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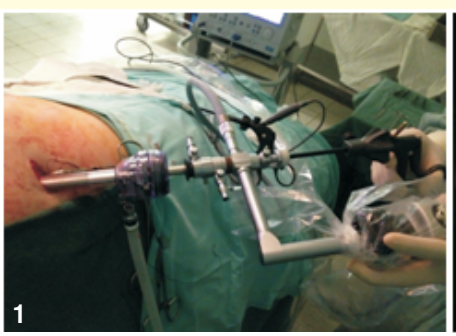

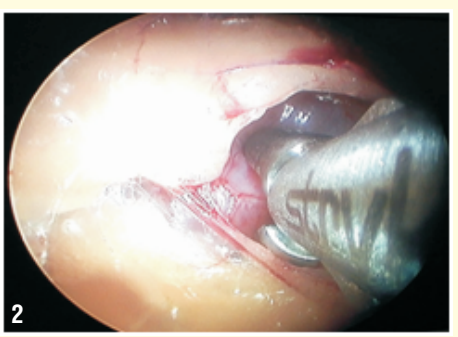

Figure 1 - Positioning of trocar and use of nephroscope for retroperitoneoscopy.
Figure 2 - Sampling renal parenchyma with a toothed biopsy forceps, through the nephroscope working channel. (Page 169)

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EDITOR'S COMMENT

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Global evaluation of men – check-up and follow-up

Women, after childhood are rapidly attended by Gynecologists, even during puberty. They become their physicians and responsible for their follow-up. On the other hand, men routinely remain for a long period of time unattended until the 5th decade of life, when, in the best of scenarios, they visit a lot of professionals of several specialties.

We could draw a long discussion about the need of medical attention between these two periods of life, but we will stick to check-up and follow-up of adult men. Usually as Urologists we are the first doctors these men interact with and at that moment we could play a definite role in providing global health evaluation.

For more than one decade Brazilian Society of Urology has launched campaigns to promote Urologists as the doctor of men. With that in mind, it is important that we recognize which are the actual needs of periodical medical care for these men.

Which is the minimal evaluation should we propose to an adult man?

Basically it is necessary a detailed anamnesis and physical exam in order to evaluate several body systems. On the contrary, since there are plenty of subsidiary exams and tests available for each specialty, it is important to stablish which are important for our target population, in order to evaluate these men efficiently. The guidelines of medical specialties provide information on this matter. They are not absolute rules, but allow for a specialty approach based on medical literature with high level of evidence. Another important aspect to be considered is that in the last 80 years we moved from an infectious diseases scenario to a pattern similar to richer countries, with mainly cardiovascular and neoplastic diseases (1). We must take into account the high prevalence of such illnesses when we decide which routine periodic evaluation to adopt.

Several models and scores were developed in order to create "*Cardiovascular Risk Stratification*", and the parameters are a mandatory part of this evaluation. Basic characteristics as age, smoking, diabetes mellitus, blood pressure, total cholesterol and fractions HDL and LDL can help define the risk of cardiovascular diseases as low, intermediate or high. This evaluation should be usually made since 40 years old and on, and the individuals with familial history of cardiovascular diseases must anticipate this approach in 10 years (2). Rest electrocardiogram, a noninvasive exam, easy to perform, may be proposed for asymptomatic men routinely, and echocardiogram must be reserved for hypertensive adults. Some exams, although popular, are not still fully validated and are not routinely indicated. For example, exercise testing, calcium score and carotid ultrasound are suggested by cardiologists for intermediate and high risk individuals (3).

It is also notorious based on the foregoing, that metabolic parameters significant role in the evaluation of adult man. Investigation of a potential glucose intolerance, for example, should begin at 45, repeated at intervals of one to three years. The dosage of

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fasting blood glucose is critical in diagnosis, and glycated hemoglobin Suggested following the glycemic control (4-6).

Also, metabolic parameters are important for the evaluation of adult men. Androgen Deficiency in Aging Males (ADAM), or adult hypogonadism, is often discussed in scientific meetings and in the press and is a recurrent topic in medical daily practice. The well documented annual lowering of total testosterone level, associated to elevation of SHBG, is better evaluated with the use of the calculation of Free Testosterone. The most reliable formula is the one proposed by Vermeulen et al (7, 8). But it is important to stress that androgenic evaluation is not routinely performed in adult men, only if there are symptoms that suggests it (7). And since some symptoms of androgen deficit are the same as presented by men with hypothyroidism, it is important to provide TSH and free T4 dosage for differential diagnosis (9).

All the above depicted evaluation is relevant, since those clinical and laboratorial parameters are directly related to several diseases, such as dyslipidemia, glucose intolerance, obesity, hypothyroidism and hypogonadism, that have common metabolic pathways.

The second main cause of death of men is tumor, so screening for these diseases is crucial. It is observed high levels of mortality due to lung cancer, followed by prostate cancer (the most prevalent in our country) and gastrointestinal tumors, according to the data of the Ministry of Health (10).

In order to detect early lung tumors, it is important to investigate smoking and to perform low dose radiation thorax computerized tomography, the ideal method for detection, although with high cost. This approach, although not completely endorsed by the medical societies, is indicated for asymptomatic adult males between 55 and 80 years old, with a history of smoking 30 packs-year and that still smokes or that quit along the last 15 years (11).

In relation to gastrointestinal system, the most important periodic evaluation is for bowel cancer. According to the recommendations of the National Institute of Cancer, it is important to provide faecal occult blood exam and colonoscopy every 10 years or less, according to risk, for patients with 50 or more years old (12, 13). On the other hand, endoscopy is only indicated by gastroenterologists for patients with symptoms or with history of familiar cancer.

At this point, being this a Urological journal, it would not be necessary to stress the importance of screening of early prostate cancer. But due the controversies published by the American Task Force and Guidelines of the American Urological Association, I decided to stress the guidelines of the Brazilian Society of Urology and Brazilian Medical Association that recommends annual evaluation of prostate to every man with 50 years of age or more, as long as life expectancy exceeds 10 years (14). It is mandatory to perform PSA dosage and digital rectal exam annually during periodic urological

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exams. Urinary tract ultrasound, routinely performed by urologists, usually is expanded to total abdominal ultrasound. This non-invasive and low cost exam allows a thorough exam of intra-abdominal organs, important for global evaluation of men.

Several other exams and diagnostic tests can be ordered during initial or periodic evaluation of adult men, beyond the scope of this paper. Male population is getting older worldwide, and demands for more health care other than only genital and urinary. In 2010, the population of men with 40 or more years old was approximately 34 million and this number will double until 2050, according to the Brazilian Institute of Geography and Statistics (IBGE) (15). In the last 50 years, global life expectancy raised around 20 years, but from the 80s, life expectancy of Brazilian people surpassed world media, and today we have reached 74 years (15, 16). Basic sanitation programs, technological advances, development of new and more efficient drugs are the main sponsors of this achievement. However, when we divided life expectancy curves according to gender, there is a world favorable difference for women (16). Lower life expectancy of men may be due to historical and cultural barriers (for men to expose their eventual fragilities), alleged lack of time for consulting, or the fact that he judges himself as the home provider. It is also observed higher levels of morbidity and mortality of diseases that are potentially treatable. Men go to the doctor less frequently.

The concept of global attention to health allows for, once the initial barrier is transposed, the Urologist to provide total medical care for the male patient. Next decade will be recognized as the 4P Medicine: predictive, custom (personal), preventive and participant. These 4 Ps must represent how we doctors must act as providers of global and total attention to men's health.

"Research is Medicine became fully fragmented in specialties. If you see a doctor due to lung disease, he is not interested in your kidneys or in your heart.... So I thing that most points must be reintegrated, beyond specialties... we will need more of the old times Medicine"
(Sidney Brenner – Nobel Prize of Medicine)

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DIFFERENCE OF OPINION

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Focal Cryotherapy in Low-Risk Prostate Cancer: Are We Treating the Cancer or the Mind?

The Cancer

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Key words: focal cryoablation, focal treatment, cryoablation, cryotherapy, focal cryotherapy, cryosurgery, prostate cancer

INTRODUCTION

In the era of PSA screening, prostate cancer faced a dramatic increase in incidence. Early detection of asymptomatic disease leads to majority of patients being diagnosed at earlier clinical stages (1). Currently, up to 90% of the patients diagnosed with prostate cancer in United States have localized disease (2). With modern cancer treatments available, patients and physicians struggle to decide among available treatment options with curative intent. Physicians and patients need to select which treatment modality will treat their cancer without morbidity. Thus, we had a surge of the development of less invasive treatments including laparoscopic and robotic surgeries, and ablative therapy.

Overtreatment and Less Invasive aggressive therapy for Localized Prostate cancer

In the PSA era, overtreatment of prostate cancer patients became a clinical and public health controversy. Therefore, active surveillance became popular and recommended in selected localized, low and intermediate prostate cancer patients (3, 4). Conversely, the lack of aggressive treatment after diagnosis of cancer may lead 50% of patients enrolled in watchful waiting cross to active treatment in a period of 5 years post-diagnosis (5, 6). Another issue is the limitations of ultrasound guided biopsies that cannot accurately grade the disease since the pathological upgrade of prostate specimens after radical prostatectomy is often seen when compared to pre-operative pathological findings (7-10).

In addition one cannot forget the emotional burden of the diagnosis of cancer and anxiety that frequently drives patients in active surveillance to seek for active treatment (11). Currently, aggressive treatment may be necessary in patients with moderate/high-risk prostate cancer (3, 4).

Unfortunately, there is no cookie cutter solution for prostate cancer patients and individual preferences, beliefs, and social economic status play a pivotal role in patient's decision making. Minority status, age, marital status, race, and D'Amico risk stratification are associated with patients who opt for less invasive treatment of localized prostate cancer (12, 13).

The American (AUA) and European Urological Associations (EAU) recommend active surveillance and monotherapy treatment options for men with low-risk prostate cancer. While, for patients with intermediate or high risk prostate cancer, the mono or multimodal therapies may achieve better cancer control (3, 4).

In 2008, the AUA's best practice statement on cryosurgery affirmed that cryosurgery is an option for patients with organ confined disease (14).

The advent of new generation cryotechnology machines, smaller probes with better control of the ice ball and better ultrasound definition made prostate cryoablation well-established and accepted worldwide technique to treat localized prostate cancer minimizing risk of urinary incontinence, erectile dysfunction, and recto-urethral fistulas when compared to earlier experiences (15-17).

Potentially, targeted or focal cryoablation of prostatic tumors may treat localized diseases decreasing the morbidity and reducing the number patients over treated with aggressive and debilitating treatments (14). The concept of targeting the cancer inside the prostate without collateral damage to the rectum, neurovascular bundles, bladder neck, and urinary sphincter is attractive and evolving (18, 19).

Controversy still exists regarding the benefits of aggressive therapy (radical prostatectomy) versus non-aggressive management of prostate cancer and the lack of survival benefits with surgery, as seen in The Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the Scandinavian Prostate Cancer Group SPCG-4 trial (20, 21).

Critics of focal cryoablation of localized prostate tumors argue that prostate cancer is known to be multifocal. A dominant lesion is often accompanied by other smaller low-grade lesions. However, with novel genetic profiling tests and better understanding of the index lesion we can better select patients for this specific treatment modality. The index lesion is associated with the highest Gleason grade, presence of lymph node metastasis, genetic profiling and other pathological determinants of progression (22-25).

Recently, the Cryo Online Data (COLD) Registry reported 1160 patients that had focal prostate cryoablation, showing an increase from 2.1% (1999) to 38.2% (2007) of cryoablation patients that received this targeted therapy for localized prostate cancer (26).

The biochemical recurrence-free survival (ASTRO criteria) for patients stratified by risk group after focal therapy was similar to whole gland cryoablation at two years clinical follow-up (26). Pathological recurrence rates during follow-up were also similar when comparing focal cryoablation with whole gland cryoablation. Since the eligibility criteria for focal cryotherapy was not defined and this study was done retrospectively, further analysis should be done.

Similarly, a small prospective study evaluating focal cryoablation (hemi-ablation) was conducted in 56 patients with unilateral low-grade prostate cancer. A total of 86% of the patients had negative biopsies during the follow-up (27).

Why cryoablation has a bad reputation?

During early cryoablation experience, the use of liquid nitrogen and inability to create a controlled ice ball, archaic ultrasound technology and absence of urethral warmers resulted in high incidence of rectourethral fistula and urinary incontinence. Moreover, these events occurred in whole gland cryoablation and in post-radiation salvage therapy patients (15, 16, 26, 28). Currently, these complications are less frequent due to the new technology and they seldom during focal cryotherapy (26). In addition, patients that had normal erectile function before focal cryoablation were more likely to maintain function after the focal treatment (58%) when compared to whole gland treatment (32.3%) (26).

Post-Radiation Targeted Therapy

While salvage treatment of failed post-radiotherapy patients can result in high complication rates associated with surgery and miss the opportunity for curative treatment (29). The complication rates for robotic-assisted salvage radical prostatectomy were as high as 47% with Clavien III-V in 35% of the patients. Within three years of follow-up, potency was maintained in only 23% of the patients and urinary control was achieved in only 45% of the patients (30). Open radical prostatectomy also had high complication rates with urinary continence rated ranging from 36 to 81%, erectile function in less than 30%, and biochemical recurrence-free probability from 37 to 55% within 5 years. The estimated cancer-specific survival at 10 years ranged from 70 to 83% (31). Salvage focal cryotherapy achieved 95.3%, 72.4%, and 46.5% biochemical-free survival at 1, 3, and 5 years of follow-up (32). A total of 3.3% of patients experienced rectourethral fistula, 5.5% experienced incontinence, and 50% of the patients maintained sexual function after salvage treatment (32). The oncological outcomes of focal prostate cryoablation reported are comparable to open salvage radical prostatectomy with improved functional outcomes and lower complication rates. Sexual function after salvage focal cryotherapy has shown to be better when compared to whole gland salvage cryotherapy (32).

It appears that the cryoablative technology is efficient even in cases of radiation failure prostate cancer. Salvage whole gland cryoablation and focal cryoablation seem as reasonable options for curative treatment of this select group of patients (32-35).

FUTURE

The options for the management of prostate cancer are transitioning to active surveillance and less invasive procedures (12, 15, 16, 36-38). The effectiveness of the treatment of localized prostate cancer will rely on accurate detection and localization of the prostate cancer cells in the body and the clinical relevance of these findings so we can efficiently select the right patients to the right treatment.

Three-dimensional computer models, alternative biopsy techniques, target biopsies, and tumor markers are potential tools that can be used to aid this task (37, 39-43).

We are still trying to understand the effects of the U.S. Preventive Services Task Force (USPTF) report discouraging PSA screening due to the imbalance of risks outweighing the benefits of prostate cancer diagnosis (44). However, it is our hope that the pre-PSA era of advanced stage prostate cancer at the time of diagnosis does not return to haunt us.

Despite the lack of randomized clinical trials comparing focal cryoablation of the prostate with other treatment modalities, the oncological and functional outcomes are pointing to a promising therapy for patients with localized disease (26, 33, 35, 45). One should not considered the focal cryoablation as "placebo" for patients that are good candidates for active surveillance but elect for an aggressive treatment option. The reality is that what we believe to be an ideal candidate for active surveillance may have a more aggressive cancer cell population or radiation resistant cells that can be treated with cryoablative technology.

Finally, the anxiety caused by the word cancer can affect the quality of life of patients and set stage to a well-known clinical challenge; "the sword of Damocles", patients that cannot enjoy life with the idea of untreated cancer.

However, data are sought after to understand the selection of optimal patients for focal cryotherapy.

CONCLUSIONS

Targeted or focal cryoablation of prostate tumors is a promising curative therapy for localized prostate cancer. Oncological outcome is comparable to available standard therapies with better functional outcomes and reduced morbidity when compared to whole gland cryotherapy. Challenges to effectively select the optimal patient for focal cryotherapy will depend on complete understanding of clinical relevance and imaging methodologies to detect localized prostate cancer cells in the body.

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DIFFERENCE OF OPINION

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The Mind

Focal Cryotherapy in Low-Risk Prostate Cancer: Are We Treating the Cancer or the Mind?

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INTRODUCTION

Since the late 1980s, the widespread use of PSA for opportunistic prostate cancer screening allowed treatment at an earlier stage, and at least in part, was responsible for a 30-40% decline in prostate cancer mortality (1). However, the stage migration favoring early localized disease, inevitably also brought the downstream effects of a diagnosis, including the enthusiasm for aggressive treatment of virtually all men who are diagnosed, driven by a myriad of forces: - inability to precisely determine the long-term risk of harm without treatment, - factors other than disease characteristics such as the limitation of using evidence to inform practice (2), and perverse incentives that often drive physician recommendations (3), commensurate with the adoption of robot-assisted laparoscopic radical prostatectomy (4, 5).

Consequently, considering the relatively high prevalence and ease of detecting, mainly low-risk cancers (6), the benefits of PSA introduction to clinical practice came with the substantial cost of over diagnosis and over treatment of many men, raising the question of whether PSA screening is associated with more harm than benefit (7).

Considering the lead-time of 6-12 years afforded with PSA testing and the generally long natural history of prostate cancer (8), high-level evidence supports the low risk of harm without treatment from favorable-risk prostate cancer in older men.

In fact, while an estimate of number needed to screen (NNS) or number need to treat (NNT) at a single point in time can be misleading, and also sensitive to comorbidity status at baseline, using a bootstrap approach the 95% CIs for NNS can be as wide as 323 to 1052 and NNT 11 to 35 to prevent one prostate cancer death at >10 years (9).

In the PSA era, Parker et al. (10) estimated the 15-year risk of prostate cancer mortality to be 0-2%, for men aged 55-74 years diagnosed with a Gleason score of ≤6 and managed conservatively, such as due to considerable lead time, curative intervention is unlikely to improve health for those with a <20 year life expectancy.

Even for those patients that to a large extent would not be considered favorable risk by today's classification schemes and did not have screen-detected prostate cancers, when aged ≥65 years, no overall, cancer-specific, or metastatic-free survival benefit was associated with surgical treatment when compared with no treatment at 12 years, suggesting the probable absence of a cancer-specific survival benefit well beyond 12 years in The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) (11).

Trying to minimize the impact of over diagnosis, a consensus conference also recommended "consideration be given to changing the term used to describe low-grade prostate cancer to one other than cancer" (12). The problem is that the cancer grade, which is the strongest predictor of cancer-specific mortality with or without treatment of prostate cancer, can be misclassified in as high as almost half of cases when evaluating 12 core biopsies and radical prostatectomy specimens (13).

Then, a primary concern with a surveillance option is the underestimation of cancer grade on a prostate biopsy that could potentially compromise long-term cancer control. This uncertainty drives many physicians to recommend curative intervention fearing the real chances of risk underestimation, generating wide variations in practice patterns of management for favorable-risk prostate cancer (5).

In this regard, in an attempt to limit the uncertainty regarding the long-term risk of a prostate cancer that is found to be of low grade on a prostate biopsy, subclassification of men as very-low-risk disease is associated with a lower likelihood of adverse features at the time of radical prostatectomy, and biochemical recurrence after treatment (14, 15), when compared with those with low-risk disease. However, this strategy denies the benefits of active surveillance to many men with indolent disease who do not fit the more stringent criteria.

An additional sensitive point is the unanswered question about the extent, if any, to which a man on surveillance who undergoes delayed intervention risks losing the opportunity for control of disease (5). However, it could be argued that deaths occur in men who had advanced disease to begin with, and that surveillance usually does not compromise length of life (16).

While the 15-year risk of death from another cause for a man age 65 years would be ≈ 40% (17), a man with a very-low-risk prostate cancer entering an active surveillance program who chose surgery if biopsy re-classification occurred, would have over a 10-year period, a 10% risk of having a Gleason score 3 + 4 on surgical pathology and a 15-year risk of a prostate cancer death of < 1% postoperatively; and over 10 years a 13% risk of a Gleason score 4 + 3 on surgical pathology, and a 15-year risk postoperatively of a prostate cancer death of ≈1% (5). It was estimated that as compared to active surveillance for favorable risk prostate cancer, the average projected increase in life expectancy with immediate radical prostatectomy was 1.8 months (18). In the end, death in men on active surveillance occurs most commonly from cardiovascular disease, and death from pros¬tate cancer is rare.

In terms of quality of life of men age 65 years managed with surveillance and curative intervention, active surveillance was associated with the longest quality-adjusted life expectancy (QALE) and surgery the shortest, but the results were highly dependent on a man's preferences with respect to living with cancer and having it treated (19).

In other words, under the most optimistic assumptions regarding postsurgical erectile dysfunction and incontinence, a man age 67 years in average health with low-risk prostate cancer, would experience ≈10 years of side effects for each additional year of life gained (20).

In support of exploring patient preferences for living with cancer and side effects of treatment as part of shared decision making, while definitive treatment brings a low probability of adding years to life in the low risk scenario, management options with lower side-effect profiles (e.g. focal therapy) might be associated with a lower cost in a broad perspective.

The enormous disparity between the prevalence of histological prostate cancer and the lifetime risk of mortality from prostate cancer (≈2%) emphasizes that most low-risk patients should not be treated at all. However, the burden of active surveillance, related to its psychological impact, repeated biopsies and associated morbidities, cost and risk of missing the treatment window, needs management.

TREATING MINDS?

It is well accepted that given the alarmingly high rates of over treatment for prostate cancer (11), any man with favorable risk prostate cancer should understand that without treatment, harm from disease is unlikely in the first decade. However, progression of disease could occur in some men resulting in harm without treatment in the second decade after diagnosis and beyond (5).

In this context, the impact of living with ''untreated'' cancer must be considered when deciding whether to undergo active surveillance; patients and clinicians must weigh the psychological burden of living with prostate cancer and manage the uncertainty associated with gaps in the published literature.

Although one must acknowledge that those patients choosing surveillance may have made this decision because they experienced low anxiety and distress and are psychologically prepared in advance, the surveillance process can also impose a burden (21). For example, events such as a screening visit or follow-up PSA measurement evoke an increase in concern that decreased significantly after a normal result (22).

Suggesting an additional psychological burden in terms of anxiety over the uncertainty of the future or fear of losing the opportunity for a cure as important drivers of treatment (23), up to 18% of patients initially under active surveillance for very-low-risk prostate cancer might be over-treated with no evidence of progression (24).

Supporting the hypothesis that even very-low-risk prostate cancer when untreated undermines psychosocial domains, we recently showed that when focal cryoablation, brachytherapy and active surveillance are offered in an equal access protocol, those choosing surveillance were older, presented higher hopelessness (BHS) and lower general health perceptions (SF-36) scores than patients opting for focal cryoablation and brachytherapy, p=0.0014, p=0.0268 and p=0.0168, respectively. Patients on brachytherapy had higher IPSS scores compared to those under focal cryoablation and surveillance, p=0.0223. For all included patients Spearman correlation (r_s) was very strong between BHS and general health perceptions (r_s=-0.800, p<0.0001), and weak/moderate between age and BHS (r_s=0.405, p=0.026) and between age and general health perceptions (r_s=-0.564, p=0.001) (25).

In an attempt to avoid living with ''untreated'' cancer, and filling the gap between surveillance and radical definitive treatment (radical prostatectomy and external radiation), focal therapy might in some circumstances represent the halfway between the hypothetical under-treatment and over-treatment (25).

As decisions about treatment receipt are unquestionably influenced by cancer related fear (26), men should be provided with more psychosocial support to perhaps delay treatment and the ensuing decrements in health related quality of life (HRQoL). In such a scenario, psychological support may be indicated during active surveillance in a selected group of patients (27), and eventually a focal therapy offered to avoid unnecessary radical treatment.

One should consider that patients might leave active surveillance prostate cancer programs motivated by their own personal criteria for seeking treatment, which may differ from formal clinical or physician criteria (23). Thus, we believe that there is a need to re-examine the psychological distress and the directed support patients under active surveillance are getting.

FOCAL THERAPY

Both active surveillance and focal therapy are based on the rationale that tissue preservation is important when it is possible, however focal therapy adds morbidity to surveillance.

While most low-risk tumors do not need treatment, for those cases that need treatment after reclassification, a nerve-sparing radical prostatectomy may be the most rational option for the youngest and healthiest patients.

Considering the relatively short follow up of focal therapy cohorts, recent evidence suggests that focal treatment can rescue some patients that are uncomfortable with the concept of “untreated” cancer, thus avoiding unnecessary radical treatment (treating their minds). However, a strategy of adding focal therapy to active surveillance to broaden the group of men that will be able to adopt a tissue preserving strategy is yet to be proven in terms of oncological safety in avoiding radical therapy at the whole-gland level (28).

Uncertainty that remains relates to the durability of outcomes over the longer term and the comparative effectiveness of focal therapy as compared to other treatments. In the future, improvements in diagnostic precision (shared by active surveillance strategy), and also in ablation precision are needed for focal treatment advancements (28).

FUTURE

The USPSTF advocates against PSA screening because risks likely outweigh benefits (7). However, to avoid a return to the pre-PSA era when men with prostate cancer typically presented with advanced incurable disease, an alternative solution would be to treat selectively after diagnosis, offering treatment based on the patient’s disease characteristics, co-morbidity risks, and personal preferences. This would likely result in a decrease in the NNT for each death avoided (29), eventually leading to a re-consideration of acceptance of the value of prostate cancer screening.

While we await improved markers of an indolent and lethal phenotype, and better imaging to monitor favorable-risk disease (30), active surveillance is an underutilized management approach that could reduce overtreatment (31). Focal therapy might be considered an important theoretical part of an active surveillance program as a tissue- sparing alternative for men that wish treatment for a favorable risk cancer.

Before acceptance of focal treatment as an oncologically effective approach, there are important unanswered questions: Can focal treatment really alleviate the psychological burden of men unable to live with “untreated” cancer with acceptably low morbidity, avoiding unnecessary radical treatment? Is focal therapy an alternative to active surveillance that could reduce cost and morbidity and thus be of higher value as compared to surveillance?

CONCLUSION

The standard of care for most men with screen detected low-risk prostate cancer in most evidence-based guidelines is active surveillance. Focal therapy, which is not yet an accepted treatment in any guideline, may complement active surveillance for those men that do not tolerate living with "untreated" cancer, further minimizing the overtreatment rates. In the last scenario, there is no evidence to support that focal treatment is acting beyond patients' minds.

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REVIEW ARTICLE

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Accuracy of Percutaneous Core Biopsy in the Diagnosis of Small Renal Masses (≤4.0 cm): A Meta-analysis

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ABSTRACT

Objective: To use meta-analysis to determine the accuracy of percutaneous core needle biopsy in the diagnosis of small renal masses (SMRs≤4.0 cm).
Materials and Methods: Studies were identified by searching PubMed, Embase, and the Cochrane Library database up to March 2013. Two of the authors independently assessed the study quality using QUADAS-2 tool and extracted data that met the inclusion criteria. The sensitivity, specificity, likelihood ratios, diagnostic odds ratio (DOR) and also summary receiver operating characteristic (SROC) curve were investigated and draw. Deek's funnel plot was used to evaluate the publication bias.
Result: A total of 9 studies with 788 patients (803 biopsies) were included. Failed biopsies without repeated or aborted from follow-up/surgery result were excluded (232 patients and 353 biopsies). For all cases, the pooled sensitivity was 94.0% (95% CI: 91.0%, 95.0%), the pooled positive likelihood was 22.57 (95% CI: 9.20-55.34), the pooled negative likelihood was 0.09 (95% CI: 0.06-0.13), the pooled DOR was 296.52(95% CI: 99. 42-884.38). The area under the curve of SROC analysis was 0.959±0.0254.
Conclusion: Imaging-guided percutaneous core needle biopsy of small renal masses (SMRs≤4.0 cm) is highly accurate to malignant tumor diagnosis with unknown metastatic status and could be offered to some patients after clinic judgment prior to surgical intervention consideration.

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Nephrostomy, Percutaneous; Biopsy; Carcinoma, Renal Cell

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INTRODUCTION

Renal cell carcinoma (RCC) is in the top 15 most common malignancies of both men and women and incidence has steadily increased since 1975 (1). Increasingly, these malignant tumors are recognized more frequently as small masses (2). CT-guided and sonographically guided percutaneous biopsy of small renal masses seemed to be effective in early reports. Several studies of renal mass biopsy have demonstrated high degrees of accuracy between 86%-95.5% (2-5), with accuracy for the Fuhrman nuclear grade at 46%-85% (4, 5). The sensitivity and specificity have been high with values between 93%-100% (3, 4, 6). The accuracy of percutaneous biopsy on small renal masses (≤4 cm), however, has not been widely debated and might be owing to tumor mobility and difficult needle penetration. We still believe that there has been a paucity of data on biopsy performance for small renal masses that could be extracted and summarized.

No large randomized controlled trials comparing percutaneous to other methods of metastatic detection are available; we set out to review the available literatures on percutaneous renal mass biopsies. Therefore, this meta-analysis included only well-designed, comparative studies in order to mainly evaluate the safety and accuracy of percutaneous core needle biopsy in diagnosis of patients presenting with small renal masses (SMRs≤4.0 cm). The purpose of this meta-analysis is to determine the diagnosis accuracy of images-guided percutaneous needle biopsies of small renal masses in adult patients.

MATERIALS AND METHODS

Search strategy

A Medline search of the English-language Literature searches were performed to identify reviews of well-designed, comparative studies on the accuracy of percutaneous core needle biopsies in diagnosis of RCC in patients presenting with small renal mass. The search included words identified in the whole text as well as in the Medical Subjects Heading (MeSH) terms: 'kidney', 'renal mass', 'renal cell carcinoma', ' percutaneous', 'needle', 'diagnosis', 'biopsy', 'accuracy'. The following databases were used: Pubmed (1966-March 2013), Embase (1974-March 2013), the Cochrane Library (2011 issue 5). No language restrictions were used. Publications addressing evaluated renal masses or recurrent disease after radiofrequency ablation or nephrectomy were excluded.

Eligibility criteria

Publications were included in the meta-analysis if the pre-set inclusion of below were met: (1) the renal lesions had to be limited in size (≤4cm) and location (kidney mass); (2) all histological diagnoses of large-core needle biopsy specimens had to be confirmed by either surgical pathology or follow-up (defined as a minimum of 12 months in at least 90% of the patients). (3) The absolute number of benign and malignant diagnoses had to be derivable; (4) Renal core biopsy was performed under ultrasonography or CT guidance using local anesthesia and an 18-G core biopsy gun. Exclusion criteria included masses >4.0 cm in any dimension and biopsy of tumor masses outside the kidney, lacking of confirmed by surgical pathology or adequate follow-up for the mass diagnosis, vague patients counting and different biopsy tools and methods, others which could not meet our eligibility criteria.

Data Extraction and Quality Assessment

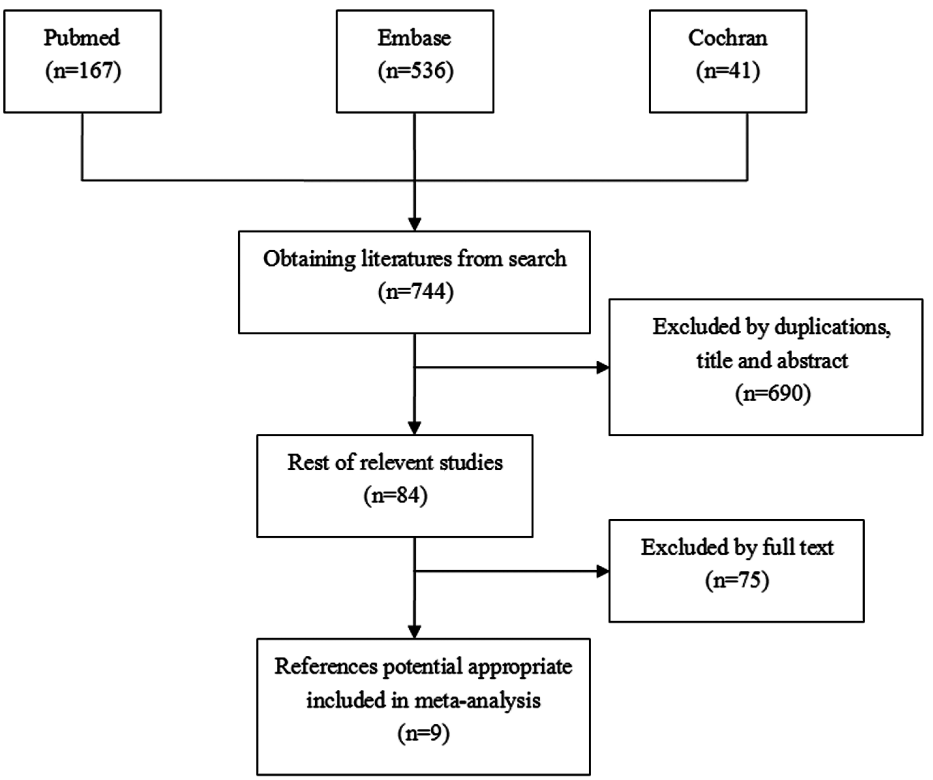
A total of 744 papers were obtained in our initial search, 690 of which failed to meet our inclusion criteria. Of the 84 studies remaining, 75 publications were excluded for lacking follow-up data (22 papers), unsatisfactorily confirmed histological diagnoses on needle biopsy (16 papers), failed to allow absolute patient small mass number to be derived (≤4 cm)(37 papers). Only 9 studies (7-15) were included (Figure-1).

The aim of our study was to evaluate the accuracy of percutaneous core needle biopsy of small renal masses (≤4 cm), especially for the malignancy. The results of the percutaneous renal mass biopsy were defined as positive if the pathologic examination presented a RCC, a metastasis, or a specific extrarenal malignancy invading the kidney. In all other cases, the biopsy results were considered negative, including those specimens in which cytopathology revealed malignancy not otherwise specified (i.e. the malignant cells were found, but the type of tumor could not be specified).

All positive percutaneous renal mass biopsy results (i.e. identification of a specific malignancy) which were confirmed by surgical procedure, surgical pathology or follow-up information (individuals refusing surgery however proved malignancy in a follow-up) were considered true-positive. The false-positive rate was defined as zero because there usually no positive biopsy results would outcome benign mass. Studies were included if patients with negative percutaneous renal mass biopsies were followed up to confirm negative or metastasis.

If the malignancy was not identified or characterized, the results of percutaneous renal mass biopsies were still considered negative despite the resulting malignancy identification could lead to different management. If either surgical pathology or follow-up confirmed the percutaneous renal mass biopsy negative result, we characterized the

Figure 1 - Flow chart for Study and sample search strategy.



biopsy result as true-negative. If the final diagnosis and the diagnosis based on the initial results of the percutaneous renal mass biopsy were discordant, also including the malignancy not specified initially, the results of the biopsy were defined as false-negative. Our use of these methodological definitions is in accordance with a similar large prospective study (16).

Quality assessment of the study was assessed by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist (17). Briefly, QUADAS-2 is a 4-domain tool, the last domain of which assists authors of systematic reviews in rating: 1) bias and 2) applicability. The risk of bias is assessed in four key areas: patient selection, index test, reference standard, and flow and timing. Concern for applicability is assessed in three key areas: patient selection, index test, and reference standard. For both categories, risk of bias and concern for applicability, the individual criteria were classified as low risk, high risk, or unclear and the results were presented using tables from the QUADAS web site (www.quadas.org) (Table-1 and Figure-2).

Data analysis

One author extracted the data from included studies and entered them into the data extraction form. A second reviewer checked the extracted data to ensure data quality. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned that corresponding author would decide.

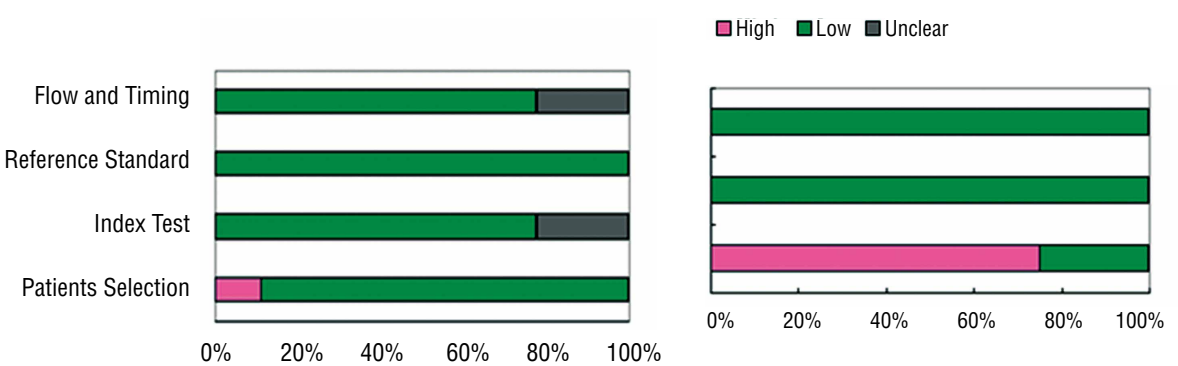
The 2x2 data were summarized in forest plots of sensitivity and specificity for each study. We calculated and assessed the true positive rate (TPR, sensitivity), specificity, likelihood ratios, diagnostic odds ratio along with 95 % confidence intervals (CI). Since the false positive rate was de-

Table 1 - Quality Assessment for 9 studies (QUADAS 2).

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
A Volpe et al.	☺	☺	☺	☺	☹	☺	☺
C.Thuillier et al.	☺	?	☺	?	☹	☺	☺
E.Lechevallier, et al.	☺	☺	☺	☺	☹	☺	☺
Frank J. et al.	☺	☺	☺	☺	☹	☺	☺
I. Eshed et al.	☹	☺	☺	☺	☹	☺	☺
M. J. Leveridge et al.	☺	☺	☺	☺	☺	☺	☺
Rou Wang, et al.	☺	☺	☺	☺	☺	☺	☺
S. Rybikowski et al.	☺	?	☺	?	☹	☺	☺
Stuart R. et al.	☺	☺	☺	☺	☹	☺	☺

☺ Low Risk; ☹ High Risk; ? Unclear Risk

Figure 2 - Graphical Display of 9 studies results (QUADAS-2).



a: proportion of studies with low, high, unclear risk of bias

b: proportion of studies with low, high, unclear Concerns regarding Applicability

fined as 0, a correction was required to make 2x2 tables rational. Thus, a correction value of ½ was added to all cells in the 2x2 matrix. Heterogeneity was assessed by means of the Cochran Q and I^2 test. Heterogeneity was classified as not likely contributory (I^2=0%-40%), moderate (I^2=30%-60%), substantial (I^2=50%-90%), or considerable (I^2>75%) (18). Pooled summary of sensitivity and specificity was calculated by using the DerSimonian and Laird random-effects models for weighted

if present. To assess the diagnostic accuracy of the percutaneous core needle biopsies of small renal masses, we used the Rutter and Gastonis version of formulas for constructing summary receiver operating characteristic (SROC) curve. To identify if publication bias was present in our study, we calculated the diagnostic odds ratio inverse of the square root of the effective sample size from Deek's funnel plots for all included studies.

Meta-analysis in this study was conducted with the Meta-Disc software package (Clinical Biostatistics Unit, Ramony Cajal Hospital, Madrid, Spain) (version 1.40) and Stata (version 11, College Station, TX, USA); probability values of less than 5% were considered significant.

RESULTS

Search results and characteristics of studies

Our initial search yielded 744 literatures and the process of study selection is summarized in Figure-1. In total, there were 1020 patients and 1156 percutaneous core needle biopsies in 9 studies. All failed biopsies without repeat biopsies or quit from follow-up/surgery result were excluded (232 patients and 353 biopsies). Finally, 788 patients and 803 percutaneous core needle biopsies were included in our meta-analysis and Table 2 summarizes the main characteristics of included studies.

Quality assessment

Table-2 and Figure-2 summarized the methodological quality of our nine studies assessment by QUADAS-2 tool. If the answers to all questions of a domain are judged as 'yes' indicating low risk of bias, then this domain will be judged to be at low risk of bias. In advert, if one judged as 'no' would indicate 'high risk', the potential bias might exist. 'Unclear' indicated insufficient information to determine whether partial verification was present.

Of the 9 studies' risk bias, 8/9 provided clear definition of an exclusion criteria, one study just described the basic information about subjects without exclusion criteria and thus scored "high risk". Two studies (8, 14) did not show enough information about the methods in details clearly, and also did not described an exact time of interval between the biopsies and follow-up of patients. Studies where language differences were thought to exist were scored 'unclear' in the index tests bias and patient flow and timing domains which we were not sure about in these studies. The remaining studies presented a clear interpretation in all the questions of domains and scored well. In relation to applicability, patient selection criteria in 2/9 studies were in accordance to our analysis inclusion criteria and scored well, the other 7 studies might have some different aims, neither some patients were not applicable for our inclusion criteria and were excluded from our analysis. So we considered it might have high risk bias in patient selection domain. The other two domains scored well for all studies.

Diagnostic accuracy

Because of our definition about the true positive, which is the specific malignancy biopsies could be confirmed by surgery procedure or follow-up final diagnosis, the false positive could not exist, that's to say, if the cytopathology report of the biopsies defined a malignancy, the corrected benign results conducted from surgery procedure or follow-up would mostly never happened. So the specificity would be calculated as 100%.

The pooled sensitivity was 94.0% (95% CI: 91.0%, 95.0%, p=0.28), with I2 of 17.7% (no likely contributory), specificity was 100% (95% CI: 98.4%, 100%, p=1), with I2 of 0% (no likely contributory). The pooled positive likelihood was 22.57 (95% CI: 9.20-55.34, p=0.54), the pooled negative likelihood was 0.09 (95% CI: 0.06-0.13, p=0.13) (Figure-3).

The pooled DOR was 296.52 (95% CI: 99. 42-884.38, p=0.36). The overall diagnostic accuracy according to the results of SROC curve analysis was 0.959 ± 0.0254 and the overall diagnostic accuracy (Q*) was 0.903 ± 0.037 (Figure-4). Thus, percutaneous core needle biopsies to diagnose malignancy in small renal masses (≤4 cm) is a highly accurate method.

Publication bias

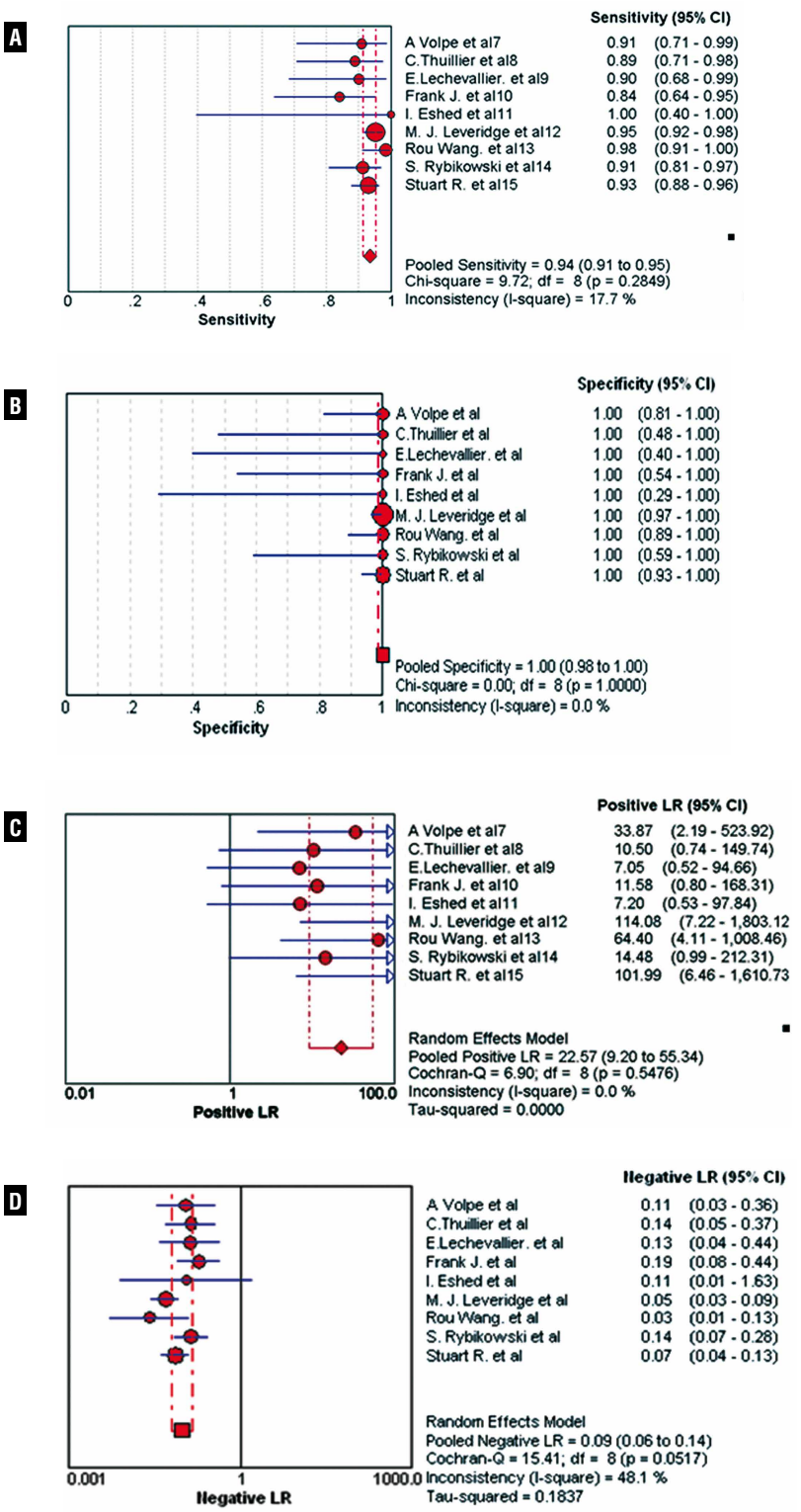
Deek's funnel plots of diagnostic odds ratio inverse of the square root of the effective sample size was constructed to assess the publication

Table 2 - Basic characteristics of the included studies of using 18 gauge needles biopsy on ≤4 cm renal mass.

Study	Country and published time	Research Time	Patients (eligible/ all)	Biopsy (eligible/ all)	Nondiagnostic biopsy	RB (≤4 cm)	Follow-up (months)	TP	FP	FN	TN	Excluded patients number and reason
A Volpe et al.[7]	Canada 2008	Jan 2000 - May 2007	40/91	40/100	16/100	2/16 (M:1/2)	22	20	0	2	18	51pts lack surgery or follow-up confirmation
C.Thuillier et al.[8]	France 2008	Feb 1998- Nov 2006	32/53	32/53	6/53	0/12	52	24	0	3	5	21 pts lack surgery or follow-up confirmation
E.Lechevallier, et al.[9]	France 2000	Jun 1995- Oct 1997	26/26	30/73	11/30	3/11 (M:2/3)	14	18	0	2	3	1 pts failed and quit and 6pts unclear
Frank J. et al.[10]	U.S 2002	Oct 1990 - March 2001	31/113	31/115	NC	NC	32	21	0	4	6	82 pts tumors diameter >4.0 cm
I. Eshed et al.[11]	Israel 2003	Jan 1996 - Aug 2001	6/22	7/22	1/6	1/1 (NC)	>12	4	0	0	3	16 pts tumors diameter > 4.0 cm
M. J. Leveridge et al.[12]	Canada 2011	Jan 2000 - Dec 2009	291/294	291/345	67/345	12/67 (M:8/12)	25	221	0	11	59	1 pts lost follow-up 57 biopsies unclear
Rou Wang. et al.[13]	U.S 2009	Feb 1999 - Oct 2006	90/106	93/110	10/110	1/10 (M:0/1)	13	60	0	1	32	9 pts quit and 7 pts lost follow-up (lack surgey or follow-up)
S. Rybikowski et al.[14]	France 2008	Jan 2001 - Oct 2006	63/65	68/70	12/70	4/12 (M:2/4)	19	52	0	5	7	2 pts lost follow-up
Stuart R. et al.[15]	Australia 2012	1998- 2009	209/250	211/268	54/268	18/54 (M:10/18)	19-36	146	0	11	54	18 pts lost follow-up 23 pts diagnosis failed
Total	-	-	788/1020	803/1156	NC	>41		566	0	39	187	-

NC= not clear; **M=** malignancy; **pts=** patients; **RB=** repeat biopsy

Figure 3 - Forest plots of index.



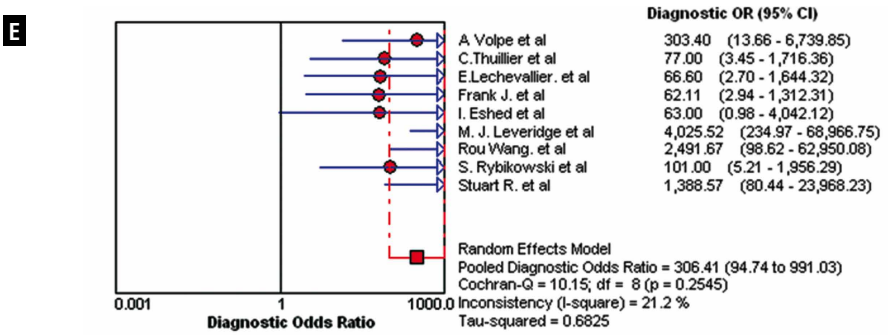
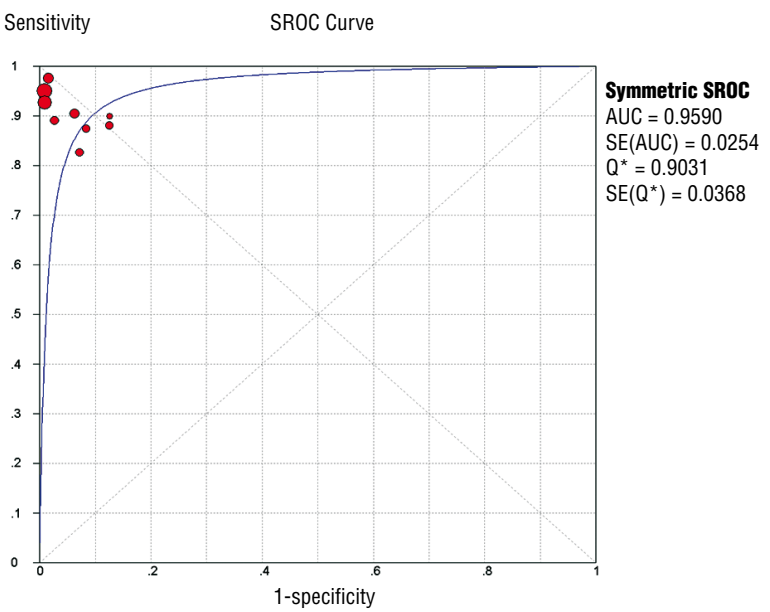


Figure 4 - SROC curve.

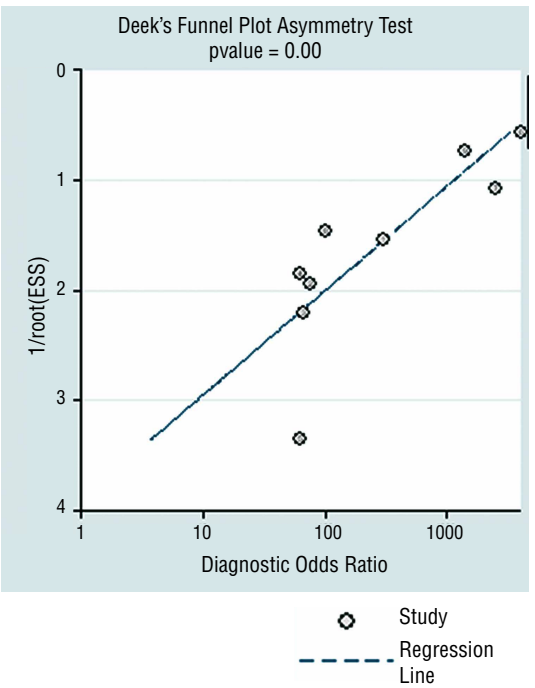


bias of literature. The shape of the funnel plots revealed a bit asymmetry (p=0.00, Figure-5). An existing publication bias were indicated; the reason for this might be related to the presence of a potential publication bias, a language bias, inflated estimates in smaller studies, and the lack of publication of small trials with opposite results.

COMMENTS

Recent advances in radiological examinations have improved small renal mass malignancy diagnosis accuracy. In many cases, if an enhanced effect in radiographic appeared, renal lesions were assumed to be malignant and patients were directed toward surgery intervention mostly. However, some solid and complex cystic lesions cannot be well defined and diagnosed by images; and urologists still encounter some masses that cannot be definitively categorized as either benign or malignant, especially for small renal masses (≤4cm). Therefore, percutaneous needle core biopsy is becoming an efficient tool in the characterization of incidentally discovered SRMs in the diagnosis for some uncertain renal lesions. In our analysis, data of the pooled sensitivity, pooled positive likelihood, pooled

Figure 5 - Deeks' Funnel plots of publications bias.



negative likelihood was similar to many literature reviews demonstrating that renal mass biopsy has an overall success rate above 90% (19, 20).

Accuracy might be defined by several variables, including the diagnostic ability to subtype/grade tissue, as well as the ability to obtain an interpretable tissue specimen to conduct a consistent diagnosis. The RCC subtype was not routinely provided; however available, the accuracy for RCC subtype is estimated at nearly 96.6% (13). Tissue grade, another diagnosis index, was not reported as high accuracy as the subtype reports. Some studies showed that the biopsies accuracy for the Fuhrman nuclear grade was lower at 46%-85% (4, 5).

In respect to the complication rates of the percutaneous biopsy, numerous studies (4-6) have already presented enough evidences that there is a very low complication rate. The most common complications observed are bleeding, syncope, flank pain, pneumothorax, etc. The most feared potential complication is tumor seeding, however, similar to several other analyses (4-7) no contemporary study has observed this complication. In the 9 included studies of our meta-analysis, the major complications and mortality reports were extremely low.

As observed in many meta-analysis of diagnostic test, the concept of the false negative remains a complex issue. Some patients received an indeterminate biopsy on their mass, which does not precisely determine subtype even it was a malignancy. Moreover, some patients' mass may be compounded by some existence of hybrid tumors containing elements of benign and malignant histology after surgical intervention, such as oncocytoma related to chromophobe RCC (21). In all such cases the event was defined as false negative. Only truly identified subtype of the benign / malignancy could be recognized as true negative/positive. This definition, while strict, is much in accordance with similar studies (10, 13).

In our analysis of 9 included studies, there were 71.5% biopsies (561/788) that were true positive malignancy and 29.7(233/788) truly benign, the ratio between malignancy and benign was 2.4:1 which agrees nicely to others' reports (5, 12, 13, 20). As the high morbidity of malignancy in SRMs suggests a probably trend toward over treatment of these mass with surgery intervention, some reports indicate that only one third of SRMs would become significant if managed conservatively (22). Some studies showed that biopsy could alter management in 41%-61% of cases (5, 6, 16).

If the patient receives an initially non-diagnostic biopsy, repeat biopsy is recommended. In our analysis, repeat biopsy was carried out in 41 patients and 23 patients were malignancy after repeat biopsies in 9 studies. Laguna and colleagues (23) analyzed published renal-mass biopsy series and determined that repeat biopsy or surgical resection of tumors followed indeterminate biopsy in 46.4% of cases, and that repeat biopsy identified cancer in 71% of cases. That means that if normal, insufficient tissue or necrosis obtained from the initial biopsy is caused by technical failure, a repeat biopsy is necessary with respect of 70% malignancy morbidity in SRMs.

Like other meta-analyses of diagnostic tests, our work has limitations. We have tried to identify and calculate all the studies about diagnosis accuracy of the percutaneous core needle biopsies of the small renal mass (≤4.0 cm). By means of an extensive Medline-based search, we aimed to retrieve and extract all published data available regarding SRM

percutaneous core needle biopsy diagnosis of malignancy. Some published studies may have been overlooked due to our strict exclusion criteria. Given diagnostic accuracy studies require large sample numbers and long follow-up periods with which to facilitate metastatic events, it seems likely studies of this magnitude would miss follow-up data and generate bias. Furthermore, publication bias (a lower probability of the publication of negative results) was more difficult to avoid than it would have been in a meta-analysis of a randomized controlled trial. Future studies should follow the Standards for Reporting of Diagnostic Accuracy recommendations and also include enough subjects.

CONCLUSIONS

Our meta-analysis identified that imaging--guided percutaneous core needle biopsy of small renal masses (SMRs≤4.0 cm) is highly accurate in differentiating benign from malignant tumors. We propose percutaneous core needle biopsies be offered to adapted patients prior to consideration of surgical intervention. Accordingly, a number of unnecessary nephrectomies might be avoided by tissues biopsy pathology.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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"I will not cut, even for the stone": origins of urology in the hippocratic collection

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ABSTRACT

The Hippocratic Collection, including the most of ancient Greek medicine, remains still interesting, despite the recent advances that transformed definitely the urological healing methods. Considering the patient as a unique psycho-somatic entity and avoiding high risk surgical manipulations were the leading principles dictating the everyday practice. Contemporary physicians can still learn from the clinical observations in times of complete absence of laboratory or imaging aid, from the prognostic thoughts, the ethics, and the philosophical concepts, represented by the Hippocratic writings, tracing into them the roots of Rational Medicine in general and Urology in particular.

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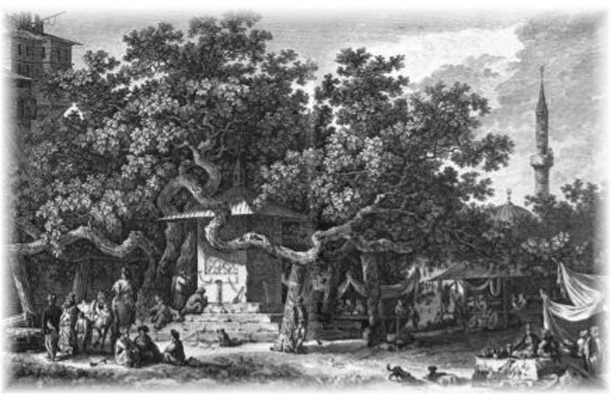
INTRODUCTION

I will not cut, even for the stone, but I will leave such procedures to the practitioners of that craft (1).

The roots of a rational approach to medicine, particularly to that of the objective observation by the bedside of the patient, are attributed to Hippocrates, a member of a family of well-known physicians on the island of Kos (2) (Figure-1). He lived and flourished in a very particular period in classical Greece, the golden age of Pericles (5th century), when many dominant personalities made too many significant contributions to Western civilization (3). Among the scientific achievements of this period, the Hippocratic medicine developed the main concepts of the medical specialties. Some topics in Urology, such as uroscopy and stone disease, are presented here. The main references derived from the famous Hippocratic treatise entitled Aphorisms, an anthology of seven sections containing medical truths included in one or two phrases, like epigrams.

The most important healing methods are surgery (including the use of knife, lancet, and cautery), blood-letting, baths, drugs, ointments and plasters, fomentations and control of lifestyle (diet and exercise). There were no reliable anesthetics and antiseptic agents, making a surgical operation quite adventurous and painful, while

Figure 1 - The famous plane tree in the island of Kos, native place of Hippocrates, under which the great physician of classical era teached young medical students (Engraving by Comte de Choiseul-Gouffier, Voyage pittoresque de la Gréce, 1782).



physicians and patients agreed on the avoidance of this procedure. Historians often comment that Hippocratic medicine delayed the development of Urology by condemning the cutting of the bladder for a stone's excision, but only the inexperience was condemned. On the contrary, the performance by the specialists was favored pre-announcing the future urological surgeons (4).

This paper intends to present the contributions of the Hippocratic writings to two main branches of the urologic specialty: the uroscopy (macroscopic urine observation) and the theory of the renal stone formation, both based on the study of the original Greek text.

Urological contributions of the hippocratic collection

A detailed study of Corpus Hippocraticum reveals several disorders of the urinary tract (5). The observations concerning the anatomy and physiology of the related organs and the etiology and treatment of various urological diseases seem accurate. Furthermore, the theory of stone formation is still valid and the diagnostic interpretations of the macroscopic urine examination (uroscopy) are still respectful (6). It is emphasized that no other system or organ of the human body gives us so much diagnostic or prognostic information by its excretion as does the urinary tract: The urine must be observed to see how far it resembles that passed in health. The less it resembles healthy urine, the more diseased it is; the more it resembles it, the healthier it is. (Aphorisms VII, 67). The analysis of the urinary system in those times, where anatomic dissections were not allowed was rare and coincidental. The holistic approach combining information clinical observations from all organs added to the urologic experience and concluded to interpretations accepted until today. Moreover, the reluctance of undertaking cutting of the stone by cystotomy seems as evidence of evaluating the dangers and preserving the principle primum non nocere (Epidemics I, 11). Hippocrates considered that the physician must have two special principles in mind, namely, to do good or to do not harm.

Some operations on the kidney were not avoided; pyonephrosis and renal abscess were considered as operable cases and drainage by deep loin incision was recommended. For many centuries, cystotomy tended to cause severe disability and even death. Some complications were also reported such as the leakage of urine, common also after incisions on other organs (bowel). The most severe complication of cystotomy seemed to be gangrene and necrosis of the testis, due to the cut of the spermatic cord (2). The Hippocratic advice to the physicians was to avoid this procedure if possible, introducing the category of high risk operation, only for specialists, and attempting to protect the patients from untrained healers. Herodotus mentioned some specialists he met during his visit to Egypt: doctors for eyes, teeth, the abdomen and for obscure internal diseases (7).

One of the most typical examples refers to the need for differentiating the upper from the lower urinary tract infection: (8) Small fleshy objects, the shape of hairs, in the urine which is thick, mean there is a discharge from the kidneys (Aphorisms IV, 76) and When blood clots in the urine are accompanied by strangury, abdominal and perineal pain, it is the parts about the bladder which are affected (Aphorisms IV, 80). The astuteness of the objective clinical observations in times of deteriorated anatomic knowledge is impressive (9). Most of the anatomic passages of the Corpus seem to have been based on animal dissection or

secret human dissection (3). It is noteworthy that Hippocrates baptized many of the urological terms and diseases, such as lithiasis (=stone disease), cystitis, cystotomy, nephritis, orchitis, strangury and many others. However, it was possible to recognize the kidney and the bladder dysfunction and their clinical manifestations in disease.

The theory of renal stone formation

The Hippocratic concept of renal and bladder stone formation were based on detailed clinical observation and uroscopy (7). The possible ways of genesis of lithos (Greek word for stone) are described in several treatises of the Corpus.

The presence of a sandy sediment or of stones in the urine means that originally tumors grew in relation to the aorta and suppurated. Then stones were squeezed out through the blood-vessels together with urine into the bladder (On the Nature of Man, 14).

In one of the treatises attributed directly to Hippocrates (10) On Airs, Waters, and Places, a hygiene-oriented epidemiologic text, the qualities of water were considered responsible for stone formation. Drinking water collected from many different sources may be dangerous for stone disease, gravel and strangury:

When two sorts of water are mixed they quarrel with one another and will leave sediment of sand and it is by drinking this that the diseases mentioned above are cause.

The Hippocratic text offers more clinical observations:

If the neck of the bladder becomes inflamed and does not allow the urine to pass the densest and cloudiest part of urine is gathered together. The gravel formed coalesces to form a stone, preventing the urine from being passed. Great pain is thus caused.

A special mention for stone disease in childhood is notable, as it was unusual to focus on pediatric problems and, furthermore, to distinguish male and female children urological problems, based on the anatomic differences of the urethra.

Female children are less liable to stone because the urethra is short and wide and the urine is passed easily in males it is not straight and it is narrow as well. Moreover, girls drink more than boys (On Airs, Waters, Places, 9).

The patient's age plays a main role in stone formation: Sedimentation after urination is more frequent in children. It is because they are warmer (Epidemics VI, part 3, 7) and sandy urinary sediment shows that a stone is forming in the bladder (Aphorisms IV, 79). For the treatment of lithiasis, fluid intake is recommended (wine mixed with abundant water) or stronger drugs: By giving a medication to a patient with a stone, they have propelled the stone into the urethra by the force of medication so that it has passed with the urine (On Diseases I, 8).

Hippocratic uroscopy observations

The contribution of the Corpus to the development of uroscopy is priceless and his work on this field of Urology reflects the function not exclusively of the urinary system but of the whole body. Hippocrates studied the acute diseases and the evolution of urine during the stages of chronic diseases and emphasized on the constant appearance of certain elements in the urine. Colorless urine is bad; it is especially common in those with disease of the brain (Aphorisms IV, 72). The short phrase indicates a reduced ability to concentrate the urine and may refer to chronic renal failure or to diabetes insipidus (the latter unknown in 5th century BC).

The sudden appearance of blood in the urine indicates that a small renal vessel has burst (Aphorisms IV, 78). It may signify necrotizing renal papillitis due to ischemic necrosis.

Bubbles appearing on the surface of the urine indicate disease of the kidneys and a prolonged illness (Aphorisms VII, 34). It may refer to chronic inflammatory activity in the glomeruli and may be identified with the term chronic glomerulonephritis (11).

It is impossible in a short article like this to include all the urologic knowledge of the Hippocratic physicians, acquainted through long experience. However, the symptoms of bladder disease (ulcer, tumor, psoriasis, lithiasis and inflammation) are all recognized by the urine appearance and the changes of this appearance. In the Aphorisms Hippocrates sums up much of what is of relevance to

Urology. In fact, of the total 420 aphorisms, about 30 belong to the urologic specialty. With a general conclusion, the high incidence of urologic diseases in the prolonged age is clearly shown: Diseases of the kidneys and of the bladder are difficult to cure in the aged (Aphorisms VI, 6).

CONCLUSIONS

The most valuable contribution of ancient Greek medicine represented by the Corpus Hippocraticum to urology constitutes of the uroscopy diagnostic results and the theory of stone formation, as well as of the exact knowledge of cutting the stone by non-specialists. On the other hand, as an antidote to overconcentration of technology, the Hippocratic medicine offers its humanistic principles (ethics and deontology, health professionals by the patient's bedside) concerning the disturbances of the psycho-somatic world and placing the guidelines for the appropriate and early treatment of the diseases of the urological system. The Father of Rational Medicine predicted the necessity for specialized physicians with certain surgical abilities and broad medical knowledge, establishing in some way the specialty of Urology. Today's urologists can still learn from the prognostic thoughts, the ethical principles, the philosophic concepts and the humane messages of Hippocrates.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Risk groups in bladder cancer patients treated with radical cystectomy

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ABSTRACT

Objective: To stratify patients with bladder cancer into homogeneous risk groups according to statistically significant differences found in PFS (progression-free survival). To identify those patients at increased risk of progression and to provide oncological follow-up according to patient risk group.

Materials and Methods: A retrospective study of 563 patients treated with radical cystectomy (RC). In order to determine which factors might predict bladder tumour progression and death, uni- and multivariate analyses were performed. The risk groups were identified according to "inter-category" differences found in PFS and lack of differences, thus revealing intra-category homogeneity.

Results: Median follow up time was 37.8 months. Recurrence occurred in a total of 219 patients (38, 9%). In 63% of cases this was distant recurrence.

Only two variables retained independent prognostic value in the multivariate analysis for PFS: pathological organ confinement and lymph node involvement. By combining these two variables, we created a new "risk group" variable. In this second model it was found that the new variable behaved as an independent predictor associated with PFS. Four risk groups were identified: very low, low, intermediate and high risk:

- Very low risk: pT0 N0
- Low risk: pTa, pTis, pT1, pT2 and pN0
- Intermediate risk: pT3 and pN0
- High risk: pT4 N0 or pN1-3.

Conclusions: We retrospectively identified 4 risk groups with an independent prognostic value for progression-free survival following RC.

Differences in recurrence patterns after RC between risk groups have led us to set different intervals in monitoring for cancer.

ARTICLE INFO

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Urinary Bladder Neoplasms; Cystectomy; Pathology

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INTRODUCTION

Bladder cancer is major health problem in Spain, with high incidence and elevated mortality (1-3). Radical cystectomy is the standard treatment for patients with muscle-invasive bladder cancer, however this is generally insufficient. In fact, it is very important to identify those at high risk of progression because these patients could benefit from adjuvant treatment and closer monitoring. Other authors (4, 5) have opted to divide patients into homogeneous risk groups according to statistically significant differences found in PFS and CSS (cancer-specific survival). A novel development in this study is the identification of the new risk group "Very low risk", which includes patients with a lower probability of suffering

from disease progression. These patients are therefore less likely to require adjuvant treatment, and follow-up intervals may also be more distanced. We propose a follow-up strategy for RC-treated bladder cancer patients that identifies most cases of recurrence while at the same time avoids monitoring patients too closely. This implies in a reduction of costs related to tests and number of visits.

While it is true that our study is not a multidisciplinary project, we believe that our single-center study includes a sample sufficiently large to draw conclusions similar to those drawn from studies undertaken by multidisciplinary groups (6). The aim of the present study was establish risk groups and tailor follow-up accordingly with a schedule appropriate to the likelihood of progression.

MATERIALS AND METHODS

Patient Population

We retrospectively reviewed all patients who underwent radical cystoprostatectomy and pelvic lymphadenectomy for bladder cancer with curative intent at Miguel Servet University Hospital between 1975 and 2007. The study population consisted of 599 patients who underwent radical cystectomy. Thirty-six patients were eliminated from the study due to missing data. Therefore, analysis was performed on the 563 remaining patients.

Radical cystoprostatectomy and lymphadenectomy were always performed according to standard protocol; indications for cystectomy did not change during the time period studied. Cystectomy is indicated in patients with invasive bladder carcinoma, endoscopically uncontrollable superficial bladder cancer and high risk bladder tumors and for those with BCG-resistance bladder tumors. Radical cystectomy and limited pelvic lymph node dissection were performed in 84% of the patients. In only 10 cases it was performed an extended pelvic lymphadenectomy. It is true that currently, this procedure is routinely performed in most cases.

All cystectomy specimens were subjected to routine pathological examination. In the last two decades the same pathologist examined the specimens microscopically. Primary tumors and lymphadenectomy were restaged based on the 2002 UICC TNM system.

Statistical analysis

"FileMaker Pro 11.0, version 11.0 v2" (FileMaker Inc©) was used as database software and "PASW Statistics 18, version 18.0.0" (IBM©) was used as statistics software.

Paper-based patient records were reviewed and data were analyzed for possible predictive factors. Univariante analysis was performed using the Kaplan-Meier (or Mantel-Haenszel) test. Significant variables ($p<0.05$) and those close to significance ($p<0.1$) from univariate analysis were analyzed using backwards multivariate analysis with the Cox proportional hazards regression model. To search for a clinical application and to check the strength of the model, a new model was set up, with the combination of the statistically most powerful variable taken from multivariate analysis. We created a new variable called "risk groups", to try to identify any differences in PFS and CSS between the different categories of this variable. The risk groups identified were compared using the Kaplan-Meier method and log-rank test.

RESULTS

Cystectomy was indicated for muscle-invasive bladder cancer (MIBC) in 493 patients. In the remaining 70 patients, the indication for cystectomy was superficial bladder cancer. In these 70 cases, 33 underwent cystectomy for multifocal recurrence of NMBC (non muscle-invasive bladder cancer) such as TaG1-2 T1G1-2, 36 patients for recurrent high-grade tumours (TaG3, T1G3, and CIS) and in one case the reason for cystectomy was not specified. These data are summarized in the chart below (Figure-1).

The variables investigated in patients treated with cystectomy in the period of study were grouped into: pre-, peri- and post-cystectomy variables, as shown in Table-1.

At the time of cystectomy, median patient age was 65.3 years (IQR 13.1). In the analysis by decades it can be seen that patients were progressively older, with statistically significant differences.

Median follow-up time was 37.8 months (IQR 83.4, range 1,1-288,2). Of note are those variables that underwent changes over the decades

Figure 1 - Indication of radical cystectomy.

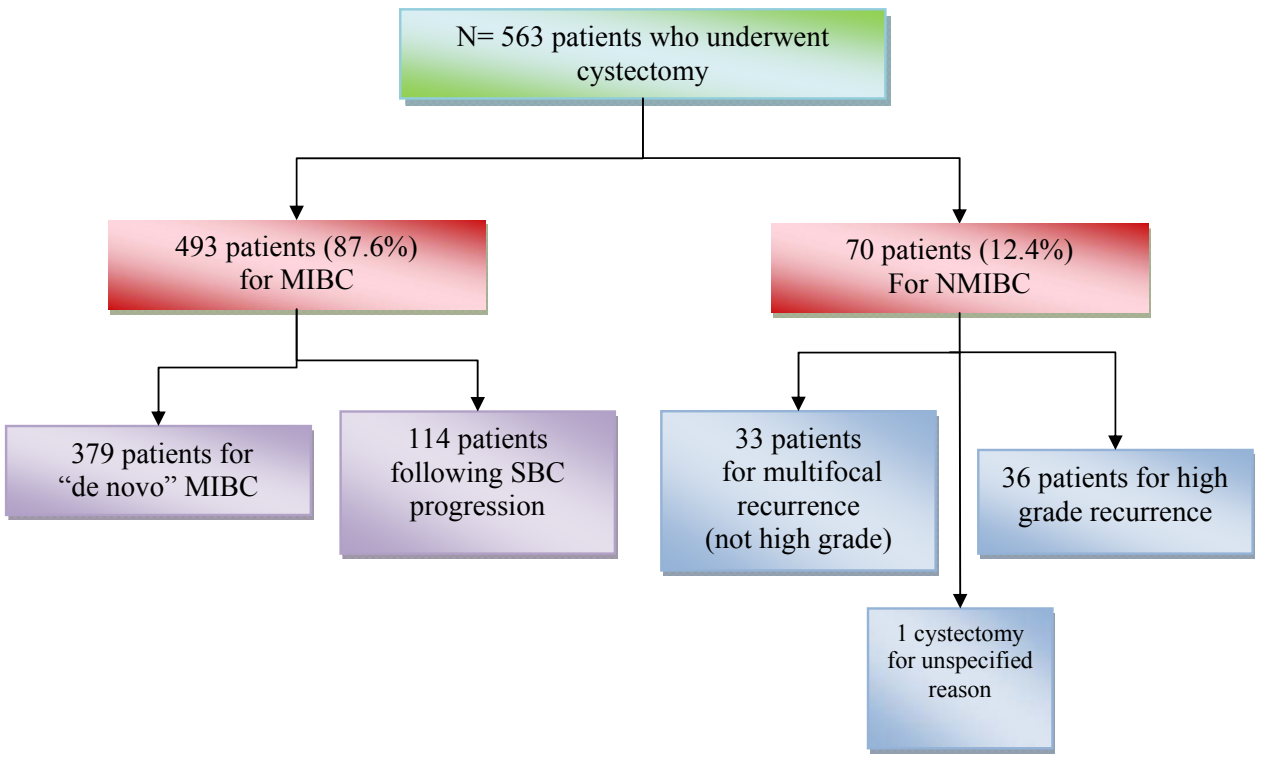


Table 1 - Variables studied.

Variables Pre-Cystectomy	Variables Peri-Cystectomy	Variables Post-Cystectomy
Gender	Transfusion	Hospital stay
Age	Type of catheterisation	Follow-up
Smoker	Ureteral reimplantation	Adjuvant CT
Alcohol	Pathological stage (pT)	Major perioperative complications
Risk occupation	Tumour grade	Minor perioperative complications
Living environment	Lymph node involvement (pN)	Late-onset complications
Comorbidity	Presence of CIS	Tumour recurrence in UUT
Clinical presentation	p53	
Clinical stage of TURBT	Anatomical pathology Terminal ureter	
History of UC in UUT	Ureterectomy	
Neoadjuvant CT	Anatomical pathology type	
	Organ confinement	
	Tumour in UUT concomitantly with BC	

TURBT = Transurethral resection of bladder tumour; **SBC =** superficial bladder cancer; **UC =** urothelial carcinoma; **UUT =** upper urinary tract; CT: chemotherapy; **BC =** Bladder cancer

studied, such as for example the number of units transfused (p<0,00), length of hospital stays and the number of complications (p<0.03). All these variables decreased in number/duration. Conversely, continent urinary derivations (p<0.00) increased during the study period. In terms of studied tumor characteristics no clear differences were observed over the four decades of the study. In the percentage of patients with organ-confined tumors there were no statistically significant differences (p=0.714). In the case of lymph node involvement prevalence increased over the decades, but not significantly (p=0.250).

Progressive disease occurred in 219 patients of the total series (38.9%). We classified recurrence as: local, regional lymph node and distant. Local recurrence: we considered this to be the appearance of local recurrence in the pelvis urothelial tumor, surgical site and/or urinary tract without distant involvement. Locoregional nodal recurrence: this included pathological lymph node involvement and distant metastasis.

In patients who progressed, the predominant type of progression was distant metastasis in 63% of cases. Mean PFS (progression-free survival) in the 563 patients was 157 (144.2-169.9) months (the median could not be calculated).

It can be observed that almost all events (recurrence from bladder cancer) occurred in the first two years of follow up. In fact, by the end of the second year of follow-up, 77% of the events had already occurred. There was a 73% probability of survival in the first year, falling to 55% at the end of the fifth year, with little further change to the end of the tenth year (51%) (Figure-2 and Table-2).

In patients who progressed, n=219 (38.9%), median progression-free survival was 9.7 months (CI 95% 8.3-11.1); there were no differences in PFS by type of progression. Progression appeared to occur shortly before lymph node recurrence (median PFS=8.6 months [6.3-11]), but significant differences were found in the univariate analysis.

Univariante analysis demonstrated that pathological organ confinement, lymph node involvement, tumour grade, terminal ureter involvement and the administration of adjuvant chemotherapy were variables that were significantly

Figure 2 - PFS in 563 patients.

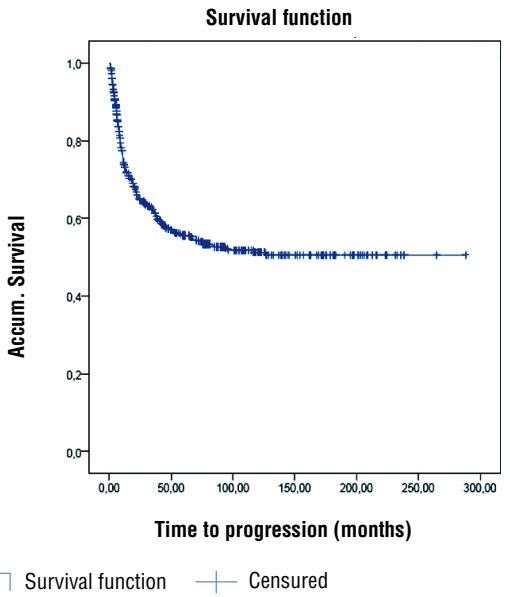


Table 2 - Mean PFS in the whole series.

T (months)	Cumulative survival probability
12m	83.1%
36m	65.5%
60m	61.5%
120m	55.2%

associated with lower progression-free survival (Table-3).

In the multivariate analysis (Table-4) we entered the significant variables detected in the univariate analysis and found that pathological organ confinement and lymph node involvement were independent variables that were significantly associated with PFS.

In order to identify patients at increased risk of urothelial disease progression or recurrence following cystectomy, we developed a classification system based on the multivariate predictive variables for PFS: pathological organ confinement and lymph node involvement. We created a new variable called “risk groups”, using a combination of the two previous variables (pT and pN), in order

Table 3 - Univariante analysis of predictive factors for PFS.

Long rank (Mantel-Cox)	Chi²	Df	Sig.	Variable	% patients
Organ confinement	66.035	1	0.000	≤ pT2	54%
				> pT2	46%
Pathological lymph node status	105.106	1	0.000	pN0	74%
				pN+	26%
Tumour grade	8.651	2	0.013	G_1-G_2	27%
				G3	73%
Terminal ureter	5.621	1	0.018	Normal	90%
				pathological	10%
Adjuvant CT	7.511	1	0.006	-	6%

PFS = progression-free survival; **CT =** chemotherapy

Table 4 - Multivariate analysis. Predictive model for PFS.

Variable	B	SE	Wald	GI	p	O.R.	95% CI for EXP(B)	
							Lower	Upper
Pathological organ confinement	1.077	0.283	14.445	1	0.000	2.936	1.685	5.117
Lymph node involvement	0.861	0.214	16.219	1	0.000	2.365	1.556	3.595

PFS = progression-free survival

to identify any differences in PFS between the different categories of this variable.

We analysed the survival for each pT variables (pT0 vs. pTa-Tis-T1 vs. pT2 vs. pT3-4) and pN variables (pN0 vs pN1-3). We observed clear differences between the patients with pT0 and the group stages PTa, pTis, pT1, pT2, and of course among the rest of groups, which led us to differentiate between a group of very low risk, separating it from the rest. According to this analysis, four independent groups were identified (Table-5).

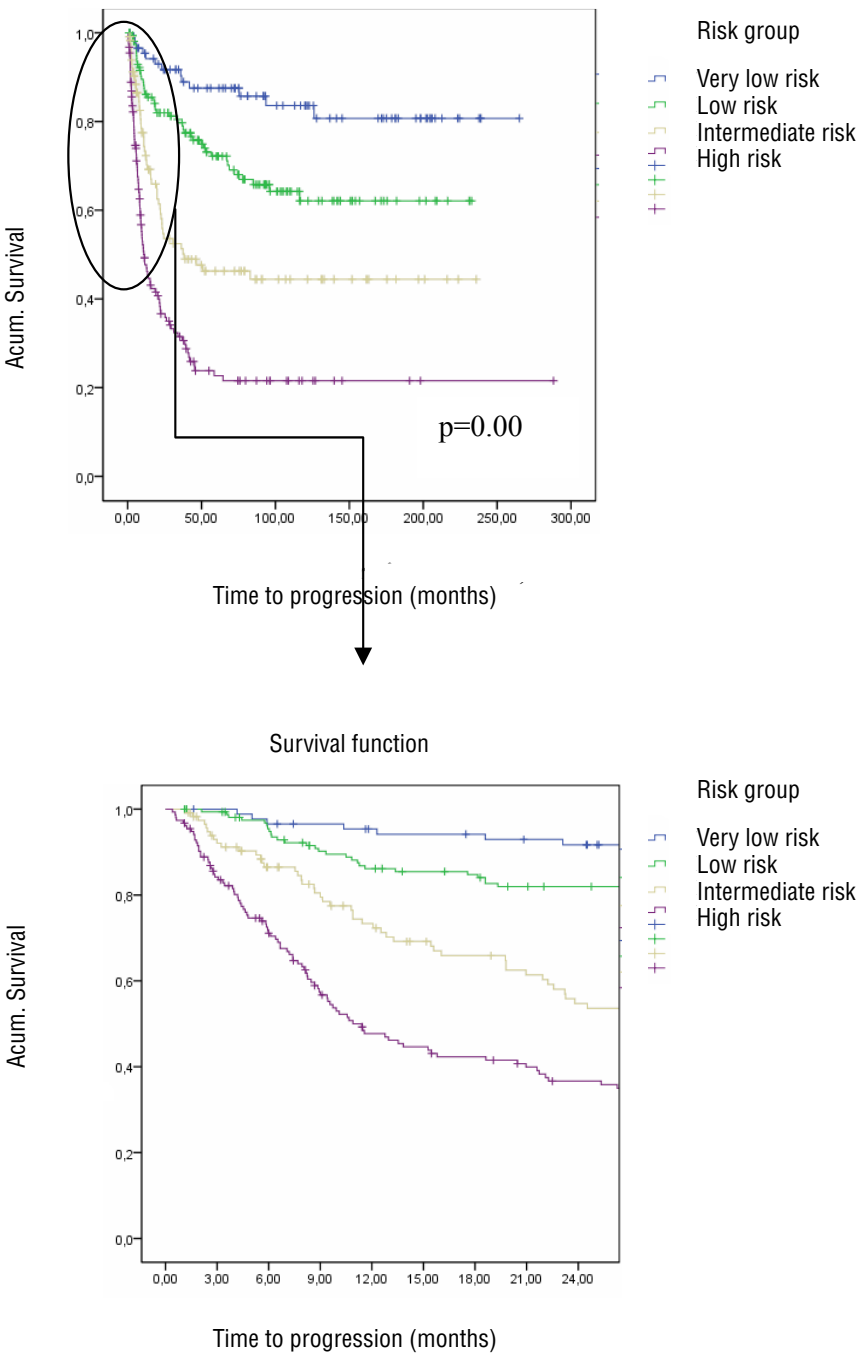
With respect to the survival graph (Figure-3), firstly it can be seen that there are statistically significant inter-category differences ($p<0.001$), which appear to confirm the homogenous nature of the composition of the four categories. Of note are the findings in PFS in the

Table 5 - Risk groups.

"Risk group" variable	
Categories	Description
Very low risk	pT0 and pN0
Low risk	pTa, pT1, pTis or pT2, and pN0
Intermediate risk	pT3 and pN0
High risk	pT4N0 or pN1-3

"Intermediate risk" and "High risk" groups. It is particularly striking that events occur so early in these groups. After two years of follow-up, 84% (45 out of 53) events relating to progression have appeared in the "Intermediate risk" group, and 84% (89 out of 105) in the "High risk" group.

Figure 3 - PFS by risk group.



Risk groups	p-value	OR
Very low vs. high	0.00	9.7
Low vs. high	0.00	4.25
Intermediate vs. high	0.00	2.04

The survival graphs show that the risk of progression stabilizes. This is similarly reflected in the survival table (Table-6). This shows the probability of reaching a certain time point, in the post-cystectomy follow-up, without progression.

In this second model it was found that the new "risk group" variable behaved as an independent predictor associated with PFS.

From the data of Table-7 it can be deduced that a patient in the high risk group has an OR of progression that is 9.7 times (1/0.103) higher than patients with a very low risk. The same high risk patient has an OR that is 4.25 times (1/0.235) higher for progression than low-risk patients.

DISCUSSION

This study was undertaken primarily due to the high rates of incidence and mortality of bladder cancer in Spain and in our region, Aragon. Rates are above the mean for Europe (7, 8), and this, together with the marked ageing of population, suggests that the upward trend will continue.

In the literature there are several studies on the prognostic value of different variables such as stage, lymph node and lymphovascular involvement, type of urinary diversion, margin status, etc. on invasive bladder cancer progression and survival. However, organ confinement and lymph node involvement are repeatedly found to be independent risk factors for PFS and cancer-specific mortality in most series (4, 9, 10).

In a study at Gregorio Marañón Hospital (4), both pathological stage and lymph node involvement were found to be independent predictors for cancer-specific survival. In that study the authors, like us, also constructed a second model by grouping local stage (pT) and lymph node involvement (pN) into risk groups in order to study CSS. Thus, the association by risk group allowed them to predict the risk of death from bladder cancer more reliably, and to identify patients in whom cystectomy is insufficient and who could benefit from adjuvant treatment.

Solsona (5) also stratified patients by risk. In this study, the records of 298 patients who un-

Table 6 - Survival table (PFS) by "Risk group".

PFS by "Risk group". Survival table							
Categories		End 1st year	End 2nd year	End 3rd year	End 4th year	End 5th year	End 10th year
Very low	pT0 and pN0	0.954	0.917	0.903	0.875	0.875	0.836
Low	pTis, pTa-1, pT2 and pN0	0.861	0.82	0.797	0.758	0.722	0.621
Intermediate	pT3 and pN0	0.734	0.547	0.525	0.476	0.463	0.444
High	pT4 or pN1-3	0.485	0.367	0.315	0.238	0.227	0.215

Table 7 - Subvariables that retain independent statistical significance for PFS.

Variable		B	ET	Wald	gl	P	Exp(B)	95% CI forEXP(B)	
								Lower	Upper
Risk Group	High vs very low	2.27	0.296	59.088	1	0.00	0.103	0.58	0.184
	High vs low	1.44	0.177	66.600	1	0.00	0.235	0.166	0.333
	High vs intermediate	0.715	0.169	17.853	1	0.00	0.489	0.351	0.682

derwent cystectomy were retrospectively analysed and risk groups were established based on lymph node involvement, pathological stage and prostatic stromal involvement as predictors of mortality in the multivariate analysis. Their figures for 5-year CSS, by risk group, were 86.4% for the low risk group (P1-2N0St-), 64.4% for the intermediate risk group (60.9%-65.3%) (P1-2N1St-, P3N0St-, HR=2.7) and 28.1% (0%-47.7%) for the high risk group (N2-3, P4, St+, N1P3, HR=8.7). These figures were not far off our 5-year CSS of 89% for the very low risk group, 75% for low risk, 54% for intermediate and 30% for low grade (data not shown).

Sonpavde (11) investigated bladder cancer risk following cystectomy using pathological factors to facilitate an indication for adjuvant treatment. This series was more similar to ours in terms of sample size and study time (although the follow-up period was longer in their study), and it was also found that pathological stage was a predictor. Like us, these authors constructed a model with prognostic groups and found that stage, lymphovascular involvement and poorly-differentiated cells were predictors of PFS. They distinguished three groups according to the presence of the three variables in the multivariate analysis, assigning a score of 0-4, according to the presence of these variables, and depending on the cumulative score, they divided patients into low, intermediate and high risk groups.

In the case of the Abol-Enein and Ghoneim group (12), which involved a large series because of the high incidence of bladder cancer in Egypt, these authors concluded that PFS predictors are lymph node involvement, stage, lymphovascular invasion and type of urinary diversion. Using these four variables, patients were stratified into four risk groups ranging from low risk (T1,N0, LV-, orthotopic diversion) to maximum risk (T4,N+, LV+, rectal diversion), comparing survival curves and likelihood of progression among these groups. They found a 5-year PFS of 64.5%, which does not differ greatly from our figure of 55.6%. Like these authors, we divided patients into categories or risk groups, with two objectives. Firstly, in reference to follow-up we aimed to identify risk of progression and detect this as early as possible. The second objective was to identify candidates for adjuvant treatment, with the final objective of increasing CSS.

In our study, differences in progression patterns after radical cystectomy suggest the need for varied follow-up protocols for each group. We proposed a stage-based protocol for monitoring of patients with bladder cancer treated with radical surgery that captures most recurrences while limiting over-investigation. Multicenter studies are consistent with our study, showing that in most patients the tumor recurs in the first two years after radical cystectomy and over half of these recurrences are distant (6).

Table-6 shows the probabilities of progression-free survival at a certain time point according to risk group. Looking at how to apply these data in clinical practice, we can draw up guidelines and recommendations for monitoring these patients. To date, there has been no consensus on how to follow up these patients after surgical intervention. Available guidelines include the National Comprehensive Cancer Network and the European Association of Urology recommendations, which acknowledge the need for risk-stratified surveillance but do not clearly delineate any protocols (13, 14) .The ESMO (European Society for Medical Oncology) guidelines, by contrast, do not address any stage-specific surveillance regimen (15).

In the very low risk group, patients could be followed up less frequently from the second year onwards. This would not be recommendable in the low risk group until the third year, when the probability of progression becomes stable. In contrast, patients in the intermediate and high risk groups should continue six monthly follow-ups until the fourth or fifth year. However, there is a high probability of progression and early-onset of events in the intermediate and high risk groups during the first months of follow-up, especially in the high risk group. 15% of patients in this group experience progression by the end of the third month and 48% by the end of the first year. The risk of progression is almost 10 times higher than in the very low risk group and two times higher in comparison with the intermediate risk group. For this reason we suggest three-monthly follow-up for the first year in the high risk group, as shown in Table-8. Later, the probability of progression drops,

Table 8 - Follow-up recommendations.

Risk group	1st year	2nd year	3rd year	4th year	5th year	6th-10th year
Very low	Six monthly	Six monthly	Yearly	Yearly	Yearly	Yearly
Low	Six monthly	Six monthly	Six monthly	Yearly	Yearly	Yearly
Intermediate	Four monthly	Six monthly	Six monthly	Six monthly	Yearly	Yearly
High	Three monthly	Six monthly	Six monthly	Six monthly	Yearly	Yearly

so follow-up can be performed at six-monthly intervals until the probability of progression stabilises (in the 4th year). In the low risk group, patients could be followed up less frequently from the third year onwards, when the probability of progression stabilises. Faysal et al. (6) proposed stage-based protocols for surveillance of patients with bladder cancer based on recurrence patterns that coincide with our group in terms of the frequency of visits especially in the first year of follow-up in patients with very high risk of recurrence.

Since there is such a high probability of progression in the intermediate and high risk groups, intensive follow-up of these patients is clearly essential. However, the aim must be to prevent progression from occurring or to delay it as much as possible. Therefore, an assessment should be made of whether to administer adjuvant chemotherapy in these two groups of patients.

It is true that there are no randomised trials that demonstrate the superiority of adjuvant chemotherapy in MIBC treatment, but until such studies are available, we would recommend that chemotherapy - preferably within the framework of a clinical trial - as it is one of the few tools at our disposal that lengthens CSS.

Our study has several potential limitations, including those inherent to any retrospective study. For example, the variable margin status; this was not studied in the early years of the study period and therefore could not be included in the study. Extent of surgery, such as the upper limit of lymph node dissection, changed slightly and was not consistent during the study period. Our median follow-up time may seem short (37.8 months) however these are patients with an ominous prognosis. Furthermore, this is a single institution study. Findings must be evaluated externally in a larger patient cohort and validated prospectively for practical use.

CONCLUSIONS

Non-organ confinement and lymph node involvement in radical cystectomy specimens are factors that retain independent prognostic value in progression-free survival in the multivariate analysis. We retrospectively identified four risk groups (very low, low, intermediate and high) with an independent prognostic value for progression-free survival following radical cystectomy. This would be useful in order to provide information to patients and physicians and to improve stratification for future clinical trials. This would serve to optimize indications for treatment, avoiding excessive monitoring and reducing costs.

ABBREVIATIONS

PFS = progression-free survival
RC = radical cystectomy
CSS = cancer-specific survival
MIBC = muscle-invasive bladder cancer
NMBC = non muscle-invasive bladder cancer

CONFLICT OF INTEREST

None declared.

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Quality of life after high-dose-rate brachytherapy monotherapy for prostate cancer

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ABSTRACT

Purpose: There is little information in the literature on health-related quality of life (HRQOL) changes due to high-dose-rate (HDR) brachytherapy monotherapy for prostate cancer.

Materials and Methods: We conducted a prospective study of HRQOL changes due to HDR brachytherapy monotherapy for low risk or favorable intermediate risk prostate cancer. Sixty-four of 84 (76%) patients who were treated between February 2011 and April 2013 completed 50 questions comprising the Expanded Prostate Cancer Index Composite (EPIC) before treatment and 6 and/or 12 months after treatment.

Results: Six months after treatment, there was a significant decrease ($p<0.05$) in EPIC urinary, bowel, and sexual scores, including urinary overall, urinary function, urinary bother, urinary irritative, bowel overall, bowel bother, sexual overall, and sexual bother scores. By one year after treatment, EPIC urinary, bowel, and sexual scores had increased and only the bowel overall and bowel bother scores remained significantly below baseline values.

Conclusions: HDR brachytherapy monotherapy is well-tolerated in patients with low and favorable intermediate risk prostate cancer. EPIC urinary and sexual domain scores returned to close to baseline 12 months after HDR brachytherapy.

ARTICLE INFO

Key words:
Prostatic Neoplasms; Brachytherapy; Quality of Life

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INTRODUCTION

Management options for patients with low or intermediate risk prostate cancer and a life expectancy of less than 10 years include active surveillance (1), radical prostatectomy (2), external beam radiation therapy (EBRT), low-dose rate (LDR) brachytherapy monotherapy (3, 4), or high-dose-rate (HDR) brachytherapy (5, 6). Since cure rates are similar among these treatment options (7), health-related quality of life (HRQOL) is an important factor in a patient's decision-making process (8).

In prostate cancer patients, physician-assessed HRQOL changes do not correlate with patient-assessed changes. Physicians under-estimate HRQOL changes and over-estimate improvement in symptoms relative to patients (9). Discrepancies are particularly large for symptoms like pain and fatigue (9). As a result, it is important to measure patient-assessed HRQOL. The Expanded Prostate Cancer Index Composite (EPIC) is a validated questionnaire used to assess HRQOL in prostate cancer patients. EPIC includes 4 domains: urinary, bowel, sexual, and hormonal (10). There are summary (i.e., overall) scores and function and bother subscale scores for each of the 4 domains. The urinary domain has 2 additional subscales: incontinence and irritative/obstructive. Domains

and subscales are scored using a 0-100 grading system, with a higher score indicating a higher quality of life.

HRQOL changes in prostate cancer patients undergoing radical prostatectomy, LDR brachytherapy monotherapy or EBRT vary significantly between treatment modalities (11). There has been only one prior report on HRQOL changes due to HDR brachytherapy monotherapy for prostate cancer (12). As a result, we studied HRQOL changes in this select group of patients.

MATERIALS AND METHODS

Recurrence risk was defined according to the National Comprehensive Cancer Network (NCCN) guidelines (13). Low recurrence risk was defined as patients with clinical T1-T2a disease, prostate-specific antigen (PSA) <10 ng/mL, and a Gleason score ≤6. Intermediate recurrence risk patients were those with clinical T2b-T2c disease, PSA=10-20 ng/mL, or a Gleason score =7. Intermediate risk patients were subdivided into "favorable" and "unfavorable" groups. Favorable intermediate risk patients were defined as those with a Gleason score of 3+4=7, ≤cT2b disease, and ≤50% positive core biopsies (5). Low risk and favorable intermediate risk patients may be treated with HDR brachytherapy monotherapy (5, 6, 12, 14). Unfavorable intermediate risk patients had a Gleason score of 4+3=7, cT2c disease, or >50% positive core biopsies (15, 16). Patients with unfavorable intermediate risk prostate cancer and patients who received intensity modulated radiation therapy (IMRT) or androgen deprivation therapy were excluded from this study.

After obtaining institutional review board approval, we treated 84 low risk and favorable intermediate risk prostate cancer patients with HDR brachytherapy monotherapy at the H. Lee Moffitt Cancer Center & Research Institute between February 2011 and April 2013. After providing informed consent, patients underwent HDR brachytherapy monotherapy to the prostate to 2,700-2,800 cGy in two 1,350-1,400 cGy fractions separated by 2-3 weeks. Over a one-year period following HDR brachytherapy, approximately half of the patients were placed on phosphodiesterase-5 inhibitors such as one sildenafil 50 mg tablet by mouth three times per week for erectile dysfunction. Use of phosphodiesterase-5 inhibitors was based upon patient preference.

HRQOL was assessed using the most recent version of EPIC. Sixty-four of 84 (76%) patients completed the 50-question form prior to HDR brachytherapy monotherapy, i.e., at baseline, and 6 and/or 12 months after treatment. Characteristics of these 64 patients are presented in Table-1. Patients who failed to complete the 50-question EPIC questionnaire commonly stated that it was too long. Mean follow-up was 9 months.

In accordance with prior reports (12, 17, 18), we calculated mean EPIC scores for each time point. Pre-treatment EPIC scores were compared to scores obtained 6 months and 12 months after treatment using a Student's t-test. Linear regression was used to analyze the relationship between patient characteristics (body mass index (BMI),

Table 1 - Patient characteristics.

Number of Patients	64
Mean Follow-up	9 months
Age at Diagnosis, mean (range)	65 years (48-83)
BMI, kg/m^2, mean (range)	29.5 (22.0-43.0)
PSA, ng/mL, median (range)	5.3 (1.0 – 16.1)
Prostate Size, cc, median (range)	54 (24-108)
AJCC Clinical T Stage	
T1c	58
T2a	5
T2b	1
Gleason Score	
3+3=6	43
3+4=7	21
NCCN Recurrence Risk Group	
Low	39
Intermediate	25

AJCC= American Joint Committee on Cancer; cc:cubic centimeters; **NCCN=** National Comprehensive Cancer Network; **PSA=** prostate-specific antigen.

age, prostate volume, PSA, Gleason score, and recurrence risk group) and EPIC scores.

RESULTS

Pre-treatment urinary overall, function, bother, incontinence, and irritative/obstructive scores were 87, 91, 85, 87, and 85, respectively (Figure-1). Six months after treatment, urinary overall, function, bother, incontinence, and irritative scores decreased to 76, 79, 75, 76, and 75 respectively ($p<0.01$). Twelve months after treatment, all urinary scores had increased and were not significantly different from baseline values.

Pre-treatment bowel overall, function, and bother scores were 95, 90, and 95, respectively (Figure-2). Six months after treatment, there was a significant decrease in bowel overall, function, and bother scores to 86, 84, and 86 respectively ($p<0.001$). Twelve months after treatment, bowel overall and bother scores increased to 88 and the bowel function score had increased to 86. These scores remained statistically below baseline values.

Pre-treatment sexual overall, function, and bother scores were 46, 43, and 53, respectively (Figure-3). Six months after treatment, there was a significant decrease in sexual overall and bother scores to 34 and 42, respectively. Twelve months after treatment, sexual overall and bother scores increased and were not statistically different from baseline values.

Pre-treatment hormonal overall, function, and bother scores were 91, 88, and 92, respectively (Figure-4). Six months after treatment, there was a non-significant decrease in sexual hormonal scores. Twelve months after treatment, hormonal scores had decreased further. However, they were not significantly below baseline.

There was no association between patient characteristics and EPIC scores.

Figure 1 - EPIC urinary overall, function, bother, incontinence, and irritative/obstructive scores before HDR brachytherapy monotherapy and 6 and 12 months after treatment.

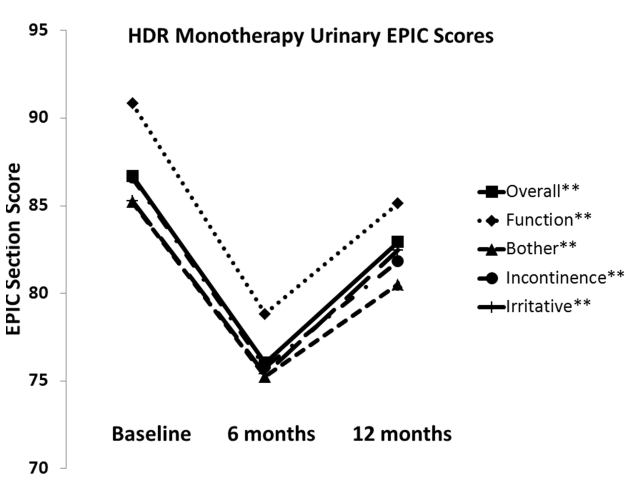


Figure 2 - EPIC bowel overall, function, and bother scores before HDR brachytherapy monotherapy and 6 and 12 months after treatment.

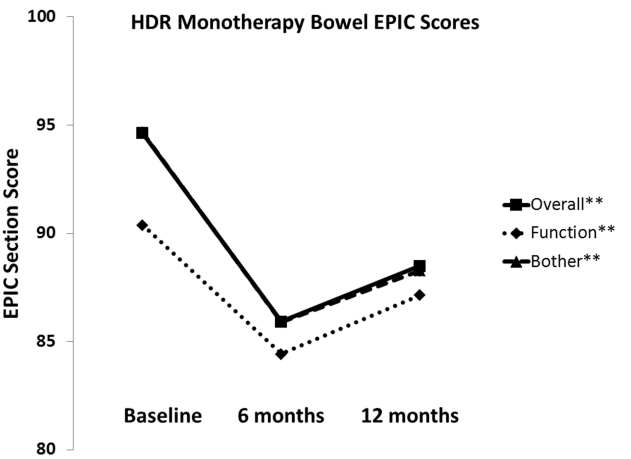


Figure 3 - EPIC sexual overall, function, and bother scores before HDR brachytherapy monotherapy and 6 and 12 months after treatment.

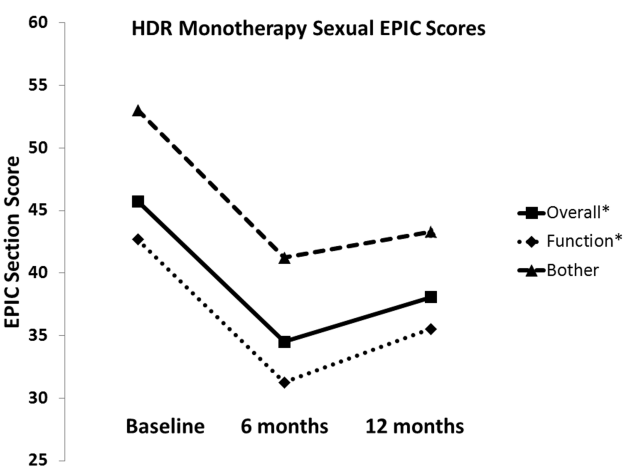
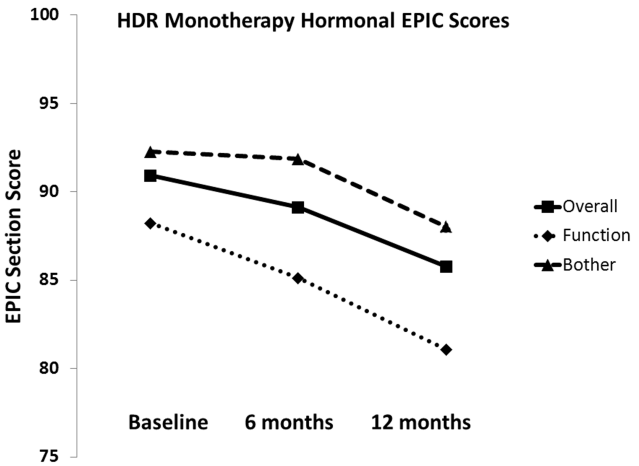


Figure 4 - EPIC hormonal overall, function, and bother scores before HDR brachytherapy monotherapy and 6 and 12 months after treatment.



DISCUSSION

Morton et al. (19) reported HRQOL changes in intermediate risk prostate cancer patients who received EBRT and an HDR brachytherapy boost without androgen deprivation therapy. Patients experienced clinically significant decreases in EPIC urinary, bowel, and sexual overall scores 12 months and 24 months after treatment. In contrast, the EPIC hormonal overall score did not change significantly due to radiotherapy. Similarly, in this study, the EPIC bowel overall score remained significantly below baseline 12 months after radiotherapy (Figure-2); however, the decrease in the EPIC hormonal overall score was not statistically significant (Figure-4).

To date, only one study has reported patient-assessed HRQOL changes in prostate cancer patients treated with HDR brachytherapy monotherapy. Barkati et al. (12) treated 79 low and intermediate risk prostate cancer patients with HDR brachytherapy monotherapy. Seven patients also received neoadjuvant androgen deprivation therapy. They observed a decline in EPIC scores across all 4 domains as early as one month after treatment. Urinary, bowel, and hormonal scores recovered 3 months after HDR brachytherapy monotherapy. This compares favorably with our findings, where EPIC urinary and sexual scores did not improve until 12 months after HDR brachytherapy (Figures 1 and 3). EPIC scores may have taken longer to improve after HDR brachytherapy in this report because we delivered a higher biologically effective dose of radiotherapy (14). Barkati et al. observed that urinary, bowel, and hormonal scores remained stable 3-48 months after treatment. Also, they reported a decline in sexual overall scores as early as one month after treatment with no recovery thereafter. Patients' ages were similar to this study. However, baseline sexual overall scores were lower in this report. As in the report by Barkati et al., baseline sexual scores in this study were considerably lower than urinary, bowel, and hormonal scores (Figures 1-4). Like Barkati et al., we observed a significant decrease in sexual overall and bother scores at 6 months (Figure-3). However, in this report, there was improvement in sexual scores at 12 months. This was probably due to early use of a phosphodiesterase-5 inhibitor after brachytherapy in approximately half of our patients (20).

Marina et al. (21) used the Common Terminology Criteria for Adverse Events v4 grading system to determine incidence rates of erectile dysfunction 3 years after HDR brachytherapy monotherapy vs. IMRT. Rates of erectile dysfunction requiring medical intervention for both HDR brachytherapy monotherapy and IMRT were low and equivalent.

In this study, 64/84 (76%) prostate cancer patients treated with HDR brachytherapy monotherapy completed 50 questions comprising the most recent version of the EPIC questionnaire. Similarly, others have reported 36-78% compliance rates (12, 22). Since men who did not complete the form commonly stated that it was too long, we have switched to a 26-item, short-form version of EPIC in an effort to improve patient compliance (23, 24).

CONCLUSIONS

HDR brachytherapy monotherapy is well-tolerated in patients with low and favorable intermediate risk prostate cancer. EPIC urinary and sexual domain HRQOL scores returned to close to baseline 12 months after treatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Short-term prophylaxis with ciprofloxacin in extended 16-core prostate biopsy

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ABSTRACT

Objective: To evaluate the safety, efficacy and possible complications of 16-core transrectal prostate biopsies using two doses of ciprofloxacin for prophylaxis of infectious complications.
Materials and Methods: Sixteen-core prostate biopsies were performed on a number of patients with different signs of potential prostate cancer. Complications were assessed both during the procedure and one week later. After the procedure, urine samples were collected for culture. The rate of post-biopsy complications, hospital visits and hospitalizations were also analyzed. Ciprofloxacin (500 mg) was administered two hours before, and eight hours after the procedure.
Results: The overall rate of post-biopsy complications was 87.32%, being 5.4% of those considered major complications due to hemorrhage, or to urinary retention. Eight patients required hospital treatment post-biopsy. Fever occurred in just one patient (0.29%). There was no incidence of orchitis, epididymitis, prostatitis, septicemia, hospitalization, or death. The urine culture showed positive results in five patients (2.15%).
Conclusion: One-day prophylaxis with ciprofloxacin proved to be safe and effective in the prevention of infectious complications following 16-core prostate biopsies.

ARTICLE INFO

Key words:
prostate; prostatic neoplasms; biopsy; complications

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INTRODUCTION

Excluding skin cancers, prostate cancer (PCa) is the most common cancer in men and the second cause of death, only after lung cancer. The estimated new cases of PCa and death in the United States (USA) in 2014 were 233,000 and 29,480, respectively (1). In Brazil, the number of deaths in 2011 was 13,129 and the estimated new cases for the year 2014 will be 68,800 (2).

The method of choice for final diagnosis of Pca is transrectal ultrasound (TRUS)-guided biopsy (2). Despite various studies in the literature that demonstrate low rates of complications and good tolerance to the procedure (3, 4), it is still considered invasive and not entirely free of complications. For some patients, it is an arduous and painful exam. Furthermore, the procedure cannot guarantee the absence of Pca, even with a negative result. Due to the aforementioned issues, there is great interest in making the exam as safe, fast and efficient as possible, along with the lowest rates of complications achievable.

The main complications related to prostate biopsy may be immediate, such as rectal bleeding (1.3 to 33.1%), hematuria (13 to 65%), vaso-vagal response (0 to 2.8%), and delayed, such as fever (1.7 to 6.6%), hemospermia (5.1 to 50.4%), persistent

dysuria (0 to 7.2%), infection (2.5 to 9.2%), acute prostatitis (0 to 1.8%) and urosepsis (0 to 8%) (5, 6).

There are many measures that can be taken in prostate biopsies in order to minimize post-procedural complications. Such measures include prior evaluation of patient co-morbidities; intestinal preparation; administration of prophylactic antibiotics; indication of the ideal number and location of biopsies to be performed; use of anesthesia or sedation; and appropriate room with all the material necessary for the intervention on emergency situations (6, 7).

Antibiotic prophylaxis generally reduces the risk of infectious complications following TRUS guided biopsy (8). Oral quinolones are the most common prophylactic antibiotics, either alone or in combination with other antibiotics; optimal dosing and treatment period vary, but in the last few years increased resistance to quinolones has been reported associated with a rise in severe infectious complications after biopsy (4, 9).

The aim of this present study was to evaluate the complications, possible risk factors, outcomes, safety and efficacy of TRUS guided biopsy with removal of 16 fragments, using two doses of ciprofloxacin as prophylaxis against infectious complications.

MATERIALS AND METHODS

The present prospective study was conducted from January 2011 to February 2012 within the Department of Urology, Botucatu Medical School - UNESP after the approval of the Research Ethics Committee. A sample of 351 patients was submitted consecutively to TRUS prostate biopsies. The criteria for inclusion in the study were: digital rectal exams suggestive of neoplasia; elevated prostate specific antigen (PSA) (higher than 4.0 ng/mL in men over the age of 55 and higher than 2.5 ng/mL in men under the age of 55); PSA density greater than 0.15 ng/mL; and annual increase rate of PSA higher than 0.75 ng/mL. Carriers of coagulopathies, individuals with urinary tract infections (whether diagnosed at the time of biopsy or in treatment), and those who refused informed written consent were excluded from the study.

After consulting the patient's medical records, parameters such as age, race, serum total PSA (current and previous), free PSA, free PSA / total PSA and biopsy indication were analyzed. Prior to ultrasound, a digital rectal exam was conducted. Prostate volume and nodule presence were determined via ultrasound. Complications during the procedure were rectal bleeding, urethral bleeding, hypotension, vaso-vagal response, hypoxia, nausea, vomiting, pain and urinary retention.

The biopsy was performed on an outpatient basis, in a room equipped with all material necessary for emergency intervention. Sedation and anesthesia were realized by the administration of 50 mcg fentanyl citrate and 5 mg midazolam. The biopsies were performed by two experienced urologists. On the morning of the procedure, rectal enema was performed with 250 mL, and antibiotic prophylaxis was achieved with the oral administration of ciprofloxacin 500 mg two hours prior to the procedure, and again eight hours after it. The procedure was performed with the patient in the left lateral position with his thighs flexed. The procedure was performed using a Dornier transrectal ultrasound equipment, with a 6.5 MHz multiplanar probe, auto-fire gun and 18 gauge needle.

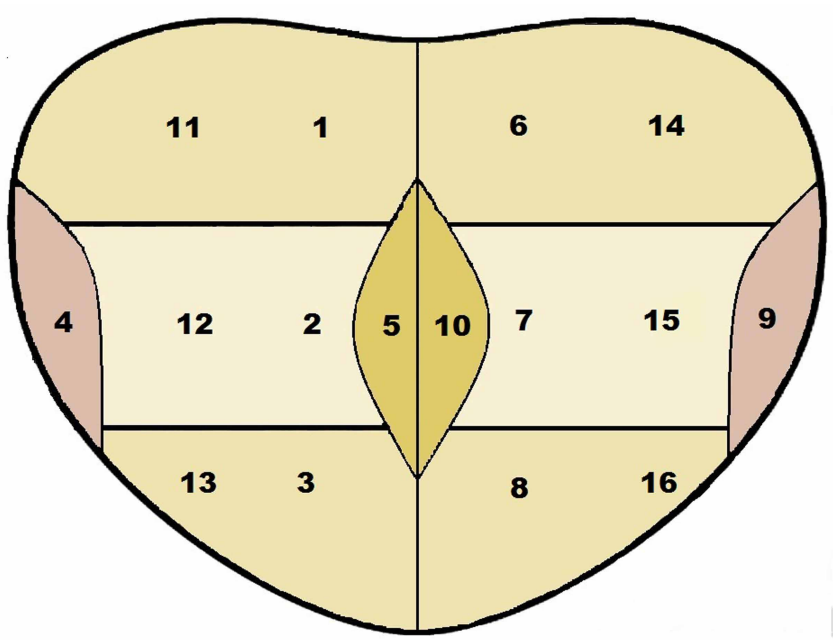
Shortly after the biopsy, urine samples were collected for culture.

Sixteen punctures were performed, obtaining cores bilaterally from the following regions of the prostate: the base, middle third, apex, medial (transitional zone), and latero-lateral. After collecting these cores, six additional punctures were made bilaterally in the more lateral regions of the base, the middle third, and the apex (Figure-1).

The positivity for diagnosis of prostate cancer was assessed as well as the overall rate of post-biopsy complications.

Seven days after the procedure, the patients returned to the clinics where they completed a questionnaire to assess possible complications resulting from the procedure such as pain, fever, hematuria, dysuria, hemospermia, and rectal bleeding. Visits to the hospital as well as hospitalizations were also analyzed.

Figure 1 – Regions where punctures were made to collect prostate cores: 1. right base, 2. right middle third, 3. right apex, 4. latero-lateral right, 5. right medial, 6. left base, 7. left middle third, 8. Left apex, 9. latero-lateral left, 10. left medial, 11. right base, 12. right middle third, 13. right apex, 14. left base, 15. left middle third and 16. left apex.



RESULTS

Of the 351 patients who underwent the procedure, the immediate complications (during and after biopsy) were rectal bleeding, intense pain, urinary retention, urethral bleeding, hypotension, vaso-vagal response (sweating, hypotension, bradycardia), nausea and vomiting (Table-1).

In 347 patients, long-term complications were hematuria, hemospermia, rectal bleeding, dysuria, pain and fever. There were no cases of sepsis and death (Table-2). We had a loss of four patients who did not return to the clinic to complete the questionnaire of long-term complications.

Positive results for PCa with the collection of 16 cores were 30.48%.

The overall rate of post-biopsy complications was 87.32%, with 5.4% of those being considered major complications, and the rest minor complications.

Eight patients sought emergency hospital care after the biopsy due to urinary retention, intense hematuria and urethral bleeding (Table-3).

After the prostate biopsy procedure, urine samples were collected for culture in 232 patients, five of which were positive (2.15%) (Table-4). Of the 351 patients submitted to the prostate biopsy, eight patients (2.27%) were catheterized with an indwelling catheter, and did not have urine samples collected.

DISCUSSION

Prostate cancer is a neoplasm with particularly insidious onset, and as with any other malignant neoplasm, there is great concern to stablish an early diagnosis. With the introduction of PSA testing in the screening for prostate cancer, there was an important advancement in the early diagnosis of the disease, making possible the detection of subclinical neoplasms in many more patients.

TRUS guided biopsy is the most accepted method for the diagnosis of prostate cancer (10). Although it is the ideal method for obtaining prostatic cores for analysis, TRUS biopsy of the prostate is considered an invasive procedure that

Table 1 - Immediate complications (during and after biopsy).

Immediate complications	N (351)	%
Rectal bleeding	30	8.54
Intense pain	17	4.84
Urinary retention	16	4.56
Urethral bleeding	9	2.56
Hypotension	3	0.85
Vaso-vagal response (sweating, hypotension and bradycardia)	2	0.57
Nausea	1	0.28
Vomiting	1	0.28
Hypoxia	0	0

Table 2 – Delayed complications.

	N(347)	%	Average (days)	SD
Hematuria	226	65.13	2.50	3.38
Hemospermia	155	44.67	4.68	7.74
Rectal bleeding	78	22.48	0.61	1.86
Dysuria	51	14.70	0.65	2.09
Pain	33	9.54	0.27	1.17
Fever	1	0.29	0.01	0.12
Sepsis	0	0	0	0
Death	0	0	0	0

Table 3 – Hospital visits post-biopsy.

Hospital visits post-biopsy	N (347)	%
Urinary retention	5	1.44
Intense hematuria	2	0.57
Urethral bleeding	1	0.28

Table 4 – Urine culture post-biopsy.

Urine culture post-biopsy	N (232)	%
Mixed flora	2	0.86
E. coli	1	0.43
Citrobacter freundii	1	0.43
Morganella morganii	1	0.43

is uncomfortable for the patient (6, 11). Considering the fact that the vast majority of men subjected to the exam show no signs of cancer, there is great concern that the procedure be as safe and effective as possible. Thus, complications should be minimized whenever possible. These complications also translate into costs. In USA, it is estimated that about 1,000,000 prostate biopsies are carried out per year (4). If one were to consider, hypothetically, if just 1% of those patients were to experience complications that required medical care and the interruption of their professional lives, the inherent cost of the procedure – both societally and on the individual level – are considerably alarming.

The positivity for CaP with collecting 16 fragments was 30.48 %; in the literature the rate is 30 to 40% (12).

The overall rate of complications after biopsy was found to be 87.32% in our study. 5.4% of those complications were considered to be major, such as hematuria and rectal bleeding for more than 7 days, infectious complications, urinary retention and death. Minor complications are mostly self-limited, resolving days after the biopsy, not causing increased morbidity to the patient. These data were also reported by other authors, such as Rodriguez and Terris (11) and Jesus et al. (6). This is important because we have given a higher probability of having some kind of complication, and patients have the right and our obligation to be alerted to this fact.

Despite occurring with great frequency, the minor complications associated with this procedure are little discussed in the literature, with the infectious complications being given much greater focus (6). Amongst the most common minor complications are those of hemorrhagic origin, such as hematuria. The results of the present study demonstrate an incidence of 65.13% of patients with hematuria, values consistent with those found in the literature (6, 13, 14).

The hemospermia in this study was the second cause of hemorrhagic complications corresponding to 44.67% of patients undergoing biopsy, also compatible with the data values from the literature (6, 14). The reported rate of hemospermia varies widely among studies, this variation may reflect cultural issues, absence of sexual activity, social stigma, or different perceptions of importance as well as differences in data collection among studies (timing and method of assessment) (9). Hemospermia is the type of hemorrhagic complications that worries and frightens the patient submitted to prostate biopsy and more common in sexually active patients.

As the third most common complication in the present study, rectal bleeding was reported in 22.48% of the patients submitted to biopsy. Other studies relate an incidence of rectal bleeding that varies from 1.3% to 37.1% of biopsied patients (6, 11, 13, 14). Almost all patients had rectal bleeding after prostate biopsy, assessment of immediate bleeding was subjective. Patients who had little bleeding were not considered in the study and patients with severe rectal bleeding who underwent treatment or observation were considered.

Infectious complications are less common than hemorrhagic, but present a greater risk of morbidity to the patient. Several recent studies describe increased rates of hospitalization after prostate biopsy, specifically because of infectious complications. Severe sepsis has been reported in 0.1% to 3.5% of patients, with Escherichia coli being the most common bacteria involved (4, 13, 15). In the present study, only one patient (0.29%) presented with fever and chills on the second day post-biopsy, which lasted only one day after beginning a 7-day course of ciprofloxacin. 51 patients (14.70%) presented with dysuria, but without the presence of infection, and no patient developed sepsis. Some authors consider asymptomatic bacteremia an infectious complication, though the majority only considers bacterial presence a complication when accompanied by clinical symptoms (16). Dysuria and pollakiuria are symptoms that are only considered infectious when accompanied by other symptoms of infection (positive urine culture, fever, chills, orchitis, or prostatis). Dysuria and pollakiuria can be the result of irritative factors after prostate biopsies such as edema or clots that obstruct the passage of urine through the urethral canal.

The post-biopsy urine culture was positive in five patients (2.15%) from a total of 232 samples. Only one patient with positive urine culture evolved with symptomatology, developing urinary retention. Although not frequently seen, asymptomatic bacteriuria was reported by Fong et al. (17) in 7% of the patients in their study in which two types of antibiotics were compared. The presence of positive urine culture is associated with the use of antibiotic prophylaxis, the type of antibiotic used, and the presence of urinary tract infection prior to biopsy (8, 17).

One strategy to reduce infectious complications is rectal cleansing; a Cochrane review concluded that enema plus antibiotics reduced the risk of bacteremia (relative risk [RR]: 0.25; 95%CI, 0.08–0.75) compared with antibiotics alone (7). The problem of infection after TRUS-guided biopsy has long been recognized in many studies, with bacteraemia occurring in almost all and bacteriuria in 13–36% of men when a placebo or no antibiotic prophylaxis is used (7-9).

Currently, the use prophylactic antibiotics to minimize infective complications are routinely used, but such therapy does not completely eliminate infection and there is no consensus about antibiotic choice, dose, route of administration and duration of therapy (9). In a systematic review, Zani et al. (7) showed that antibiotic prophylaxis is effective in the prevention of infectious complications after prostate biopsy and that a variety of classes of antibiotics are effective. The quinolone class (ciprofloxacin) was the most widely researched class, with the greatest number of studies and subjects dedicated to its research. There were no definitive studies to confirm that long duration antibiotic courses (three days) are superior to short duration courses (one day), or that multiple dose treatment is superior to single dose treatment.

Antibiotic prophylaxis most commonly uses fluoroquinolones (ciprofloxacin), largely due to a broad spectrum of antibacterial activity, including most aerobic microorganisms residing in the bowel, good oral bioavailability (70% to 80%), extended half-life (4 to 5 hours), high concentration in both urine and prostate tissue, and post-antibiotic effect suppressing bacterial growth lasting for 2 to 6 hours (8, 18). Thus, ciprofloxacin becomes a logical candidate for the prophylaxis of urinary tract infections in patients undergoing prostate biopsy. However, recent studies have described an increase in infections after prostate biopsy by fluoroquinolone-resistant E. coli (19, 20).

A new strain of E. coli recently emerged from phylogenetic group B2, sequence type 131 (ST131), characterized by its ability to combine a set of extra-bowel virulence factors with antimicrobial resistance, principally against fluoroquinolone (21, 22). Recent studies have emphasized that E. Coli ST131 is capable of spreading in the community and rates of fluoroquinolone-resistant bowel colonization can rise amongst men who undergo prostate biopsies (23, 24).

An increase in fluoroquinolone-resistant E. coli strains has been observed in certain localities, remaining below 5% in most places, however, certain areas have seen more significant increases, such as São Paulo, Brazil, wherein the density of these strains has continued to grow even further in recent years (19).

Quinolone-resistant strains of E. coli will become even more common in the future. For areas in which the rate of infection from prostate biopsy remains high, the exclusive use of alternative prophylactic antibiotic regiments, or alternatives used in combination with fluoroquinolones, may be useful in the reduction of rates of complications (25, 26).

The low rate of infectious complications observed in our study may be due to a population less exposed to antibiotics and a lower incidence of E. coli strains resistant to ciprofloxacin, demonstrating the efficacy and safety of short-term prophylaxis with ciprofloxacin in our location.

Eight patients (2.30%) in a total of 347 patients were hospitalized, five of them due to urinary retention. In our study there was no hospitalization resulting from post- biopsy complications. In literature hospitalization rates range from 0.1 to 3.4% (5, 6, 11, 13, 15).

In our study, 16 patients (4.56%) presented with urinary retention, a number significantly greater than those seen in comparable studies. Only in the study of Deliveliotis et al. (27) occurred a similar rate (4.6%) of urinary retention. The cause of urinary retention can be explained perhaps by collecting fragments in transition zones near the prostatic urethra, prostate volume, lower urinary tract symptoms (LUTS) pre biopsy or the number of cores collected. In our study, we collected two cores from the transition zone (one core bilaterally), which may have resulted in injury and inflammation near the urethra, thus explaining the increase in rates of urinary retention. Biopsy in the transition zone has a low rate of detection of PCa (1.8%), and does not improve the number of positive re-biopsies. There is currently no indication for the collection of cores from the transition zone (28). In our sample of 351 patients, only one patient (0.28%) was diagnosed with PCa due to collection from the transition zone, reinforcing the lack of necessity for the biopsy of this region. Raaijmakers et al. (13) demonstrated that an increase in prostate volume is associated with hematuria of over three days' duration ($p<0.001$) and acute urinary retention ($p=0.009$). The mean prostate volume in the 16 patients who developed urinary retention in our study was 50.12 cm^3, which is not statistically different from patients who did not experience this complication. According to the data obtained in this

study, Rodriguez and Terris (11) did not demonstrate any association with prostate volume and morbidity. Zisman et al. (29) reported a relationship between prostate biopsy and LUTS, a transient voiding impairment or acute urinary retention might be precipitated by biopsy, especially in patients with a transition zone volume >42 mL and with a baseline IPSS of >20. In our study we did not performed the evaluation of LUTS in pre biopsy period. It seems logical that the greater the number of cores collected, the greater the damage to the prostate, but in many studies comparing biopsies with varying numbers of cores collected, there were no statistically significant differences regarding complications associated with prostate biopsy (5, 30, 31).

CONCLUSIONS

Prophylaxis with a single-day course of ciprofloxacin in this study proved to be effective, with low rates of infectious complications, even in extended biopsies. These findings demonstrate that ciprofloxacin remains the gold-standard drug for antibiotic prophylaxis in this procedure.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The referred manuscript is a large sample study and demonstrated good results in terms of low overall incidence of symptomatic urinary tract infection. These results denoted that ciprofloxacin still was effective in promoting antibiotic prophylaxis in the population evaluated despite the current increase in bacterial resistance rates faced by fluoroquinolones. This observation permits emphasize that population variability may play an important role on the selecting process of antibiotics for prophylaxis purposes. Consequently, knowledge of the bacterial resistance profile from the local population is paramount for optimizing post-biopsy infectious complications results. However, this study results have limitations, a control group was not designed for comparisons and therefore its evidence level was reduced to grade III. Other aspect is that post-biopsy urine culture was positive in four asymptomatic patients and was not considered as an infection event. Asymptomatic bacteriuria can lead to oligosymptomatic urine/prostate colonization causing eventual urinary tract infection onset in the future.

Is the era of empiric fluoroquinolones for prostate biopsy prophylaxis over?

Prostate biopsy is the gold-standard method for diagnosing prostate cancer. The procedure is most commonly performed through a transrectal approach, which can expose the genital and urinary tract to Gram-negative enterobacteria infection, especially caused by E. coli (1).

A Cochrane review on prophylaxis for transrectal prostate biopsy revealed a significant reduction in bacteriuria, urinary tract infection, bacteremia, fever and hospitalization after prostate biopsy with antibiotics compared to placebo. Definitive evidences of superiority of long-term or multiple-dose compared to short-term or single--dose antibiotic prophylaxis protocols were not demonstrated (2). Several reports have not shown significant difference between single-dose/1-day and 3-day prophylactic regimens (3-5). In addition, the American Urological Association has recommended antibiotic prophylaxis maintained for less than 24 hours in transrectal prostate biopsies (6). In this scenario, a short-term protocol may offer advantages of cost savings with potentially fewer drug related resistance.

Other efforts for reducing post-biopsy infection rates have been investigated. The use of enemas in association with antibiotic prophylaxis was also evaluated by Cochrane review. A reduced risk of bacteremia was identified when this association was applied compared to antibiotics alone, although no differences were found in fever or infection endpoints (2).

Patient-specific and procedure-specific characteristics were also described as possible potential risk factors for higher post-biopsy infection rates: increased comorbidity scores, untreated asymptomatic bacteriuria, history of prostatitis, urinary tract infection, prostate size, indwelling urinary catheters, presence of bladder stones, inadequately treated diabetes mellitus, number of biopsy cores and number of repeat biopsy procedures (7).

The choice of the prophylactic antibiotic type has been empirical and guided by the expected bacterial spectrum at the operative site, antibiotic susceptibility, drug pharmacokinetic and pharmacodynamics properties (8). Fluoroquinolones have traditionally been used as the primary prophylactic agent for prostate biopsy due to excellent urinary and prostatic penetration providing optimal coverage against key pathogens (9).

Despite the fact transrectal prostate biopsy has been widely considered a safe procedure for a long period of time and associated with low infectious complications rates, contemporary prospective and retrospective reports have currently shown a surprisingly increase on post-biopsy infectious rates from 1% to 4% over the past fifteen years (10, 11). Parallel to this trend, studies have also shown a dramatically increase in the prevalence of fluoroquinolone-resistant E. coli strains (12). These findings have progressively changed the optimal scenario found by fluoroquinolones to effectively promote antibiotic prophylaxis in transrectal prostate biopsies.

Another important issue is that the previous controlled randomized trials that first evaluated the empirical use of antibiotic prophylaxis before transrectal prostate biopsies were performed when levels of resistance to commonly used antibiotics were generally low (2).

In this respect, recent reports demonstrated presence of fluoroquinolone-resistant bacteria in 50-90% of patients with post-biopsy symptomatic infections. Additionally, the presence of fluoroquinolone–resistant pathogens in the rectal flora preoperatively, has been considered the most important risk factor for post-biopsy infection. The risk of harboring fluoroquinolone-resistant bacteria in the faeces was evaluated and increased remarkably on those who have received fluoroquinolones within the past 6 months or after international travel to countries with high levels of antibiotic resistance (12-14).

In this regard, non-randomized trials applied rectal swab cultures for preoperative assessment of rectal flora susceptibility and performed a targeted antimicrobial therapy based on its susceptibility profile. The targeted antibiotic prophylaxis was associated with a notable decrease in the incidence of infectious complications as well as a decrease in the overall cost of care (15).

Currently, these new attempts for a more individualized and optimized antibiotic prophylaxis based on the susceptibility profile of the rectal flora of each patient reached a new milestone of a new era on the way for reducing post biopsies infection rates. However, additional larger randomized prospective studies are still needed to further evaluate the efficacy and cost-effectiveness of this new strategy and compare it to the traditional empirical prophylaxis approach.

On the other hand, new biopsy technology as the MRI-transrectal ultrasonography (MRI--TRUS) fusion-guided-3D targeted biopsies has potential to reduce the number of repeated biopsies (16,17). Consequently, it may reduce the amount of antibiotic used for prophylaxis and therefore possibly contribute for reducing antibiotic resistance in the future.

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ORIGINAL ARTICLE

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A cross-sectional study of cryptorchidism in children: testicular volume and hormonal function at 18 years of age

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ABSTRACT

Purpose: To evaluate the relationship between unilateral or bilateral criptorchidism, patient age, primary location of the gonad and modality of treatment with testicular volume and hormonal status at 18 years in patients diagnosed and treated for cryptorchidism during childhood.

Materials and Methods: Testicular volume, LH, FSH, and testosterone were evaluated in 143 young men at 18 years treated in childhood for unilateral (n=103) or bilateral (n=40) cryptorchidism.

Results: Unilateral cryptorchidism: Location of testis was prescrotal in 36 patients, inguinal in 52 and non-palpable in 15. The mean volume was 9.7 mL compared to 16.2 mL. for the spontaneously descended testicle in unilateral cryptorchidism. However, 22 patients who received HCG had a significantly bigger testis (11.8 mL.) than those treated with primary surgery (9.2 mL). The results showed a significant positive correlation between testicular volume and patient age at treatment.

Bilateral cryptorchidism: Location of testis was prescrotal in 34 cases, inguinal in 40 and 6 patients with non-palpable testicles. Mean volume at 18 years was 12.9 mL, greater than unilateral cryptorchid testis (9.7 mL) but smaller than healthy contralateral in unilateral cases (16.2 mL). There were significant differences in the testicular growth for bilateral patients with testicular descent after being treated with HCG (14.4 mL) in respect with those untreated (11.1 mL) or those who underwent primary surgery (11.4 mL). There was a significant positive correlation between the testicular volume and palpable (12.4 mL) or non-palpable testis (10.4 mL). There was a correlation between unilateral or bilateral cryptorchidism and levels of FSH.

Conclusions: Testicular volume and hormonal function at 18 years for patients diagnosed and treated for cryptorchidism during childhood are strongly influenced by whether the undescended testis was unilateral or bilateral. Location of the testes at diagnosis or age of initial treatment exerts no definite effect on testicular volume improvement or hormonal levels at 18 years of age.

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INTRODUCTION

Incomplete descent of one or both testicles from the abdominal cavity, through the inguinal canal into the scrotum (cryptorchidism) is a multifactorial etiology abnormality that affects 1-1.8% of male infants (1). It is reported to be associated with infertility and testicular cancer (2). To minimize these complications is mandatory the placement and fixation of the testis in

the scrotum (2, 3). It is not known the ideal age for surgical treatment and which is the ideal therapy (4). However, based on several studies that show that undescended testes undergo early and progressive deterioration, the recommended age for treatment has been decreasing gradually as we have improved our understanding of spermatogenesis (3, 5).

Testicular damage may be secondary to the abnormal position of the testis. This damage is basically characterized by a progressive reduction in germ cell number and size of the seminiferous tubules with peritubular fibrosis and hyalinization, resulting in a decrease of the number of Leydig cells. These facts may affect the production of sexual hormones promoting testicular atrophy with subsequent infertility (6-8). Hence, the testicular volume and hormone levels are related to reflect the spermatogenesis and are considered to be indirect indicators to predict the potential for fertility. (9-11). But it is also possible that the undescended testis has been inherently atrophic (12-14); therefore, early correction of cryptorchidism would be less important (15-17).

A cross-sectional observational transverse study was performed to evaluate the relationship between age at treatment, location of the gonad and type of treatment (hormonal and/or surgical therapy) on testicular growth and hormonal function at 18 years of age in patients treated for unilateral or bilateral cryptorchidism during childhood. To the best of our knownledge, this is the first reported survey of longitudinal long--term follow-up of patients with cryptorchidism.

PATIENTS AND METHODS

Study population

The study population consisted of 143 boys who were born before 1993 and were diagnosed as having unilateral (103 cases) or bilateral (40 patients) primary cryptorchidism. Patients with retractile testis, endocrine diseases, chromosomal abnormalities, incomplete data or dysmorphic features were excluded from the study. The mean age at effective treatment was 7.42±3 years. All these patients were evaluated at 18 years of age and divided in two separate groups: unilateral and bilateral cases.

DESIGN OF THE STUDY AND FOLLOW-UP DATA

Design of study

A cross-sectional observational transverse study at 18 years of age of boys diagnosed and treated of unilateral or bilateral cryptorchidism during infancy and/or childhood period.

Physical examination

Physical examination included assessment of testis position obtained by gentle manipulation. Testis position was classified as pre-scrotal (between external inguinal ring and scrotum), inguinal, or nonpalpable. Testicular volume was measured using a Prader orchidometer (a chain with 13 numbered beads of increasing size from 1 to 30 mL).

Testicular ultrasound

After the physical examination, testicular volume was measured with ultrasonography at 18 years of age. All ultrasound examinations were performed with a 12-MHz linear transducer. To measure the testicular volume, the scanner was placed on the inguinal region or on the scrotum. Three separate transverse and longitudinal images were recorded for each testis to assess the volume. After maximum length, width and height were obtained in the ultrasound, the testicular volume was calculated using the empiric formula of Lambert first described in 1951. The Lambert equation (length x width x height x 0.71) estimates the ellipsoid testicular volume more accurately. The testicular volume estimated by Prader orchidometry correlated closely with the measurements by ultrasonography (18).

Surgical and/or hormonal therapy

According to the protocol established in our hospital, hormonal therapy was offered to all cases as first line treatment. Boys who accepted were given human chorionic gonadotropin hormone (HCG) intramuscularly twice a week for five weeks. Each injection was 250 IU for children under two years, 500 IU. for children between 2 and 6 years, and 1,000 IU for ages 6 to 11 years, following the recommendations of the expert group of WHO in cryptorchidism (19). Patients

who refused or did not respond to hormonal treatment, underwent surgery for correction of undescended testes according to the standard surgical orchidopexy technique (20). Effective age of treatment was considered once the testis was definitely located in the scrotum after hormonal and/or surgery.

Follow-up

All patients were followed at the outpatient clinic in the first year at one, 3, 6 and 9 months after treatment (medical or surgical). Then, they were reviewed annually until age 18. At the age of 18, a physical examination was performed in all patients, checking the location of the testes and their size using a Prader orchidometer. True testicular volume was determined by ultrasonography and the empiric formula of Lambert. One pediatric surgeon (RVC) performed more than 95% of the clinical examinations. Blood samples were analyzed in all adolescents for FSH, LH and Testosterone levels. Hormonal levels were measured using an immunometric monoclonal assay. Semen analysis was realized only in a small number of adolescent's patients who voluntary provided a semen specimen after ejaculation. Patients were definitely discharged once informed of the laboratory results and concerns about potential of fertility and risk of testicular malignancies.

Statistical analysis

The mean, median, and range were calculated using standard methodology. Data were reported as means when normally distributed, and medians when non-normally distributed. Categorical variables are presented as absolute numbers and percentages, continuous variables as means, standard deviations, minimum and maximum range. Means were compared using the chi-squared or Fisher exact test and medians were compared using the non-parametric Mann-Whitney U test. Differences in proportions among categoric data were assessed using the Fisher exact test. All data were analysed by the statistical package SPSS for Windows, version 18.0 (SPSS, Chicago, IL, USA). Statistical significance was set at $p<0.05$.

ETHICAL APPROVAL

The Local Ethical Committee of the University Hospital of Santiago de Compostela, Spain approved the study. Informed consent was obtained from all parents of the patients who agreed to participate in the study.

RESULTS

The mean age at referral for undescended testis was 7.42 years (range 1-13). Of the 143 boys diagnosed with undescended testis, the anomaly was bilateral in 40 and unilateral in the remaining 103. Of these 103 boys, the anomaly was on the left in 45 (43.7%) and on the right side in the remaining 58 (56.3%). In all cases the testicular volume was measured by Prader orchidometry and ultrasonography.

Unilateral Cases

Among unilateral cases (Table-1) only 15 patients had non-palpable testis (14.5%) and 88 had a palpable gonad. Of these 103 unilateral patients, 26 patients refused hormone treatment. Treatment with HCG induced the descent in 22 testes (28.6%) for a total of 77 patients. The descent of those located in the inguinal region was 3/39 (7.7%) and 19/32 (59.4%) of those located high scrotal. Unilateral non-palpable testis in patients who received HCG therapy did not respond (0/5). We performed an orchidopexy in 81 patients with unilateral disease, 26 primary and 55 subsequent to failure of medical treatment. In 20% (3/15) of non-palpable unilateral cases, a very atrophic testicle was found during the surgical procedure. The volume of undescended testicle in unilateral cases was significantly smaller in size (median 9.7 mL) than its counterpart normal testicle (median 16.2 mL). The hormone levels were within normal ranges in all cases, mean 4.01 IU/L for FSH, 4.32 IU/L for LH and 6.75 ng/mL for testosterone. Testicular volume of patients with scrotal descent after HCG treatment (22 cases) was significantly higher (mean 11.8 mL) in respect to those who were operated after failure of hormonal therapy (mean 9.2 mL.) and those who underwent primary surgery (mean 8.6 mL)

Table 1 - Unilateral cryptorchidism (n=103). Features based on testis location and therapy used (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST-Testosterone).

	Testis Location								
	Pre-Scrotal (36)			Inguinal (52)			Non Palpable (15)		
Treatment	Hormonal therapy		CX	Hormonal therapy		CX	Hormonal Therapy		CX
Groups	A	B		A	B		A	B	
Patients	19	13	4	3	36	13	0	6	9
FSH (UI/L)	3.6	3.9	3.8	4.9 (*)	3.7	4.4	4.03		3.8
Range	(1.7-7.6)	(3.3-8.8)	(2.5-6.0)		(2.6-5.9)	(2.3-9.2)	(3.4-4.6)		(2.3-8.4)
LH (UI/L)	3.5	5.9	4.7	6.2 (*)	3.8	3.3	3.93		3.25
Range	(3.1-5.5)	(2.6-7.5)	(3.4-5.8)		(2.8-5.1)	(2.8-5.4)	(3.1-4.6)		(2.7-4.3)
TEST. (Ng/mL)	5.2	5.4	6.1	10.1 (*)	6.3	5.6	10.0		5.3
Range	(4.8-9.1)	(4.1-6.8)	(5.3-9.8)		(5.2-8.1)	(4.5-6.6)	(4.6-18.2)		(3.9-11.9)
Age Treatment (months)	84.6	98.7	140.7*	121.2 (*)	92.6	81.1	57.9		87.5
Range	(44.1-99.5)	(53.5-137.3)	(131-143)		(37.2-137)	(30.4-140.0)	(28.7-99.7)		(71.5-113.4)
Testicular Vol.									
Affected testis	13.0 (10.0-17.8)	11.3 (7.8-22.6)	9.4 (8.8-10.2)	10.7 (7.8-12.5)	10.1**** (7.3-13.0)	11.9** (8.05-14.4)	6.3** (0.1-9.1)		4.6 *** (0.1-10.5)
Non affected testis	13.5 (10.5-18.0)	16.7 (13.1-22.1)	9.8 (8.3-12.3)	22.9 (11.0-24.3)	14.8 (11.8-18.5)	15.8 (11.9-21.3)	16.4 (10.3-23.7)		19.7 (16.0-30.6)

(*) Only 1 case with data
*p < 0.05; ** p <0.01; *** p < 0.005; **** P <0.001

(p=0.019). However, hormone levels were similar in all groups without any statistically significant differences.

In this survey, testicular volume of the palpable testes was significantly greater than non-palpable ones (mean 11.0 mL vs. 7.6 mL). However, volume of the contralateral testes was significantly lower in the group of palpable testes. Thus, the total testicular volume (ie, sum of the volumes of both testes estimated by Lambert's equation or Prader orchidometry) in both groups of patients related to unilateral criptorchidism (palpable and non-palpable) was similar. In patients with retained testicles in the inguinal position, the volume was significantly lower in respect to its counterpart, regardless of type of treatment. No differences in hormone levels according to the situation of the gonad were noticed (Table-1). In boys treated before 2 years of age (Table-2) there was a further development of both the undescended testicle (median 13.4 mL) and healthy scrotal counterpart (median 17.1 mL) in respect to the patients treated after 2 years of age (11.0 mL and 14.7 mL respectively). However, FSH, LH and testosterone levels did not show statistically significant differences in these two groups of patients.

Bilateral Cases

In patients with bilateral cryptorchidism (Table-3) 6 cases had non-palpable testes but 74 had palpable ones. Of all bilateral cases, 5 pa-

Table 2 - Unilateral cryptorchidism (n=103) Features based on age and therapy (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST-Testosterone).

	< 2 years			2-6 years			> 6 years		
	Hormonal therapy		CX	Hormonal therapy		CX	Hormonal therapy		CX
	A	B		A	B		A	B	
FSH (UI/L)	4.0 (*)	3.5	5.3 (*)	2.3	4.1	3.5	4.0	3.8	3.8
Range		(2.5-5.4)		(1.1-7.0)	(2.5-5.7)	(2.2-8.0)	(2.0-9.5)	(3.2-6.3)	(2.5-7.6)
LH (UI/L)	2.8 (*)	4.2	2.7 (*)	3.2	4.8	3.1	5.1	3.8	3.5
Range		(3.3-5.6)		(3.2-3.5)	(2.9-5.9)	(2.9-3.3)	(3.2-6.1)	(2.7-5.1)	(3.3-5.8)
TEST (Ng/mL)	4.9 (*)	7.5	5.6 (*)	6.7	5.9	4.6	5.2	5.9	6.0
Range		(5.5-16.6)		(5.3-9.9)	(4.4-8.2)	(3.8-6.6)	(4.8-10.1)	(4.8-7.8)	(4.5-9.1)
Age at treatment (months)	11.9 (8.6-15.7)	18.3 (14.5-21.3)	17.8 (17.3-20.1)	37.2 (27.5-60)	50.1 (34.2-54)	36.0 (28.5-59)	96.2 (80.5-121)	80.9 (46.3-126)	128.7* (87.6-142)
Testic. Volume									
Affected testis	17.2 (11.4-23.0)	11.2 (9.3-13.5)	11.9 (0.1-15.0)	15.4 (11.8-18)	8.3*** (6.5-11.1)	11.2 (7.1-12.4)	11.5 (8.9-15.8)	10.9*** (7.7-13.8)	9.0*** (4.8-11.4)
Non-affected testis	18.5 (18.0-19.0)	15.0 (12.1-17.5)	17.9 (12.3-33.2)	15.3 (10.3-18)	16.7 (13.4-20)	14.0 (11.2-18)	12.1 (10.6-21.6)	14.6 (11-19.9)	15.8 (10-22.9)
Patients	2	5	3	4	20	4	16	30	19

(*) Only 1 case with data
* p < 0.05; ** p <0.01; *** p < 0.005; **** P <0.001

tients refused hormone treatment (10 testes). HCG therapy induced the descent of 14 testes (20%), two of them located inguinal (5.4%) and 12 pre-scrotal (41.37%). Descent after hormonal therapy was not noticed in cases of non-palpable testes (6 patients). 10 primary and 56 secondary orchidopexies were made in bilateral cryptorchidism. Of the three non-palpable bilateral cases, a severe atrophic testicle was found during surgical procedure (3/6, 50%). The mean testicular volume of the undescended testes in the bilateral group (12.93 mL) was significantly greater than the unilateral group (9.7 mL). However, this testicular measurement was significantly lower than the normal value for the healthy contralateral testes in unilateral cryptorchidism (16.2 mL). The hormone levels were within normal ranges in all bilateral patients except in six cases. Mean hormonal values in bilateral cases were 11.28 IU/L for FSH, 4.83 IU/L for LH and 5.73 ng/mL for testosterone.

The mean volume of the 14 testes that descended after treatment with HCG (14.4 mL) was significantly greater than the non-responders group (11.1 mL) or even than the group of patients who underwent orchidopexy without previous hormonal therapy (11.4 mL). A significant reduction in testicular size was noticed in cases of non-palpable bilateral testis (10.4 mL) in respect to palpable ones (12.4 mL). In these particular patients with bilateral criptorchidism and non-palpable testes, the FSH levels were significantly lower in relation to palpable cases (15.6 vs 10.4 IU/L). Similar results were obtained with LH levels (6.7 vs 4.4 IU/L) and Testosterone values (3.7 vs 6.1 ngr/mL).

In patients with bilateral cryptorchidism treated before two years of age, we noticed mean testicular volume measurements significantly smaller (10.3 mL) than those treated after two years (12.1 mL). Comparing these two separate

Table 3 - Bilateral cryptorchidism (n=80) Features based on testis location and therapy used (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone).

	Pre-Scrotal (34)			Inguinal (40)			Non-Palpable (6)
	Hormonal Therapy		CX	Hormonal Therapy		CX	Treatment
	A	B		A	B		B
Patients	12	19	3	2	31	7	6
FSH (UI/L)	9.2	6.6	13.9	-	5.3	17.1	15.6
Range	(3.0-10.8)	(3.5-10.1)	(13.9-22.3)		(2.3-13.2)	(7.5-19.7)	(15.6-15.6)
LH (UI/L)	4.2	3.4	4.0	-	4.8	5.9	6.7
Range	(3.1-9.6)	(2.5-4.9)	(4.0-5.9)		(3.4-7.7)	(4.8-8.8)	(6.7-6.7)
TEST. (Ng/mL)	7.5	5.6	5.9 (*)	-	5.7	6.0	3.7
Range	(6.0-8.4)	(5.3-6.4)			(5.3-6.6)	(2.5-8.5)	(3.7-3.7)
Age at Treat.	96.3	109.1	114.0	29.6	82.9	100.2	55.5
(Months)	(71.8-102.5)	(61.0-125.7)	(88.6-115.0)	(29.6-29.6)	(30.6-130.0)	(37.1-103.0)	(47.8-127.9)
Testic. Volume	15.40	12.6	11.2	13.5	10.3	11.7	10.4
Range	(10.9-16.7)	(9.0-18.5)	(10.5-12.0)	(12-15.0)	(7.6-14.7)	(5.1-13.1)	(1.8-18.1)

(*) Only 1 case with data.

groups of bilateral cases (treated before and after two years of age), hormonal levels were significantly different too: FSH (3.0 vs 9.0 IU/L), LH (5.1 vs 5.5 IU/L) and Testosterone (6.5 vs 6.0 ngr/mL) (Table-4). Statistical analysis results indicated that the mean volume of undescended testicle showed a strong positive relationship with type of cryptorchidism (unilateral or bilateral). Testicular volume is smaller in unilateral cryptorchidism; however, total testicular volumen is greater in unilateral cases in relation to bilateral patients due to the compensatory effect of the healthy contralateral one. Accurate determination of hormonal levels at 18 years of age in our study also showed a significant elevation of FSH levels in bilateral cryptorchidism (p=0.001), with slight increase in LH levels. Testosterone values were significantly lower in bilateral patients in relation to unilateral cases. There was statistically significant difference between the two groups.

DISCUSSION

Since testicular volume plays a definitive role in potential of fertility in young adults, accurate measurement is supposed to be relevant in the follow-up of cryptorchid patients. Testicular volume in otherwise healthy young adults is aproximately 18-20 mL (10, 21). Hypoplasia is considered in those with volume less than 14 mL (22, 23) or those with a difference greater than 3 mL in relation to the healthy contralateral (24). Volume loss was shown to have progressive deleterious effects on the future fertility status. The minimum testicular size for good fertility is approximately 12 mL (22). Total testicular volume (ie, sum of the volumes of both testes) of approximately 30 mL is indicative of normal testicular function. We consider that an accepted normal testicular volume at 18 years of age is 14-16 mL (22, 24). Since approximately 70%-80% of tes-

Table 4 - Bilateral cryptorchidism (n=80) Features based on age and therapy (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST- testosterone).

AGE	< 2 years	2 - 6 years			> 6 years		
	Treatment	Treatment		CX	Treatment		CX
Groups	B	A	B		A	B	
FSH (UI/L)	3.7	2.8	9.5	-	10.6	6.6	15.5
Range	(1.9-6.3)	(2.5-3.2)	(5.0-15.6)		(9.2-11.3)	(3.5-11.3)	(9.1-21.0)
LH (UI/L)	5.1	10.4	4.6	-	3.3	3.8	5.3
Range	(4.3-5.7)	(4.2-16.7)	(2.7-7.2)		(2.4-7.2)	(2.8-7.9)	(4.2-8.1)
TEST. (Ng/mL)	6.5	6.1	5.4	5.9 (*)	7.5	5.6	5.8
Range	(4.0-6.6)	(4.4-7.9)	(4.1-6.3)		(6.6-9.8)	(5.3-5.9)	(2.5-8.5)
Age at Treat.	20.4	43.7	47.4	37.0	100.5	119.5	101.6
(Months)	(16.1-23.4)	(29.6-71.8)	(33.6-61.0)	(36.9-37.2)	(95.3-111.3)	(92.4-139.8)	(91.5-112.2)
Testic Volume	10.3	15.0	10.3	6.6	13.9	12.1	14.5
Range	(7.4-18.9)	(12.4-16.1)	(6.6-19.6)	(1.2-12.1)	(10.0-17.2)	(8.8-15.4)	(6.7-12.8)
Patients	7	6	15	2	8	34	8

(*) Only 1 case with data

ticular mass consists of seminiferous tubules, testicular volume is largely a reflection of spermatogenesis (23, 25-27). The testicular volume has been one of the most important endpoints predicting the outcomes of cryptorchid patients related to spermatogenesis. Since it is not usually possible to perform semen analysis in pediatric age group and established clinical criteria to properly define the favourable outcomes are absent, the improvement in the testicular volume has been considered to be the most relevant indirect measure for potential of fertility in adolescents patients (28, 29).

Vast majority of authors reported a significant decrease in testicular volume in cryptorchid patients (10, 24, 30-33), more evident in high locations (30) and in patients treated later during childhood (33). However its not clear if age at referral of hormonal therapy can achieve an improvement in testicular size (33, 34, 36-38).

According with other authors (39, 40) our results showed a marked decrease in the volume of the cryptorchid testis related to the healthy contralateral in unilateral cases. Our rate of testicular volume loss in respect to healthy contralateral in unilateral cases is 34.76% and in bilateral patients is 23%; both are similar of the percentages refered by other studies (24). Although we have used the contralateral healthy testis as a control, it would be interesting for future studies to include a real control group of normal age-matched adults to compare both hormone levels and testicular volume.

Since the location of the testicle before treatment is strongly related to the ipsilateral testicular volume catch-up growth rate at 18 years of age, our results showing an improvement in size after hormonal therapy on both unilateral and bilateral groups are consistent with those reflected in the reviewed literature due to the more caudal location of these testes (3). This volume catch-up growth rate depends on location before treatment but is not related to the type of therapy employed. Likewise, the lower catch-up growth rate of non-palpable testis at 18 years of age may be explained by the high location inherent to these testicles, and is

non-related to the treatment modality. However, in unilateral cryptorchidism there is a remarkable improvement in the contralateral testis growth and there are no differences in the total testicular volume in relation to the bilateral group.

However, some authors underestimated the correlation of testicular volume with sperm count of semen profiles (41). According with others, we think that testicular volume had the strongest positive correlation with sperm density, followed in decreasing order by total sperm count per ejaculate, total motile sperm count per ejaculate, and percentage of motile sperm (24).

Likewise, the benefit of early treatment or adjuvant hormonal treatment does not seem clear (10, 42, 43). Our study showed that in patients with unilateral cryptorchidism treated before 2 years of age, testicular growth was markedly higher for both the undescended testis and the healthy contralateral, compared with those treated after 2 years of age. In bilateral cryptorchidism, by contrast, there is a decrease in catch-up growth testicular rate in the group of patients treated early. Furthermore, these growth differences do not reflect changes in hormone levels at 18 years of age in both age groups (treated before and after two years). Nevertheless, the small number of cases treated before two years of age may influence our statistics workup. Anyway, in the group of patients with unilateral criptorchidism, the early treatment (before two years of age) had a markedly improvement in testicular growth in relation to those treated later. Although animal studies have confirmed the positive effect of early orchiopexy in bilateral cryptorchidism and the little benefit of additional hormone therapy (44), we didn't find these results in our series.

One of the relevant findings of our study is that hormonal treatment before surgery does not appear to exert any beneficial effect in testicular growth at 18 years of age. There are no significant differences in cath-up growth testicular rate and hormone levels between patients undergoing primary surgery and those who were operated on after hormonal treatment failure. We found a significant improvement in testicular size in patients whose testes descended with HCG treatment alone.

Some authors have reported a weak correlation between testicular size at orchiopexy, and lower ratios of paternity, hormone levels, sperm count and testicular volume in adult patients (45, 46). According with others, we found a strong positive correlation between lower FSH levels (a marker of spermatogenesis) and high location of the testicle (9, 47, 48).

We didn't find a direct relationship between testicular volume of the undescended testes and hormone levels in patients at 18 years of age. However, we noticed that in bilateral cryptorchidism, FSH levels were significantly higher than in unilateral patients, despite having the larger volume of the healthy contralateral testes and equal total testicular volume. A possible explanation theory is that there are embryologic and etiopathogenic differences between the unilateral and bilateral criptorchidism (49-51). Anyway, what seems evident is that with only one testicle located in scrotum, the potential of fertility may be preserved (52).

CONCLUSIONS

In conclusion, the current study shows that the testicular volume and hormonal function at 18 years of age for patients diagnosed and treated for cryptorchidism during childhood are positively and strongly influenced by whether the undescended testis was unilateral or bilateral. Location of the testes at diagnosis or age of initial treatment exerts no definite effect on testicular volume improvement or hormonal levels at 18 years of age.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The efficacy of immediate versus delayed antibiotic administration on bacterial growth and biofilm production of selected strains of uropathogenic Escherichia coli and Pseudomonas aeruginosa

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ABSTRACT

Purpose: The treatment of urinary tract infections (UTI) with antibiotics is commonly used, but recurrence and antibiotic resistance have been growing and concerning clinicians. We studied whether the rapid onset of a protective biofilm may be responsible for the lack of effectiveness of antibiotics against selected bacteria.

Materials and Methods: Two established uropathogenic *Escherichia coli* strains, UTI89 and CFT073, and two *Pseudomonas aeruginosa* strains, PA01 and Boston-41501, were studied to establish a reliable biofilm formation process. Bacterial growth (BG) was determined by optical density at 600 nm (OD 600) using a spectrophotometer, while biofilm formation (BF) using crystal violet staining was measured at OD 550. Next, these bacterial strains were treated with clinically relevant antibiotics, ciprofloxacin HCl (200 ng/mL and 2 µg/mL), nitrofurantoin (20 µg/mL and 40 µg/mL) and ampicillin (50 µg/mL) at time points of 0 (T0) or after 6 hours of culture (T6). All measurements, including controls (bacteria -1% DMSO), were done in triplicates and repeated three times for consistency.

Results: The tested antibiotics effectively inhibited both BG and BF when administered at T0 for UPEC strains, but not when the antibiotic administration started 6 hours later. For *Pseudomonas* strains, only Ciprofloxacin was able to significantly inhibit bacterial growth at T0 but only at the higher concentration of 2 µg/mL for T6.

Conclusion: When established UPEC and *Pseudomonas* bacteria were allowed to culture for 6 hours before initialization of treatment, the therapeutic effect of selected antibiotics was greatly suppressed when compared to immediate treatment, probably as a result of the protective nature of the biofilm.

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Key words:
urinary tract infection; antibiotic therapy; biofilm formation; bacterial growth

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INTRODUCTION

Uropathogenic *Escherichia coli* (UPEC) is the leading cause of urinary tract infection (UTI) and, in the United States alone, health care costs for UTI surpass $1.5 billion per year (1-4). UTIs rank among the most common bacterial infectious diseases encountered in clinical practice, with the occurrence of UTI in the United States estimated at 12-50% for women and 3% for men (3, 5). In patients with bladder or catheter-associated infections, the primary etiologic agents associated

with UTIs are strains of E.coli and *Pseudomonas aeruginosa* (P.aeruginosa) respectively. Therefore, this study focused attention on well-established strains of these two bacteria.

Currently, antibiotics represent the most effective treatment against UTI. However, some patients exhibit recurrent infections and/or appear to develop resistance to antibiotics (4, 6). Several studies have indicated that the production of bacterial biofilm, a large bacterial community that forms following bacterial adhesion and colonization to surfaces and in which bacteria are held together by exopolysaccharides (7) secreted by the bacteria, contributes to antibiotic resistance (8). A mature biofilm can contain a community of cells and provide a matrix for chemical signaling and message relay between individual cells (5, 9). Thus, we were interested in determining the role of biofilm production by E.coli and P.aeruginosa bacteria strains as one of the major contributors to antibiotic resistance. To study the biofilm formation by bacteria treated with antibiotics, two established strains of E.coli (UTI89 and CFT073) and two well-characterized strains of P.aeruginosa (Boston-41501 and PA01) were selected.

We first determined the time course of the growth of each bacteria strain and biofilm under different culture conditions. We also examined whether different pH conditions, consistent with the range of urine pH in humans, had any impact on bacterial growth and biofilm formation. Based on these optimized culture conditions, we examined the effect of clinically relevant antibiotics on the bacterial growth and biofilm formation. Furthermore, we evaluated whether different treatment schedules of antibiotics have any impact on bacterial growth and biofilm formation.

MATERIALS AND METHODS

Study Design

Following the evaluation of the impact of biofilm performance under different culture conditions and pH ranges, biofilm formation obtained from established strains of E.coli and P.aeruginosa was assessed in the presence of commonly used antibiotics in the treatment of urinary tract infections. The timing of antibiotic treatment on biofilm formation and bacterial growth was also studied to determine the effect of delayed therapy.

Bacterial strains

E.coli UTI89 and E.coli CFT073 were obtained from Harry Mobley (University of Michigan); both strains have been sequenced. E.coli UTI89 is a prototypic cystitis isolate (1) and E. coli CFT073 is a prototypical UPEC isolate cultured from blood and urine of a patient with pyelonephritis (10). P.aeruginosa-Boston 41501 was purchased from American Type Culture Collection (Manassas, VA), and P.aeruginosa-PA01 was obtained from Kevin McIver; only PA01 has been sequenced. Antibiotics (Ampicillin, Ciprofloxacin and Nitrofurantoin) were purchased from Sigma-Aldrich (St. Louis, MO) and used at the following concentration ranges: Ciprofloxacin HCl (Cipro: 200 ng/mL and 2 µg/mL), Nitrofurantoin (Nitro: 20 µg/mL and 40 µg/mL), and Ampicillin (Amp: 50 µg/mL). DMSO was used as a solvent to dilute all the antibiotics. The final concentration of DMSO was 0.1%. Biofilm formation was not affected at this low concentration of DMSO.

Determination of Minimum Inhibitory Concentration (MIC) by the microdilution method

MIC for E.coli and P.aeruginosa strains were assessed by varying concentrations of Ciprofloxacin, Nitrofurantoin, and Ampicillin assessing bacterial growth through CFU counts as previously described (11). An adjusted inoculum of the overnight growth organism was introduced into LB broth containing serial dilutions in 96 well plates, from 0.0015 µg/mL to 100,000 µg/mL of an initial antibiotic solution, with approximately $5x10^5$ CFU/mL inoculum. Results were observed after 18 hours of incubation at 37°C. The MIC was defined as the lowest concentration to inhibit visible growth (11).

Bacterial culture condition and growth assay

Each bacteria was cultured to log phase at 37°C in 3 mL Luria-Bertani (LB, pH 7.4) broth with no supplementation. Bacterial suspensions were diluted 1:100 and plated 100 µl into a 96-well plates containing LB broth with 1% glucose (Sigma-Aldrich). The plates were incubated at 37°C with agitated shaking (AS) at 250 rpm) or no agitation

(static environment (SE)) for 6-72 hours or incubated in LB broth with different pH environments (pH 5 to 8) for 24-48 hours. Bacterial growth was determined by optical density at 600 nm (OD_{600}) using a spectrophotometer. Furthermore, serial dilutions of culture were performed and plated for colony forming units (CFU).

For adjusting different pH in LB broth, either hydrochloric acid or sodium hydroxide was used to either decrease or increase the pH, respectively, to 5, 6, 7 and 8. Media was then filtered through a 0.2 µm sterile syringe filter (Corning, Inc., Corning, NY). Each bacterium was added into aliquots of sterile pH-adjusted media and pH was measured using pH indicator strips (EM Science, Cherry Hill, NJ) before and after incubation.

Crystal violet staining for biofilm assay

We followed the methodology for biofilm assay as previously described (8) with minor modifications. Briefly, after determining bacterial growth density, the supernatant was discarded, and attached bacteria and biofilm were washed twice with sterile water. The attached biofilm was stained with 100 µl of 0.4% crystal violet (Sigma-Aldrich) for 15 minutes at room temperature. The wells were rinsed twice with sterile water, then air dried. The biofilm-retained crystal violet was eluted with 100 µl of 100% ethanol and incubated for 5 minutes at room temperature on a shaker (175-200 rpm). The OD_{555} was determined using a spectrophotometer.

Statistical analyses

Each experiment was repeated three times for consistency, with samples in triplicate. Data were presented as the mean ± SEM, and the differences between two groups compared by the Student's t test. Statistical significance ($p<0.05$) was shown by asterisks (*) above the bars on the graphs.

RESULTS

Determination of culture condition for bacterial growth and biofilm production

As shown in Figure-1A, the time course study indicated that the growth of both E.coli strains, UTI89 and CFT073, reached a plateau in 6 hours. The AS condition was more favorable for UTI89 while no significant difference was noted for CFT073 in either condition. For CFT073, the biofilm production gradually increased under either condition, while UTI89 formed biofilm by 6 hours which stayed fairly consistent thereafter (Figure-1B). For P.aeruginosa Boston-41501, the bacterial growth reached a plateau around 24 hours with no significant difference observed in AS or SE conditions (Figure-1C). In contrast, P.aeruginosa PA01 continued to grow in AS condition from 24 to 72 hours, as compared to SE condition (Figure-1C).

Overall, both Boston-41501 and PA01 P.aeruginosa strains showed more robust biofilm production than both E.coli strains (Figures 1C and D). Noticeably, under AS condition, Boston-41501 exhibited tremendous biofilm production capability in a time-dependent manner even when bacterial growth reached a plateau at 24 hours (Figure-1D). For Boston-41501, although the biofilm production pattern remained similar in both AS or SE conditions, the biofilm production in the SE condition was significantly lower than in the AS condition (Figure-1D). For PA01 strain in AS conditions, it appeared that biofilm production was established at 6 hours and did not increase further over time (Figures 1C and D). In contrast, for PA01 strain under SE condition, bacterial growth reached a plateau within 24-48 hours but biofilm continued to increase in a time-dependent manner (Figures 1C and D). Taken together, with the exception of PA01, AS conditions appeared to be more favorable for both growth and biofilm production for all the bacterial strains tested in this study.

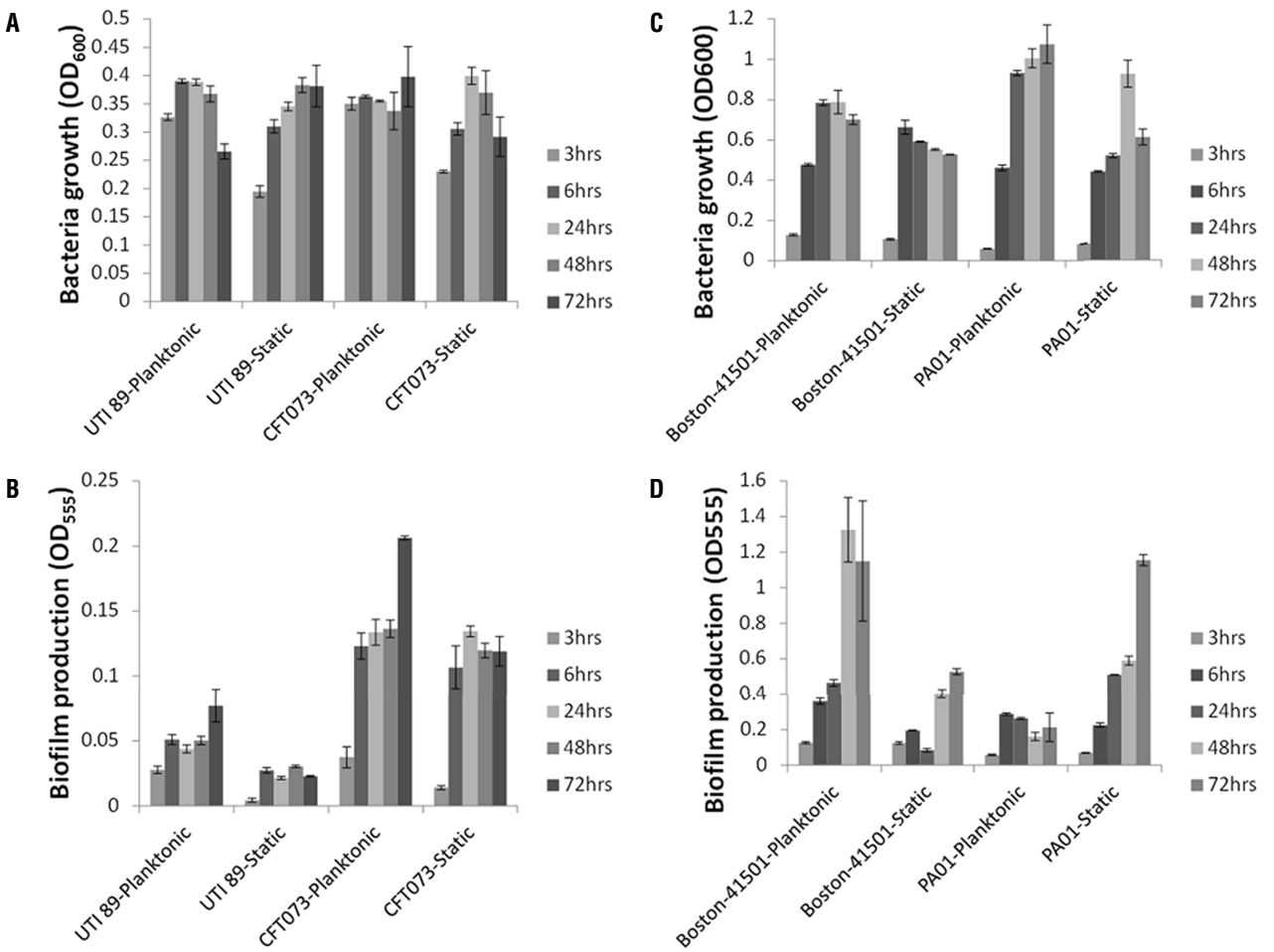
Effect of pH

As indicated in Figure-2, the different pH levels did not affect the growth or biofilm formation of our E.coli and P.aeruginosa strains, with the exception of the more acidic conditions (pH 5). P.aeruginosa strains were able to bring pH levels back to a consistent level (neutral pH) across the study at 48 hours.

Effect of antibiotics on bacterial growth and biofilm production

To assess the role of antibiotic concentration on biofilm, we initially determined the MIC of an-

Figure 1 - Time course analysis of growth and biofilm patterns.

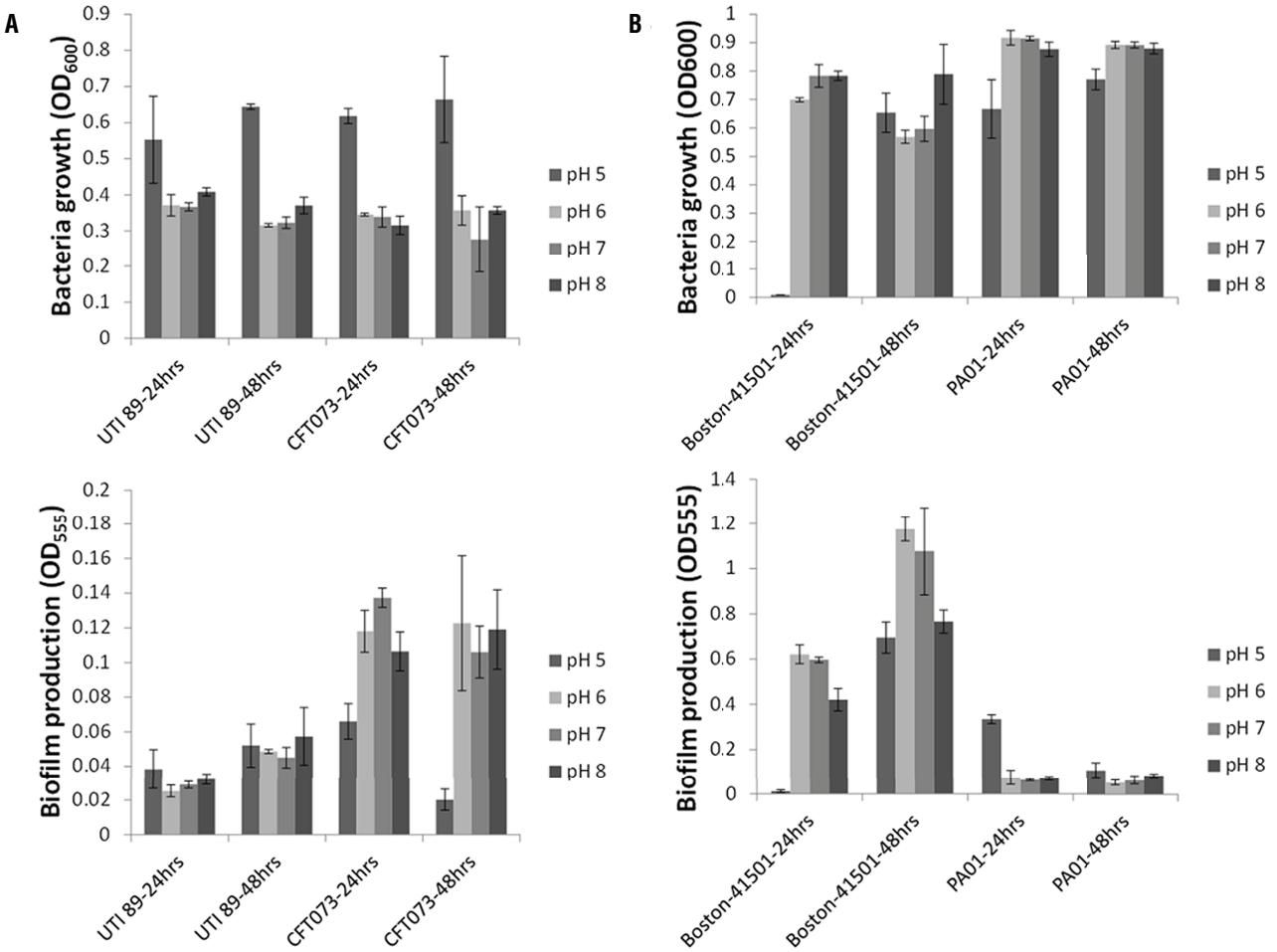


tibiotic tested for our selected strains of E.coli and P.aeruginosa. Antibiotics used in this study were chosen based on their common clinical use. For Ciprofloxacin, MIC was 100 µg/mL for all selected strains. For Ampicilin, MIC was 100,000 µg/mL for P.aeruginosa PA01, 10,000 µg/mL for P.aeruginosa Boston-41501, and 1,000 µg/mL for both E.coli strains. For Nitrofurantoin, MIC was 400 µg/mL for both P.aeruginosa (Boston-41501 and PA01) strains, 100 µg/mL and 20 µg/mL for UTI 89 and CFT 073 respectively. The dosage reported in urine is 2 µg/mL (8, 12) for Ciprofloxacin and between 25 and 400 µg/mL for Nitrofurantoin. Therefore, to make this study relevant, we used concentrations of antibiotics similar to the concentrations found in urine, which are significantly lower than the MIC. Ampicilin was used primarily as a negative control in a similar range used for the other two antibiotics.

As shown in Figures 3A and B, all antibiotics were able to significantly inhibit both bacterial growth and biofilm production for both UTI89 and CFT073 at 24 hours when antibiotics were added at Time 0. For UTI89 and CFT073, Ampicilin appeared to be less effective than Ciprofloxacin or Nitrofurantoin for inhibiting bacterial growth and biofilm production. Taken together, for UTI89 and CFT073, antibiotics can effectively inhibit both growth and biofilm production when administered at baseline (Table-1).

For P.aeruginosa strains, only Ciprofloxacin was able to significantly inhibit bacterial growth while Nitrofurantoin and Ampicilin failed to inhibit bacterial growth even when these antibio-

Figure 2 - Effect of different pH levels on bacterial growth and biofilm production over 48 hours.



tics were added at Time 0 (Figure-4A). Interestingly, for both strains, Ciprofloxacin at 200 ng/mL or 2 µg/mL and Ampicilin at 50 µg/mL significantly inhibited biofilm production. Surprisingly, Nitrofurantoin increased biofilm production in both strains (Figure--4B). Antibiotics also effectively inhibited both growth and biofilm production of P.aeruginosa when they were administered at baseline (Table-1).

Subsequently, E.coli and P.aeruginosa strains were cultured for 6 hours prior to receiving antibiotic treatment for an additional 24 hours. As shown in Figures 5A and B, E.coli bacterial growth and biofilm production were not inhibited by any of the antibiotics.

For Boston-41501, Ciprofloxacin still remained effective for both bacterial growth and biofilm production inhibition when it was added 6 hours after the initial plating of bacteria (Figures 6 A and B). However, a significant inhibition of biofilm production by Ciprofloxacin was only detected at 2 µg/mL for the PA01 strain. Nitrofurantoin was not only an inefficient antibiotic for either P.aeruginosa strain but its presence stimulated their biofilm production (Figure-6B). Ampicillin failed to inhibit bacterial growth of both P.aeruginosa strains (Figure--6A) but it showed significant inhibitory effect on biofilm production (Figure-6B).

DISCUSSION

Recurrent urinary tract infections represent a major clinical challenge as they affect a

Figure 3 - Effects of antibiotic treatment on E.coli from Time 0. Asterisks (*) show statistical significance as compared to bacteria with no treatment (P<0.05).

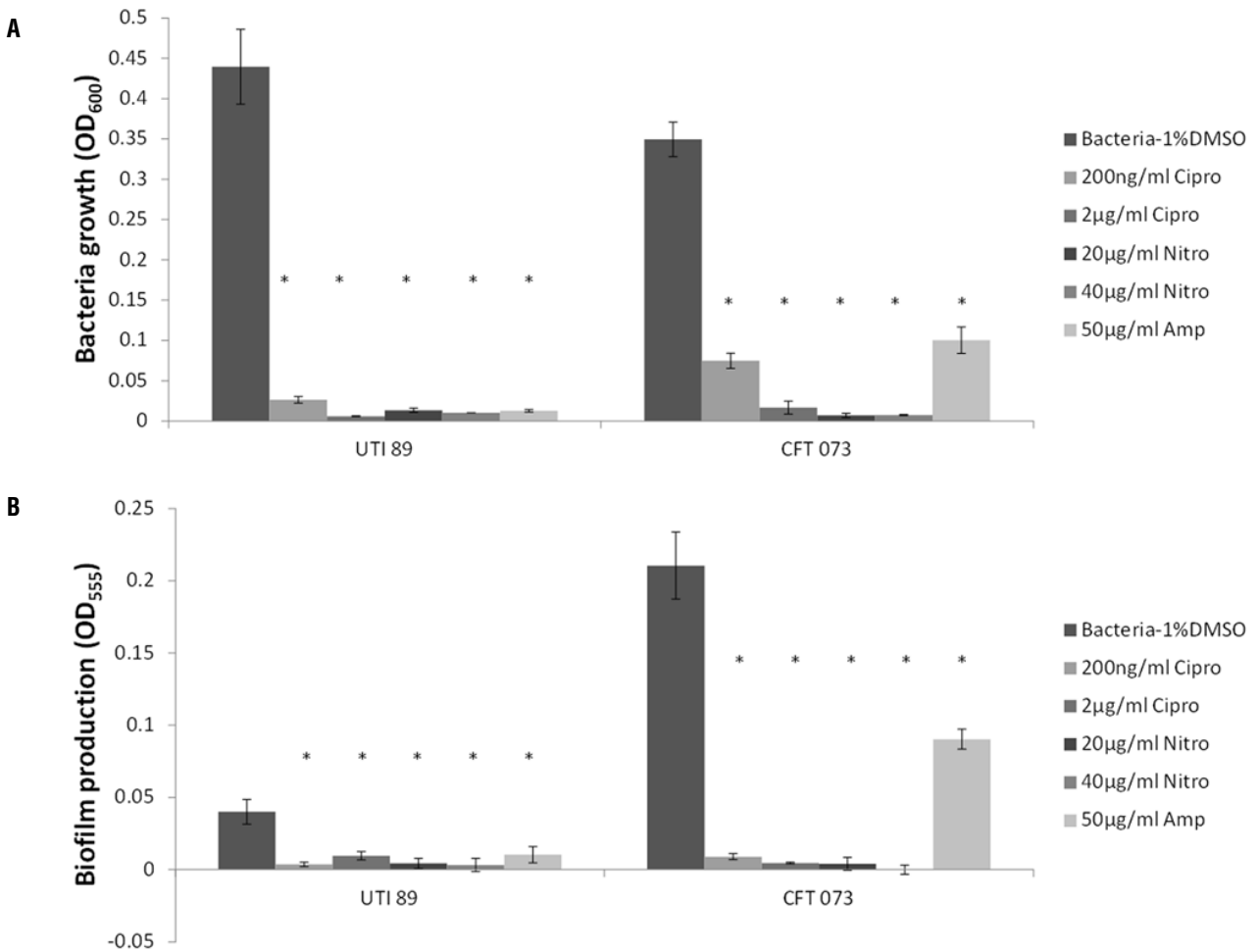
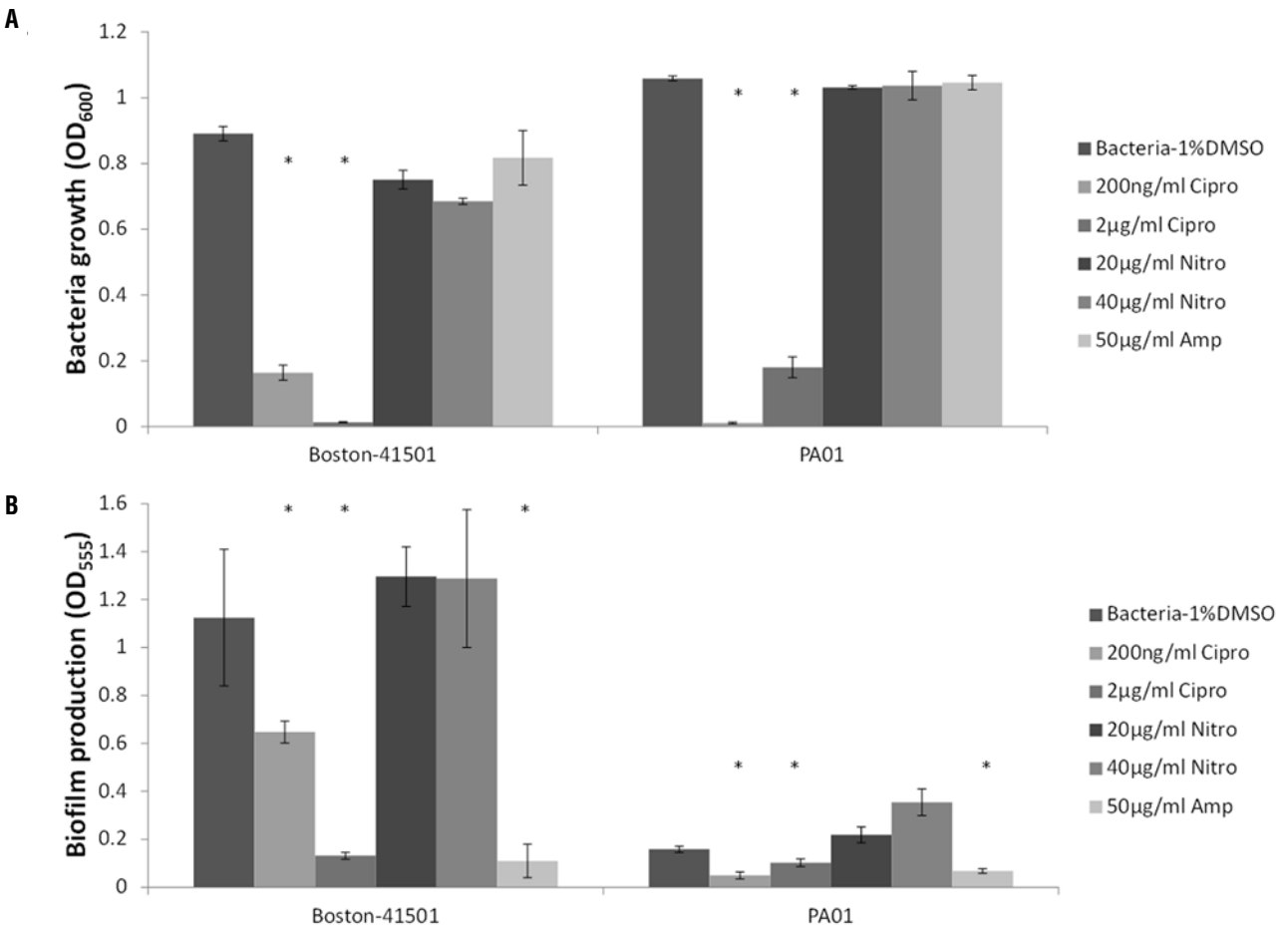


Table 1 - Inhibition of bacterial growth and biofilm formation of E. coli and P. aeruginosa by treatment of different antibiotics at initial bacterial plating.

		Antimicrobial agents[a]		
Determinations	Bacterial strains	Cipro	Nitro	Amp
Bacterial growth	UTI89	+	+	+
	CFT073	+	+	+
	Boston-41501	+	–	–
	PA01	+	–	–
Biofilm formation	UTI89	+	+	+
	CFT073	+	+	+
	Boston-41501	+	–	+
	PA01	+	–	+

[a] **Cipro =** Ciprofloxacin; **Nitro =** nitrofurantoin; **Amp =** ampicillin; **+ =** statistical significance; **- =** without statistical significance.

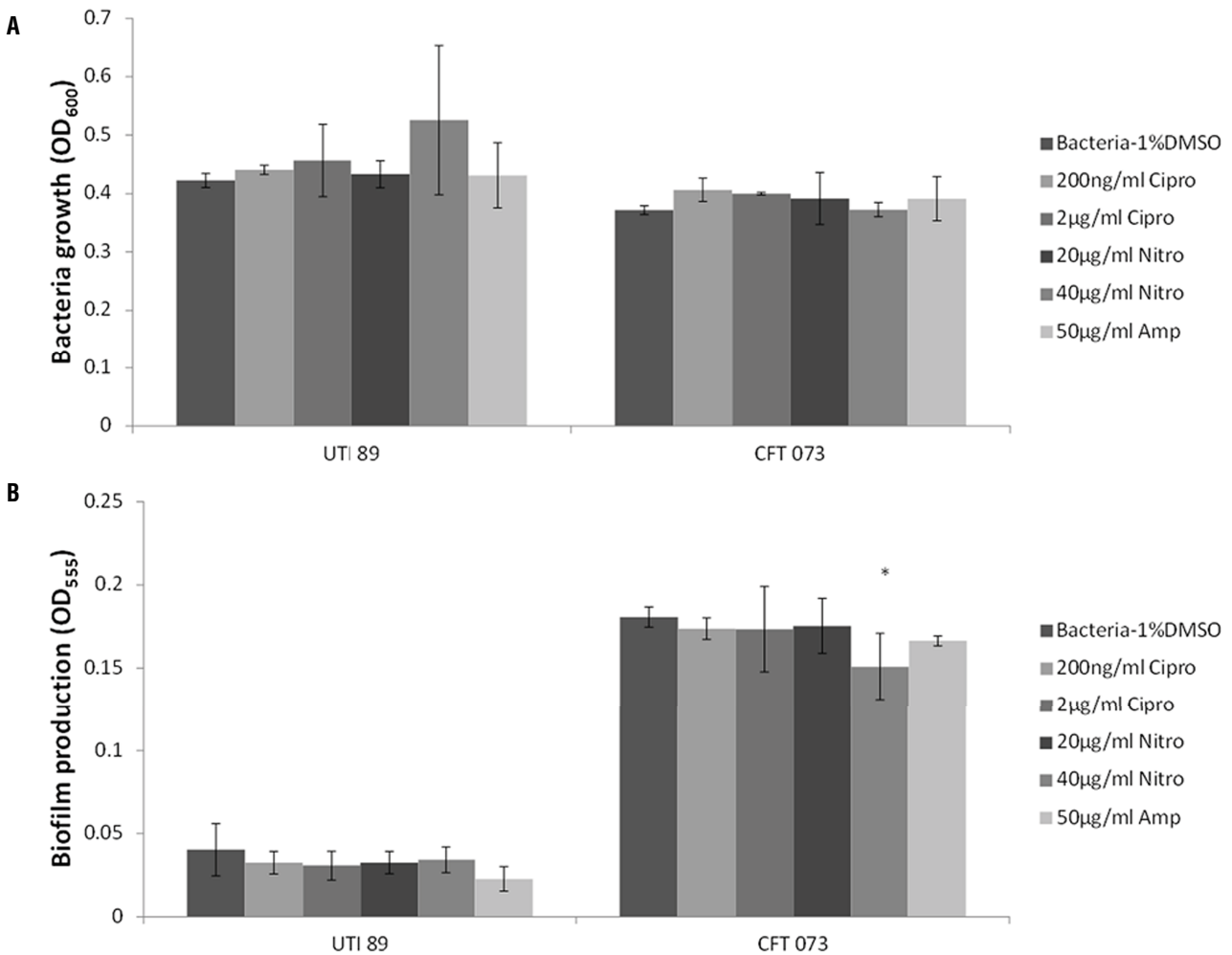
Figure 4 - Treatment of P.aeruginosa with antibiotics from Time 0. Asterisks (*) show statistical significance as compared to bacteria not treated (P<0.05).



large proportion of women after a first UTI episode (13). Different theories have been proposed to explain recurrence, including periurethral colonization and persistence of quiescent intracellular reservoirs inside a protective biofilm in the bladder (14). Other factors such as estrogen deficiency, the composition of the surface glycosaminoglycan of the bladder, the host response, and the acidity of the urine have also been implicated in this complex process. Even when patients are treated with culture-directed antibiotic therapy, some will develop a clinical lack of response, prompting a switch to a different antibiotic regimen after a few days, while others seem to respond initially but promptly recur after the completion of the antibiotic treatment course. These clinical observations suggest several plausible mechanisms, including a sub-therapeutic concentration of urinary antibiotics to effectively eradicate the bacterial infection, or an intra-vesical mechanism of bacterial protection against the antibiotics, such as a protected site for the bacteria inside a biofilm.

In this study, we selected bacteria known to be good biofilm formers, such as uropathogenic E.coli UTI89 and CFT073. We added two strains of P. aeruginosa as these bacteria are capable of producing extremely robust and generous biofilms and are among the most challenging UTIs to eradicate in patients. Since most bacteria, including those used in this study, form biofilms, we decided not to include non-biofilm forming bacterium as a control. These strains were sub-

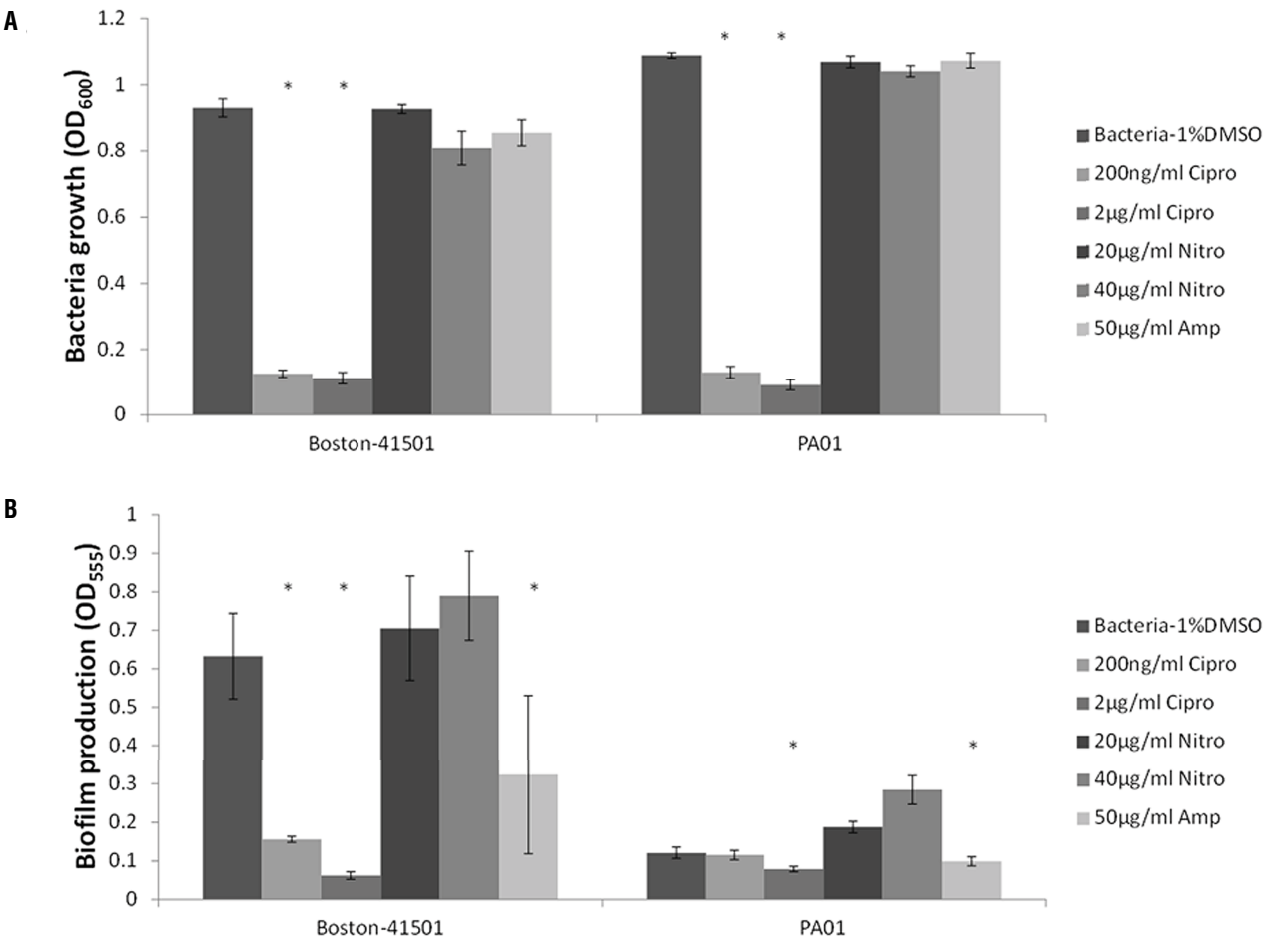
Figure 5 - Treatment of E.coli with antibiotic after untreated growth for 6 hours. Asterisks (*) show statistical significance to negative control (P<0.05).



jected to various environmental changes like movement and pH variations to determine how such changes would impact the biofilm assay results, our goal being to produce a very reliable biofilm assay for our next study. With the exception of P.aeruginosa PA01, we found that agitated conditions were more conducive to bacterial growth and biofilm formation. In general, bacterial growth of E.coli UTI89 and CFT073 reached a plateau within 6 hours after plating; however, biofilm formation continued. Although bacterial growth between CFT073 and UTI189 was similar, CFT073 produced more biofilm than UTI89. P.aeruginosa Boston-41501 reached a bacterial growth plateau at 24 hours but biofilm continued to grow in a time-dependent manner. P.aeruginosa PA01 likewise reached a growth plateau at 24 hours and biofilm production reached a plateau at 6 hours in agitated conditions. However, PA01 was able to continue producing biofilm in a time-dependent manner in static conditions (Figure-1). With our findings, we established that agitated conditions would be optimal for our future work.

Since urine pH in patients varies from pH 5 to 8, we investigated whether variations in pH would impact the bacterial growth or biofilm formation of each strain. Our results indicated that, except in more acidic conditions (pH 5), variations

Figure 6 - Treatment of P.aeruginosa with antibiotics after untreated growth for 6 hours. Asterisks (*) show statistical significance when compared to negative control (P<0.05).



in pH did not play a significant role in the inhibition of bacterial growth or biofilm production. For P.aeruginosa, at 48 hours, the strain of bacteria was able to overcome pH variations and neutralize the acidic conditions (Figure-2).

Equipped with a reliable biofilm formation assay, we then tested the effect of some of the most widely prescribed antibiotics for UTI to elucidate bacterial growth and biofilm production patterns at different time points and with different antibiotic concentrations (8, 15). Immediate treatment of either E.coli strains with Ciprofloxacin, Nitrofurantoin, or Ampicilin at various concentrations showed significant decreases in both bacterial growth and biofilm production (Figure-3 and Table-1). However, we observed a different behavior with both P.aeruginosa strains when treated immediately with antibiotics: only Ciprofloxacin was able to significantly inhibit both bacterial growth and biofilm production at both concentrations for both strains (Figure-4). A key finding of this study was that when administered at 6 hours, none of these antibiotics were able to stop E.coli bacterial growth or biofilm formation. Furthermore, Nitro increased biofilm production for P.aeruginosa, seemingly serving as a nutrient factor.

Clinically, it would be difficult to treat patients with UTI symptoms with antibiotics immediately, and even so, the biofilm may be completely formed when symptoms start. This observation could explain the trend to UTI recurrence in some women (16). In fact, some patients known to experience recurrent episodes of urinary tract infections are at times prescribed antibiotics to

have on hand to treat themselves as soon as their symptoms restart. This approach has several shortcomings, including the potential for unnecessary treatments in the absence of a culture-proven urinary tract infection and an increased risk of bacterial resistance over time. On the other hand, clinicians are sometime tempted to empirically initiate therapy while waiting for the culture results to return. Considering our data in selected strains of E.coli and P.aeruginosa known for their biofilm formation performance, such a clinical decision may be very relevant. However, caution is required as one limitation of this study is the complexity of the biofilm and the challenges of extending in vitro observations to the in vivo situation. Although there is mounting evidence on the role of biofilm resistance to antibiotics as part of the recurrence process (17), the data in humans remains weak.

Nitrofurantoin has recently been incriminated for its long-term risks (pulmonary fibrosis, peripheral neuropathy, dosing adjustment in renal insufficiency) (18, 19) to the point that its current use requires sometimes a complex clearance process. It is important to note its counter-effect leading to biofilm growth stimulation in this study, which may explain its lack of initial effectiveness or durable response even in patients with culture--proven sensitivity.

In summary, antibiotics can be very effective for the uropathogenic E.coli strains selected in this study if the treatment can be applied early on. For P.aeruginosa strains, Ciprofloxacin is the best agent to inhibit bacterial growth and biofilm production even when the agent is given when bacterial growth reached a plateau. In some situations, Nitrofurantoin can stimulate biofilm production.

ABBREVIATIONS

UTI = urinary tract infections
UPEC = uropathogenic *Escherichia coli*

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Stage IIA and IIB testicular seminoma treated post-orchiectomy with radiation therapy versus other approaches: a population-based analysis of 241 patients

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ABSTRACT

Objectives: To evaluate post-orchiectomy utilization of radiation therapy (RT) versus other management approaches in stage IIA and IIB testicular seminoma patients.
Materials and Methods: Two hundred and forty-one patients with stage IIA and IIB testicular seminoma were identified between 1988 and 2003 using the Surveillance, Epidemiology, and End Results (SEER) database.
Results: Median follow-up was 10 years. Patients with stage IIA disease underwent RT more frequently than those with stage IIB disease (72% vs. 46%, respectively; P<0.001). There was no significant change in RT utilization for stage IIA or IIB disease between 1988 and 2003 (P = 0.89).
Conclusions: Between 1988 and 2003, stage IIA patients underwent RT more often than stage IIB patients in the United States. There was no significant change in RT utilization for stage IIA or IIB disease during this time period. Based on reports describing excellent progression-free survival with cisplatin-based chemotherapy, this approach has increased in popularity since 2003 and may eventually become the most popular treatment approach for both stage IIA and IIB testicular seminoma.

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INTRODUCTION

Testicular cancer is the most commonly-diagnosed malignancy in men between the ages of 20 and 45 years. The American Cancer Society estimates that there were 7,920 new cases and 370 deaths due to testicular cancer in the United States (U.S.) in 2013 (1). Eighty percent of testicular seminoma patients present with stage I disease and 11% present with stage II disease (2). Standard of care post-orchiectomy for stage IIA and IIB testicular seminoma is radiation therapy (RT) or cisplatin-based combination chemotherapy (3, 4).

Prior studies of RT for stage IIA and IIB testicular seminoma have involved fewer than 130 patients (5-8). The purpose of this study is to analyze utilization of RT vs. other management approaches for stage IIA or IIB testicular seminoma in a relatively large number of patients

based upon an analysis of the Surveillance, Epidemiology and End Results (SEER) database.

MATERIALS AND METHODS

The SEER program created by the National Cancer Institute (NCI) includes population-based cancer registries from 20 selected geographic areas in the U.S., covering approximately 28% of the national population. Data is submitted to the NCI registry on an annual basis without "identifiable" private information, and the NCI makes the data available to the public for research purposes. As a result, this study was exempt from Institutional Review Board review. Patient data was obtained via a query of the SEER dataset (November 2012 edition). The population for this study consisted of patients diagnosed with stage IIA and stage IIB pure testicular seminoma. Patients treated between 1988 and 2003 were identified using the following extent of disease codes for the primary tumor: T1: 10, 20, 30, and 40; T2: 15 and 45; T3: 50; and T4 60 and 70. For regional lymph nodes, extent of disease code one was used for N1 disease and code two was used for N2 disease. In the SEER database, patients are listed simply as having received RT or not having received RT. The database does not state the management approach that was used post-orchiectomy in patients who did not undergo RT. Also, it does not state whether a particular treatment approach (RT vs. other) was based upon physician recommendation or patient preference. In addition, RT and chemotherapy details, including dosages, are not included in the SEER database. Moreover, initial volume of nodal disease, relapse-free survival including sites of relapse, and non-lethal toxicities are not included. Patients in whom the stage grouping was unknown were excluded. Stage IIC disease was excluded because cisplatin-based combination chemotherapy for good-risk patients as defined by the International Germ Cell Cancer Collaborative Group (IGCCCG) constitutes the standard of care (9), precluding a statistical analysis of RT vs. other management approaches. There is no consensus on the definition of educational level. A low educational level was defined in this study as a high school graduation rate of <75%, a moderate educational level was defined as a high school graduation rate of 75-85%, and a high educational level was defined as a high school graduation rate of >85%.

Statistical analysis was performed using SAS 9.2 and JMP 7 (SAS Institute Inc., Cary, NC). Survival analysis was carried out using Kaplan-Meier estimates. The log-rank test was used to test for differences in survival. A non-parametric test of medians was used to assess continuous variables. A P-value less than 0.05 was considered to be statistically significant. The Cox proportional hazard model was used for univariate and multivariate analyses to assess the effect of patient characteristics on outcomes.

RESULTS

Patient Characteristics

One hundred and forty-five of 241 (60%) patients had stage IIA testicular seminoma and 96/241 (40%) patients had stage IIB testicular seminoma in the SEER database between the years of 1988 and 2003. Patient characteristics are presented in Table-1.

Stages IIA and IIB Combined

Median follow-up was 10 years. Twenty-two of 241 (9%) patients died. For stages IIA and IIB combined, the 5-, 10-, and 15-year overall survival (OS) rates were 95%, 91%, and 89%, respectively. The 5-, 10-, and 15-year cause-specific survival (CSS) rates were 98%, 97%, and 97% respectively.

Stage IIA vs. IIB

Race, age, educational level, and marital status did not correlate with patient selection for RT. Patients with T1 disease underwent RT more frequently than those with T3 disease (64% vs. 16%, respectively; P<0.001). Also, patients with stage IIA disease underwent RT more frequently than those with stage IIB disease (72% vs. 46%, respectively; P <0.001). There was no significant change in RT utilization for stage IIA or IIB disease between 1988 and 2003 (P = 0.89). Causes of death in stage IIA and IIB patients are presented in Table-2.

Table 1 - Characteristics of Stage IIA and IIB Testicular Seminoma Patients.

	All Patients (n = 241)		Radiotherapy (n = 136)		No Radiotherapy (n = 105)		
Characteristic	n	%	n	%	n	%	P
Age (years)							
18-39	139	58%	76	55%	63	45%	0.52
40-76	102	42%	60	59%	42	41%	
Marital Status							
Single	97	40%	52	54%	45	46%	0.59
Married	125	52%	75	60%	50	40%	
Divorced	16	7%	8	50%	8	50%	
Unknown	3	1%	1	33%	2	67%	
Race							
White	219	91%	127	58%	92	42%	0.12
Non-White	22	9%	9	41%	13	59%	
Year of Diagnosis							
1988-1991	14	6%	7	50%	7	50%	0.89
1992-1995	43	18%	23	53%	20	47%	
1996-1999	52	22%	31	60%	21	40%	
2000-2003	132	54%	75	56%	57	44%	
Educational Level							0.47
Low	65	27%	37	57%	28	43%	
Intermediate	102	42%	56	55%	46	45%	
High	74	31%	43	58%	31	42%	
Primary Tumor (T)							
T1	150	62%	96	64%	54	36%	<0.001
T2	39	16%	23	59%	16	41%	
T3	18	7%	3	16%	15	84%	
T4	5	2%	3	60%	2	40%	
TX	29	12%	11	38%	18	62%	
Regional Lymph Nodes							
N1*	96	40%	69	72%	27	28%	<0.001
N2†	145	60%	67	46%	78	54%	

*Stage IIA
†Stage IIB

Table 2 – A) Causes of Death in Stage IIA Testicular Seminoma Patients, B) Causes of Death in Stage IIB Testicular Seminoma Patients.

A

Cause of Death (n=9)	Radiotherapy (n=69)	No Radiotherapy (n=27)
Testicular Cancer	2	2
Lung Disease	1	1
Acute Myeloid Leukemia	0	1
Accident	0	1
Unknown	0	1

B

Cause of Death (n=13)	Radiotherapy (n=67)	No Radiotherapy (n=78)
Unknown	1	3
Testicular Cancer	1	2
Heart Disease	2	1
Lung Disease	1	0
Infection	0	1
Colon Cancer	0	1

Patients with stage IIA disease who received RT had a 5-, 10-, and 15-year OS rate of 96% compared with 88%, 77%, and 77%, respectively, for those who underwent other management approaches (P = 0.008; Figure-1). The 5-, 10-, and 15-year CSS rate for stage IIA disease was 97% for RT compared with 96%, 92%, and 92%, respectively, for other management approaches (P = 0.30).

Improved OS (P = 0.03; Figure-2) was noted in patients with stage IIB disease who received RT (5-, 10-, and 15-year OS rates of 98, 96%, and 88%, respectively) as opposed to no RT (5-, 10-, and 15-year OS rates of 90%, 86%, and 86%, respectively). The 5-, 10-, and 15-year CSS rate was 98% for stage IIB patients who received RT compared with 98%, 96%, and 96%, respectively, for those who underwent other management approaches (P = 0.60).

Univariate and Multivariate Analyses

On univariate analysis, race, educational level, marital status, treatment year, and T and N stage were not associated with OS or CSS. Increasing age was associated with worse OS (P = 0.009), but not CSS (P = 0.11). Age was associated with worse OS on multivariate analysis as well, adjusting for race, T and N stage, year of treatment, use of RT, marital status, and educational level. The use of RT correlated with improved OS (HR 0.30; 95% CI: 0.12-0.74; P = 0.008) but not CSS (P = 0.35) on univariate analysis. The use of RT correlated with improved OS on multivariate analysis as well (HR 0.40; 95% CI: 0.15-0.90; P = 0.02).

DISCUSSION

The bulk of retroperitoneal adenopathy is the most important prognostic factor in stage II disease (5). There have been no prospective, randomized trials involving stage IIA or IIB testicular seminoma due to the rarity of such patients. As a result, treatment recommendations have commonly been guided by reports from single institutions (3).

Figure 1 - Overall survival for stage IIA testicular seminoma patients managed with radiation therapy vs. other approaches.

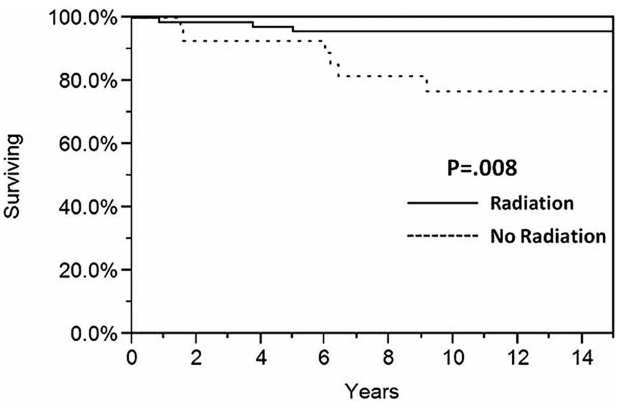
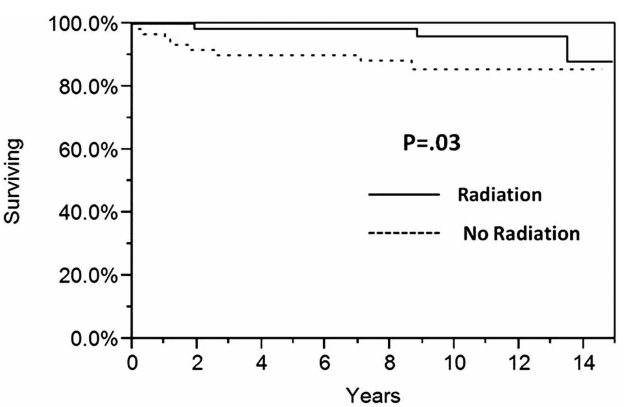


Figure 2 - Overall survival for stage IIB testicular seminoma patients managed with radiation therapy vs. other approaches.



One limitation of the SEER database is a lack of randomization with regards to treatment. Other limitations include a lack of treatment details in the no RT group such as chemotherapeutic agents and doses.

In a highly curable disease such as stage IIA and IIB testicular seminoma, prevention of long-term complications of treatment is a priority. Retroperitoneal RT increases the relative risk (RR) of second non-germ-cell malignancies, including gastric (RR 4.1), pancreatic (RR 3.8), and colon (RR 1.9) cancers (10). Also, several groups have reported that retroperitoneal RT results in a twofold or greater risk of cardiovascular disease beyond 15 years, particularly when prophylactic mediastinal/supraclavicular RT is added (11-13). Late effects are less well-defined for chemotherapy than they are for RT (10). The deleterious effects of 3-4 cycles of cisplatin-based chemotherapy on fertility are transitory, reversible, and dose-dependent (14). Huyghe et al. (14) suggested that RT has a more deleterious effect on fertility than chemotherapy in testicular cancer patients. However, RT in that study was antiquated by today's standards. Fertility can be preserved when the RT dose to the remaining testis is reduced to less than 2 Gy (15, 16). The cumulative incidence of spermatogenesis as a function of time appears to be similar after modern RT and cisplatin-based chemotherapy (16-18). A low but increased risk of development of acute myeloid leukemia is associated with chemotherapy, especially when etoposide is administered in high cumulative doses (19). Travis et al. (10) observed significantly increased risks of solid cancers among testicular cancer patients treated with RT alone (RR = 2.0, 95% CI = 1.9 to 2.2), chemotherapy alone (RR = 1.8, 95% CI = 1.3 to 2.5), and both (RR = 2.9, 95% CI = 1.9 to 4.2). Huddart et al. (12) observed an increased incidence of cardiovascular events in germ cell tumor patients treated with cisplatin-based chemotherapy. van den Belt-Dusebout et al. (20) reported that retroperitoneal RT strongly increases the risk of second malignancies but not of cardiovascular disease, whereas chemotherapy increases the risks of both second malignancies and cardiovascular disease. In addition, cisplatin-based chemotherapy has been associated with nephrotoxicity, ototoxicity, and neuropathy (21), especially when a large number of cycles of cisplatin is given. Fossa et al. (22) observed that men treated with chemotherapy (with or without RT) in 1975 or later had higher mortality from all non-cancer causes (standardized mortality ratio (SMR) = 1.34, 95% CI = 1.15 to 1.55), all circulatory diseases (SMR = 1.58, 95% CI = 1.25 to 2.01), all infections (SMR = 2.48, 95% CI = 1.70 to 3.50), and all respiratory diseases (SMR = 2.53, 95% CI = 1.26 to 4.53). Active surveillance is not a management option post-orchiectomy for stage IIA and IIB disease; however, it is the preferred approach for stage IA and IB disease (23).

This report is the largest study of stage IIA and stage IIB testicular seminoma in the litera-

ture. The 5-year OS and CSS rates of 96-98% for RT are comparable with other reports (5, 8). Based on a median follow-up of 10 years in this study, RT was associated with improved OS in stage IIA (Figure-1) and IIB (Figure-2) disease. Patients who underwent RT had similar known characteristics such as age to those who did not undergo RT (Table-1). However, this study was not randomized. As a result, the improved OS in patients who received RT may be due to selection bias. Also, patients in the RT group could have received a single cycle of neoadjuvant carboplatin chemotherapy prior to RT, which reduces the risk of relapse (21). In addition, stage IIA and stage IIB testicular seminoma patients in the no RT group may have been treated with 4 cycles of single-agent carboplatin chemotherapy, which results in worse OS and progression-free survival than cisplatin-based chemotherapy (24, 25). In this report, no patients died of acute myeloid leukemia or infection in the RT group, whereas 2 patients died of these causes in the no RT group based on a median follow up of 10 years (Table-2). Most second malignancies and major cardiac events occur more than 15 years after RT (8, 13). As a result, longer follow-up is necessary to assess late toxicity and OS. Only 7 of 22 (32%) deaths in this study were due to testicular seminoma (Table-2). Consequently, statistical power was limited for the assessment of CSS.

Chung et al. (5) reported 5-year relapse--free survival rates of 92% and 90%, respectively, for stage IIA and stage IIB testicular seminoma patients who underwent RT. Similarly, Classen et al. (6) reported 6-year relapse-free survival rates of 95% and 89%, respectively, for stage IIA and stage IIB patients who were treated with RT.

Modified dog-leg RT to 30 Gy in 15 fractions remains the preferred approach by most investigators for stage IIA testicular seminoma in the absence of a horseshoe kidney, inflammatory bowel disease, or a history of RT (3, 4, 26, 27). If one of these 3 contraindications to RT is present, then cisplatin-based combination chemotherapy is recommended (3, 4, 26, 27). Prophylactic mediastinal/supraclavicular RT is no longer given for stage II testicular seminoma due to its late toxicity (13, 28).

In most studies, more than 80% of stage IIA patients received RT (5, 7, 29). Similarly, 82% of stage IIA patients in this report received RT. Nevertheless, cisplatin-based chemotherapy for good-risk testicular seminoma patients as defined by the IGCCCG (9) has gained in popularity over the past decade (30). One advantage of cisplatin--based chemotherapy is that it can eradicate carcinoma in situ in the remaining testis and prevent or postpone the development of an invasive cancer in some patients (17).

The Spanish Germ Cell Cancer Group conducted the first study of cisplatin-based chemotherapy as frontline therapy in stage IIA testicular seminoma patients (30). None of the 19 stage IIA patients relapsed. Also, in the Swedish and Norwegian Testicular Cancer Project (SWENOTECA) study (29), none of the 6 stage IIA patients who received cisplatin-based chemotherapy relapsed. Based on the impressive progression-free survival in these two studies, the European Society for Medical Oncology (31) recommends cisplatin--based chemotherapy or modified dog-leg RT to 30 Gy in 15 fractions, with no preference for one treatment option over another, for stage IIA testicular seminoma.

Cisplatin-based chemotherapy used to be reserved for stage IIB patients with high-volume disease, e.g., multiple lymph nodes measuring 3.1-5.0 cm (3, 4). The Spanish Germ Cell Cancer Group conducted a study that included 54 patients with low-volume, e.g., a solitary retroperitoneal node measuring 2.1-3.0 cm, or high-volume stage IIB disease. Patients were treated with three cycles of cisplatin, etoposide, and bleomycin (PEB) or four cycles of cisplatin and etoposide (PE) (30). Median follow up was 72 months. The 5-year progression--free survival rate for stage IIB patients was 87%. The SWENOTECA study included 67 stage IIB patients with low-volume or high-volume disease who were treated with cisplatin-based chemotherapy (29). None of them relapsed based on a median follow-up of 5.2 years. Based on the excellent progression-free survival in the SWENOTECA study, version 1.2014 of the National Comprehensive Cancer Network Clinical Practice Guidelines (32) and the European Society for Medical Oncology (31) recommend three cycles of PEB chemotherapy for all stage IIB patients, regardless of tumor burden. If there is a contraindication to bleomycin

such as a reduction in lung capacity, emphysema, current or a history of heavy smoking, or poor renal function, then four cycles of PE may be used (31). Modified dog-leg RT to 36 Gy in 18 fractions also constitutes a treatment option for stage IIB patients in whom chemotherapy would be unsuitable (31) or who have a solitary retroperitoneal node measuring 2.1-3.0 cm (32).

One treatment that has been investigated for stage IIA and IIB testicular seminoma is a single course of neoadjuvant carboplatin chemotherapy followed by para-aortic RT to 30-35 Gy. In a series involving 51 patients, there have been no relapses after a median follow up of 55 months (21). Eight per cent of patients experienced grade 3 hematological toxicity and 2% developed grade 3 nausea. These results are promising; however, additional investigation is needed (3, 30).

CONCLUSIONS

Stage IIA testicular seminoma patients in the U.S. underwent RT more often than stage IIB patients between 1988 and 2003. There was no significant change in RT utilization for stage IIA or IIB disease during this time period. Cisplatin--based chemotherapy has produced excellent progression-free survival and, as a result, may eventually become the most popular treatment approach for both stage IIA and IIB testicular seminoma.

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Comparison of imaging modalities for detection of residual fragments and prediction of stone related events following percutaneous nephrolitotomy

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ABSTRACT

Introduction: Achieving stone free status (SFS) is the goal of stone surgery. In this study it is aimed to compare effectiveness of unenhanced helical computerized tomography (UHCT), KUB and ultrasonography (US) for detection of residual RFs and predicition of stone releated events following percutaneous nephrolitotomy (PNL).

Materials and Methods: Patients underwent PNL for radiopaque stones between November 2007 and February 2010 were followed. Patients were examined within 24-48 hours after the procedure by KUB, US and UHCT. For stone size 4 mm was accepted as cut off level of significance.Sensitivity and specificity of KUB and US for detection of RFs and value of them for prediction of stone related events were calculated.

Results: SFS was achieved in 95 patients (54.9%) and when cut off value of 4 mm for RFs was employed, SFS was achieved in 131 patients (75.7%). Sensitivity was 70.5% for KUB, and 52.5% for US. UHCT was shown to be significantly more efficient for detection of RFs compared to both KUB (p=0.01) and US (p=0.001). When cut off level of 4 mm employed, sensitivity of KUB and US increased to 85.7% and 57.1%. Statistical significant superiority of UHCT still remained (p value vs. KUB: 0.03 and p value vs. US: 0.008).

Conclusion: UHCT is the most sensitive diagnostic tool for detecting RFs after PNL. It has higher sensitivity regardless of stone size compared to KUB and US. Additionally UHCT has higher capability of predicting occurrence of stone related events.

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INTRODUCTION

The achievement of stone free status (SFS) is the primary goal of any treatment modality for stone disease. Residual fragments (RFs) are associated with such potential short and long-term sequelae, as renal colic, urinary tract infection (UTI),stone regrowth, need for hospitalization and additional intervention (1).

Percutaneous nephrolitotomy (PNL) is currently one of the most commonly employed surgical procedures for the treatment of renal stones and especially indicated in large or complex stone cases. Following PNL, diagnosis of RFs is crucial in the early postoperative period while percutaneous access is still in place. Depending on the SFS, further interventions can be employed (2).

The use of diagnostic tools for determination of RFs during the early postoperative period is controversial. The use of any imaging modality has its advantages and disadvantages. Plain kidney-ureter-bladder radiography (KUB), ultrasonography (US), unenhanced helical computerized tomography (UHCT), antegrade pyelography and

flexible nephroscopy through renal access site are the choices (2). The superimposition of bowel gas, feces and soft-tissue calcifications as well as the presence of obesity, faint radiopaque stones, and nephrostomy tubes decrease the accuracy of these diagnostic modalities (3, 4). UHCT, in conjunction with image reconstruction, was prospectively compared to other imaging modalities, KUB and US for the detection of RFs and found to have significant superiority (3, 5, 6).

The sensitivity of the UHCT reached 100% and this method has been accepted as the gold standard for detection of residual stones. However clinical significance of RFs detected through UHCT is unclear and besides, performing UHCT is costly and causes radiation exposure. Therefore its role in the prediction of occurrence of stone related events and deciding for any additional interventions should be clarified. Although diameter of 4-5 mm is generally accepted as the cut off, size of the residual stone does not always correlate with clinical significance (7, 8). Apart from size follow-up of patients for occurrence of stone related events and application of additional interventions should be performed to determine the fate of RFs.

In this study, it is aimed to compare effectiveness of UHCT, KUB and ultrasonography for detection of RFs and predicition of stone releated events following PNL.

PATIENTS AND METHODS

Patients underwent PNL for radiopaque renal stones between November 2007 and February 2010, in Ankara University Hospital Department of Urology and were followed prospectively. All patients were evaluated with intravenous urography preoperatively.

All patients were examined within 24-48 hours after the procedure by KUB, US and UHCT. US was performed by a single radiologist especially experienced in ultrasonographic examination of urinary system (EO). KUB and UHCT images were investigated by a single clinician (MIG) and presence of any RFs along with size and location were recorded. For stone size, 4 mm was accepted as cut off level of significance.

Unenhanced helical scanning was performed using a 4 row multislice LightSpeed Plus CT scanner (GE Medical Systems, Milwaukee, Wisconsin). Images were obtained from the upper border of 10th rib to the lower border of the symphysis pubis using 4 mm slice thickness.

Patients were followed prospectively and stone related events were recorded. Stone related events were defined as renal colic, stone regrowth, need for hospitalization and additional intervention. Outcome measures were sensitivity and specificity of KUB and US for detection of RFs and value of the imaging modalities for prediction of stone related events.

UHCT was accepted as the gold standard for detection of RFs, and sensitivity of KUB and US were calculated. Sensitivity was defined as the number of positive test results divided by the overall number of positive cases using the gold standard. Statistical significance was determined by use of Pearson chi-square test and P value of <0.05 was accepted for statistical significance.

RESULTS

Totally 173 PNL cases were performed and one stage procedure was performed in all of the cases. Access through 1 caliceal puncture was performed in 148 patients (85.5%), and multiple access was performed in 25 cases (14.5%). Mean age of the patients was 48.4 ± 7, 1 and 113 of the patients (65.3%) were males. Median follow-up of patients was 9 months (3-36 months).

SFS with RFs of any size was achieved in 95 patients (54.9%) using UHCT as the gold standard test to diagnose RFs. When cut off value of 4 mm for RFs was employed, SFS was achieved in 131 patients (75.7%). Sensitivity was 70.5% (55 of 78 cases) for KUB, and 52.5% (41 of 78 cases) for US when RFs of any size was considered. UHCT was shown to be significantly more efficient for detection of RFs compared to both KUB ($p=0.01$) and US ($p=0.001$). When cut off level of 4 mm was employed, sensitivity of KUB increased to 85.7% (36 of 42 cases) and US increased to 57.1% (24 of 42 cases). Statistical significant superiority of UHCT still remained (p value vs. KUB: 0.03 and p value vs. US: 0.008). Sensitivity values of the ima-

ging modalities are summarized in Table-1. Considering specificity, neither KUB nor US resulted in any false positive results. Therefore specificity of both modalities were calculated as 100%.

Considering stone related events, among the 78 patients with RFs of any size in UHCT, 36 patients (46.1%) experienced an event. Distribution of stone related events is summarized in Table-2. Regarding ancillary procedures, shock wave lithotripsy was employed in 12 patients and additional surgery was needed for 8 patients (PNL: 4 patients with renal stones ≥2 cm and ureterorenoscopy: 4 patients with ureteral or renal stones<2 cm). Of these 36 patients with a stone related event, 25 of them were shown to have RF in KUB and 18 of them were shown to have RF in US. Seven and six patients that underwent surgery were found to have RFs in KUB and US respectively. For prediction of stone related events, UHCT was found to be superior to KUB (p=0.01) and US (0.001).

Table 1 - Sensitivity values of imaging modalities for detection of RF's following PNL.

	Sensitivity			
	All stones	P value vs. UHCT	Stones > 4 mm	P value vs. UHCT
UHCT (%)	100		100	
KUB (%)	70.5	0.01	85.7	0.03
US (%)	52.5	0.001	57.1	0.008

Table 2 - Stone related events within the 78 patients with residual fragments following PNL.

	Number of patients (%)
Renal colic episode	23 (29.4)
Stone regrowth	10 (12.8)
Shock wave lithotripsy	12 (15.3)
Additional surgery	8 (10.2)

DISCUSSION

Aim of surgical treatment for urinary calculi is achieving SFS. However the cut off level for SFS and selection of the appropriate imaging modality is controversial. It is clear that complete stone removal after PNL is crucial for preventing recurrence and regrowth of stones and further need for additional procedures (3, 5). This makes postoperative imaging for RFs necessary.

KUB is one of the most commonly used imaging modality for detection of RFs following PNL. Main advantages of KUB are its cost and lower radiation exposure.

Majority of urinary calculi are radiopaque, however RFs are sometimes difficult to be seen on plain abdominal radiographs because of their size, location, and also to the presence of stents and tubes and bowel loops (3, 9). US is noninvasive and does not cause radiation exposure, and can directly visualize residual fragments in the upper collecting system as small as 2 mm diameter. It also gives information on dilation of the collecting system (10). However, routine follow-up with only US for the detection of RFs after PNL is not advised, because its sensitivity is directly affected from the presence of a nephrostomy tube, and postoperative debris in the collecting system (3).

UHCT is currently the imaging modality of choice for evaluation of SFS, detection and localization of RFs after PCNL (3, 5, 8, 11,12). Sensitivity and specificity of UHCT was shown to exceed 90%, for all types of stones, with the exception of indinavir stones (13). High sensitivity results and widespread availability of UHCT restricts the utilization of flexible nephroscopy for the detection of RFs after PNL.

The superiority of UHCT over KUB for detection of RFs was shown in the study of Park et al. (5). In their study stone free rates of 62.3% and

20.8% were detected when KUB and UHCT were used respectively. In another study, sensitivity of KUB and US was investigated, regarding UHCT as the gold standard imaging modality.

Sensitivity of KUB and US to detect RFs of radiopaque stones was 62.9% and 48.6% for KUB and US respectively (3). Similarly, in our study only radiopaque stones were considered and sensitivity of KUB and US were found to be 70.5% and 52.5% for KUB and US , respectively. However in their study Osman et al. detected no significant difference for detection of RFs of radiopaque stones of >5 mm. Based on this result they concluded that utilization of UHCT for radiopaque stones should not be routine (3). In our study, 4 mm was accepted as the cut off value and for detection of RFs above this cut off level, sensitivity of KUB increased to 85.7%. But despite this increase, sensitivity of UHCT was still significantly greater than KUB.

Based on the results of previous studies, use of KUB, US or UHCT for detection of RFs following PCNL is still controversial. The data indicates that UHCT is the best method for detection of RFs, but the superiority is especially prominent for smaller stone fragments (<4-5 mm). However, size of the RF does not always correlate with the presence of stone related events. Sometimes even small fragments of 2 mm can cause significant obstruction or act as a nidus for further stone regrowth especially in infection stones. For this reason we evaluated the stone related events during the follow-up and found out that, over 30% of the cases with a stone related event were reported to have no RFs in KUB, although they have RFs in UHCT images. Additionally these results are maintained from a population with radiopaque stones and this gap between the two imaging modalities would increase if radiolucent stones are also included. When US is considered, RFs were detected only in half of the patients with a stone related event and RFs in UHCT images. On the other hand, in our study more than half of the patients with a RF in UHCT images did not experience a stone related event. Therefore the question of unnecessary utilization of UHCT should also be kept in mind as UHCT is expensive and causes significant radiation exposure.

Optimal timing for utilization of imaging modalities for detection of RFs is also a subject of debate. In many centers, as in our center, an imaging is performed routinely at postoperative day 1, but this is probably associated with increased false--positive results from stone dust postoperatively, and also RFs that would pass spontaneously during the early postoperative period without causing any stone related events are also detected. Therefore imaging at the end of the first month after surgery is considered optimal (5, 14, 15). Results of our study demonstrates the results of these 3 imaging modalities in the early postoperative period.

CONCLUSION

UHCT is found to be the most sensitive diagnostic tool for detecting RFs after PNL in the early postoperative period. It has higher sensitivity regardless of stone size compared to KUB and US. Additionally UHCT has higher capability of predicting occurrence of stone related events.

ABBREVIATIONS

SFS = stone free status
RFs = Residual fragments
UTI = urinary tract infection
PNL = Percutaneous nephrolitotomy
KUB = kidney-ureter-bladder radiography
US = ultrasonography
UHCT = unenhanced helical computerized tomography

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Perineostomy: the last oportunity

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ABSTRACT

Objective: To review the technique and outcome of perineal urethrostomy or urethral perineostomy and to identify factors related to the procedure failure.
Material and methods: We studied 17 patients who underwent perineal urethrostomy between 2009-2013 in a single hospital. Success was defined as no need for additional surgical treatment or urethral dilatation. We reviewed the clinical data related to age, weight, previous urethral surgery, diabetes, hypertension, ischemic cardiopathy, lichen sclerosus and other causes and studied their association with the procedure failure (univariate analysis). We completed the analysis with a multivariate test based on binary regression.
Results: The average follow-up was 39.41 months. From all the causes, we found Lichen Sclerosus in 35%, idiopathic etiology in 29% and prior hypospadia repair in 18%. Postoperative failure occurred in 3 patients, with a final success of 82.4%. The binary regression model showed as independent risk factors ischemic cardiopathy (OR: 2.34), and the presence of Lichen Sclerosis (OR: 3.21).
Conclusions: The success rate with the perineal urethrostomy technique shows it to be a valid option above all when we preserve the urethral blood supply and plate. Lichen sclerosus and ischemic vascular problems are risk factors to re-stenosis.

ARTICLE INFO

Key words:
Perineum; Lichen Sclerosus et Atrophicus; Balanitis Xerotica Obliterans

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INTRODUCTION

There are numerous methods for the treatment of anterior urethral stricture, from simple dilatation, to endoscopic procedures and urethroplasties, with variable success rates but often very high. However, when the stenosis affects the anterior urethra, finding a suitable process becomes a challenge. Pan-urethral stenosis can have multiple causes, but when the etiology is lichen sclerosus (LS) or balanitis xerotica obliterans (BXO) the use of multiple grafts forces us to look for non-skin graft sources (1, 2). Factors associated with failure in the reconstruction are previous hypospadias surgery, urethroplasty and pelvic radiation due to oncological processes (3-5).

If the anterior urethra is not suitable for successful reconstructive procedures because of severe, complex and refractory stenosis, we can consider the perineal urethra (perineal urethrostomy or perineostomy) which lies proximal to the stenosis and distal to the striated sphincter, not only to prevent bladder damage but also renal. Some patients reject a second or third urethral stage and decide to keep perineal micturition. This technique is widely accepted as the first step in a sequential reconstruction process or as the only step if an adequate reconstruction is not possible (6-9). This technique is always offered to older patients or patients who would not undergo long reconstructive urethroplasty procedures, or as a single solution to the presence of a LS.

In our study we describe the use of perineal urethrostomy in a varied group of patients in which LS is not the only cause of the pan-urethral stenosis. Importance is given in the technique to maintain the urethral plate and thus the entire urethra vascularization, as do other authors (10). The concept of urethra marsupialization was described in 1914. Its application to the Leadbetter perineostomy was initiated in 1960, and improved by Johanson and Blandy following the principles of Turner-Warwick (7, 11). In 1968, the use of the inverted U-scrotal flap was defined (7). The scrotal flap is difficult to achieve in patients who are very obese or have altered perineal anatomy, therefore other forms of skin pedicle grafts are performed, in order to avoid the risk of complications as high as 30% in some series (6).

This study details the surgical technique and reviews in our cohort the clinical performance of perineal urethrostomy, and it evaluates statistically the variables associated with the success of the procedure.

MATERIALS AND METHODS

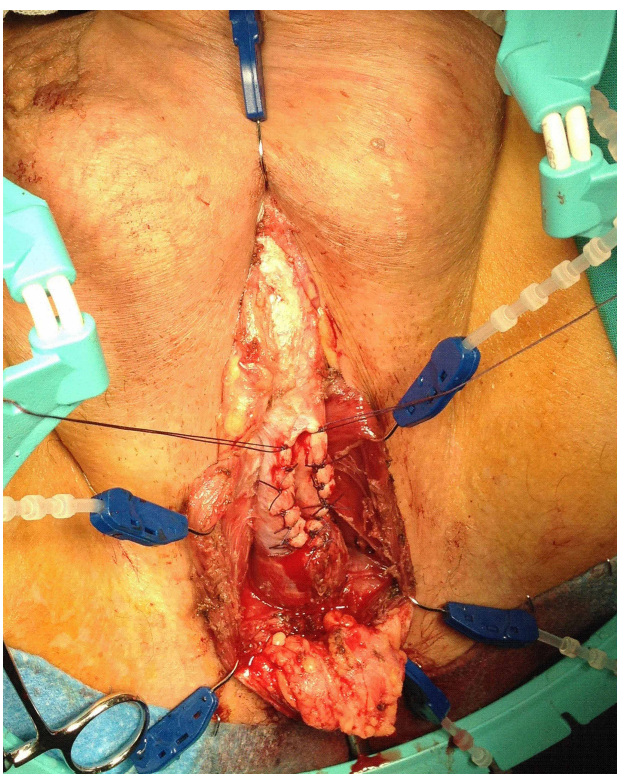
A retrospective study of all perineal urethrostomies carried out and followed-up between 2009-2013 in a single center was performed. We reviewed different clinical variables. Success was defined as no need for additional surgical treatment or urethral dilatation.

We conducted a univariate and multivariate analysis to determine factors associated with the risk of failure, using chi-square and ANOVA tests for qualitative and quantitative variables respectively, and a logistic regression was used to the multivariate analysis. Analyses were performed using SPSS Statistics software version 17.0.

SURGERY TECHNIQUE

The patient is usually placed in a high lithotomy position and loco-regional anesthesia is applied. An inverted U-shaped incision is made, placing the tip of the U in the upper portion of the perineum where the scrotum ends in order to create a complete non-tense pedicle, which includes fat, on the urethral plate. The bulbocavernosus muscle is separated to expose the bulbar urethra, which is sectioned 4-6 cm longitudinally, and then hemostatic sutures are employed on the edges (Figure-1).

Figure 1 - Urethrotomy and hemostatic sutures.

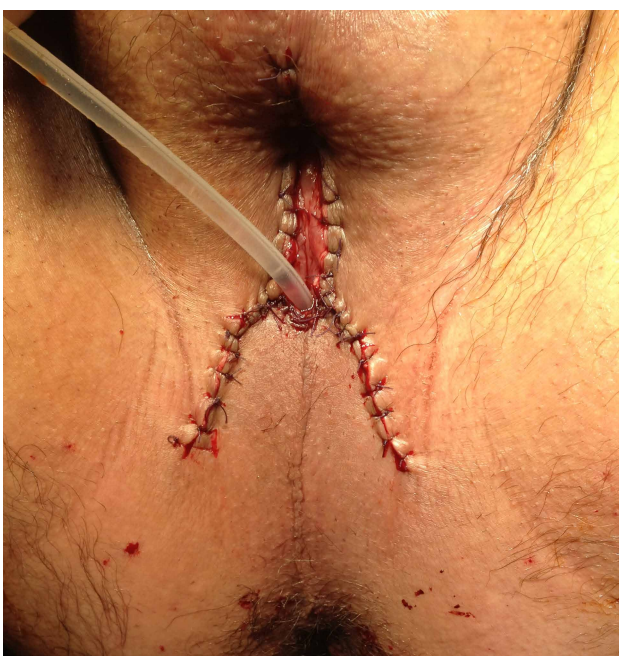


Then we proceed with the urethral calibration up to the bladder to avoid unnoticed deeper stenosis. The ventral incision can be extended to membranous urethra free of stricture. Perineum skin is sutured to the edges of the ventral urethrotomy, preserving the urethral dorsal plate. The apex of the U is sutured to the proximal edge of the urethrotomy, using an absorbable suture polyglactin (Vicryl) 3-0 or 4-0. Once the process of suturing the skin edges to the urethrotomy is complete, there are two incisions remaining, which are then sutured (Figure-2). The complete urethrostomy has two entrances, one proximal leading to the bladder and the other distal leading to the penis.

The urethra is not sectioned in its entirety, only longitudinally, maintaining blood flow

in the corpus spongiosum. A Foley 16F silicon catheter is inserted.

Figure 2 - Post-surgical appearance.



Postoperative course

The patient ambulates on the afternoon of the operative day. The catheter is left in place for 10 days to promote complete healing of the suture. Patients are discharged from the hospital the day after surgery.

Uroflowmetry and urine culture are repeated every 4 months in the first year and annually thereafter.

RESULTS

From 2009-2013, 17 patients with a mean age of 65.88 years (range 50-92) underwent perineal urethrostomy. The etiology of pan-urethral stenosis was multifactorial in many cases, idiopathic in 5 (29%), LS or BXO in 6 (35%), prior hypospadias repair in 3 (18%), and one case of penile carcinoma, one of radiotherapy, and one iatrogenic case. In many cases, repeated episodes of infection overlap contributed to increased urethral stricture.

In all patients, pan-urethral stenosis was defined as a stenosis which affected the whole anterior urethra (Figures 3 and 4). Five patients (30%) presented suprapubic catheterization. Previous surgery of urethroplasty was found in 6 patients (35.3%), and internal urethrotomy in 8 (47%), with 87.5% of these having undergone two previous internal procedures.

Among the medical history of interest, chronic ischemic heart disease was observed in 6 patients (35%), diabetes mellitus in 6 (35%) and hypertension in 10 medicated patients (59%). The average weight was estimated at 79.82 kg (65-106), with an age of over 60 in 10 patients.

The mean follow-up was 39.41 months (3 months-91 months), with all patients receiving complete follow-up. Immediate complications were related to perineal wound bleeding in one case, and maintenance of urinary catheter for longer time due to delayed perineal wound in three cases.

Postoperative stenosis or failure occurred in 3 patients with a final success rate of 82.4%. All patients undergo calibration tracking. The mean time to failure diagnosis was 4 months (2-6 months).

We performed a univariate analysis to identify causes related to failure of the procedure and development of new stenosis. The results are shown in Table-1.

When a binary regression study was carried out the presence of ischemic heart disease (OR 2.34, 95% CI [1.08 to 4.98]) and the presence of LS (OR 3.21, 95% CI [1.00 to 4.89]) were shown as independent factors associated with procedure failure. Results are shown in Table-2.

DISCUSSION

The concept of complex anterior urethral stricture includes pan-urethral stenosis affecting bulbar and penile urethra simultaneously and patients with urethral strictures who have previously undergone failed urethroplasty. The LS is the most common cause of pan-urethral stricture (12), and failed hypospadias correction is the major cause of anterior complex stricture (13, 14). It remains difficult and controversial to recom-

Figure 3 - Panurethral stenosis. Retrograde urethrography.

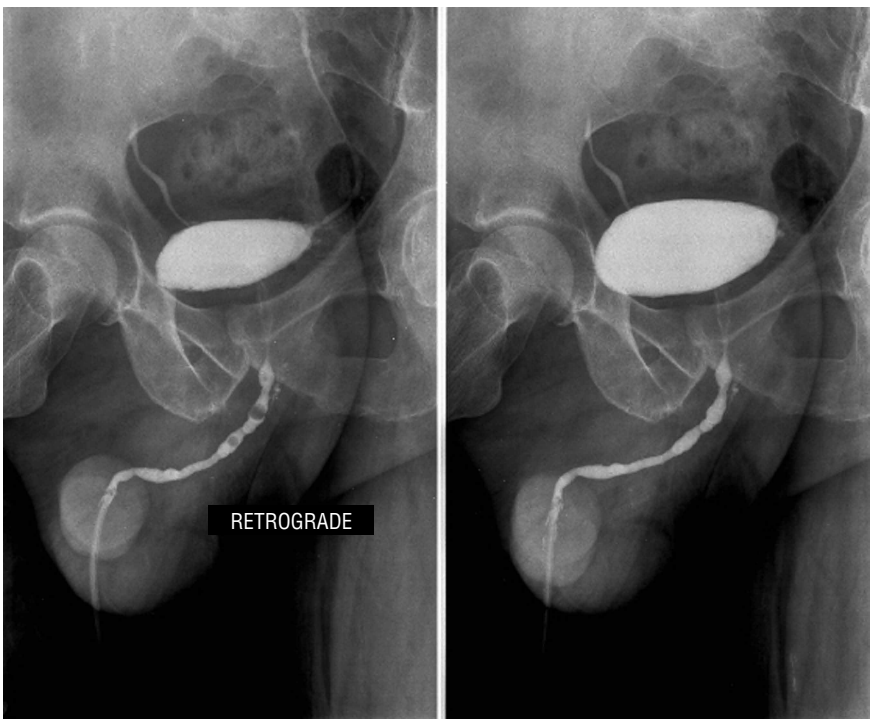


Figure 4 - Panurethral stenosis. Voiding urethrography.

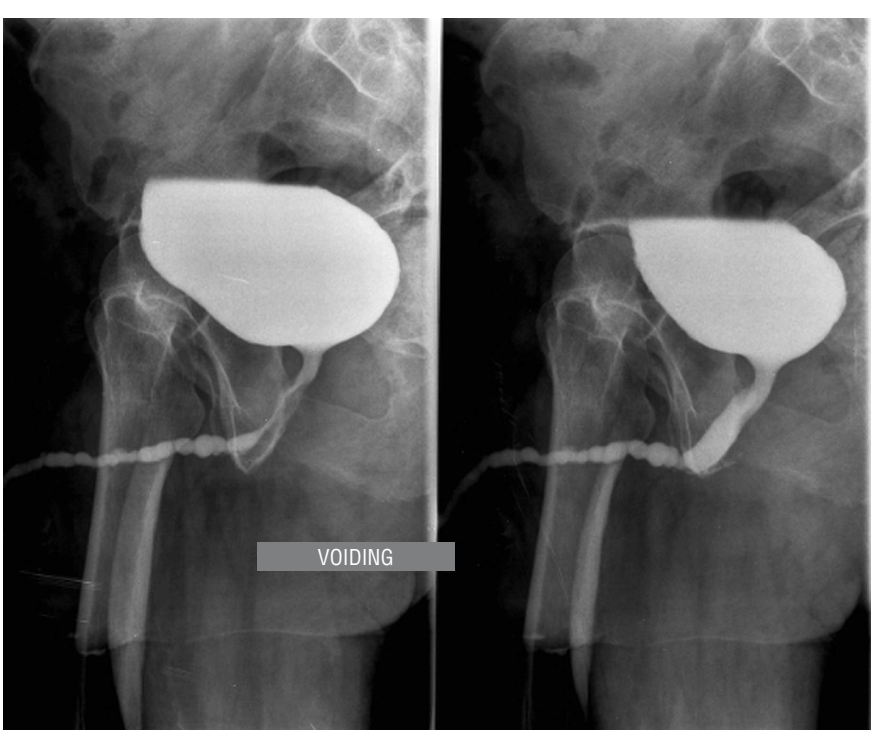


Table 1 - Variables related to procedure success.

Qualitative Variables	RR	95.0% CI	P-Value*
Ischemic heart disease	4.67	1.71-12.72	0.01
Diabetes	2.33	0.74-7.38	0.20
Hypertension	2.00	0.97-3.38	0.10
Previous urethroplasty	1.75	0.94-2.75	0.15
Previous Urethrotomy	2.33	0.98-6.56	0.07
Previous Radiotherapy	1.16	0.94-1.44	0.48
Previous Hypospadia repair	1.26	0.96-1.67	0.37
Penile Cancer surgery	1.27	0.97-1.67	0.37
Lichen sclerosus	3.50	1.52-8.01	0.02
Quantitative variables	**Group success average**	**Failure Group average**	**p-value**
Age	62.57	81.33	0.02
Weight	81.57	71.67	0.13
Number of previous Urethrotomies	0	1.14	0.06

*Statistical significance based on univariate analysis and Student's t – test.

Table 2 - Odds Ratio (Binary regression).

Variables	P value*	RR	95.0% CI	
			Inferior	Superior
IHD	0.03	2.32	1.08	4.99
BXO	0.02	3.21	1.00	4.89

IHD = Ischemic heart disease; **BXO =** Balanitis xerotica obliterans
*Statistical significance based on multivariate analysis.

mend a particular technique in these cases (15). Most studies of perineal urethrostomy have LS as the underlying disease. The LS is a chronic dermatological autoimmune inflammation that causes discomfort and morbidity that involves both urinary and sexual problems (itching, pain, phimosis and weak stream). The true incidence and prevalence is unknown. The age of onset is between the ages of 40 and 50, although it has been reported in adolescents and children. Its name has generally been LS, but urologic literature has referred to it as BXO (balanitis xerotica obliterans). Its exact etiologic risk factors remain unknown; suggesting an autoimmune dysregulation, viral or bacterial infection, local trauma, chemical irritation or hormonal dysfunctions. Diagnosis and treatment forms vary from author to author. In 1979 the urological literature, unlike the dermatological literature, emphasized on the BXO urethral involvement.

In the 70´s, Mallo et al. (16) and Herschorn et al. (17) showed histological findings of LS in the penile urethra. By contrast Khezri et al. (18) pursued that urethral damage was limited

only to squamous meatus and the fossa navicularis without affecting the urethra. In 1998, Mundy et al. (19) published that 25% of urethral stricture was due to LS. Barbagli et al. (20) in their 1999 work, described a percentage of 30% with pathological diagnosis of LS, with involvement of the pan anterior urethra in 52% and a higher incidence in patients with failed hypospadias. In a 2011 Barbagli et al. update (12), the authors found positive results in 85% of biopsies, with bulbar urethra damage of 0%. It is unclear why in some patients the complete anterior urethra is damaged showing a pan-urethritis radiological pattern (21) and why the bulbar or posterior urethra is not affected, which suggests a different epithelial origin as an explanation.

On the other hand, it has been thought that the urethral damage in patients with LS is not due to the disease itself, but because of the damage from continued expansion and infections. Venn et al. (19) surmised that changes to more proximal urethra may be due to chronic obstruction caused simply by emptying stenotic meatus, which leads to increased pressure and swelling of the posterior periurethral glands. It takes over 10 years for the disease to progress and affect the complete urethra. If the disease is limited to the skin it can be treated early with topic steroid treatment such as clobetasol propionate 0.05% or tacrolimus (22). Its purpose is to avoid the bother of the disease and prevent anatomical changes such as stenosis or malignant transformation, seen in 4-8% of cases (2, 23-29). Although some authors advocate the complete removal of the urethra to prevent the development of cancer, it may not be necessary as the urinary diversion would allow the drying of the distal urethra stopping the progression of LS and the cancer risk (30). Furthermore, patients with failed hypospadias show a high incidence of associated LS.

When the disease progresses despite medical treatment, we have the possibility of periodic urethral dilations, meatotomies, urethral removal or non-skin graft substitution, oral or tongue mucosa in sequential procedures and even definitive perineal urethrostomy. Heroic repair measures in one procedure are not usually justified due to the anticipated high failure rate (6, 9). Some patients decide after many previous procedures, not to have the second half of the procedure after a successful perineal urethrostomy (6). Other authors recommend using genital skin or bladder mucosa for repairing complete defects, but the low number of patients and limited follow-up prevent a conclusion being reached. The involvement of the perineostomy by LS has also been described, requiring subsequent surgical revision with low rates of success (15).

Intervening in early stages of the disease with a neo-meathotomy may involve stopping the spread of the disease. Peterson et al. reached success rates of 100% for perineal urethrostomy in 52 patients (9), Kulkarni et al. report 72% (15) arguing that the difference between the two series is due to the low number of previous urethroplasties in the first cohort, which could be considered a risk for subsequent strictures. Breyer et al. (21) stated that strictures greater than 4 cm or previous failed urethroplasty are predictive of failure. On the other hand, we observed a success rate of 100% in patients with no previous urethroplasty reaching significance in the univariate analysis. Similar to Barbagli´s study (6), our major causes of stricture are the presence of LS and idiopathic (65%). These authors achieved a success rate of 70% and defined as risk factors for failure, youth, prior urethroplasty and the presence of LS with no statistical study.

Our success rate reached 82.4%. Although we could think a priori that the presence of radiation or surgery for penile carcinoma are factors for recurrence of stenosis, we did not find any statistical significance in our study probably due to the small number of these antecedents in the patient group. Radiation and ischemic scar are associated in many cases. In the same way erectile dysfunction is defined as an early symptom in the development of ischemic heart disease, we found that ischemic heart disease leads to poorer healing and greater failure of our perineostomies. If we eliminate patients with ischemic heart disease, we have a success rate of 100%. For authors like Elhilali et al. (31), the incidence of urethral stricture is surprisingly high in patients with significant cardiac surgery. Urethral ischemia plays an important role in the development of stenosis.

Therefore, the existence of the LS along with ischemic heart disease requires the use of non-skin terminal perineal urethrostomy techniques but those that maintain the highest degree of vascular flow in the urethral sponge as used in our group, similar to that reported by Myers et al. (10). We have acquired the experience in this technique from the two-stage procedures of Blandy et al. (7), which do not perform a complete section of the urethra, but a longitudinal open urethrotomy sutured to the skin edges, also carried out by Barbagli et al. (6). It is a misconception that in perineal urethrotomies of 2 cm it is necessary to prolong the incision to 4 or 6 cm as a prerequisite for success (10). Other authors propose the removal of the stenotic urethra, allowing greater mobility of the proximal urethra to suture the flap to the skin without stress, particularly in obese patients.

Our study has some limitations such as the small number of patients and its retrospective character. Although there are no questionnaires that assess patient satisfaction with the procedure and its finality, apparently it has been accepted by all patients, even more when it was not their first urethral surgery or they have severe limiting clinical problems in urination. In other series, younger patients had higher acceptance rates than patients older than 70. The acceptance of the procedure was shown by Barbagli et al. in their cohort (6). The perineostomy might not be accepted for religious, cultural, hygienic or psychological reasons, but, in fact, many patients already urinate while sitting when they reach this urethral situation (6, 9). Furthermore, the technique is fast and of little difficulty in its implementation and allows a quick return to normal physical activity, useful in older patients with comorbidity and multi-stepped and a fibrous urethral plate. Only those patients with damage or disease of the dorsal plate may receive a dorsal buccal mucosa urethral graft of adequate length to allow a suitable perineal urethrostomy and less retractable scar. The buccal mucosa is used in the subsequent repair of the perineal urethral stricture which continues to suffer from LS, and where Y-V repair procedures are inadequate because the disease affects the skin surrounding the perineal stoma.

CONCLUSIONS

Perineostomy is a valid alternative for patients with unfavorable urethral pathology (LS, failed previous urethroplasty, hypospadias repair history, prior pelvic radiation) or for individuals who do not to be submitted to more urethral or perineal urethroplasties.

Perineal urethrostomy success rate is affected principally by age, the presence of LS and ischemic vascular problems.

The preservation of the dorsal plate and longitudinal vascularization of the corpus spongiosum are advantageous factors to reduce healing complications after completion of the procedure.

ABBREVIATIONS

LS = Lichen sclerosus
BXO = Balanitis xerotica obliterans
IHD = Ischemic heart disease

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Genital lichen sclerosus (LS) has been reported as a common progressive, sclerosing, inflammatory dermatosis disease. The incidence is 10.3% in a population of 2.096 patients (1). It is more prevalent in women than men (6:1-10:1). In women, this disease occurs, in general, in the menopause period, and in males at the age of 30-50 years. Surprisingly, it has also been reported in adolescents and children (2, 3).

In females, it affects the anogenital area (85-98%) and extragenital area (15-20%) (4). The differential diagnosis should include lichen planus, lichen simplex chronicus, vitiligo, alopecia, psoriasis and vulvar intraepithelial neoplasia (5). In males, this disease can affect, in the sequence, the foreskin and glans penis (57%), urethral meatus (4%), and can involve the anterior urethra (20%) (4).

Urethral involvement by LS normally starts at the meatus and inches up to the anterior urethra until it reaches the bulb, involving the epithelial/spongiosus tissue displaying dilations and well demarcated stricture (panurethral stenosis, i.e., alternative multiple strictures in the anterior urethra). In the initial stage, degeneration of basal cell layer and inflammatory infiltration (lymphocytes, hyperkeratosis of the epithelium and stratum malpighii atrophy) have been verified (6).

The initial treatment, when the disease is limited to the foreskin/glands, consists in the application, topically or intralesionally, of steroids (clobetasol propionate, mometasone aceponate or betamethasone dipropionate cream or ointment) or emollients that might be used to inhibit chronic inflammatory processes (4, 7). As an alternative, pimecrolimus or tacrolimus can also be used (they have significant anti-inflammatory activity). Some benefits that are obtained, by reversing histological changes noted in the LS are known (2, 6). If the LS is confined to the foreskin, especially if the prepuce becomes tightened and nonretractile, circumcision is recommended. The possibility of cure by circumcision in the initial stages, i.e., when still located, is 92% (1, 6, 8), without recurrence signals. It is suggested that circumcision specimens always be sent for histological evaluation (to ensure diagnosis). As a strong association between LS and spongiosus cells carcinoma (SCC) has been reported (5), it is necessary to confirm the existence of LS and rule out SCC. It has been estimated that the risk of malignancy in male and female genitalia is 4-8% (9). For that reason, the treatment of panurethral strictures should never be managed with dilation or instrumentation.

Depasquale et al. noted that patients with LS limited to the glans penis and foreskin and who were submitted to circumcision alone did not show recurrent signals of LS at long-term surveillance (4). The perineal urethrostomy is commonly used as first step for staged reconstruction of the urethra (10, 11). With older patients or those with multiple failed repairs, with serious morbidity, or with histologically severe disease, the possibility of perineal urethrostomy might be discussed with the patient, especially elderly patients already accustomed to seat voiding. Moreover, failure in fibrotic hypospadias repair and postradiation stenosis in many situations requires a perineal urethrostomy. Because of many iterative interventions, many patients, by personal option, surprisingly have chosen this procedure as definitive, reporting satisfaction and acceptance (10).

In conclusion, to date the etiology of LS is not known. The pathology of this disease can lead to scarring causing serious alterations in the lower urinary tract function and also sexual dysfunction in males and females.

The diagnosis is eminently clinical, but it must be confirmed by histological evaluation. Treatment with corticosteroids has been effective enough. Surgical treatment is indicated when the foreskin, the coronal glans, the meatus or the urethra are involved.

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ORIGINAL ARTICLE

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Intrarectal ice application prior to transrectal prostate biopsy: a prospective randomised trial accessing pain and collateral effects

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ABSTRACT

Objectives: To analyze the efficacy of intrarectal ice application as an anesthetic method prior to transrectal ultrasound (TRUS) guided prostate biopsy.
Materials and Methods: A total of 120 consecutive men were included into the study prospectively. Patients were equally randomized as group 1 and 2 with 60 patients each. Ice was applied as an anesthetic method 5 minutes before procedure to the patients in group 1. Patients in group 2 were applied 10 ml of 2% lidocaine gel 10 minutes before procedure. Twelve core biopsy procedure was performed for all patients. The pain level was evaluated using a visual analogue scale (VAS).
Results: Median pain score was 3.5 (1-8) in group 1 and 5 (1-8) in group 2. There is significantly difference between groups regarding the mean sense of pain level during the procedure. (p=0.007) There was also no difference in complications between two groups about presence and duration of macroscopic hematuria and rectal bleeding.
Conclusions: Intrarectal ice application prior to TRUS prostate biopsy has an effect on reducing pain. Development of new techniques about cold effect or ice can make this method more useful and decrease complication rates.

ARTICLE INFO

Key words:
Ice; Prostate; Biopsy; Anesthesia

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INTRODUCTION

Several studies have shown that 80-96% of patients undergoing transrectal ultrasound (TRUS) guided prostate biopsy reported that they suffered a disturbing pain from this procedure (1, 2). Hence, any anesthetic method is considered to be required prior to TRUS prostate biopsy.

As yet, various anesthetic methods including intrarectal lidocaine gel and periprostatic anesthetic material application have been tried. A method which is easily-applicable, painless and not leading to any additional complication should be chosen as an anesthetic agent prior to TRUS prostate biopsy. Intrarectal lidocaine gel is an easily-applicable method among others. However, factors limiting its efficacy include superficial application, absorption of little fraction of drug into systemic circulation and insufficient penetration to periprostatic tissues. Although periprostatic injection provides an efficient pain control, it has disadvantages including painful application and more frequent complication rates due to additional injections. However, it has currently been reported as a safe, easily-applicable and quite efficient method among all other methods (3).

In this study we aim to analyze the efficacy of intrarectal ice application as an anesthetic method prior to TRUS prostate biopsy. Besides its antinociceptive effect, ice can slow down nerve conduction, reduce muscle spasm and prevent post-traumatic edema (4). Ice has been used for

relieving various kinds of pains for many years and its efficacy has also been known.

No study is available in literature regarding intrarectal ice application for TRUS prostate biopsy. However, ice is being used for various muscle-skeletal pathologies and some simple surgical procedures.

It has been known that ice has a vasoconstrictor impact on vessels. We are of the opinion that ice could reduce rates of rectal bleeding and hematuria seen after biopsy.

MATERIALS AND METHODS

The study was designed as a prospective randomized clinical trial comparing two methods during a period of 6 months at the Department of Urology, Faculty of Medicine, University of Kocaeli. Biopsy indication criteria were abnormal digital rectal examination (DRE) and elevated serum PSA levels higher than 4 ng/mL. Inclusion criteria were all patients who were eligible for prostate biopsy. Exclusion criteria for this study included a history of transrectal prostate biopsy; a bleeding diathesis and/or anticoagulant treatment; anal or rectal pathologies such as hemorrhoid, anal fissure or anal stricture; a history of lidocaine allergy; use of analgesic or narcotic drugs; and an inability to rate a visual analogue scale. Oral Ciprofloxacin prophylactic therapy (2x500 mg/day) was used for all the patients 1 day before biopsy and continued for the next 3 days. A Fleet enema was administrated in the morning of biopsy for bowel cleaning. Biopsies were performed with the patient in the left lateral decubitus position using Toshiba SSA-550A ultrasonography machine with 6 Mhz 150° endorectal probe (PVT-651VT) and automatic biopsy gun with 18 gauge biopsy needles by the same urologist.

Ethics committee approved the study and informed consent was obtained from each patient for biopsy and this randomized study. Patients were equally randomized using previously prepared cards in envelopes as group 1 and 2 with 60 patients each. Ice was applied as an analgesic method 5 minutes before procedure to the patients in group 1. Patients in group 2 received 10 ml of 2% lidocaine gel 10 minutes before procedure. No additional analgesia was utilized in any groups. Firstly digital rectal examination was performed, and subsequently analgesic method was administered. Prostate was analyzed in sagittal and coronal sections then diameters of prostate and seminal vesicles were measured. Finally, 12 core biopsies were taken. Blinding could not be possible since all interventions were made by the same urologist and patients were aware of ice application. But the pain scores were assessed by another blinded physician.

The 10-point linear Visual Analogue Scala (VAS) was used to assess the pain score. Scores between 1-3 were considered as mild pain, 4-7 as moderate and 8-10 as severe. The patients were asked the question of "How much pain do you feel in a simple blood draw procedure?" and the score obtained was considered as threshold pain value. One and three weeks after biopsy patients were assessed regarding complications. Pain during the anesthesia and probe insertion were expressed by categorical variables (none, mild, moderate and severe) and during TRUS prostate biopsy by VAS score. SPSS® 13.0 software was used for statistical analyses. Student t-test and Mann Whitney U tests were used for continuous variables and Fisher's Exact Test for categorical variables as statistical methods.

Ice application technique

Firstly, middle finger space of the large size glove was filled with water and taped from its bottom part then frozen (Figure-1). During the anesthesia procedure, ice mould lubricated with Vaseline was inserted into the rectum adjacent to the prostate. Five minutes later, ice mould was pulled out of rectum, which was semi-melted.

RESULTS

A total of 169 patients were evaluated for eligibility. Seventeen patients were excluded because they met the exclusion criteria and thirty-two patients rejected to sign the written informed consent. Finally 120 patients were included into the study (Figure-2). Both groups were similar in terms of abnormal DRE numbers, age of patients, serum total PSA levels, mean prostate volume,

Figure 1 - Ice mould.

mean duration of procedure and mean threshold levels (Table-1).

Median pain score was 3.5 (1-8) in group 1 (ice) and 5 (1-8) in group 2 (lidocaine gel), with significant difference regarding the mean sense of pain during the procedure (p=0.007). Statistical power was calculated as 0.80 with a two-sided 5% significance level and a sample size of 60 patients per group using post hoc analysis (mean±sd group1 and 2 were 3.8±1.5 and 4.6±1.6 respectively).

No difference was detected in pain levels during the probe insertion; however, there was an obvious difference in pain levels during anesthesia between two groups (Tables 2 and 3). Distribution of pain level is shown in Figure-3. None of

Figure 2 - Study flow diagram.

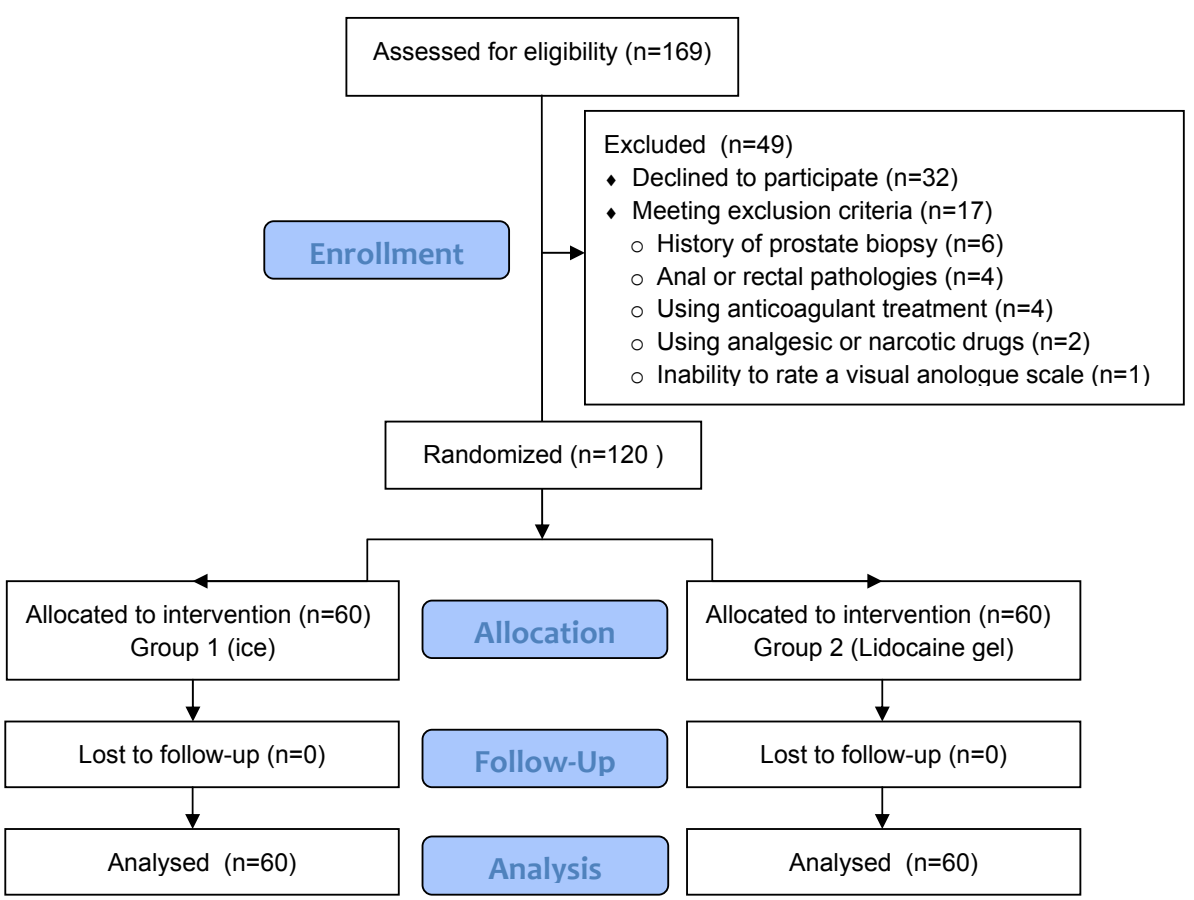


Table 1 - Distribution of 2 groups according to various features (Group 1: ice, Group 2: lidocaine gel).

	Group 1	Group 2	p Value
Total patient number (n)	60	60	
Abnormal DRE number, n(%)	15 (25%)	19 (31.7%)	0.544*
Median age (IQR)	64.0 (49-80)	66.0 (41-82)	0.507
Median Total PSA (IQR)	7.7 (1.2-70.0)	6.8 (0.6-29.6)	0.152
Number of patients with cancer, n(%)	24 (40%)	18 (30%)	0.339*
Median Prostate Volume (IQR)	53.1 (11.3-153.2)	47.4 (16.3-122.9)	0.118
Number of patients developing rectal bleeding n (%)	16 (26.7%)	19 (31.7%)	0.688*
Median duration of rectal bleeding (IQR)	0.0 (0.0-10.0)	0.0 (0.0-7.0)	0.884
Number of patients developing hematuria n (%)	41 (68.3%)	40 (66.7%)	1.00*
Median duration of hematuria (IQR)	1.5 (0.0-14.0)	1.5 (0.0-21)	0.457
Median threshold level (IQR)	1.5 (1-4)	2 (1-4)	0.525
Median duration (minutes) of procedure (IQR)	7.3 (5.5-10.0)	7.0 (5.0-10.5)	0.244

Student t-test, Fisher's Exact Test*

Table 2 - Comparison of pains felt during application of anesthetic method, probe insertion and throughout the procedure between the groups (Group 1:ice, Group 2: lidocaine gel).

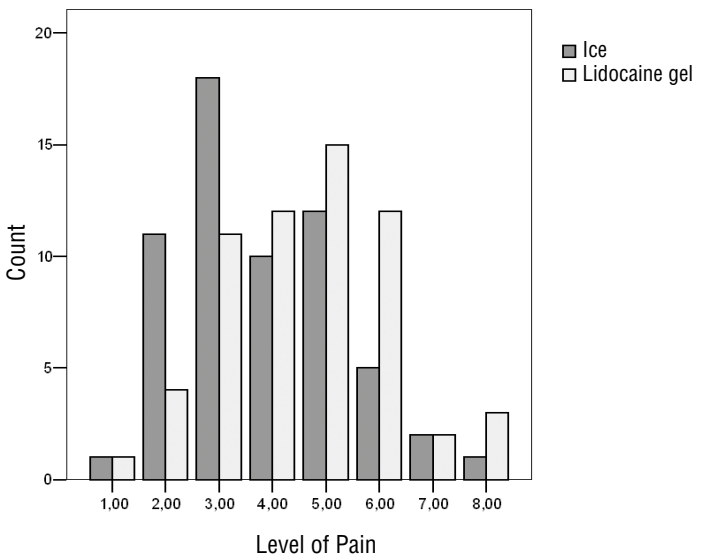
	Group 1	Group 2	p Value
Total number of patients	60	60	
Number of patients feeling pain during anesthesia, n (%)	25 (41.7%)	0 (0%)	0.000*
Number of patients feeling pain during placement of probe, n (%)	18 (30%)	27 (45%)	0.131*
Median pain score felt during the procedure (IQR)	3.50 (1-8)	5.0 (1-8)	0.007

p: p value, Student t-test, Fisher's Exact test*

Table 3 - Levels of pain felt during application of anesthetic method in both groups (Group 1: ice, Group 2: lidocaine gel).

	Pain during the application of anesthetic method n (%)				
Method	**None**	**Mild**	**Moderate**	**Severe**	**Total**
Group 1	35 (58.3%)	22 (36.7%)	1 (1.7%)	2 (3.3%)	60 (100.0%)
Group 2	60 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	60 (100.0%)

Figure 3 - Distribution of pain level during TRUS prostate biopsy. (Group 1:ice, Group 2: lidocaine gel).



the patients who received lidocaine gel felt pain during the procedure, though 22 of those who received ice felt mild (36.7%), 1 moderate (1.7%) and 2 severe (3.3%) pain (Table-3).

When the ice group is divided into two groups according to the presence of pain during application of ice, no difference was detected in pain level during the procedure between two groups (p=0.088) (Table-4).

Vasovagal syncope developed in one patient from lidocaine gel group. Urinary retention developed in no patient. No difference was detected between groups about presence and duration of macroscopic hematuria and rectal bleeding (Table-1). No abundant bleeding requiring treatment developed in patients. 100.000 colony/CFU Escherichia coli were detected in one patient with complaint of dysuria in lidocaine gel group and was treated with antibiotics.

DISCUSSION

Prostate biopsy has been considered as gold standard in diagnosis of prostate cancer since Hodge et al. described TRUS guided systematic sextant prostate biopsy technique in 1989 (5). TRUS prostate biopsy has a critical role in urological practice and is generally used in urology clinics as an outpatient procedure.

Although TRUS prostate biopsy is well tolerated in most patients, it also causes a disturbing pain (6). According to the studies, 19-25% of the patients feel moderate or severe pain (7-9).

Table 4 - Comparison of mean pain scores during the procedure in ice group according to presence of pain during the ice application.

	Pain during the application of ice	
	None	Mild to severe
Number of patients feeling pain during the application of ice, n (%)	35 (58.3%)	25 (41.6%)
Median pain score during the procedure in ice group (IQR)*	3.0 (1-8)	4 (2-7)

p: 0.088, Mann Whitney U test*

Bastide et al. reported in their study that 80% of patients without local anesthesia felt a significant discomfort and approximately half of them underwent less than 6 core biopsy (2). It was reported that high numbered biopsy protocols increase the possibility of diagnosis of prostate cancer in recent years (10); however, it is considered that high number of biopsies will cause more pain (11). Therefore, the requirement of an anesthetic method during prostate biopsy is accepted by many urologists.

Up to now, many protocols have been developed as anesthetic methods and studies performed. Intrarectal lidocaine gel is an easily-applicable and simple method so it is widely being used by urologists. However, factors limiting its efficacy include topical application, absorption of little fraction of drug into systemic circulation and insufficient penetration to periprostatic tissues. Some studies in literature indicate that the effect of lidocaine gel is suboptimal (12-14).

Periprostatic neural blockage (PNB) is currently the most popular method in recent studies. Various studies have been conducted about PNB regarding the way, number and amount of local anesthetic infiltration and their efficacy has also been shown (6, 15-20). But in one study no difference was detected between the periprostatic injection and lidocaine gel groups (21).

PNB does not ameliorate the pain during the placement of ultrasound probe into the rectum because it is applied afterwards (22). It has been shown that patients feeling pain during placement of probe also felt much more pain during biopsy and their tolerance decreased (23, 24). Besides, injection may also cause pain in proportion to the number of injections (19). In a study, application of PNB and intrarectal lidocaine combination was shown to be more effective than PNB alone and this combination method has been recommended (25).

Numerous studies have been conducted on complications and side effects of PNB, and no statistical difference has been detected between placebo and PNB groups (26-28). In a study conducted by Obek et al., no statistical difference was detected about frequency of urinary infections requiring hospitalization although bacteriuria rates were high (26).

PNB combined with lidocaine gel or alone has been presented as an easily-applicable and safe method, and is currently considered as a gold standard method (3).

General anesthesia may overcome the pain issue during TRUS prostate biopsy but it should be considered that it is not without risk and it could have a significant impact on manpower and financial resources (3). There are several approaches that can be used for this purpose including entonox, propofol, midazolam etc. Barbosa et. al. reported in their study that the intensity of postoperative pain was significantly higher in patients who received only propofol. Fentanyl-propofol had no postoperative pain but two cases of intraoperative respiratory depression, possibly due to the interaction fentanyl-propofol, were observed (29). In consequence of this results, combined local anesthesia is also necessary. Because general analgesia is a complicated treatment due to relatively high costs and the need for operating room conditions, it should only be used in special situations.

Ice has been used as an anesthetic agent for pain related to muscle-skeletal system pathologies and simple surgical procedures for a long time, and its efficacy is well-known. In a review, it was reported that the application of intense cold to traumatic injuries and surgical sites were important steps in 18th and 19th century anaesthesia and local tissue temperature could be brought down by the application of ice and salt by the surgeon (30).

There are two studies in the literature about anal hypothermia; one of them is a frozen finger made from a surgical glove for local anal hypothermia to treat acute painful prolapsed piles (31) and the second one is using an anal cooler (a cylindrical plastic device) to reduce pain after rubber band ligation for hemorrhoids (32). The first study reported that the frozen finger reduced the pain and swelling of painful prolapsed piles. In the subsequent study, no additional benefit was found. No study is available in literature regarding intrarectal ice application for TRUS prostate biopsy.

Ice has some impacts such as slowing down neural conductance, reducing muscle spasms and preventing edema secondary to trauma together with antinociceptive effects (4). Because of these effects, we analyzed the efficacy of ice applica-

tion as an anesthetic method prior to TRUS prostate biopsy in this study. Mean pain scores during the procedure were compared among the groups of intrarectal ice and lidocaine gel in this study, and we found significant differences between two groups (p=0.007). Also, no difference was detected between two groups about feeling pain during the placement of probe. These results indicate that intrarectal ice application prior to TRUS prostate biopsy may have an effect on reducing pain during the procedure.

There are two main disadvantages in use of this method which is performed via intrarectal application of ice mould obtained by glove finger. Firstly, because ice is applied before the procedure, its cold effect on tissues decreases over time. In our study, ice mould was applied during 5 minutes intrarectally and then the procedure begun after it had been taken out. Hence, it is obvious that the anesthetic effect would decrease over time after the ice mould is taken out. Secondly, patients felt pain at the time of the ice application. None of the patients that received lidocaine gel as an anesthetic method felt pain. But in the ice group 22 patients (36.7%) felt mild pain, one felt moderate (1.7%) and two patients (3.3%) felt severe pain while ice was placed through anus. After the ice mould was placed, patients reported a sense of coldness which was not uncomfortable during the 5 minutes. The ice group was divided into two groups as painful and painless application of ice mould to explore the possibility of its effect on the level of pain during the procedure then the main pain levels were compared. No significant difference was determined between both groups (Table-4).

At the beginning of this study, our opinion was that the complication rates of biopsy would be lowered via intrarectal ice application because of its vasoconstrictor effect on vessels. However, we did not detect any significant difference between groups about duration of rectal bleeding and hematuria after biopsy. We think that this result may be related to using the ice at the beginning of the procedure and its effect decreases overtime. If this cold effect can be kept all along the procedure by using new techniques, its combined use with available methods (ice+lidocaine gel or ice+PNB) or using post-procedure ice for biopsy complications, complication rates may decrease and it may provide additional benefits.

CONCLUSIONS

In conclusion, the ice application seems to be effective to reduce the pain during prostate biopsy. The aim of this study was to show that we can have the benefit of cold effect to reduce pain during prostate biopsy. It should be admitted that our method in this present form is difficult to be considered an alternative to easily applicable lidocaine gel or PNB which is quite effective. Development of new techniques about cold effect or ice can make this method more useful and decrease complication rates. Also, its combined use with available methods may provide additional benefit.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Pioneering in the urological scenario, the cooling interest was refreshed by the IBJU in an elegant prospective randomized trial assessing intrarectal ice application prior to transrectal prostate biopsy, revisiting ice for its embryonic use of analgesia/anesthesia (1). In fact, the use of cold as a therapeutic agent has an exciting and long history and hypothermia is receiving unprecedented attention from the medical and scientific communities nowadays.

Since Hippocrates time, cryotherapy has been used for local analgesia, inhibition of local blood circulation and oedema. Baron de Larrey, a French army surgeon during Napoleon's Russian campaign, packed the limbs in ice prior to amputations to render the procedures painless. Freezing temperatures using iced salt solutions was also described producing reduction in tumor size and amelioration of pain in England (James Arnott, 1845-51) (2, 3).

Besides, after brutally applied in the concentration camps, hypothermia became associated with the atrocities exposed at the war trials in Nürnberg and after lying dormant for decades, to date with further improvements in apparatus and imaging techniques we are facing a resurgence of interest in the cooling and freezing properties for medical use, including modern cryosurgery with increasingly growing clinical use in urology, mainly for prostate and kidney cancers (3, 4).

Behind the high-tech establishment, the longstanding ice seems to be "the flavor of the moment", struggling to prove that the simple and primitive might overcome the complex and new.

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ORIGINAL ARTICLE

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Insulin-like growth factor (IgF)-I, IgF binding protein-3, and prostate cancer: correlation with gleason score

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ABSTRACT

Introduction: Non-androgenic growth factors are involved in the growth regulation of prostate cancer (PCa).
Objective: This is the first Brazilian study to correlate, in a population of patients operated for PCa, PSA, total testosterone, insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein-3 (IGFBP-3) with Gleason score and to compare with a control group with benign prostate hyperplasia (BPH).
Materials and Methods: This retrospective single-center study included 49 men with previously diagnosed PCa and 45 with previously diagnosed BPH. PSA, testosterone, IGF-I, IGFBP-3 were determined in both groups.
Results: PSA and IGFBP-3 levels were significantly higher in the PCa group as compared to the BPH group ($p<0.001$ and $p=0.004$, respectively). There was a significant difference when we compared the PSA before surgery ($p<0.001$) and at the inclusion in the study ($p<0.001$) and IGFBP3 (0.016) among patients with Gleason <7, ≥7 and BPH. In the PCa group, PSA, testosterone, IGF-I and IGFBP-3 levels were comparable between Gleason <7 and ≥7. Conclusions: Our data suggest that in localized PCa, the quantification of PSA and, not of IGF-1, may provide independent significant information in the aggressiveness. IGFBP-3 could be a biochemical marker of disease control in PCa patients.

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Key words:
Prostatic Neoplasms; Prostatic Hyperplasia; Insulin-Like Growth Factor I; Insulin-Like Growth Factor Binding Protein 3

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INTRODUCTION

After non-melanoma skin cancer, prostate cancer (PCa) represents the most frequently diagnosed cancer in adult men with an annual incidence of approximately 50 cases per 100.000 men (1).

Androgens are considered the primary growth factors for prostate epithelial cells. However, other non-androgenic growth factors are involved in the growth regulation of PCa cells (2).

Insulin-like growth factor-I (IGF-I) is a potent mitogen for normal and cancerous cells and exerts the mitogenic action by increasing DNA synthesis and by stimulating the cell cycle progression (3). In addition, IGF-I also inhibits apoptosis (4). IGF-I has direct mitogenic and anti-apoptotic

effects on normal and transformed prostate epithelial cells and has been implicated in the pathogenesis of PCa (5, 6). The interaction between IGF-I and IGF-IR is regulated by the IGF-binding proteins (IGFBPs). Of the circulating binding proteins, IGFBP-3 is the most abundant one (7). At tissue level, IGFBP-3 regulates the mitogenic activity and inhibits the anti-apoptotic effect of IGF--I (8). Furthermore, IGFBP-3 has been linked to induction of apoptosis (9).

Several epidemiologic studies have suggested that high-normal serum IGF-I levels may be concordant with a higher risk of PCa (5, 10). It was observed a 38% increased odds of prostate cancer risk comparing highest vs. lowest quintiles of IGF-I (11). The largest systematic review of studies reporting on the association of IGF-I with the risk of PCa was published in 2009 (12). It included both retrospective and prospective studies (n=42 studies) and demonstrated that the published literature is consistent with an average 21% increase risk of PCa per standard deviation increase in IGF-I. They also showed a stronger association of IGF-I with more aggressive and advanced cancers. The probable inverse association between IGFBP-3 and PCa risk was only seen in retrospective, but not prospective studies.

A possible explanation for variability in normal IGF-I levels was proposed. Johansson et al. hypothesized that genetic variation in the 3' region of the IGF-I gene influences levels of circulating IGF-I and, therefore, PCa risk (13).

The prognosis of PCa is associated with Gleason score of the surgical specimen. It is considered a good prognosis if a Gleason score up to six (14). In 2005, the International Society of Urological Pathology (ISUP) modified the Gleason score system in order to get an accurate Gleason grade (15).

To date, in the Brazilian population, there is no study that correlates serum levels of IGF-I and IGFBP-3 with Gleason score in surgical specimens.

This study evaluated, in a population of patients operated for PCa, serum PSA, testosterone, IGF-I and IGFBP3 levels and correlated with Gleason score of the surgical specimens. All findings were compared with a control group with benign prostate hyperplasia (BPH).

MATERIALS AND METHODS

Patients

This retrospective single-center study included 49 men with previously diagnosed PCa and 45 men with previously diagnosed BPH, recruited from the outpatient urology clinic. All PCa patients were submitted to radical prostatectomy from January 2007 to April 2010 and time elapsed between surgical intervention and inclusion in the study varied from 3-48 months. On the basis of the histological grade obtained at surgery, PCa patients were divided into two groups: Gleason score < 7 and Gleason score ≥7. This information was obtained from patient's records. The evaluation of prostatectomies specimens was done using the current grading system. All BPH patients were submitted to transurethral or suprapubic prostate resection at least five years before the inclusion in the study and presented with stable PSA values and digital rectal examination of the prostate without changes.

Reasons for ineligibility included patients with hepatic failure, uncontrolled diabetes mellitus, hypo or hyperthyroidism, GH deficiency, acromegaly, malnutrition and diseases that could interfere in serum levels of IGF-I and IGFBP-3. All subjects entered the study after obtaining written informed consent according to a protocol approved by the Ethics Committee.

Clinical parameters

All patients had the following data collected: age, preoperative serum PSA levels and type of surgery. For patients with PCa, Gleason score and complementary treatment were also documented.

Hormone assays

Serum IGF-I, IGFBP-3 and total testosterone levels were determined by chemiluminescense immunometric assays. Total PSA serum levels were measured by electrochemiluminescense assay before surgery - PSA_1 and at the inclusion in the study - PSA_2.

The low detection limit of IGF-I measured by Immulite 2000 kit DPC is 20 ng/mL and the

intra and inter-assay CVs are 3.6 and 6.6%, respectively. The standards are calibrated against the first International Reference Reagent WHO 87/518 and IGF-I was expressed in mass units and age-related standard deviation scores (SD--scores). Group 0: -2 SD to zero and group 1: zero to +2 SD.

All serum samples were collected in the early morning after an eight-hour fasting period.

Statistical analysis

Analyses were performed by SPSS (version 16.0, SPSS, Inc., Chicago, IL). In the descriptive analysis, the categorical variables were expressed by their percentages and frequencies, whereas the numerical variables were expressed as mean ± standard deviation (SD). The Mann--Whitney test was performed for comparison between two groups and the Kruskal-Wallis test was used to compare the numerical variables among three groups. Comparisons between categorical variables were done by χ^2 test. The correlations between numeric variables were studied using the Spearman's correlation test. A p-value less than 0.05 was considered significant, except for comparisons between two of the three groups (PCa with Gleason <7, PCa with Gleason ≥7 and BPH), when p-values <0.017 were considered significant (Bonferroni post hoc analysis).

RESULTS

Patients' characteristics

Ninety-four men entered this study: 49 (65.5±6.2 years-old, median 65) with previously diagnosed histologically confirmed prostate adenocarcinoma and 45 (66.8±8.0 years-old, median 67) with histologically confirmed BPH, without the finding of intraepithelial neoplasia. Clinical, laboratorial and pathological characteristics of the PCa and BPH cases are described in Table-1.

Considering the PCa patients, at the time of inclusion in the study, 28 had been submitted only to surgery, 10 had been submitted to surgery and radiotherapy and 11 had been submitted to surgery, radiotherapy and hormone therapy.

Comparison between PCa and BPH patients: Serum markers

Serum PSA (both before surgery and at the inclusion in the study) and IGFBP-3 levels were significantly higher in the PCa group as compared to the BPH group (p<0.001; p<0.001 and p=0.004, respectively) (Figures 1 and 2). Age, serum testosterone and IGF-I levels did not significantly differ between the two groups (Table-1). Categorizing IGF-I in SD--scores there was no statistically significant difference between the PCa and BPH groups.

A negative correlation was observed between PSA (both before surgery and at the inclusion in the study) and testosterone levels (r=-0.36,

Table 1 - Clinical, laboratorial and pathological characteristics of PCa and BPH patients.

	PCa patients	BHP patients	p
n	49	45	-
Age, years	65.5±6.2	66.8±8.0	0.500
PSA_1, ng/mL	8.7±4.1	3.6±1.7	**< 0.001**
PSA_2, ng/mL	0.2 ±0.4	3.4±1.0	**< 0.001**
Testosterone,ng/dL	446.1±161.5	542.3±144.3	0.756
IGF-I, ng/mL	126.8±42.0	126.7±40.8	0.976
IGFBP3, ng/mL	3.5±0.8	3.0±0.8	**0.004**
Gleason <7	26	-	-
Gleason ≥7	23	-	-

PSA_1= PSA before surgery; **PSA_2**= PSA at the inclusion in the study

Figure 1 - Serum PSA levels (before surgery) in patients with prostatic hyperplasia and prostate cancer. Statistical significance was determined by Mann–Whitney's test. The lower and upper bars represent the first and third quartiles respectively. The line across the box represents median value. The lines above and below the box represent the highest and lowest values, excluding outliers.

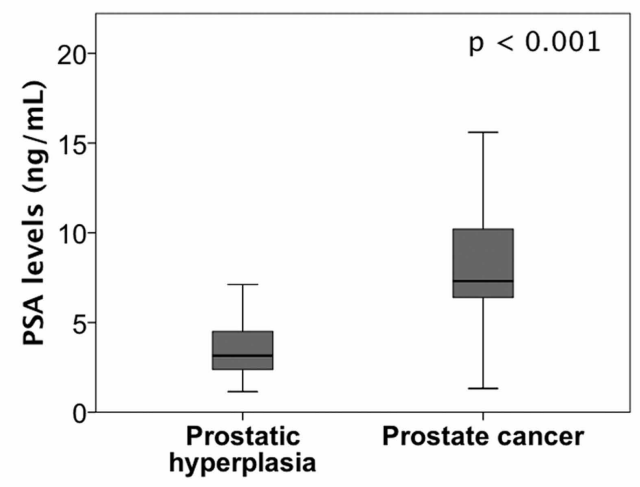
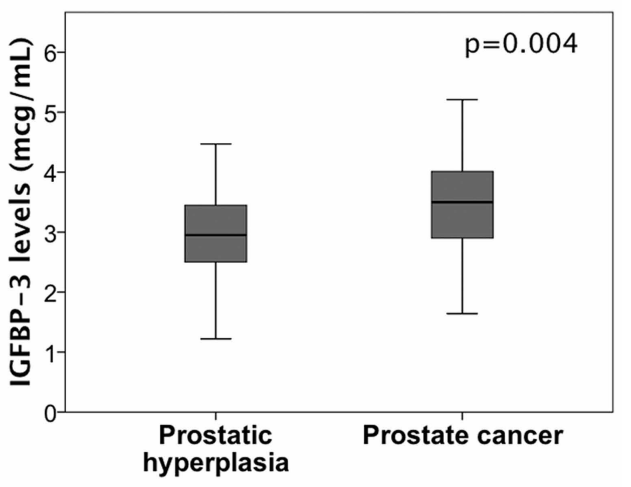


Figure 2 - Serum IGFBP-3 levels (at the inclusion in the study) in patients with prostatic hyperplasia and prostate cancer. Statistical significance was determined by Mann-Whitney's test. The lower and upper bars represent the first and third quartiles respectively. The line across the box represents median value. The lines above and below the box represent the highest and lowest values, excluding outliers.



IGFBP - 3 levels (mcg/mL)

PSA levels (ng/mL)

p=0.014 and r=-0.43, p=0.005, respectively). A positive correlation was observed between IGFBP3 and testosterone levels (r=0.39, p=0.008).

Age, serum markers and the Gleason score

In the PCa group, serum PSA, testosterone, IGF-I and IGFBP-3 levels were comparable between Gleason score <7 and Gleason ≥7 cases (Table-2). Categorizing IGF-I in SD-scores (group 0: -2 SD to zero and group 1: zero to +2 SD) there was no statistically significant difference between patients with Gleason score <7 and Gleason ≥7. There was a significant difference when we compared the PSA levels before surgery (p<0.001) and at the inclusion in the study (p<0.001) and IGFBP3 levels (0.016) among patients with PCa Gleason <7, PCa Gleason ≥7 and BPH. PSA levels (both before surgery and at the inclusion in the study) were higher in patients with PCa Gleason <7 and PCa Gleason ≥7 (p<0.001, both) than in those with

Table 2 - Clinical and laboratorial characteristics of PCa cases according to Gleason score.

	Gleason < 7	Gleason ≥7	p
n	26	23	-
Age, years	65.0±6.9	66.0±5.2	0.452
PSA_1, ng/mL	7.9±3.4	9.6±4.8	0.288
PSA_2, ng/mL	0.2±0.4	0.3±0.4	0.368
Testosterone,ng/dL	418.1±121.1	477.7±195.6	0.326
IGF-I, ng/mL	130.0±38.0	123.1±46.7	0.316
IGFBP3, ng/mL	3.4±0.8	3.5±0.8	0.833

PSA_1= PSA before surgery; **PSA_2**= PSA at the inclusion in the study

BPH. IGFBP3 levels were higher in patients with Gleason ≥7 (p<0.016) than in those with BPH. There was no difference in PSA (both before surgery and at the inclusion in the study) and IGFBP3 levels between patients with PCa Gleason <7 and ≥7. There was no difference in IGFBP3 levels between patients with PCa Gleason <7 and BPH.

A negative correlation was observed between PSA at the inclusion in the study and testosterone levels (r=-0.30, p=0.04).

DISCUSSION

This study analyzed and compared the serum levels of PSA, IGF-I and IGFBP-3 as possible markers of PCa, according to the aggressiveness of the tumor in terms of Gleason score. For this reason, we selected a population of previously diagnosed PCa, all our tumor cases had been submitted to radical prostatectomy. As a control group, we included patients with previously diagnosed BPH, all of them submitted to transurethral or suprapubic prostate resection at least five years before the inclusion in the study and with stable disease. We consider that this group of BPH patients represents a reliable sample of patients without PCa.

In our population, only serum PSA and IGFBP-3 levels, not IGF-I, were significantly higher in the PCa group than in the BPH group. A possible explanation for this was that the IGF-1 was assessed only after surgery. Marszalek et al. and Sciarra et al. (16, 17) did not find significant variations in IGF-I levels between PCa and control cases. Differently to our study, they did not evaluate IGFBP-3 levels and Marszalek et al. (16) did not have the possibility to analyze the results in terms of the Gleason score of the surgical specimens. Since IGFBP-3 is a substrate for PSA, by proteolytically cleavage (18), PCa patients with undetectable PSA levels are expected to have higher IGFBP-3 levels. The inverse correlation between PSA and IGFBP-3 could make IGFBP-3 a possible biochemical marker of disease control in PCa patients.

There is a known variability in IGF and gene sequencing among race groups that can influence disease incidence (19). Brazil has a heterogenic population that can limit these results. Recently, Schumacher et al. (20) conducted a comprehensive analysis, utilizing a resequencing and tagging single-nucleotide polymorphism (SNP). They have identified a novel IGF-I SNP, not associated with IGF-I blood levels, which showed preliminary evidence for association with PCa risk among Caucasians.

In this study, serum PSA, testosterone, IGF--I and IGFBP-3 levels were comparable between PCa cases with Gleason score <7 and Gleason ≥7. These findings are consistent with previous studies that demonstrated no significant variations in PSA and IGF-I according to the tumor Gleason score (16-18). As in our population, Ismail et al. (21) also found no significant difference in IGFBP-3 levels between patients with Gleason score <7 and Gleason ≥7. The negative findings of our study are in agreement with other series suggesting that IGF--I serum levels provide no significant information considering aggressiveness of PCa. Moreover, it differs from epidemiological studies that also showed a stronger association of IGF-I with more aggressive and advanced cancers (12).

CONCLUSIONS

This was the first Brazilian study that correlated serum levels of IGF-I and IGFBP-3 with Gleason score in surgical specimens.

Our data suggest that in clinically localized PCa, the quantification of PSA and, not of IGF-I, may provide independent significant information in the aggressiveness of PCa. IGFBP-3 could be a biochemical marker of disease control in PCa patients.

CONFLICT OF INTEREST

None declared.

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Continued administration of antithrombotic agents during transperineal prostate biopsy

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ABSTRACT

Purpose: To determine the safety of continued administration of antithrombotic agents during transperineal (TP) prostate biopsy.

Patients and Methods: A total of 811 men who underwent transrectal ultrasound (TRUS)-guided TP biopsy from January 2008 to June 2012 at our two institutions were retrospectively analyzed. Among these 811 men, 672 received no antithrombotic agents (group I), 103 received and continued administration of antithrombotic agents (group II), and 36 interrupted administration of antithrombotic agents (group III). Overall complications were graded and hemorrhagic complications were compared (group I with group II) using propensity score matching (PSM) analysis.

Results: An overall complication rate of 4.6% was recorded. Hemorrhagic complications occurred in 1.8% and they were virtually identical in all the three groups, and no severe hemorrhagic complications occurred. One patient in group III required intensive care unit admission for cerebral infarction. PSM analysis revealed no statistical difference between groups I and II with regard to the incidence of gross hematuria, perineal hematoma, and rectal bleeding. Multiple regression analysis revealed that hemorrhagic complications were associated with lower body mass index (<21 kg/m^2, P=0.0058), but not with administration of antithrombotic agents.

Conclusions: Continued administration of antithrombotic agents does not increase the risk of hemorrhagic complications; these agents are well tolerated during TP biopsy.

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INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and sixth leading cause of cancer-related death in men worldwide (1). Its incidence has increased substantially in recent years in many countries.

As a result of prolonged life span, the generation with a risk for prostate cancer coincides with that with a history of cardiovascular disease. Anticoagulant and/or antiplatelet agents (henceforth referred to as antithrombotic agents) are used for the prevention and treatment of thrombosis in patients with cardiovascular disease. Prostate cancer can be detected using a combination of digital rectal examination (DRE), serum prostate-specific antigen (PSA) concentration and magnetic resonance imaging (MRI). However, definitive diagnosis is only possible through a prostate needle biopsy. Therefore, antithrombotic agents are routinely discontinued before the procedure to avoid hemorrhagic complications (2, 3).

However, evidence has shown that discontinuation of antithrombotic agents can trigger serious

and potentially fatal embolic complications. The odds ratio for ischemic stroke after aspirin interruption was 3.4 in patients with a history of ischemic heart disease (4). Of 526 patients in whom warfarin treatment was interrupted before dental surgery, five suffered serious embolic complications, and four of these patients died (5). The new edition of the American College Chest Physicians' authoritative clinical practice guidelines for the prevention and treatment of venous thromboembolism suggested continuation of warfarin for minor dermatological procedures and cataract surgery. They also suggested that thromboprophylaxis with aspirin in patients with cardiovascular disease should not be interrupted prior to major or minor surgery (6).

To avoid thrombosis triggered by discontinuation of antithrombotic agents, transrectal (TR) prostate biopsy under continued antithrombotic agents has been attempted with minor increase of biopsy-related bleeding (7-14). Recently, introduction of transrectal ultrasound (TRUS)-guided transperineal (TP) biopsy led to evaluation of the TP route for biopsy purposes, which provides direct access to the peripheral apical region of the prostate, which is inaccessible via the TR route (15). However, the effect of interruption of antithrombotic agent administration before TP biopsy remains controversial. The primary goal of this study was to evaluate the safety of continued administration of antithrombotic agents during TP biopsy.

PATIENTS AND METHODS

Patients

After obtaining informed consent, 832 consecutive patients underwent TRUS-guided systematic TP biopsy to evaluate elevated PSA levels (>4ng/mL) and/or abnormal DRE findings at two Japanese institutions between July 2008 and August 2012. Patients with biochemical recurrence after prostatectomy (n=11) or radiation therapy (n=2), those with fewer than 5 cores obtained by biopsy because of high suspicion of prostate cancer (n=5), and those with simultaneous transurethral resection of bladder tumor and prostate biopsy (n=3) were excluded. Thus, 811 patients were eligible for inclusion in the present retrospective study. This study was approved by the institutional review boards of both institutions.

Table-1 lists the clinical variables examined in the three groups of patients, including age,

Table 1 - Clinical characteristics of all 811 patients and 84 pairs of patients after propensity score matching (PSM).

	All patients				Matched patients		
	Group I (n = 672)	Group II (n = 103)	Group III (n = 36)	*P*-value	Group I (n = 84)	Group II (n = 84)	*P*-value
Median (IQR)							
Age (years)	69 (63-74)	72 (67-77)	70 (64-74)	<0.0001	71 (64-76)	72 (66-77)	0.23
PSA (ng/mL)	7.5 (5.2-11.9)	8.4 (5.6-15.7)	9.7 (6.1-15.0)	0.043	7.9 (5.0-15.9)	7.6 (5.2-13.1)	0.82
Total Prostate volume (mL)	33 (25-49)	35 (26-47)	32.0 (22-51)	0.68	33 (26-51)	35 (25-46)	0.69
INR	1.00 (0.97-1.04)	1.03 (0.98-1.09)	1.02 (0.97-1.12)	<0.0001	1.01 (0.96-1.05)	1.02 (0.98-1.06)	0.13
Biopsy cores	14 (14-14)	14 (14-14)	14 (14-14)	0.74	14 (14-14)	14 (14-14)	0.96
IPSS	9 (4-16)	12 (8-16)	9 (5-15)	0.10	11 (6-18)	12 (7-17)	0.73
BMI (kg/m^2)	23.0 (21.2-24.7)	23.5 (21.6-25.1)	22.3 (21.7-24.2)	0.11	23.4 (21.7-25.1)	23.6 (21.7-25.3)	0.41
N (%)							
Local anesthesia	623 (92.7)	100 (97.1)	32 (88.9)	0.16	81 (96.4)	81 (96.4)	1.0
Abnormal DRE	123 (20.6)	29 (34.9)	10 (29.4)	0.0086	25 (29.8)	28 (33.3)	0.70

PSA level, total prostate volume, international normalized ratio (INR), biopsy cores, International Prostate Symptom Score (IPSS), body mass index (BMI), type of anesthesia, and DRE findings. The control group (group I) of 672 patients had never taken antithrombotic agents. Group II included patients who underwent TP biopsy while continuing antithrombotic therapy (n=103), including 78 patients on an antiplatelet agent (56 on aspirin, 1 on clopidogrel, and 21 on another agent), 15 on an anticoagulant (warfarin), seven on dual antiplatelet agents, and three on both the antiplatelet and anticoagulant (Table-2). Because the number of patients taking anticoagulant was too small to analyze, we combined those patients with the antiplatelet group, although these drugs have different mechanisms of action and produce a different biologic response. In group III (n=36), antithrombotic therapy was interrupted in accordance with a decision by the attending physician or at the patient's request. These agents were discontinued 7–10 days before TP biopsy and were resumed 1–2 days after completion of the procedure.

Biopsy protocol

A cleaning enema was administered before TP biopsy. For antimicrobial prophylaxis, levofloxacin (500mg) or tosufloxacin (300mg) was orally administered before the procedure. In general, the biopsy protocol included a standard systematic 14-core scheme, as described by Kawakami et al. (Figure-1) (15). When abnormal findings were observed during pre-biopsy MRI or TRUS, additional targeted biopsies were performed. With the patient in the lithotomy position, the prostate gland was imaged using an ultrasound machine (ALOKA SSD-2000, Aloka, Tokyo, Japan) equipped with a biplanar 5/7.5-MHz TR probe (ALOKA UST- 672), and TRUS-guided TP biopsy was performed using a disposable 18-gauge needle (C.R. Bard, Inc., Covington, GA, USA). TP biopsy was performed using local anesthesia consisting of 1% lidocaine (n=756) as described previously (16), spinal anesthesia (n=52), or general anesthesia (n=3). Biopsies were performed by experienced urologists (6 surgeons, mean experience of 17 years, range 6-32 years). After the procedure, the patients were hospitalized for 1 day to monitor and for treatment of any complications (i.e. acute urinary retention, hematuria or fever).

Table 2 - The detail of continuing anti-thrombotic agents.

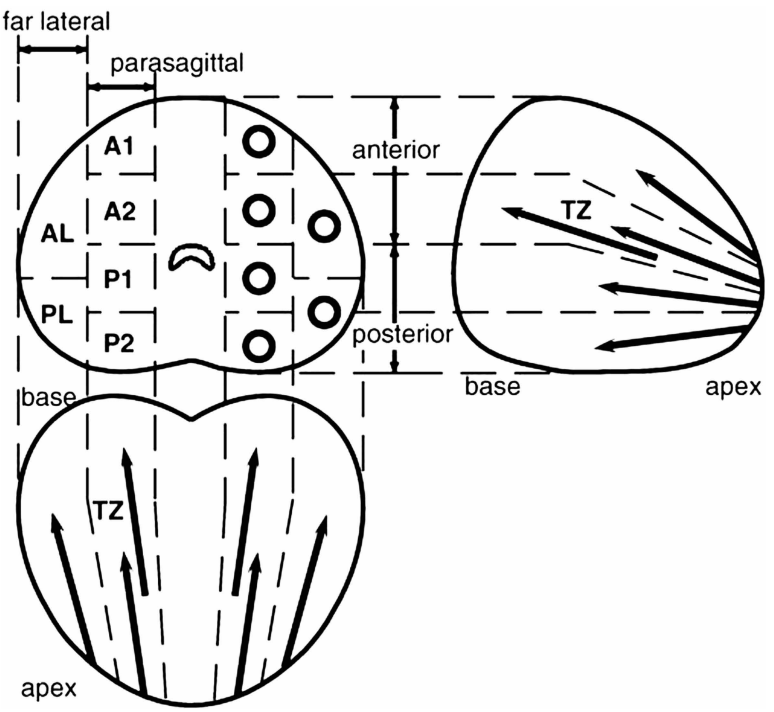
	No. of patients
Single agent	
Aspirin	56
Cilostazol	4
Clopidogrel	1
Ticlopidine	5
Warfarin	15
Others	12
Dual agents	
Aspirin and cilostazol	3
Aspirin and clopidogrel	3
Aspirin and ticlopidine	1
Aspirin and warfarin	2
Warfarin and cilostazol	1

Morbidity assessment

All patients were evaluated around 2 weeks after the TP biopsy at the first outpatient visit, during which they were asked about the incidence of bleeding-associated events and other complications. Bleeding-associated events included gross hematuria, perineal hematoma, and rectal bleeding. These events noticed at least once were included. Gross hematuria was defined as passing blood or red urine. Perineal hematoma was defined as a non-pulsatile mass >1.5cm in diameter diagnosed by visual examination and palpation of the perineum. Rectal bleeding was defined as the passage of bright blood on or in the stool due to needle penetration through the rectum. The incidence of hematospermia was not evaluated due to lack of data.

Overall complications were graded as follows: grade 1 (need for hospital admission without medication), grade 2 (need for any type of intervention including medication, catheterization or blood transfusion), or grade 3 (life-threatening complications resulting in intensive care unit management or death).

Figure 2 - 14-core scheme, as described by Kawakami et al.



Statistical analysis

Comparisons between the three groups were performed using the Mann-Whitney U test or Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Univariate logistic regression analysis was used to identify the individual clinical factors predictive of hemorrhagic complications.

Given the non-randomized nature of the study, we used propensity score matching (PSM) analysis to compare hemorrhagic events and complications between groups I and II for determining the risk of continuing antithrombotic agents during TP biopsy. Group III was excluded from the analysis as it was difficult to precisely assess the relationship between resumption of antithrombotic agents and hemorrhagic complications. PSM was applied to correct for potential selection bias and to adjust for differences in baseline clinical characteristics. To derive the propensity score in this study, patient characteristics were entered into a logistic regression model. We used the greedy nearest-neighbor matching method within a caliper of 0.2 of the standard deviation (17, 18). Matching factors included age, BMI, DRE findings, PSA level, total prostate volume, INR, IPSS, and type of anesthesia.

Statistical analyses were performed using JMP 9.0.2 (SAS Institute Inc., Cary, NC, USA) and the R 2.15.2. statistical system (R Foundation for Statistical Computing, Vienna, Austria). All P-values <0.05 was considered statistically significant.

RESULTS

Histological examination revealed the presence of prostate cancer in 383 patients (47.2%). Of 383 patients, the biopsy Gleason score was 5-6 in 61 (16.4%) patients, 7 in 181 (48.5%) patients, and 8-10 in 131 (35.1%) patients. Table-1 lists the characteristics of controls, patients continuing antithrombotic agents, and the interrupted anti-

thrombotic agents groups before and after PSM. The matching analysis resulted in 84 well-matched pairs of group I and II patients. There were no significant differences in the clinical variables among the 811 patients in the three groups, except for age, PSA level, INR, and DRE findings. In group II, higher age, longer INR, and more frequent abnormal DRE findings were observed.

Table-3 showed the incidence of complications among the three groups. Of the 811 patients included in this study, complications occurred in 37 patients (4.6%). Grade 1, 2, and 3 complications occurred in 12 (1.4%), 24 (2.9%), and one (0.1%) patients, respectively. The most frequent biopsy-related complication was urinary retention (1.2%). Although hemorrhagic complications occurred in 15 (1.8%) patients, many were grade 1 (73.3%) and no grade 3 complications occurred. One patient in group III whose aspirin treatment was interrupted 7 days before TP biopsy, was transferred to the emergency department 10 days after the procedure. The patient was diagnosed with cerebral infarction requiring intensive care unit treatment.

Table-4 showed the incidence of gross hematuria, perineal hematoma, and rectal bleeding of 168 matched patients compared with group I and group II. PSM analysis revealed that there were no significant differences in the incidence of all events between groups I and II. The incidence of hemorrhagic complications was similar in group I (2/84 patients) and group II (3/84 patients) after PSM.

Table 3 - Incidence of complications among the three groups.

Complications	Group I (n = 672)			Group II (n = 103)			Group III (n = 36)			total
	Complication grade									
	G1	G2	G3	G1	G2	G3	G1	G2	G3	
Urinary retention		9			1					10
Acute prostatitis		5			1					6
Perineal pain		3								3
Ischemic colitis		1								1
Vasovagal reflex	1									1
Cerebral infarction									1	1
Hemorrhagic complication										
Hematuria	4			2			1			7
Colt retention		2			1					3
Perineal hematoma	3	1		1						5

Table 4 - Incidence of bleeding associated events after PSM.

	Group I (n = 84)	Group II (n = 84)	P-value
Gross hematuria	39 (46.4)	38 (45.2)	0.88
Perineal hematoma	0 (0)	2 (6.1)	0.15
Rectal bleeding	0 (0)	0 (0)	1.0

Lastly, we evaluated the predictive factors for hemorrhagic complications in the 811 patients (Table-5). Univariate analysis revealed that hemorrhagic complications were significantly associated with a BMI <21kg/m^2 (P=0.0058).

COMMENTS

We conducted a retrospective study including 811 patients in whom TRUS-guided TP biopsy was performed with or without continuation of antithrombotic agents during the procedure. Our study demonstrated that antithrombotic agents did not increase the frequency of bleeding-associated events or the risk of hemorrhagic complications during TP biopsy.

An extended life span is accompanied by an increase in the incidence of prostate cancer among elderly patients with a history of cardiovascular disease. Antithrombotic agents are routinely administered to these patients to prevent thromboembolism. Until recently, antithrombotic agents were routinely interrupted before diagnostic prostate biopsy to avoid hemorrhagic complications; however, thromboembolism triggered by discontinuation of antithrombotic agents may have life-threatening consequences. Of 36 patients in whom treatment with antithrombotic agents was interrupted in this study, cerebral infarction occurred in one, who required treatment in the intensive care unit. Life-threatening risk of drug interruption-associated thromboembolism may prompt clinicians to not discontinue antithrombotic agents prior to prostate biopsy; however, the risk of drug continuation in relation to biopsy-related hemorrhagic complication remains to be determined.

The TP route has been less often employed than TR route because it appears more invasive than TR biopsy (19, 20). Recently, the introduction of TRUS-guided extended TP biopsy increased the use of the TP route because of its much lower risk of infection, rectal bleeding and potential for improved sampling from the anterior portion of the prostate, which may not be accessible via the TR route (21, 22). Although perineal hematoma is a TP biopsy-specific complication, severe cases requiring blood transfusion or endoscopic intervention have not been reported. The absence of a free cavity between the prostate and perineum may be associated with a low hemorrhagic risk after TP biopsy.

Table 5 - Univariate logistic regression analysis for predicting the risk of hemorrhagic complications.

Variable	Odds ratio (95% CI)	P-value
Age, years (≥70 vs <70)	1.48 (0.51-4.52)	0.47
PSA (≥10 ng/mL vs. <10 ng/mL)	0.48 (0.11-1.52)	0.23
Total prostate volume (≥30mL vs. <30mL)	1.74 (0.59-6.31)	0.35
INR (≥1.04 vs. <1.04)	2.72 (0.97-7.85)	0.058
Biopsy cores (≥15 vs. <15)	N/A†	0.37
IPSS (≥9 vs. <9)	0.23 (0.01-1.44)	0.18
BMI (<21 kg/m^2 vs. ≥21 kg/m^2)	4.52 (1.55-13.89)	0.0058
Local anesthesia (local vs. others)	1.04 (0.20-18.99)	0.97
Abnormal DRE	0.73 (0.24-2.68)	0.60
Continuing anti-thrombotic agent (yes vs no)	2.56 (0.70-7.65)	0.11

†N/A, not applicable.

In the present study, hemorrhagic complications occurred in 1.8% of patients and most were self-remitting. According to the PSM analysis, no statistically significant difference was found in the incidence of gross hematuria, perineal hematoma, and rectal bleeding between controls (group I) and patients who continued antithrombotic agents (group II). Univariate analysis revealed that hemorrhagic complications were not associated with antithrombotic agents. These data indicate that hemorrhagic complications are rare after TP biopsy. Continued administration of antithrombotic agents does not increase the risk of hemorrhagic events or complications.

Our findings are consistent, in part, with the findings of Kariotis et al. (11), which indicated that younger patients with lower BMI receiving aspirin were at higher risk of developing hematuria after TR biopsy. It was assumed that patients with lower BMI were more sensitive to aspirin than obese patients (23). In this study, lower BMI ($<21 kg/m^2$) was associated with hemorrhagic complications in all patients. This result suggests that patients with low BMI require careful attention and monitoring after TP biopsy.

This study has several limitations. First, this is a retrospective study, and although we utilized PSM analysis, this does not replace randomization. Second, the sample size after PSM reduced. Among 103 patients with continued antithrombotic agents, only 84 were eligible for evaluation of the incidence of bleeding-associated events and hemorrhagic complications. A major weakness of PSM is the reduction in the number of participants to avoid poor matching pairs. Third, patient complications were not followed up for >2 weeks after the biopsy; thus, the possibility of late-onset complications cannot be ruled out.

CONCLUSIONS

Continued administration of antithrombotic agents does not increase the risk of hemorrhagic complications. It is not necessary to discontinue antithrombotic agents during TP biopsy. Further multicenter prospective randomized controlled trials are needed to validate the safety of continuing antithrombotic treatment.

ABBREVIATIONS

BMI = body mass index
DRE = rectal examination
INR = international normalized ratio
IPSS = International Prostate Symptom Score
MRI = magnetic resonance imaging
PSA = serum prostate-specific antigen
PSM = propensity score matching
TP = transperineal
TR = transrectal
TRUS = transperineal ultrasound

CONFLICT OF INTEREST

None declared.

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Preoperative prostate biopsy and multiparametric magnetic resonance imaging: reliability in detecting prostate cancer

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ABSTRACT

Purpose: The aim of the study was to analyse and compare the ability of multiparametric magnetic resonance imaging (mp–MRI) and prostate biopsy (PB) to correctly identify tumor foci in patients undergoing radical prostatectomy (RP) for prostate cancer (PCa).

Materials and Methods: 157 patients with clinically localised PCa with a PSA <10 ng/mL and a negative DRE diagnosed on the first (12 samples, Group A) or second (18 samples, Group B) PB were enrolled at our institution. All patients underwent mp-MRI with T2-weighted images, diffusion-weighted imaging, dynamic contrast enhanced--MRI prior to RP. A map of comparison describing each positive biopsy sample was created for each patient, with each tumor focus shown on the MRI and each lesion present on the definitive histological examination in order to compare tumor detection and location. The sensitivity of mp-MRI and PB for diagnosis was compared using Student's t-test. The ability of the two exams to detect the prevalence of Gleason pattern 4 in the identified lesions was compared using a chi-square test.

Results: Overall sensitivity of PB and mp-MRI to identify tumor lesion was 59.4% and 78.9%, respectively (p<0.0001). PB missed 144/355 lesions, 59 of which (16.6%) were significant. mp-MRI missed 75/355 lesions, 12 of which (3.4%) were significant. No lesions with a GS≥8 were missed. Sensitivity of PB and mp-MRI to detect the prevalence of Gleason pattern 4 was 88.2% and 97.4%, respectively.

Conclusions: mp-MRI seems to identify more tumor lesions than PB and to provide more information concerning tumor characteristics.

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INTRODUCTION

In recent decades, an increase in prostate cancer (PCa) diagnosis occurred because of the introduction of PSA into clinical practice and an increase in the number of biopsy samples, leading to an increase in cases with low-grade disease on prostate biopsy (PB) and a pathological migration towards earlier stage tumors (1).

After the diagnosis of PCa, some factors have a negative prognostic value, such as tumor volume (TV) and Gleason Score (GS). The current definition of clinically significant disease is PCa with a TV≥0.5 mL and/or a pathologic GS >6 (2, 3). To predict a significant PCa prior to surgery, urologists use parameters such as the PSA value, digital rectal examination (DRE), and PB results (bioptic GS, number of positive samples

and percentage of biopsy cores positive for PCa), separately or in combination in nomograms (4). Despite the use of these tools, tumor size and aggressiveness are often underestimated (5). Recently, some authors have emphasised the role of multiparametric magnetic resonance imaging (mp-MRI) in PCa diagnosis, taking advantage of the anatomical, morphological and functional information that it provides (6-8).

The aim of this prospective study was to analyse the ability of mp-MRI to correctly identify tumor foci in patients undergoing radical prostatectomy (RP) for PCa with a PSA <10 ng/mL and a negative DRE and to compare it with the results of PB. The secondary aims were to identify significant or insignificant lesions and to compare the ability of these results dividing our population in terms of diagnosis at first or second PB.

MATERIALS AND METHODS

Population

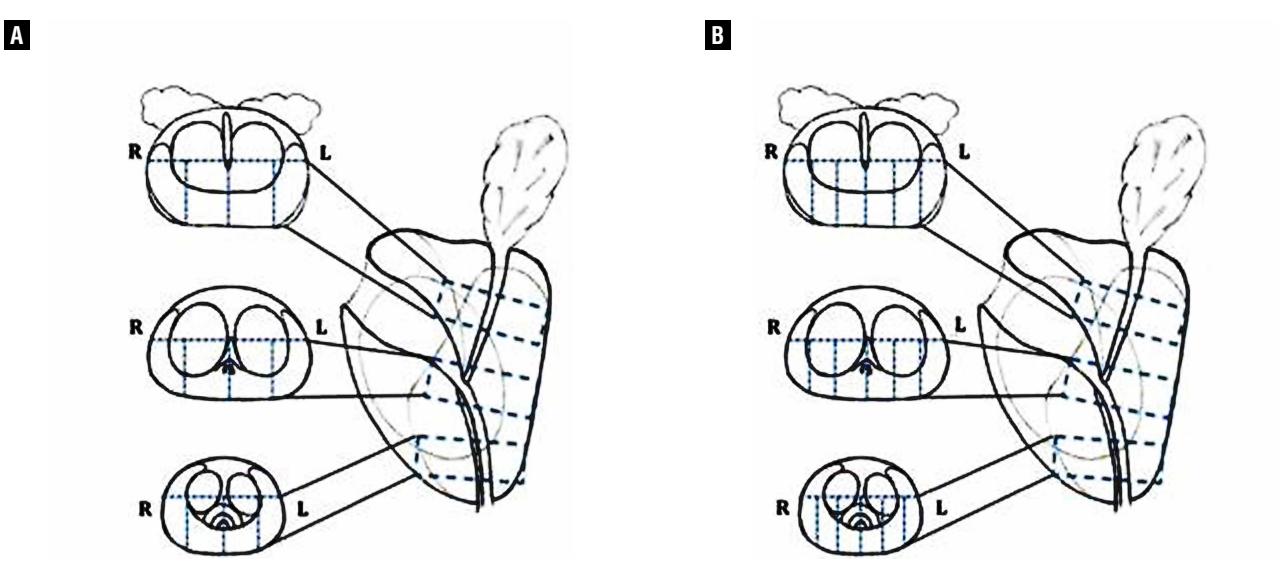
The study lasted between September 2010 and November 2012, and it was approved by the ethical committee of our institution, San Luigi Hospital in Orbassano (Turin), Italy. During this period, 178 consecutive patients with PCa diagnosed on the first or second PB who underwent mp-MRI prior to RP, as a part of preoperative evaluation, were enrolled at our institution.

For the purposes of the study, only patients with clinically localised PCa with a PSA <10 ng/mL and a negative DRE were included. The exclusion criteria involved: any previous prostate treatment (TURP, 12 patients; hormonal therapy, 4 patients); contraindications for mp-MRI (i.e., claustrophobia, presence of magnetically activated implanted devices, metallic implants in sensitive areas; 5 patients). The patients were divided into two groups: Group A, patients diagnosed at the first biopsy; and Group B, patients diagnosed at the second biopsy.

Prostate biopsy

All biopsies were performed at our institution with a transrectal approach under TRUS guidance. First biopsies consisted of 12 samples (Group A) while second biopsies consisted of 18 samples (Group B). Second biopsies were performed in cases of an initial negative PB and persistently elevated PSA, according to a systematic template. A modification of the European Consensus Meeting on the prostate MRI template (9) was used for this purpose (Figure-1).

Figure 1 - Prostate reporting scheme for first (A) and second (B) prostate biopsy with transrectal approach. Prostate gland is divided into 12 (A) or 18 (B) sectors.



mp-MRI

All patients underwent preoperative mp-MRI in the Department of Radiology of I.R.C.C. in Candiolo, using a 1.5 Tesla unit (Signa HDX, General Electric, Milwaukee, USA), with a 4-channel phased-array body coil and an endorectal coil filled with 50 mL of air for signal reception, after intramuscular injection of 20 mg butylscopolamine bromide. All patients underwent mp-MRI at least 6 weeks after PB, to reduce artefacts due to bleeding or inflammation. All mp-MRI examinations were performed according to the same protocol, using the following sequences: a panoramic T1-weighted sequence from the aortic bifurcation to the symphysis pubis for the evaluation of iliac and obturator lymphadenopathies; T2-weighted images (slice-thickness 3 mm, FOV 16 x 16 cm, NEX 2) and T1 fast spin-echo axial images (slice-thickness 3 mm, TR/TE 580/min, FOV 16 x 16 cm, matrix 320 x 256, NEX 2) were used to study prostate and seminal vesicles in axial (TR/TE 3020/85), coronal (TR/TE 3620/90) and sagittal (TR/TE 3960/110) planes. Three sequences were obtained on Diffusion-Weighted Imaging (DWI), with axial EPI sequences (slice-thickness 3 mm, TR/TE 7000/min., FOV 16x16 cm, matrix 128x128, NEX 6) with b-values of 0.600 s/mm^2, 0.1000 s/mm^2 and 0.1400 s/mm^2. Dynamic Contrast Enhanced MRI (DCE-MRI) was performed using axial FSPGR sequences with a temporal resolution of 13s, repeated for 26 times (TR/TE ~3.5/min., FOV 20x20 cm, matrix 224x192, NEX 0.5). The contrast agent (gadobutrol, Gadovist, Bayer Pharma AG, Berlin) was administered intravenously at an injection rate of 2 mL/s, followed by saline solution flush at the same rate using a power injector (Spectris, Medrad). The entire prostate was sectioned to achieve 3 mm-thick parasagittal sections. All MRI images were interpreted by the same expert uroradiologist. Positivity for neoplastic tissue was defined by the following: hypointensity in T2-weighted (T2w) images; an Apparent Diffusion Coefficient (ADC) value ≤1.05 mm^2/s with a b-value of 1000 s/mm^2 in DWI examination; an enhancing area with early intense contrast uptake followed by washout in DCE-MRI. Overall, the mp-MRI finding was considered positive if at least two of the three MRI sequences (T2w, DWI and DCE-MRI) produced suspicious findings. The presence, side and location of PCa were analysed, and for every lesion, the radiological stage, ADC and pharmacokinetic parameters were analysed using DCE-MRI. For the purpose of the study, very low ADC values were considered as an index of Gleason pattern 4 prevalence, based on the previously reported correlation between ADC and GS (10).

RP

All patients underwent robot-assisted RP at our institution.

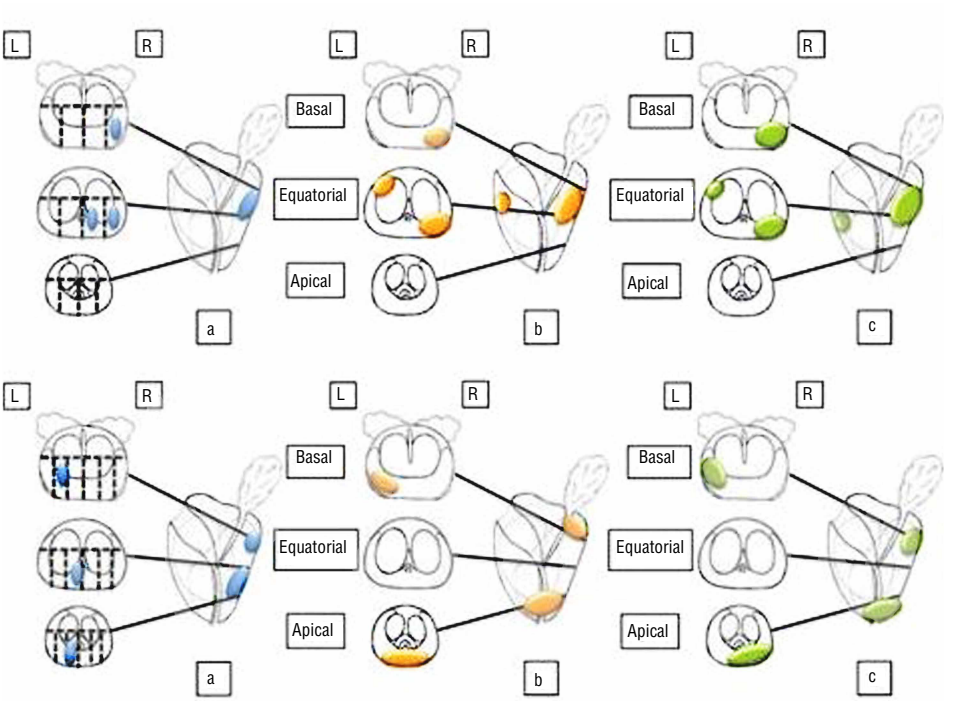
Pathologic analysis

All RP specimens were uniformly processed and submitted in their entirety for histological investigation according to the protocol of Montironi et al. (11). The entire prostate surface was treated with black ink, and the seminal vesicles and the apical and basal portions of the gland were removed to create two 4 mm sections. From the remaining gland, 4 mm-thick parasagittal sections were obtained and were further sectioned to achieve 3 mm slices (analogous to slices obtained with MRI), which were then stained with haematoxylin-eosin. Tumors were staged according to the TNM classification system, and the grading was evaluated according to the Gleason Score (12). The volume of each tumor was measured using the ellipsoid formula (length x width x height x 0.52) in mL. The pathologic analysis was conducted by the same uropathologist who was blinded to the MRI results. The following variables were analysed: tumor location, TV, and pathologic GS (pGS).

Map of comparison

A dedicated operator, blinded to patient names, noted the location of positive biopsy samples according to the European Consensus Meeting on prostate MRI (9) on a specific form. The same procedure was performed by the radiologist for the MRI report and by the pathologist for the pathology report. A map describing each positive biopsy sample was created for each patient, with each tumor focus shown on the MRI and each lesion present on the definitive histological examination (Figure-2).

Figure 2 - Example of two comparison maps between biopsy (a, a'), mp-MRI (b, b') and pathological examination (c, c'). The first case (1) was a naive patient with 12 PB samples (a), with a diagnosis of PCa in 3/12 samples on the right lobe (equatorial, equatorial lateral, basal lateral); mp-MRI (b) highlighted two areas that were suspicious for cancer: the posterolateral equatorial right with extension to the base (diameter 8x5 mm) and the anterolateral equatorial left (diameter 4x5 mm); a histological examination of the surgical specimen (c) demonstrated two tumor foci: a right posterolateral lesion on the basal plane extending to the equatorial plane (vol. 0.75 mL) and a left anterolateral lesion on the equatorial plane (vol. 0.3 mL). The second case (2) was a patient with persistently elevated PSA from whom 18 samples were collected during a second PB (a'). A diagnosis of PCa was made in 3/12 samples from the left lobe (equatorial lateral, basal median, apical median); mp-MRI (b') highlighted two suspicious areas: the posterolateral left on the basal plane (diameter 6x4 mm) and the apical posterior (diameter 14x6 mm); a histological examination of the specimens (c') demonstrated two tumor foci: a left posterolateral lesion on the basal plane (vol. 0.45 mL) and a right posterolateral apical lesion extending to the contralateral lobe (vol. 1.25 mL).



Statistical analysis

Using the tumor map obtained by the pathologic analysis as the standard reference, the overlap of the biopsy samples and mp-MRI was evaluated. Lesions were divided into groups according to the TV (<0.5 and ≥0.5 mL), the tumor location (basal, equatorial and apical) and the pGS (≤6, 7a – 3+4, 7b – 4+3, ≥8). The sensitivity of mp-MRI and PB for diagnosis was compared using Student's t-test in the overall population and in Groups A and B. Finally, the ability of the two exams to detect the prevalence of Gleason pattern 4 in the identified lesions was recorded and compared using a chi-square test. All statistical tests were performed using Statistic 7 software (Statsoft, Tulsa, Oklahoma) and p-values <0.05 were considered as statistically significant.

RESULTS

The overall population consisted of 157 patients: group A consisted of 113 patients diagnosed at the first prostate mapping, while group B

consisted of 44 patients diagnosed at the second prostate mapping. The baseline characteristics are detailed in Table-1.

The pathologic analysis identified 355 neoplastic lesions, 140 (39.4%) with a TV <0.5 mL and 215 (60.6%) with a TV ≥0.5 mL. The mean TV was 2.21±2.5 mL (median 1.55 mL; range 0.04-15.3 mL). According to the pGS, 150 (42.3%) lesions had a GS ≤6, 148 (41.7%) GS=7a (3+4), 31 (9%) GS=7b (4+3) and 26 (7%) a GS≥8. Tumor location was also analysed; 118 (33.2%) lesions were basal, 121 (34.1%) were equatorial, and 116 (32.7%) were apical.

Overall, MRI identified tumor lesions thanks to three sequences that produced suspicious findings (T2w, DWI and DCE-MRI) in 69 cases and thanks to two sequences in 211. In 36 cases, only one sequence (T2w or DWI or DCE-MRI) produced suspicious finding, so the lesion was not classified as tumour (see Materials and Methods section - mp MRI).

The sensitivities of PB and mp-MRI for identifying tumor foci, stratified by TV, tumor location and pGS, in the overall population and in the two subgroups are presented in Tables 2 and 3.

PB missed 144/355 lesions, 59 of which (40.9%) were significant: 11 with a TV ≥0.5 mL, 25 with a pGS=7 and 23 with both a TV ≥0.5 mL and a pGS=7. No statistically significant differences in the number of missed significant lesions were recorded between Groups A and B.

mp-MRI missed 75/355 lesions, 12 of which (16%) were significant: four with a TV ≥0.5 mL, six with a pGS=7 and two with both a TV ≥0.5 mL and a pGS=7. No lesions with a GS ≥8 were missed by both mp-MRI and PB.

Compared to PB, in the overall population and in Groups A and B, mp-MRI demonstrated a higher sensitivity, reaching statistical significance in most of stratifications. The results are detailed in Table-4.

The abilities of mp-MRI and PB to detect the prevalence of Gleason pattern 4 are shown in Table-5.

PB showed an accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 87.2%, 88.2%, 81.8%, 96.3%, and 56.3%, respectively, while mp-MRI showed values of 97.5%, 97.4%, 98.0%, 99.6%, and 89.3%, respectively. Pearson's correlation coefficients were 0.6067 and 0.9207 for PB and mp-MRI, respectively.

DISCUSSION

After a diagnosis of localised PCa eligible for RP, the current standard of pre-operative evaluation is based on data from biopsies of the entire

Table 1 - Baseline characteristics. Group A= first biopsy (12 samples); Group B= second biopsy (18 samples); SD= standard deviation.

	Overall population	Group A	Group B	p-value
Number of patients	157	113	44	/
Age, mean (SD), years	63.1±6.2	63.2±6	63.1±6.8	NS
PSA, mean (SD), ng/mL	5.87±2.1	5.91±2	5.73±2.2	NS
Number of positive biopsy samples, median (range)	3 (1-12)	3 (1-8)	3 (1-12)	NS
% pathological tissue, median (range)	13.5 (0.1-87)	12.5 (0.1-80)	14 (0.5-87)	NS
Bioptic Gleason Score, rate (number of patients)				
≤6	51.6%(81)	54.9%(62)	43.2%(19)	NS
7a	37.6%(59)	36.3%(41)	40.9%(18)	NS
7b	5.1%(8)	2.6%(3)	11.4%(5)	NS
≥8	5.8%(9)	6.2%(7)	4.5%(2)	NS

Table 2 - Neoplastic lesions identified by prostate biopsy. Group A= first biopsy (12 samples); Group B= second biopsy (18 samples).

		Prostate Biopsy			
		Identified overall	Identified Group A	Identified Group B	p-value
Pathologic Tumor Volume	<0.5 mL	21.4% (30/140)	20.8% (21/101)	23.1% (9/39)	NS
	≥0.5 mL	84.2% (181/215)	81.5% (123/151)	90.6% (58/64)	NS
Pathologic Tumor Location	Basal	54.2% (64/118)	51.2% (43/84)	61.8% (21/34)	NS
	Equatorial	61.2% (74/121)	58.8% (50/85)	66.7% (24/36)	NS
	Apical	62.9% (73/116)	61.4% (51/83)	66.7% (22/33)	NS
Pathologic Gleason Score	≤6	36.0% (54/150)	33.7% (36/107)	41.9% (18/43)	NS
	7a	73.0% (108/148)	71.7% (76/106)	76.2% (32/42)	NS
	7b	74.2% (23/31)	70.8% (17/24)	85.7% (6/7)	NS
	≥8	100% (26/26)	100% (15/15)	100% (11/11)	NS
Total		**59.4% (211/355)**	**57.1% (144/252)**	**65% (67/103)**	**NS**

Table 3 - Neoplastic lesions identified by mp-MRI. Group A= first biopsy (12 samples); Group B= second biopsy (18 samples).

		mp-MRI			
		Identified overall	Identified Group A	Identified Group B	p-value
Pathologic Tumor Volume	<0.5 mL	50.7% (71/140)	49.5% (50/101)	53.9% (21/39)	NS
	≥0.5 mL	97.2% (209/215)	96.7%(146/151)	98.4% (63/64)	NS
Pathologic Tumor Location	Basal	71.2% (84/118)	71.4%(60/84)	70.6% (24/34)	NS
	Equatorial	84.3% (102/121)	83.5% (71/85)	86.1% (31/36)	NS
	Apical	81.0% (94/116)	77.4% (65/83)	87.9% (29/33)	NS
Pathologic Gleason Score	≤6	55.3% (83/150)	53.3% (57/107)	60.5% (26/43)	NS
	7a	95.2% (141/148)	95.3%(101/106)	95.2%(40/42)	NS
	7b	96.8% (30/31)	95.8%(23/24)	100%(7/7)	NS
	≥8	100% (26/26)	100% (15/15)	100% (11/11)	NS
Total		**78.9% (280/355)**	**77.8% (196/252)**	**81.6% (84/103)**	**NS**

prostate gland under TRUS guidance. Thus, in men diagnosed with low-risk PCa, we observed an underestimation of the tumor grade in up to 30% of cases and the tumor burden in up to 50% of cases that was related to the biopsy technique, and it affected both the first and repeat biopsies (5). mp-MRI is the imaging technique that provides the best results for the diagnosis of significant PCa with high sensitivity and specificity values (7). Moreover, the use of an endorectal coil may

Table 4 - Comparison between sensitivity of prostate biopsy and mp-MRI in identifying tumor lesions. Results are reported by studied variables in the overall population and in Group A (first prostate biopsy) and B (second prostate biopsy).

		Sensitivity	PB	mp-MRI	p-value
Total		Overall	59.4%	78.9%	<0.0001
		Group A	57.1%	77.8%	<0.0001
		Group B	65.0%	81.6%	0.0112
Pathologic Tumor Volume	<0.5 mL	Overall	21.4%	50.7%	<0.0001
		Group A	20.8%	49.5%	<0.0001
		Group B	23.1%	53.9%	<0.0001
	>0.5 mL	Overall	84.2%	97.2%	<0.0001
		Group A	81.5%	96.7%	<0.0001
		Group B	90.6%	98.4%	0.0316
Pathologic Tumor Location	Basal	Overall	54.2%	71.2%	0.01
		Group A	51.2%	71.4%	0.0114
		Group B	61.8%	70.6%	NS
	Equatorial	Overall	61.2%	84.3%	0.0001
		Group A	58.8%	83.5%	0.0007
		Group B	66.7%	86.1%	NS
	Apical	Overall	62.9%	81.0%	0.0035
		Group A	61.4%	77.4%	0.0386
		Group B	66.7%	87.9%	NS
Pathologic Gleason Score	≤6	Overall	36.0%	55.3%	0.0012
		Group A	33.7%	53.3%	0.0059
		Group B	41.9%	60.5%	NS
	7a	Overall	73.0%	95.2%	< 0.0001
		Group A	71.7%	95.3%	< 0.0001
		Group B	76.2%	95.2%	0.0296
	7b	Overall	74.2%	96.8%	0.0291
		Group A	70.8%	95.8%	NS
		Group B	85.7%	100%	NS
	≥8	Overall	100%	100%	NS
		Group A	100%	100%	NS
		Group B	100%	100%	NS

Table 5 - Comparison among PB and mp-MRI in predicting the prevalence of Gleason pattern 4 on histopathological analysis. The prevalence of pattern 4 is evaluated on histology and biopsy with the Gleason Score ≥7b (pGS and bGS, respectively) while is predicted in mp-MRI by a very low value of the ADC on DWI. Gleason pattern 4 not prevalent is defined by Gleason Score ≤7a. The rate (number) of identified patients are shown. In the lower part of the table the Pearson correlation coefficient, both for biopsy and mp-MRI, is indicated.

		PB		mp-MRI	
		Pattern 4 prevalent	Pattern 4 not prevalent	Pattern 4 prevalent	Pattern 4 not prevalent
Histology (standard reference)	Pattern 4 prevalent	56.2% (27/48)	43.8% (21/48)	89.3% (50/56)	10.7% (6/56)
	Pattern 4 not prevalent	3.7% (6/163)	96.3% (157/163)	0.4% (1/224)	99.6% (223/224)
Pearson's correlation coefficient		**0.6067**		**0.9207**	

allow a more accurate detection rate by improving the spatial characterisation of the prostate zonal anatomy and molecular changes (13). Actually, mp-MRI is also gaining an important role because of the possibility that it offers in performing cognitive (14) or visually guided targeted PB (15-17).
In this study, compared to transrectal biopsy, mp-MRI demonstrated a significantly greater sensitivity in the entire study population (78.9% vs. 59.4%, p<0.001) and in each subgroup (TV, tumor location and pGS). Moreover, mp-MRI diagnosed the vast majority of significant lesions regarding TV (97.2% in PCa with TV ≥0.5 mL) and pGS (>95% in PCa with pGS ≥7). Although mp-MRI had a sensitivity that was statistically higher than biopsy, both had low sensitivity for detecting small lesions (TV <0.5 mL). The same results were observed when the population was divided into patients diagnosed at the first PB (Group A) or the second PB (Group B).
Despite these differences between mp-MRI and PB, it is extremely important to identify the characteristics of the missed lesions and determine whether these characteristics are actually significant.

In our study, only 12 of the 75 lesions (16%) missed by mp-MRI were significant PCas (with a TV ≥0.5 mL and/or a GS ≥7), representing 3.4% (12/355) of all identified lesions. Conversely, PB missed 144 lesions of which 40% (59/144) were significant (16.6% of all identified lesions). Interestingly, all lesions with a GS ≥8 were diagnosed by both mp-MRI and PB.

A change in GS from the PB to the resected specimen was recently reported in approximately 23-35% of cases (18). Functional imaging techniques provide information not just about tumor location and volume but also about cancer behaviour (8): less differentiated and dense cancers are associated with lower ADC values, better contrast and a higher detection rate using DWI (19, 20). Additionally, cancer foci show lower ADC values than normal prostate tissue, and these values correlate with GS (10, 21). Nevertheless, ADC values may vary depending on the technical parameters used (10). In our study, we analysed the ability of mp-MRI to identify the prevalence of the pathologic Gleason pattern 4 and observed a strong correlation (Pearson 0.9207) between Gleason pattern 4 and very low ADC values on DWI, while a good correlation was obtained using the biopsy GS (Pearson 0.6067).

Focusing on clinically not significant disease, mp-MRI correctly identified 50% of tumor lesions with a TV <0.5 mL and 55% of PCa with a GS ≤6. In our opinion, on the basis of these results, mp-MRI may be a valid diagnostic tool not only before the surgery but also in the follow up of patients included in active surveillance protocols for PCa.

The technical parameters of mp-MRI used in this study correspond to the minimal imaging requirements outlined in the recommendations of the European Consensus Meeting on prostate MRI

(9), particularly concerning the use of an endorectal coil (considered an optimal requirement).

This study was limited by the inclusion of only a single expert uroradiologist who interpreted all the mp-MRI images, which may affect the reproducibility of our results in centres without a radiologic team specialised in prostate mp-MRI. On the other hand, including only one uroradiologist minimises sources of potential bias because patients were treated and followed at the same department.

CONCLUSIONS

Our study suggested that mp-MRI allows for higher identification rate of tumor lesions than PB. Moreover, compared to significant PCa diagnosed at either the first or second biopsy, mp--MRI provides more information concerning tumor anatomy (tumor volume and location) and aggressiveness (prevalence of Gleason pattern 4). In patients with PCa with PSA <10 ng/mL and negative DRE, the data provided by mp-MRI may be useful for better therapeutic planning.

ABBREVIATIONS

PCa = prostate cancer
PB = prostate biopsy
TV = tumor volume
GS = Gleason Score
DRE = digital rectal examination
mp-MRI = multiparametric Magnetic Resonance Imaging
RP = radical prostatectomy
DWI = Diffusion-Weighted Imaging
DCE = Dynamic Contrast Enhancement
ADC = Apparent Diffusion Coefficient

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Concurrent stone stabilization improves ultrasonic and pneumatic efficacy during cystolithopaxy: an in vitro analysis

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ABSTRACT

Objective: To identify whether stabilization of larger bladder stones would improve the efficacy of combination (ultrasonic/pneumatic) lithotripsy in a phantom bladder stone model for percutaneous cystolithopaxy.

Materials and Methods: Using 1cm phantom Bego stones, a spherical model bladder was used to simulate percutaneous bladder access. A UroNet (US Endoscopy, USA) was placed alongside a Swiss Lithoclast probe through the working channel of a Storz 26Fr rigid nephroscope. Using a 30Fr working sheath, the stone was captured, and fragmented for 60seconds.

Resulting fragments and irrigation were filtered through a 1mm strainer, and recorded. Five trials were performed with and without the UN. Durability was then assessed by measuring net defects, and residual grasp strength of each instrument. Descriptive statistics (mean, standard deviations) were used to summarize the data, and Student's t-tests (alpha<0.05) were used to compare trials.

Results: The mean time to stone capture was 12s (8-45s). After fragmentation with UN stabilization, there were significant improvements in the amount of residual stone (22% dry weight reduction vs 8.1% without UN, p<0.001), number of fragments (17.5 vs 5.0 frag/stone, p=0.0029), and fragment size (3.6mm vs. 7.05 mm, p=0.035). Mesh defects were noted in all nets, ranging from 2-14 mm, though all but one net retained their original grip strength (36.8N).

Conclusions: Bladder stone stabilization improved fragmentation when used in conjunction with ultrasonic/pneumatic lithotripsy. However, due to limitations in maneuverability and durability of the UN, other tools need to identified for this indication.

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Urinary Bladder Calculi; Lithotripsy; Urinary

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INTRODUCTION

Bladder stones account for 5% of urolithiasis in industrialized countries. They are most commonly associated with urinary stasis caused by bladder outlet obstruction (1). Endoscopic management of bladder stones utilizes similar equipment and techniques as kidney stones, however poses several unique challenges.

Endoscopic lithotripsy may be performed by a transurethral or percutaneous suprapubic approach using regular nephroscopy equipment. By creating a 1cm skin incision, the percutaneous Seldinger technique for bladder access remains pre-peritoneal and does not require a formal open cystotomy. Using a sheath, fragmentation may be performed using any lithotripter through a nephroscope. The challenges shared by each lithotripter is

localization and stabilization for fragmentation and retrieval.

The stakes for complete stone clearance are high; retained fragments (especially in BOO) are a risk for future stones, acute urinary obstruction, and persistent lower urinary tract symptoms. This technique has been used safely in adults, pediatrics, and in native, augmented, and neo-bladders (2-6). The obstructive process inciting stone formation can also lead to bladder distention, diverticula formation, and chronically infected and inflamed mucosa.

Conduits, neobladders, and augmentation cystoplasties possess multiple folds, debris, mucus, foreign bodies (i.e. extruded clips and sutures). These not only increase the risk of bladder stones up to 40% in patients at two years (7), but can increase the surgical time due to stone localization, fragmentation, and retrieval. Theoretically the risk of endoscopic bladder stones management in enteric augments/conduits is increased (compared to native bladders) due to the lack of a substantial muscularis layer, and unexpected vascular injuriy during percutaneous access.

In order to reduce stone debris spillage and improve fragmentation, our objective was to study bladder stone stabilization. As no current studies have assessed simultaneous stabilization and lithotripsy through a single scope during cystolithopaxy, we assessed a novel technique using an in vitro bladder stone model, with a new entrapment device. By stabilizing a stone during fragmentation, we hypothesize that we can improve efficiency of ultrasonic and pneumatic lithotripsy.

The entrapment device used in this experiment was the UroNet Retriever™ (UN), an adaptation of gastroenterology's endoscopic RothNet, constructed to fit flexible and rigid scopes. Though its intended use is to gather coarse fragments after fracture, we sought to study its role in stone stabilization during fragmentation.

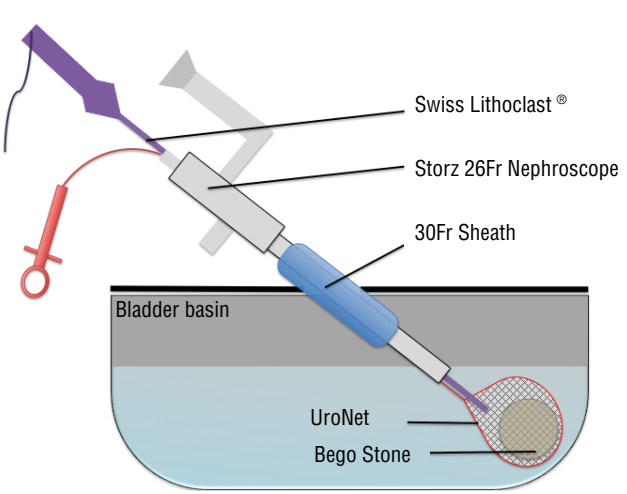
MATERIALS AND METHODS

Phantom Bego stones were created to 1cm maximum diameter, and 1±0.05 grams. BegoStone Plus™ plaster (Bego Dental, Bremen, Germany) was used with a 5:1 ratio of Bego power to water, and spherical molds were used for consistent sizing. All stones were dried and weighed prior to usage. A 600 cc round bottom rigid plastic container and urethane cover were used as a bladder model. A central aperture, accommodating a 30Fr sheath was fashioned allowing for rotational and depth manipulation of the nephroscope (modeling the mechanics of a percutaneous cystolithopaxy). A Karl Storz26 Fr rigid nephroscope was used with saline irrigation and Swiss Lithoclast™ probe (Electro Medical Systems, Nyon, Switzerland) to provide simultaneous ultrasonic and pneumatic fragmentation with continuous suction. The Swiss Lithoclast ultrasound probe used was 11.4Fr, and 403mm in length (FR-083), with a 3Fr pneumatic combination probe (EL-220) (Figure-1).

A phantom stone was placed in the bladder and subjected to 60 seconds of fragmentation, with or without UN stabilization (through the nephroscope) using a single operator. The UroNet Flexible Retriever (product no. 913604) produced by US Urology of US Endoscopy (Mentor, OH), has working length of 70 cm, 5.4Fr sheath diameter, and a 3.0x1.25 cm nylon net. Video endoscopy for scope manipulation was used to simulate routine surgical practice. Once located with the scope, the UN was advanced through the working channel, and the stone was captured.

Once stabilized by the net, the SL probe was advanced along side the UN through the

Figure 1 - Schematic bladder stone model.



working channel and directed on to the captured stone. Ultrasonic and pneumatic lithotripsy were used simultaneously at maximal power settings for 60 seconds. Stones and irrigation were then sifted through a 1mm strainer, and all retained fragments were recorded. Five trials were performed with and without the UN, during fragmentation. The number of fragments, maximum diameter of fragments, and change in dry weight were recorded. Durability was assessed after fragmentation by measuring netting defects and the change in grasp strength of the instrument.

Grasp strength testing involved trapping an 8 mm marble, and recording the closure force required to fracture the netting around the marble. These forces were then compared to brand new nets, and assessing the variation.

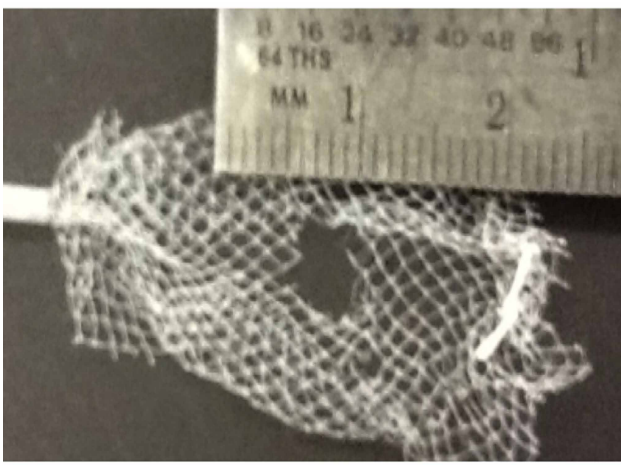
Means and standard deviations were used to summarize the data. Two tailed Student's T--tests were used (alpha <0.05) to compare results with and without UN. SPSS (version 20, Armon NY) was used for all statistical analyses.

RESULT

Mean time to stone capture, using UN through the nephroscope was 12s (range 8-45s). The average pre-fragmentation dry weight was similar for both trials (1.05 g+UN vs 1.02 g-UN), and diameters were standardized to 1 cm using the same mould for all stones.

After 60seconds of SL fragmentation, all UN captured stones were removed by withdrawing the pouch through the sheath. The remaining stones were collected from the strainer, and dried for one week. The change in dry weight when using UN was 22.6±0.02%, and 8.1±0.04% without UN (p<0.001). Lithotripsy with UN led to greater fragmentation (17±5 vs 5.0±4.1 fragments/stone, p=0.0029) and smaller average fragment size (3.6±0.51 mmvs 7.05±3.0 mm, p=0.035). Defects in the meshwork ranged from 2-14 mm, though all nets retained their original strength (36.8N), except one which was nonfunctional. This net developed a 14 mm defect too large to grasp the 8mm marble used for testing (Figure-2).

Figure 2 - UroNet Retriever with 4 mm mesh defect after lithotripsy.



DISCUSSION

Endoscopic management of bladder stones offers unique challenges, some of which can be addressed by simultaneous fragmentation and stabilization. In conjunction with dual-modality lithotripsy provided by SL, the UN aided in improving fragmentation, and significantly reduced the amount of residual stone after 60s of breakage. This advantage is not limited to a percutaneous procedure, as it could easily be performed transurethrally. However, though improvements in fragmentation efficacy were identified, several issues concerning the UN design, prevents it from being the ideal tool for this indication.

Stone capture was straight forward, though controlling both the SL and UN through the working channel could be challenging. As the net closes around a stone it is tethered at the shaft's insertion, producing a fulcrum. As they exit the scope in parallel, depth becomes the probe's major degree of freedom. With minor adjustments of the nephroscope and rotation of the UN, the captured stone can be rolled into the probe's path. Once aligned, little manipulation is needed as probe suction keeps the netted stone in place. If the option was available to remove the UN sheath, and have the netting tethered by just a string within the scope, simultaneous manipulation would be greatly improved.

Stone capture may be difficult if a stone is spherical, smooth, and greater than 2 cm in diameter. This leads to incomplete capture, and sliding of the nitinol frame off of the stone. In larger irregular stones, portions could be stabilized within the UN, fragmented and extracted, then repeated sequentially for the entire burden. However, in patients with significant stone burdens the indications for an open surgical approach should be individualized.

Bladder stone capture has been described using a laparoscopic entrapment sac through a 10 mm ports placed percutaneously in neobladders, augmented bladder, with simultaneous cystoscopic visualization (per urethra) (8). Lam et al., used a similar technique, fragmenting stones through a 30Fr sheath placed within the sac (after port removal), until small enough to remove through the 10 mm incision (6). Percutaneous management is becoming popular in both adults and children, and using larger sheaths improves drainage, accommodates rigid nephroscopes, and allows removal of larger stones/fragments (3). It has also been shown to have comparable stone free rates as open surgery, in addition to being less painful and requiring shorter admission times (4).

Holmium:Yag laser cystolithopaxy is commonly performed, with advantages in being performed transurethrally or percutaneously with both rigid and flexible instruments. A downside being laser fragmentation produces smaller fragments, and a significant amount of debris (9). We have found lasers most useful in smaller stones treated transurethrally, or when anatomic challenges are present, we use flexible instrumentation. Unintentional mucosal injuries can occur when attempting to stabilize fragments against the bladder wall during fragmentation. Lasers can also be used during stone stabilization using the UN to reduce fragment dispersion, though net damage occurs with higher settings.

Designed for stone/tissue capture for extraction in the kidney or bladder, the UN's application in stabilization during lithotripsy offers several theoretical benefits. The risk of bladder injury may be lessened as the entrapped stone is maintained between the SL probe and bladder wall. In native bladders these injuries are of minimal significance, however in bowel augments or conduits they can easily cause transmural perforations. Sequestration of fragments until the pouch can be withdrawn through the 30Fr working sheath reduces the time spent in the localization and removal of loose fragments. Keeping millimeter sized particles and 'dust' trapped within the basket reduced the amount of residual stone matter that may not clear with outlet obstruction.

These theoretical benefits however, do not outweigh the limitations of this device when used for stabilization. Difficulties in simultaneous manipulation, and durability preclude it from everyday use with concomitant SL lithotripsy. The optimal size of the stone to be captured is also relatively small, though currently not defined. Though no freed netting fragments were encountered, the risk remains in foreign bodies leading to a future nidus for stones. Though alternatives may be utilized (baskets, graspers, etc), the circumferential netting provides and ideal configuration for fragmentation, without fragment spillage. Improvements in netting durability, shaft flexibility/removability and maximal diameter of applicable stone would make for an ideal instrument. Employing nitinol baskets, though resistant to fracture by SL fragmentation, would result in a similar distribution of fragments seen in non-stabilized procedures.

Limitations of this study include in vitro modeling and short trial times. Compared to typical bladder stone procedures, our trials were relatively short. However, within this time, fragmentation was significantly improved by stabilization, even with the shortcomings of the UN. The use of a 30Fr sheath with 1 cm stone, clinically does not require fragmentation, however as the purpose of this study was to measure fragmentation potential, extraction dynamics were not specifically investigated. Our model also may amplify shortcomings in durability as Bego stones are very hard, and by using a rigid bladder model, damage caused by the SL may have been higher than in situ. As such, an obvious limitation to the routine use of this instrument is the potential need for multiple devices.

The concept of stabilization may be useful in many situations, but with the limitations in stone size, durability and simultaneous maneuverability, the UN requires significant modifications prior to routine use.

CONCLUSIONS

In conclusion, bladder stone stabilization during SL lithotripsy improves efficacy, however, in its current configuration the UroNet Retriever is better suited for post-lithotripsy fragment removal.

CONFLICT OF INTEREST

None declared.

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Is quantitative diffusion-weighted MRI a valuable technique for the detection of changes in kidneys after extracorporeal shock wave lithotripsy?

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ABSTRACT

Objective: The aim of this study was to evaluate the capability and the reliability of diffusion-weighted imaging (DWI) in the changes of kidneys occurring after extracorporeal shock wave lithotripsy (ESWL) treatment for renal stones.
Materials and Methods: A total of 32 patients who underwent ESWL treatment for renal stone disease between June and December 2011 were enrolled in this prospective study. Color Doppler ultrasonography (CDUS) and DWI were performed before and within 24 hours after ESWL. DWI was obtained with b factors of 0, 500 and 1000 s/mm² at 1.5 T MRI. Each of Resistive index (RI) and ADC values were calculated from the three regions of renal upper, middle and lower zones for both of the affected and contralateral kidneys. Paired sample t test was used for statistical analyses.
Results: After ESWL, the treated kidneys had statistically significant lower ADC values in all different regions compared with previous renal images. The best discriminative parameter was signal intensity with a b value of 1000 s/mm². The changes of DWI after ESWL were noteworthy in the middle of the treated kidney ($p<0.01$). There were no significant difference between RI values in all regions of treated and contralateral kidneys before and after treatment with ESWL ($p>0.05$).
Conclusion: DWI is a valuable technique enables the detection of changes in DWI after ESWL treatment that may provide useful information in prediction of renal damage by shock waves, even CDUS is normal.

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INTRODUCTION

The prevalence of stone disease shows an increase in the developing world. The invention and development of extracorporeal shock wave litothripsy (ESWL) in the last 25 years has brought an effective perspective to the treatment of urinary stone diseases as a non-invasive method. It is an optimal technique that may save time and resources and decrease the suffering of patients especially in the emergency department. Shock waves are non-linear waves characterized by high pressure and low frequency. When the shock waves encounters the stone, a part of energy is absorbed, a part of energy is reflected and the rest of energy is transmitted through stone. These destructive forces that are called cavitation and spalling cause stone fragmentation. The shock waves traverse renal parenchyma before reaching renal calculi and this causes some pathologic changes in the kid-

ney. The side effects of shock waves are intra renal hematomas, subcapsular hematomas, subcapsular fluid collections, perinephric soft tissue stranding, cardiac arrhythmias, fascial thickening and loss of corticomedullary junction. Histopathologic changes are observed in the form of diffuse interstitial fibrosis, focal calcification, glomerular hyanilization and sclerosis, damaged capillary vessels and acellular scars ranged from cortex to medulla. These changes results in 0.01-20% loss of renal function (1-4). Color Doppler ultrasonography (CDUS) has been used to detect the effects of ESWL on the kidneys as a noninvasive technique (5). Also, the kidney is a suitable organ for diffusion studies because of its high blood flow and its fluid transport function. Besides, it's a noninvasive technique with no need of contrast agents. Recent ultrafast sequences made diffusion studies more applicable with shorter examination times and fewer motion artifacts (6, 7). The purpose of our study was to detect the changes of kidneys after ESWL treatment by diffusion weighted imaging (DWI) and CDUS and to evaluate whether DWI has advantages in prediction of renal damage due to shock waves.

MATERIALS AND METHODS

The study protocol was approved by the local Ethics Committee. Written informed consents were obtained from all participants. During the period of June to December 2011, a total of 32 consecutive patients 23-68 years old (mean age, 41±0.6 years old), diagnosed with nephrolithiasis by abdominal X-ray and US, underwent ESWL and were enrolled in the study group. Exclusion criteria included urinary system infection, marked collecting system dilatation, renal parenchymal disease such as diabetes mellitus and hypertension.

ESWL Protocol

ESWL was performed by piezoelectric lithotriptor, Wolf Piezolith 3000 with F3 triple focus (2.5 x 16 mm / 4.0 x 25 mm / 6.0 x 30 mm). Outline X-ray and inline ultrasound was used for stone location. The stones ranged in size from 9 x 6 mm to 18 x 14 mm. Three sessions of ESWL (with interval of 3 days) were applied to all patients and the number of pulses ranged between 1600 and 2000 (mean 1880). Main supply of lithotriptor was 220-240 V/ 50-60 Hz with power consumption 1000 VA. Energy density and peak pressure applied to all patients ranged from 0.84 to 1.14 mJ / mm^2 (mean 0.98 mJ / mm^2) and 36 to 112 MPa (mean 88 MPa), respectively. DWI and CDUS were performed before and within 24 hours after 3 sessions of ESWL in all patients.

Color Doppler Ultrasound (CDUS)

All the Doppler sonographic measurements were performed by the same operator using a Toshiba Aplio SSA-770A/80 (Toshiba Medical Systems Corporation, Tokyo, Japan) scanner using with Convex array probe PVT-375AX (1.9-6 mhz) before and after ESWL in the first day. The resistive index (RI) measurements were taken at an interlobar or arcuate artery from the three regions of kidney (upper, middle and lower zones) for both the affected and contralateral kidneys.

Diffusion Weighted Imaging (DWI)

DW images were obtained with a 1.5 T whole body system (Avanto; Siemens, Erlangen, Germany) with a 33 mT/m maximum gradient capability using an eighteen channel phased-array body coil. No specific preparatory measures were required such as fasting or drinking prior to the examination. Also, no oral or intravenous contrast agent were administered. Axial diffusion weighted single-shot spin-echo echo-planar sequence with chemical shift selective fat-suppression technique (TR/TE 4738/80; matrix 192 x 192; slice numbers 36; slice thickness 5 mm; interslice gap 30%; FOV 40 cm; averages 5; acquisition time approximately 4 minutes; PAT factor 2; PAT mode generalized autocalibrating partially parallel acquisition –GRAPPA-) was performed. DW images were obtained with b-factors of 0, 500 and 1000 sec/mm^2. The phase encode direction was set antero-posteriorly in both sequences. All slices were acquired from the superior pole to the bottom of the kidneys. All images were obtained without restriction of fluid intake and without breath-holding.

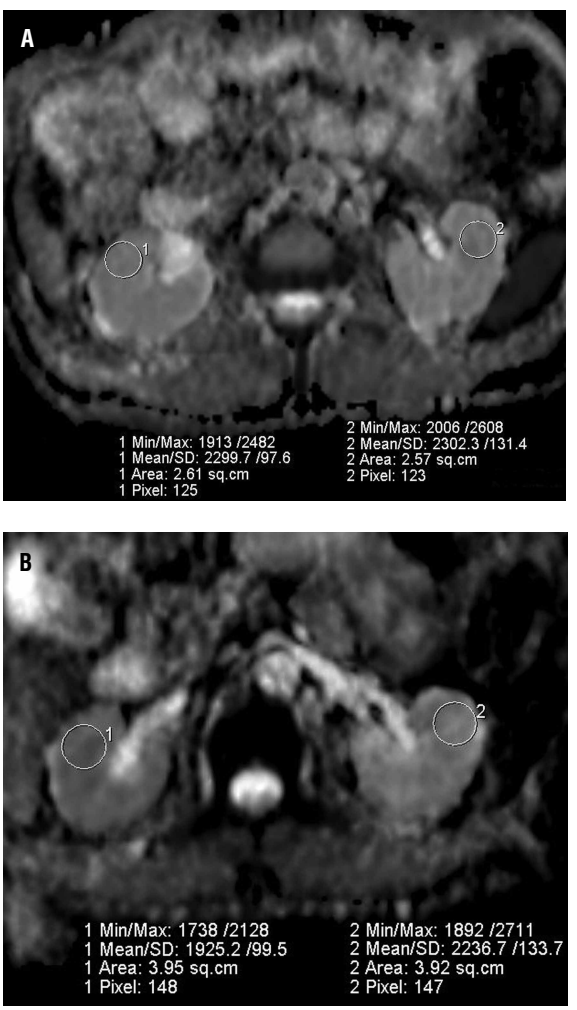
Imaging Interpretation

CDUS was performed by a single examiner with experience in sonography before and within

24 hours after ESWL. Measurements were taken three times for each region repeatedly in the three different regions of affected and contralateral kidneys (middle zone, upper, and lower poles). Averaged values were recorded for each region as the RI value.

DW images were interpreted by two readers at random order in consensus. All were of diagnostic quality with no exclusion. The DWI datasets were transferred to an independent workstation (Leonardo console, software version 2.0; Siemens AG Medical Solutions, Forchheim, Germany) for postprocessing, and the ADC maps were reconstructed. The kidneys were prospectively evaluated quantitatively with the DW sequences before and after ESWL. We measured DWI signal intensity to quantify visual conspicuity and the level of detectability. A large circular region of interest (ROI) was placed at the corticomedullary junction for the measurement of ADC values. ADC values were obtained on the different sites of kidneys. For each ADC calculation, 3 ROI measurements were taken and the average value was accepted. All measurements were repeated at different *b* values (0, 500, 1000 s/mm²). Each patient's ADC values were recorded in square milimeters per second quantitatively (Figures 1a, 1b, 2a, 2b, 2c and 2d).

Figure 1 - 56 years old male patient. Apparent diffusion coefficient (ADC) maps of treated and contralateral kidneys before (Figure-1a) and after (Figure-1b) treatment with ESWL. The ADC value is decreased from $2.29x10^{-3}$ mm^2/sn to $1.92x10^{-3}$ mm^2/sn in treated kidney. The ADC values of the contralateral kidney are $2.30x10^{-3}$ mm^2/sn and $2.23x10^{-3}$ mm^2/sn before and after ESWL treatment, respectively.



Statistical analysis

Statistical analysis was performed with the NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) packages program. The paired sample t-test was used to compare RI and ADC values before and after ESWL. A p value of less than 0.05 was considered statistically significant.

RESULTS

Color Doppler Ultrasound

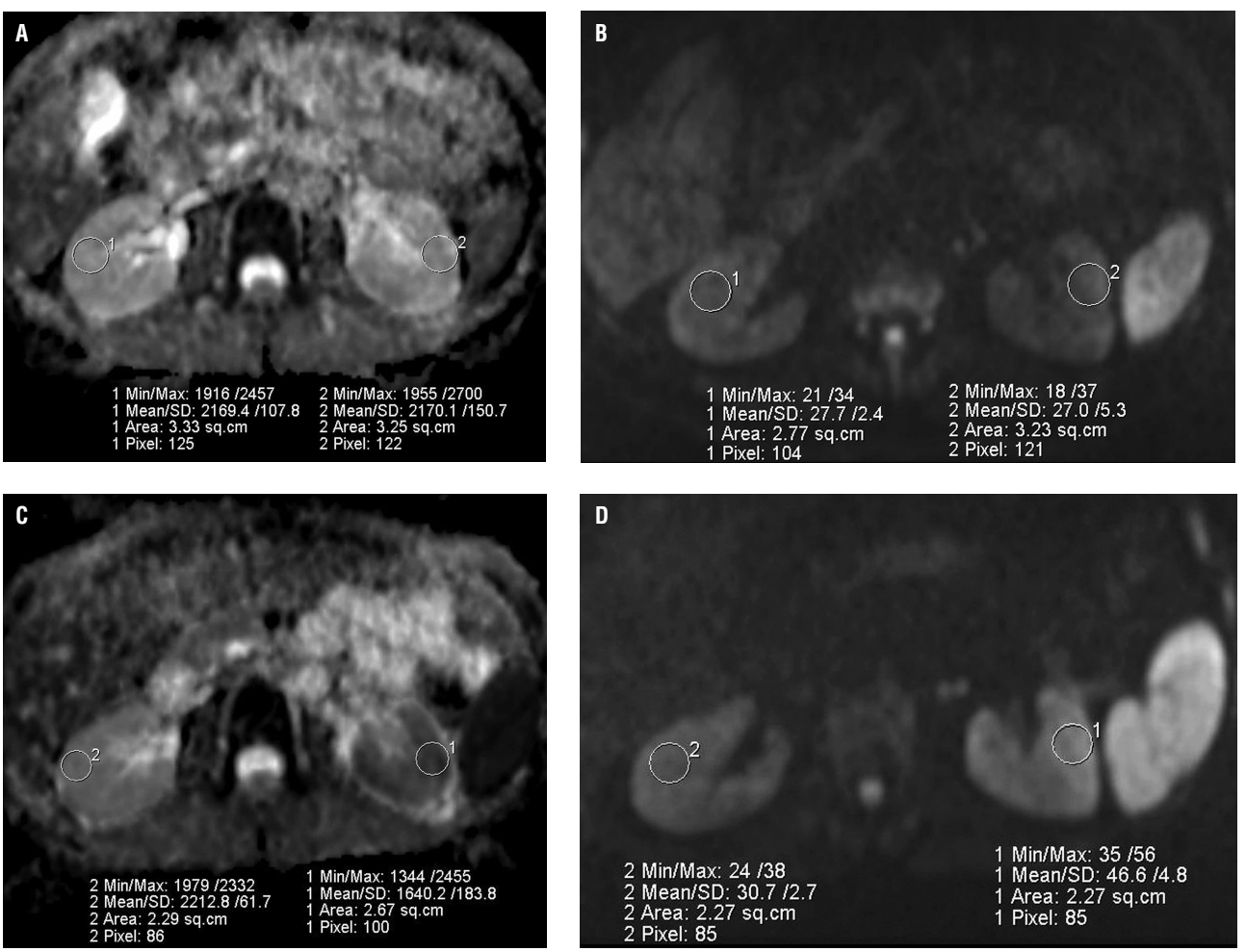
Comparison of the mean RI values before and after ESWL showed no statistically significance for both ipsilateral and contralateral kidneys ($p>0.05$). The mean RI values pre and post ESWL were 0.58 ± 0.05 and 0.59 ± 0.04 in the ipsilateral kidney, 0.58 ± 0.05 and 0.59 ± 0.05 in the contralateral kidney, respectively. The changes in the RI values before and after ESWL in certain regions are shown in Table-1.

Diffusion weighted imaging

The mean ADC values of ipsilateral kidneys with b=0, b=500 and b=1000 values before and after ESWL treatment are shown in Table-2.

Ipsilateral kidneys had statistically significant lower ADC values in all different regions compared to contralateral kidneys after ESWL (Figure-3). The changes after ESWL were conspi-

Figure 2 - 44 years old male patient. Apparent diffusion coefficient (ADC) maps and signal intensities (with b values of 1000 s/mm^2) of treated (left) and contralateral kidneys before (Figures 2a and 2b) and after (Figures 2c and 2d) treatment with ESWL. The ADC value decreased from 2.17x10^{-3} mm^2/sn (Figure-2a) to 1.64x10^{-3} mm^2/sn (Figure-2c) in the treated kidney. Signal intensity of the treated kidney with b values of 1000 s/mm^2 increased from 27.0 s/mm^2 (Figure-2b) to 46.6 s/mm2 (Figure-2d). The ADC values of the contralateral kidney are 2.16x10^{-3} mm^2/sn (Figure-2a) and 2.21x10^{-3} mm^2/sn (Figure-2c) before and after ESWL treatment, respectively. Signal intensities of the contralateral kidney with b values of 1000 s/mm^2 are 27.7 s/mm2 (Figure-2b) and 30.7 s/mm2 (Figure-2d) before and after ESWL treatment, respectively.



cuous in the middle zone ($p<0.01$). The best discriminative parameter was signal intensity with a b value of 1000 (Figure-4).

In contralateral kidneys, minimum and maximum ADC values of renal parenchyma ranged from 1.98 to 2.47x10^{-3} mm^2/sn.

DISCUSSION

ESWL has dominated the treatment of renal stone disease since its introduction in 1980. It has been a major advance in Urology which is the fragmentation of stone by means of acoustic shock waves created by an extracorporeal source. It is non-invasive, effective and very well tolerated. The shock waves generated by ESWL cause fragmentation of renal calculi by exerting on the brittle calculi mechanical stresses sufficient to exceed the tensile strength of the stone (1-4). Although the focal point of the shock wave is centered on the renal stone, the waves must pass through the soft tissues of the back and the renal parenchy-

Table 1 - The RI values of treated kidneys before and after ESWL in certain regions.

	RI		p
	Pre-ESWL	Post-ESWL	
	Mean±SD	Mean±SD	
Upper Pole	0.58±0.05	0.59±0.04	0.375
Middle Zone	0.58±0.05	0.59±0.04	0.204
Lower Pole	0.58±0.04	0.59±0.04	0.307

Table 2 - The mean ADC values of ipsilateral kidneys with b-0, b-500 and b-1000 values before and after ESWL treatment.

		Pre-ESWL	Post-ESWL	p
		Mean±SD	Mean±SD	
Upper Pole	b0	244.47±44.99	254.03±43.41	0.107
	b500	67.37±7.01	72.15±13.98	0.075
	b1000	26.87±5.84	31.18±11.55	0.014*
	ADC	2.173±0.112	2.099±0.243	0.049*
Middle Zone	b0	255.06±43.95	266.34±40.70	0.006**
	b500	68.47±9.38	75.37±13.72	0.005**
	b1000	27.15±5.81	33.40±11.60	0.001**
	ADC	2.189±0.125	2.053±0.244	0.004**
Lower Pole	b0	241.12±47.75	254.97±46.31	0.003**
	b500	65.43±9.28	69.72±11.64	0.015*
	b1000	25.56±6.95	30.56±11.26	0.012*
	ADC	2.201±0.129	2.115±0.204	0.023*

ADC ($x10^{-3}$ mm^2/sn)
*p<0.05; **p<0.01

ma before reaching the calculus. Therein lies the potential for damage to these tissues. Kaude and co-workers (8) hypothesized that the spherical shock waves passing through the kidney during ESWL produce renal contusions. Lang et al. (9) have defined renal contusion as interstitial extravasation of small amounts of urine and blood and interstitial edema. However, the treatment with shock waves carries the risk of acute injury with the potential for long-term adverse effects (8-12). Many techniques have been used to show the effects of ESWL on the kidneys, such as US, CT, MRI, laboratory findings.

CDUS is an easy, effective, noninvasive method for evaluating changes of after ESWL therapy (5, 13-15). The RI measured by CDUS is a physiologic parameter reflecting the degree of renal vascular resistance and intrarenal edema and is elevated in diseases involving the tubulointerstitial or vascular system. Our study demonstrated no significant differences in the RI of treated kidneys before and after ESWL, as Beduk et al. (13) reported. Aoki et al. (14) showed that the RI of treated kidneys significantly increased at 30 minutes after ESWL. Janetschek et al. (15) found that

Figure 3 - The mean ADC values before and after ESWL treatment in upper pole, middle zone and lower pole of treated kidneys.

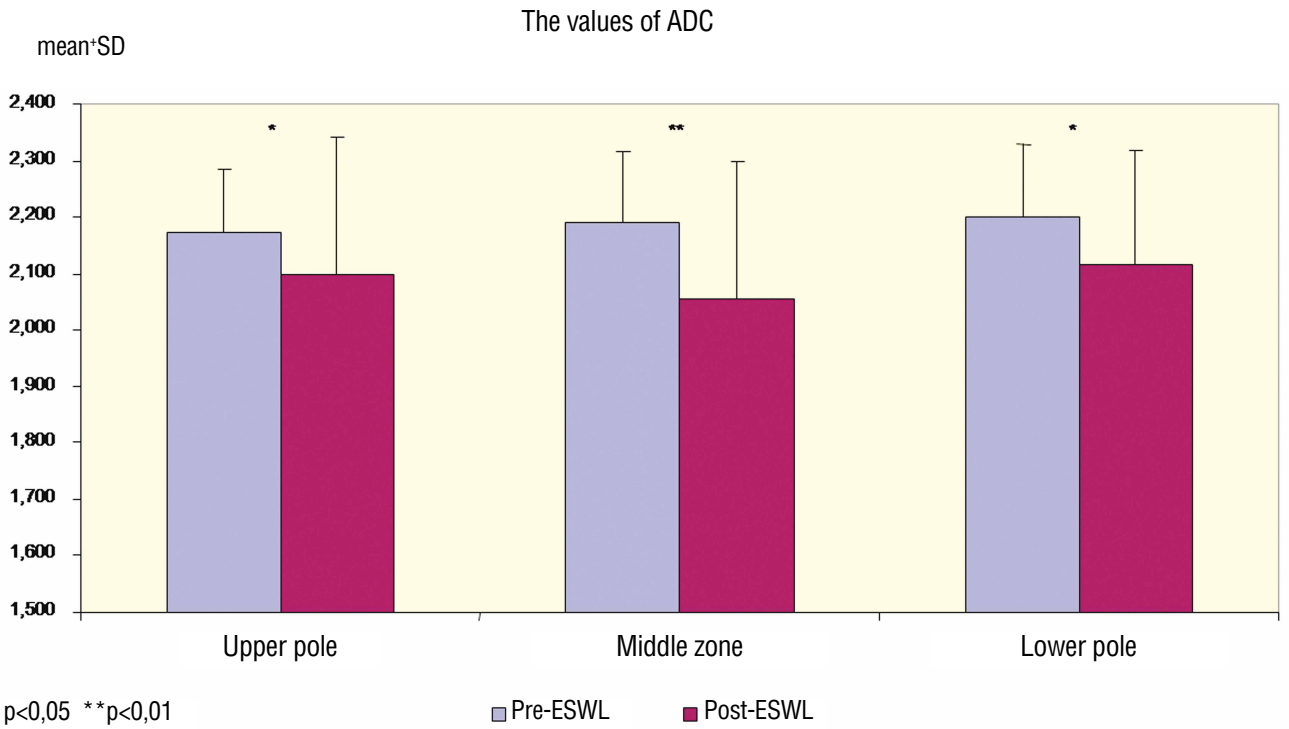
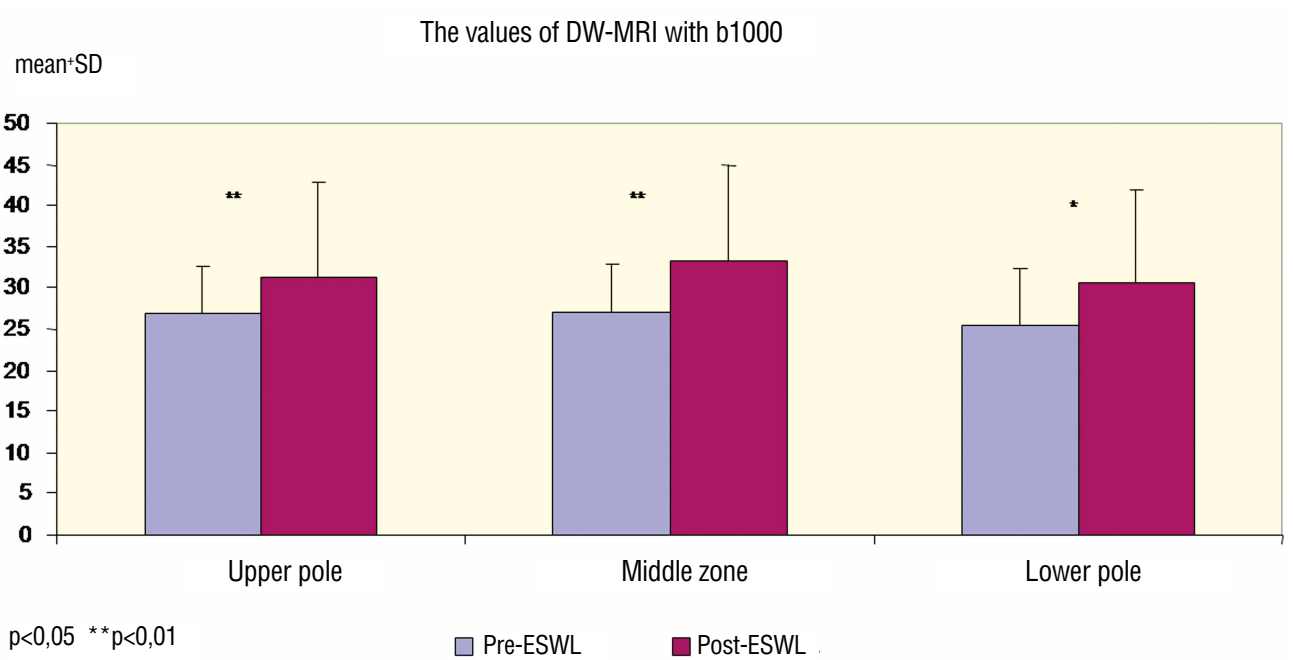


Figure 4 - Signal intensities with b=1000 s/mm² before and after ESWL treatment in upper pole, middle zone and lower pole of treated kidneys.



RI values in the treated region within 3 hours after ESWL were significantly higher in the group of patients aged >60 years.

Baumgartner et al. (10) showed the presence of abnormality in 74% of patients studied after ESWL by MR imaging. According to their results, MR imaging may be a very sensitive method to image these pathologic alterations occurring in the kidney.

The results of diffusion-weighted MRI in the kidney are still preliminary, and more research should be done (16). DWI provides information on perfusion and diffusion simultaneously in any organ; it can be used to differentiate normal and abnormal structures of tissues and it might help in the characterization of various abnormalities. Thus, calculating the ADC of low and high *b* values separately provides more specific information on kidney function (17). Thoeny et al. (18) showed the decrease in the ADC values of kidneys in patients with chronic renal failure and pyelonephritis. Chan et al. studied DWI to differentiate between hydronephrosis and pyonephrosis (7). Powers et al. (19) used a spin-echo diffusion-weighted sequence with respiratory triggering in dog kidneys, and found a drop in ADC in the unilateral renal artery stenosis that correlated with renal blood flow. Müller et al. (20) demonstrated that acute ureteral obstruction shows a quick decrease in ADC.

Researches have been processing about the long term side affects after ESWL. These possible adverse effects include a decrease in renal function, an increased rate of new stone formation and an increase in systemic blood pressure. Yokoyama and friends (21) have witnessed 1.5% of new initiative hypertension on normotensive patients after one year of ESWL. It is realized that retrospectively more than 8% of patients have suffered hypertension within the following two years (11). Uozumi et al. (22) determined a decrease of renal blood flow and delay of radionuclide urinary clearance in the affected kidney from ESWL.

In our study, renal changes after ESWL treatment were demonstrated with DWI in spite of a normal CDUS. After ESWL session, ipsilateral kidneys had statistically significant lower ADC values in all certain regions compared to contralateral kidneys. This condition can be explained by the decrease of renal blood flow or renal microcontusion arising from shock waves. ESWL centers routinely apply shock wave dosages in the range of 1500 to 2500 per treatment session. Since the possibility of an adverse effect of ESWL on the blood pressure and the lack of evidence that efficacy is enhanced by the utilization of such high doses of shock wave energy, such practices should be discouraged.

Our data suggest that DWI may be a very useful method for imaging pathologic alterations occurring in the kidney after ESWL therapy. Additionally, to our knowledge there has been no previous report relating the DWI findings in the kidneys treated by ESWL. One of the limitations of our study is that all images were obtained without any specific preparation of the patients such as fasting or drinking. However it's known that hydration has some effects on the ADC levels even though minimal.

CONCLUSIONS

DWI is a valuable technique for detection of post-ESWL changes in the kidneys even while the Doppler US is normal. Further studies specifically investigating long-term effects are warranted.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Oncological and functional outcomes of salvage renal surgery following failed primary intervention for renal cell carcinoma

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ABSTRACT

Purpose: To assess the oncologic and functional outcomes of salvage renal surgery following failed primary intervention for RCC.

Materials and Methods: We performed a retrospective review of patients who underwent surgery for suspected RCC during 2004-2012. We identified 839 patients, 13 of whom required salvage renal surgery. Demographic data was collected for all patients. Intraoperative and postoperative data included ischemic duration, blood loss and perioperative complications. Preoperative and postoperative assessments included abdominal CT or magnetic resonance imaging, chest CT and routine laboratory work. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease equation.

Results: The majority (85%) of the patients were male, with an average age of 64 years. Ten patients underwent salvage partial nephrectomy while 3 underwent salvage radical nephrectomy. Cryotherapy was the predominant primary failed treatment modality, with 31% of patients undergoing primary open surgery. Pre-operatively, three patients were projected to require permanent post-operative dialysis. In the remaining 10 patients, mean pre- and postoperative serum creatinine and eGFR levels were 1.35 mg/dL and 53.8 mL/min/1.73 m^2 compared to 1.43 mg/dL and 46.6 mL/min/1.73 m^2, respectively. Mean warm ischemia time in 10 patients was 17.4 min and for all patients, the mean blood loss was 647 mL. The predominant pathological stage was pT1a (8/13; 62%). Negative surgical margins were achieved in all cases. The mean follow-up was 32.9 months (3.5-88 months).

Conclusion: While salvage renal surgery can be challenging, it is feasible and has adequate surgical, functional and oncological outcomes.

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Key words:
Kidney; General Surgery; Carcinoma, Renal Cell; Salvage Therapy

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INTRODUCTION

The clinical and financial burden of renal cell carcinoma (RCC) is significant, with its incidence continuing to rise worldwide during the last three decades. In 2011, there were over 60,000 new cases and 13,000 deaths attributed to RCC in the United States alone (1). This rise in diagnosis is likely, at least in part, related to the increased detection of small asymptomatic renal masses using cross sectional abdominal imaging often for unrelated abdominal complaints.

Several treatment options are available for small renal masses (SRMs), including active surveillance, radical nephrectomy, nephron-sparing surgery and ablative procedures. While ablative

treatment options such as radiofrequency ablation and cryotherapy are commonly used (1, 2), there are limited data describing their long-term oncologic outcomes. In comparison, the positive oncologic outcome data for radical or partial nephrectomy are consistent, established and mature (3, 4).

Following surgery, cryoablation and radiofrequency ablation, the rate of local recurrences are approximately 3, 5 and 8%, respectively (5, 6). Importantly, the effective management of these recurrences can be challenging, particularly with the use of repeated ablative modalities that tend to have a higher failure rate (7, 8). An alternate clinical approach for the treatment of suspected RCC recurrence is salvage partial nephrectomy (SPN). Repeated salvage procedures can achieve adequate functional and oncologic outcomes but are surgically challenging and associated with surgical complications (9-11). Currently limited outcome data are available for salvage renal surgery. As such, in the present study we sought to evaluate the functional and oncologic outcomes following salvage renal surgery at a large, urban, tertiary referral center.

MATERIALS AND METHODS

Institutional review board approval was obtained for the purposes of this study. We retrospectively reviewed the records of 839 patients who underwent surgery for suspected RCC from 2004-2012. From this cohort, we identified 13 patients (1.5%) who underwent salvage renal surgery.

Demographic data was collected for this group of 13 patients. Operative reports and outpatient notes were reviewed for intraoperative and postoperative data, including ischemic duration, blood loss and perioperative complications. Preoperative and postoperative assessments included abdominal CT or magnetic resonance imaging, chest CT and routine laboratory work. Plain films, bone scans, and brain-imaging studies were performed if indicated for accurate preoperative staging. Estimated glomerular filtration rate (eGFR) was calculated (in mL/min/1.73 m^2) according to the Modification of Diet in Renal Disease equation:

eGFR=186(serum creatinine – 1.154)(age-0.203)

For female patients eGFR was multiplied by a factor of 0.742, while for African-American patients an adjustment factor of 1.212 was used.

Local recurrence with inferior vena cava tumor thrombus was present in 3 of our patients, and thrombi were classified according to Nieves and Zincke (level I-IV) (12).

RESULTS

A retrospective review of our institutional kidney cancer database identified 13 patients who underwent salvage renal surgery between 2004-2012. Of these, three of 13 (23%) required a radical nephrectomy. The majority of the patients (11/13; 85%) were male, with an average age of 64 years (Table-1). Cryotherapy was the main primary treatment modality in six of 13 (46%) patients, through an open, percutaneous or laparoscopic approach. In contrast, four of 13 (31%) patients underwent open partial nephrectomy as a primary treatment modality (Table-2).

In the patients included in the study, 11/13 (84.6%) had clinically diagnosed hypertension. Similarly, 3/13 patients (23.1%) were diagnosed as diabetic. Three patients (23.1%) had both hypertension and diabetes (Table-3). The predominance of hypertension and diabetes in our patient cohort is reflected in the profile drugs administered to patients (which included antihypertensives, diuretics, ACE inhibitors, AT1 antagonists, statins and other various agents) (Table-4).

In 12/13 patients (92.3%), recurrence occurred at the same location as the primary tumor (Table-3). In 11/13 patients (84.6%) new primary tumors occurred in the same location as the initial tumor (Table-3).

While of interest, proteinuria was not directly assessed in our study cohort. However, in 10 non-dialysis patients, mean pre- and postoperative serum creatinine and eGFR levels were 1.35 mg/dL and 53.8 mL/min/1.73m^2 compared to 1.43 mg/dL and 46.6 mL/min/1.73m^2, respectively (Table-1). In patients undergoing SPN, mean warm ischemia was 17.4 min. Mean blood loss was 647 mL for the entire cohort. In 3 of 13 (23%) patients permanent dialysis after surgery was required, which was related to the fact that

Table 1 - Summary of patient demographics, clinical data, surgical treatments and pathology.

Mean age (n)		64.2 (13)
Gender (M/F)		11/2
Primary treatment (n)	Open partial Nx	4
	Open CA (previous partial nephrectomy)	1
	Laparoscopic CA	3
	Percutaneous CA	2
	Percutaneous RFA	2
	Hand assisted laparoscopic partial Nx	1
Serum creatinine (mg/mL); (median; range; n=10)	Pre-op	1.4 (0.8-2.5)
	Post-op	1.4 (0.8-2.6)
eGFR (mL/min/1.73m^2); (median; range; n=10)	Pre-op	53.9 (41-60)
	Post-op	46.7 (15-60)
Tumor stage (n)	pT1a	8
	pT1b	2
	pT3b	3
Grade* (n)	2	2
	3	8
Pathology (n)	Clear cell	8
	Papillary	2
	Oncocytoma	2
	Fibrosis	1
Negative margins (n)		13
Follow up (months)		32.9
Distant recurrence (n)		1

*Grading data were unavailable for 3 patients due to their final pathology (2 oncocytomas and 1 fibrosis)

Table 2 - Intra and postoperative complication rates in previously published studies.

	Kowalczyk et al. (18)	Johnson et al. (10)	Bratslavsky et al. (19)	Current study
Number of patients	13	47	11	13
Number of partial nephrectomies	16	51	13	10
Primary treatment	RFA	Open partial	Open partial	RFA, cryo, open partial
Number of intraoperative complications	1	18	6	0
Number of postoperative complications	8	22	13	3

Table 3 - Details of primary treatment, tumor stage, size of relapse, solitary kidney and pathologic stage for individual patients.

Patient	Primary treatment	Tumor stage	Tumor size at relapse (cm)	Primary tumor location	Location of relapse	Location of new primaries	Solitary kidney	Pathologic stage	Tumor size at pathology (cm)
1	Laparoscopic cryo	cT1a	3.5	Right Posterior Upper Pole	Same	Same	Solitary (Anatomical)	pT1a NXMX	3.3
2	Laparoscopic cryo	cT1ab	4.7	Left Anterior Mid Pole	Same	Same	Solitary (Anatomical)	pT1b NXMX	4.7
3	Laparoscopic cryo	pT1a	2.5	Left Anterior Mid Pole	Same	Same	Solitary (Aantomical)	pT1a NXMX	2.5
4	Renal cryotherapy	cT1b	6.5	Right Medial Mid Pole	Same	Same	Solitary	pT1b NXMX	6.5
5	Left partial nephrectomy	cT1a	4	Left Upper Pole	New	New	Solitary	-	4.5
6	Right hand assisted partial nx	pT1a	4	Right Poster Lower Pole	Same	Same	Solitary	pT1aNXMX	4.0
7	2 open+cryo	pT3bN0Mx	5.5	Right Upper Pole	Same	Same	Solitary (Functional)	PT3c NXMX	5.0
8	RFAx 2	-	3.5	Left Posterolateral Upper Pole	Same	Same	Solitary (Anatomical)	-	3.5
9	right open partial	pT3bN0Mx	10.5	Right Upper Pole	Same	New	Solitary (Functional)	pT3b N0MX	10.5
10	Right open partial	pT1aNxMx	1.9	Right Lateral Upper Pole	Same	Same	Solitary (anatomical)	pT1a NXMX	1.3
11	RFA Left	pT1aN0Mx	1.5	Left Anterior Upper Pole	Same	Same	Multi (Anatomical)	-	1.3
12	Open partial	pT1b	5.5	Right Mid/ Lower Pole	Same	Same	Solitary (Anatomical)	pT1bNXMX	6x5.4
13	RFAx2	pT1aN0M0	2.5	Right mid pole	Same	Same	Solitary	-	1.6

each had a marginal renal function prior to salvage surgery and IVC tumor thrombus. A single patient had a solitary kidney.

The predominant pathological stage was pT1a (8/13; 62%), while the predominant histology was clear cell carcinoma with a Fuhrman grade 3 (Table-1). Oncocytoma was reported in 2 cases, while only a single patient had no evidence of malignancy in the resected tissue (Table-1). A negative surgical margin was achieved in all cases. In our series, three patients presented with inferior vena cava tumor thrombus, level II and III in 1 and 2 patients, respectively.

The mean follow-up was 32.9 months (3.5-88 months) and during this period only 1 patient experienced cancer recurrence 6 months following the salvage procedure. The patient underwent a combination of radiation therapy to a lumbar vertebral metastasis and tyrosine receptor kinase therapy. Three of our patients experienced complications

including prolonged ileus, cecal volvulus and a urinary fistula. All of the patients were treated conservatively consisting of nasogastric tube decompression, endoscopic decompression and double J stent (Figure-1).

DISCUSSION

Partial nephrectomy is currently considered the gold standard for the effective management of small renal masses (SRMs). In contrast, radical nephrectomy is utilized successfully in clinical scenarios in which partial nephrectomy is either not indicated or not possible from a technical perspective. Despite the benefits of partial nephrectomy and the equivalent oncologic outcomes with radical nephrectomy, it remains underused in the treatment of small renal masses.

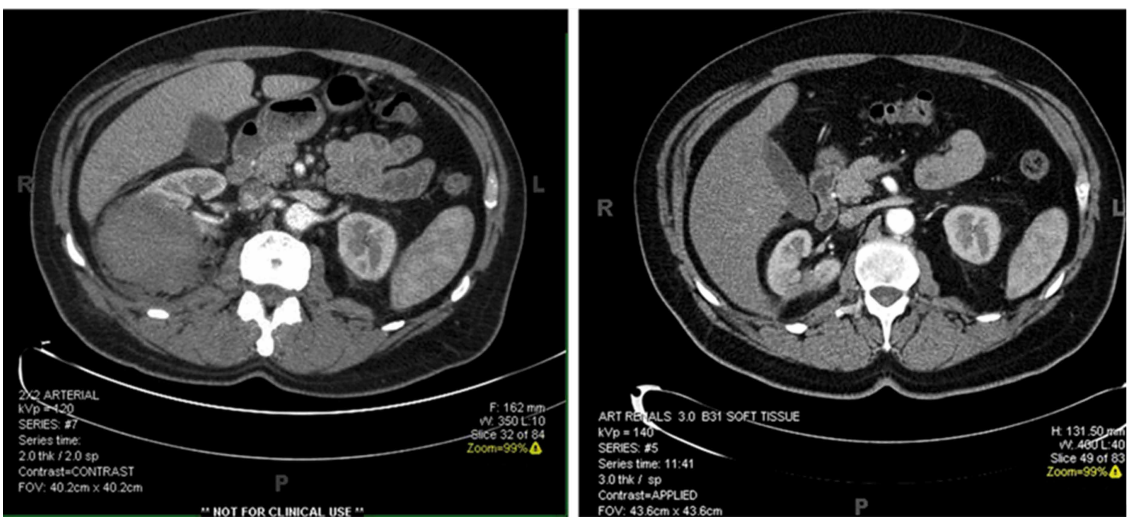
Ablative procedures are established modalities for the treatment of SRMs. A number of published studies have described excellent oncologic efficacy with ablative techniques during short and intermediate follow-up periods (5). The majority of published studies describing long term data for oncologic control are relatively small with limited follow-up and lack tumor pathologic diagnosis or are population based-studies that lack substantial details regarding patient comorbidities and demographics. However, intermediate oncological outcomes support the use of this strategy (6).

A growing number of patients opt to undergo ablation as a primary therapy, often because

Table 4 - Patient comorbidities and administered drugs.

Patient	Hypertension?	Diabetes?	Drugs administered
1	Yes	Yes	Aspirin (analgesic), carvedilol (b-blocker), Crestor (statin)
2	Yes	Yes	Aspirin (analgesic), Furosemide (diuretic), Glimepiride (sulfonylurea antidiabetic), Lupron (gonadotropin-releasing hormone antagonist, Metformin (antidiabetic)
3	Yes	No	Omeprazole (proton pump inhibitor), metoprolol (b-blocker/antihypertensive), Lisinopril (ACE inhibitor), Fexofenadine (antihistamine), atorvastatin (statin), Amlodipine (Ca channel antagonist - antihypertensive)
4	Yes	No	Amlodipine (Ca channel antagonist – antihypertensive), Carvedilol (b-blocker), Lisinopril (ACE inhibitor), Simvastatin (statin)
5	Yes	No	Atacand/HCT (AT1 inhibitor/diuretic), Spiriva (anticholinergic), Symbicort (COPD)
6	Yes	Yes	Allopurinol (xanthine oxidase inhibitor), Amlodipine (Ca channel antagonist – antihypertensive), Bisoprolol (b-blocker antihypertensive), Pantoprazole (proton pump inhibitor)
7	Yes	No	Aspirin (analgesic), Lisinopril (ACE inhibitor), Toprol (b-blocker), Simvastatin (statin)
8	No	No	None
9	Yes	No	Amlodipine (Ca channel antagonist – antihypertensive)
10	No	No	Metoprolol (b-blocker antihypertensive), Hydrochlorothiazide (diuretic), Mirtazapine (antidepressant/antiemtic), Fenofibrate (PPARa activator – cholesterol lowering)
11	Yes	No	Cardizem (Ca channel antagonist – antihypertensive), Triamterene (potassium sparing diuretic)
12	Yes	No	Hydrochlorothiazide (diuretic)
13	Yes	No	Lipitor (statin), Plavix (P2PY12 platelet inhibitor), Lotrel (Ca channel inhibitor – antihypertensive), Toprol (b-blocker), Hydralazine (antihypertensive), Hydrochlorothiazide (diuretic).

Figure 1 - CT images from a 64 year old patient who failed percutaneous cryotherapy. The patient underwent open salvage partial nephrectomy with no evidence of disease recurrence during 33 months follow-up.



of a solitary kidney, bilateral renal masses or renal insufficiency. However, these patients present challenges should they require subsequent surgery due to disease recurrence or new tumors. A recent large meta-analysis by Kunkle et al. demonstrated an increased risk of local recurrence after cryoablation and RFA compared to partial nephrectomy (13). Many of these cases of recurrence require additional treatments and repeat ablation is used most commonly. However, repeat ablation may not be advisable due to repeated ablation failures, tumor growth after ablation, large tumor size, disease progression, hilar location of a new tumor and proximity of heat sensitive structures. Another possibility may simply include the unwillingness of the patient to undergo the same treatment modality that has failed once already. In these cases, surgical intervention may be required.

There are limited reports describing the feasibility and difficulties of surgery in cases of ablation failure. These surgeries are technically challenging and complicated by severe fibrosis surrounding the previously ablated lesion. Dissections are difficult due to distortion of normal anatomical planes and a high rate of pleural injury (14). Karam et al. recently evaluated the feasibility, safety and pathologic, radiologic and functional outcomes of salvage surgery after prior renal mass ablation therapy (15). They concluded that failed renal ablation therapy can be salvaged with partial or radical nephrectomy with good intermediate outcomes. As a cautionary note, however, they noted that a high rate of adverse events and a requirement for longer follow-up in these patients. As such, patients with multifocal bilateral tumors electing ablative therapy as a primary treatment modality should be aware that new tumors may form in locations not amenable to repeat ablation. In these cases, the challenges involved in salvage surgery are not insignificant.

Barwari et al. (16) recently reviewed the role of different focal treatment modalities in the management of small renal masses. However, there are limited reports of adequate oncological follow-up or standardized assessment of complications (16). The incidence of local recurrence after open surgery or ablative procedures varies depending on the series (5, 8, 16). In the majority of the cases, post ablation recurrences are treated with a repeat ablation procedure. However, in selected scenarios, surgery is considered to be an efficacious management option. Such cases include rapid tumor growth following primary treatment, or tumors in unfavorable locations such as the collecting system or the renal hilum.

Recently published data have described the long-term impact on cardiac and renal function in patients who underwent radical nephrectomy rather than nephron sparing procedures (8, 9, 16). Kaushik et al. (17) demonstrated a four-fold increase in the risk of developing stage IV CKD following radical nephrectomy in a univariate and multivariable analysis compared with partial nephrectomy following surgery for a benign renal mass (17). In a major clinical study, Johnson demonstrated an adequate functional outcome with minimal decline in serum creatine and creatinine clearance following partial nephrectomy (10). Furthermore, Weight et al. (11) demonstrated an increased incidence of cardiovascular and renal complications, including chronic kidney disease and a requirement for postoperative dialysis, in patients who underwent radical nephrectomy as compared with nephron sparing surgery (NSS) (11). The health care impact of repeated NSS may be greater compared to undertaking an initial partial nephrectomy, due to the inherent complications of reoperative surgery and associated prolonged hospital stay. However, hemodialysis and its associated complications cost approximately $70,000 per year, per patient. As such, reoperative NSS (which is significantly less costly), may be a more cost effective option compared to dialysis (18).

Salvage surgery can be technically challenging and is often associated with significantly higher complication rates when compared with procedures performed in a virgin surgical field. In particular, an increased incidence of injury to adjacent organs such as the bowel, spleen, pancreas, liver and diaphragm, has been described (10, 11). Analyses of recurrent disease following thermal ablation have demonstrated that cryoablation is often associated with a significant degree and incidence of fibrosis and adhesive scarring around the kidney as compared to radiofrequency ablation, in which this side effect tends to be less extensive (19).

Two of our patients had multiple procedures before the salvage procedure including repeated open procedures and cryotherapy treatment. However, it did not preclude an increased number of complications.

In our series, three patients experienced significant local progression of their tumors with IVC involvement and subsequently underwent radical nephrectomy and IVC thrombectomy. Two of the patients had failed initial open renal cryoablation and the remaining patient failed an initial complex partial nephrectomy. The finding of such significant disease progression illustrates how important it is for surgeons managing renal tumors to select appropriate therapeutic strategies based on the characteristics of the primary tumor.

Three post-operative complications were managed conservatively. However, no major intraoperative complications or injuries to any adjacent organs were reported. In contrast, in other published studies intraoperative and postoperative complications occurred in approximately 44% of cases (Table-2). Six of our patients received cryoablation delivered by different approaches. An increased complication rate in patients previously treated with cryotherapy has been described previously. However, in our study group the intraoperative complications were significantly less frequent.

Following the salvage renal surgery pathology revealed nonmalignant tumors or findings including oncocytoma in two patients and fibrosis in 1 patient. Park and Weight (11, 20) investigated the role of the imaging studies and biopsies in patients who underwent RFA or cryoablation. The authors concluded that for cryoablation, contrast enhancement was a reliable tool and follow--up biopsies were of low value whereas after RF ablation, radiologic findings were not reliable and follow-up biopsies had an impact on further decision making (11, 14). In our series, none of our patients underwent a confirmatory biopsy before the salvage procedure. Surgical decisions were based on supporting imaging studies.

Limitations of the current study include the retrospective nature of this report, the small number of patients included for review, the lack of pre-operative confirmatory biopsies prior to salvage renal surgery, and of course the inherent selection bias of patients chosen for salvage renal surgery. We did not include an evaluation of patients who were refused salvage surgery or who elected observation for a suspected recurrence of their tumors. However, our findings are comparable to other small series that share similar limitations.

CONCLUSIONS

Data from this study illustrates that while a re-operation can be challenging, it is both feasible and associated with adequate surgical, functional and oncologic outcomes. While the technically challenging nature of salvage renal procedures following a primary treatment can be associated with an increased frequency of complications, this is not associated with significant renal dysfunction or adverse oncologic outcomes.

ABBREVIATIONS

SRM = Small renal mass
SPN = Salvage partial nephrectomy
RCC = Renal cell carcinoma
eGFR = Estimated glomerular filtration rate
EBL = Estimated blood loss
NSS = Nephron sparing surgery

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Validation of Portuguese version of Quality of Erection Questionnaire (QEQ) and comparison to International Index of Erectile Function (IIEF) and RAND 36-Item Health Survey

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ABSTRACT

Purpose: To validate the Quality of Erection Questionnaire (QEQ) considering Brazilian social-cultural aspects.

Materials and Methods: To determine equivalence between the Portuguese and the English QEQ versions, the Portuguese version was back-translated by two professors who are native English speakers. After language equivalence had been determined, urologists considered the QEQ Portuguese version suitable. Men with self-reported erectile dysfunction (ED) and infertile men who had a stable sexual relationship for at least 6 months were invited to answer the QEQ, the International Index of Erectile Function (IIEF) and the RAND 36-Item Health Survey (RAND-36). The questionnaires were presented together and answered without help in a private room. Internal consistency (Cronbach's α), test-retest reliability (Spearman), convergent validity (Spearman correlation) coefficients and known-groups validity (the ability of the QEQ Portuguese version to differentiate erectile dysfunction severity groups) were assessed.

Results: We recruited 197 men (167 ED patients and 30 non-ED patients), mean age of 53.3 and median of 55.5 years (23-82 years). The Portuguese version of the QEQ had high internal consistency (Cronbach α=0.93), high stability between test and retest (ICC 0.83, with IC 95%: 0.76-0.88, p<0.001) and Spearman correlation coefficient r=0.82 (p<0.001), which demonstrated the high correlation between the QEQ and IIEF results. The correlations between the QEQ and RAND-36 were significantly low in ED (r=0.20, p=0.01) and non-ED patients (r=0.37, p=0.04).

Conclusion: The QEQ Portuguese version presented good psychometric properties and high convergent validity in relation to IIEF. The low correlations between the QEQ and the RAND-36, as well as between the IIEF and the RAND-36 indicated IIEF and QEQ specificity, which may have resulted from the patients' psychological adaptations that minimized the impact of ED on Quality of Life (QoL) and reestablished the well-being feeling.

ARTICLE INFO

Key words:
Erectile Dysfunction; Quality of Erection Questionnaire; Quality of Life; Cross-cultural adaptation

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INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to obtain or maintain an erection long enough to achieve a satisfactory sexual activity. ED affects from 12 to 69% males in the world, depending on the age group (1-7). The number of affected Brazilian men ranges from 3 to 48%,

depending on the measurement instrument used, being more prevalent in individuals of low educational level, and those who are hypertensive or diabetic (8, 9).

Clinical studies commonly use questionnaires in the evaluation of ED due to their capacity to evaluate physical, psychological and social aspects (10, 11). The International Index of Erectile Function (IIEF), and its short version IIEF-5, is one of the most used instruments. The IIEF is considered the gold standard and the IIEF-5 is largely used because of its short length with only 5 questions. However, the coverage of the multiple aspects of male sexuality besides erection by both instruments is questioned (12), since they deal only superficially with the patients' perception and satisfaction with their erections (13).

With the appearance of various ED treatment options, the assessment of self-perceived penile hardness has received more attention and been the subject of studies that have led to the development of a new short and patient-friendly assessment instrument, the "Quality of Erections Questionnaire" (QEQ) (13). It measures the patients' satisfaction with their erections and identifies those who would like to undergo treatment (14).

Since the QEQ covers physical, psychological and social aspects of male sexuality and focuses more on penile hardness and the patients' individual needs, it provides a differential assessment in relation to the IIEF (14, 15). This may favor the follow-up of clinical and psychosocial response to non-pharmacological ED treatment, such as physical therapy, and changes in life style. Apart from focusing on the erectile function, it is important to determine the impact of ED on quality of life (QoL). This study describes the correlations between the QEQ and the IIEF results in the quantification of ED and the QoL measured with the RAND-36, an instrument similar to the SF-36 (16), but which has a simpler scoring system and is publicly available.

MATERIALS AND METHODS

QEQ Translation and validation

The original English version of the QEQ was made publicly available by Pfizer New York® and has been translated to Brazilian Portuguese. After obtaining the author's permission, the QEQ was translated and backtranslated by two professors fluent in English for analysis of equivalence between the versions in the two languages. Next, urologists evaluated the adequacy of the Portuguese version (Figure-1).

Subjects

After approval of this study by Unicamp's ethics committee, 197 patients from a public andrology clinic were consecutively invited during routine consultations to participate in this study from January 2009 to February 2012 (Figure-2). The patient inclusion criteria were: having had a stable sexual partner for at least six months, being literate and over 18 years of age. The exclusion criteria were refusal to participate in the study and the use of IPDE-5 between the test and retest. If the patients were already using oral or injectable ED medication, they were instructed to answer the questions considering the effect of the medication in use.

The patients were informed about the purpose of the study by the examiner privately. After giving their written informed consent, the patients were requested to fill in an evaluation sheet and answer the QEQ and RAND-36. The evaluation sheet items were age, skin color, marital status, occupation, level of education, monthly income. Concerning diseases, the patients were asked about their ability to walk with or without aid, neurological diseases, diabetes, hypertension, heart disease, androgen deficiency of the aging male (ADAM), urological examination for description of the anatomic part and type of treatment received, when ED symptoms started and whether the treatment had already been started. The patients also replied questions concerning their life style such as alcoholism, smoking, regular physical exercising and number of attempts of sexual intercourse in the previous month.

The answers were checked after the patients had answered the evaluation sheets and the patients were asked to complete any missing information. When the questionnaires were fully answered, a new date was scheduled for the QEQ retest at about 28 days after the first test.

Figure 1 - Final version of the EQF in Portuguese

Questionário de Qualidade da Ereção (QEQ)

As questões seguintes perguntam sobre a qualidade das suas ereções ao longo das últimas quatro semanas. Por favor, para cada questão assinale a opção que melhor descreve sua resposta.

Ao responder estas questões, observe as seguintes definições:

Atividade sexual inclui relação sexual, carícias, brincadeiras amorosas e masturbação.

Relação sexual é definida como penetração (entrada) na vagina da parceira.

Satisfatória é definida como atingir suas expectativas, ter sucesso na relação sexual.*

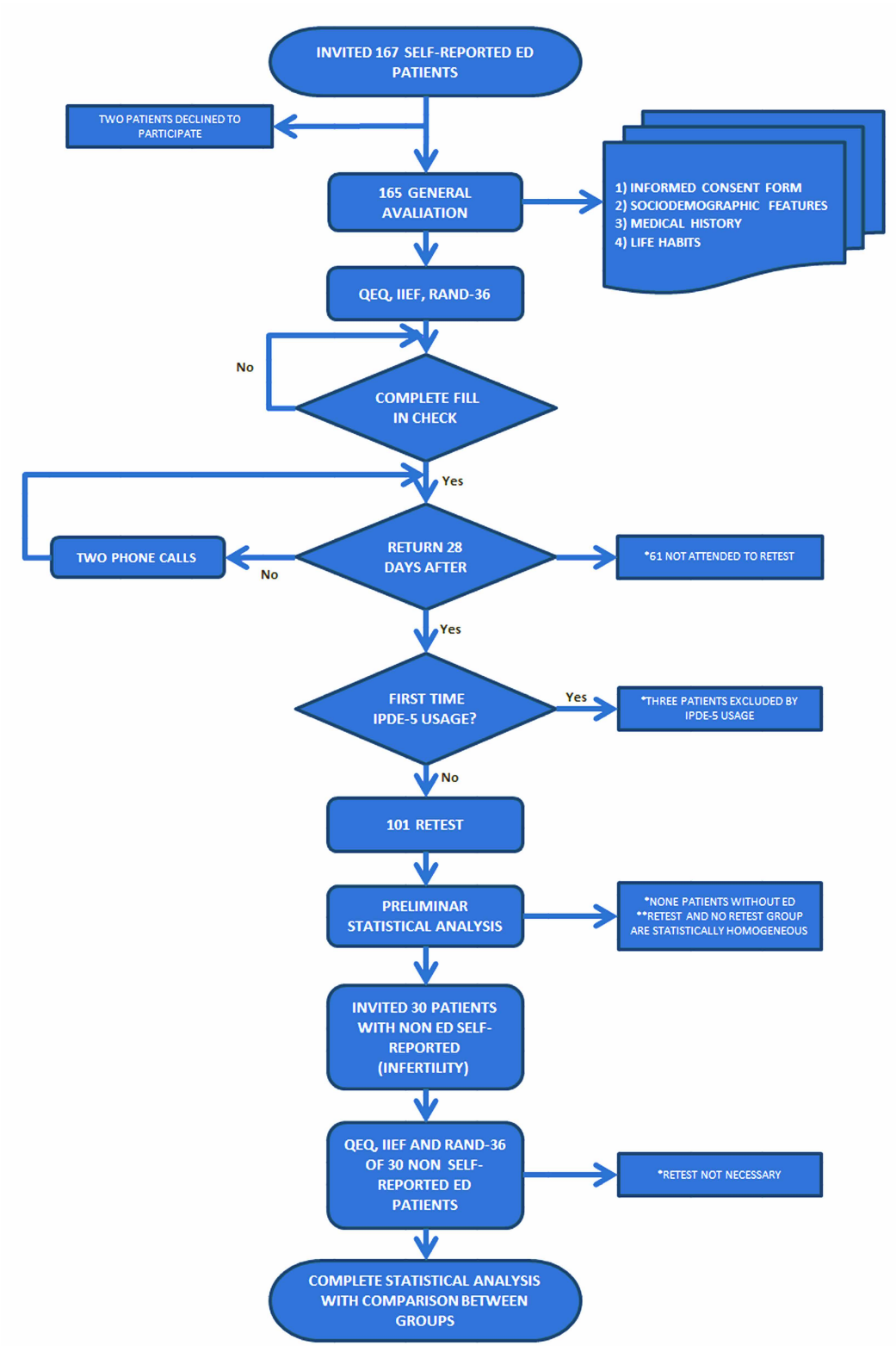
Insatisfatória é definida como falha das suas expectativas, falha do sucesso na relação sexual.*

1. Você teve ereções suficientemente duras para permitir a penetração em sua parceira
   - □*Quase sempre ou sempre*
   - □*Mais da metade do tempo*
   - □*Cerca da metade do tempo*
   - □*Menos da metade do tempo*
   - □*Quase nunca ou nunca*

2. Sua habilidade para manter sua ereção até o final da relação sexual foi:
   - □*Muito satisfatória*
   - □*Um pouco satisfatória*
   - □*Nem satisfatória nem insatisfatória*
   - □*Um pouco insatisfatória*
   - □*Muito insatisfatória*

3. A quantidade de tempo (desde que começou a atividade sexual) até que a sua ereção fosse suficientemente dura para participar de uma relação sexual foi:
   - □*Muito satisfatória*
   - □*Um pouco satisfatória*
   - □*Nem satisfatória nem insatisfatória*
   - □*Um pouco insatisfatória*
   - □*Muito insatisfatória*

Figure 2 - Study flow chart.



Instruments

To compare the instruments of measurement of sexual life and QoL, we took into account the time aspect. The questions of all the instruments used in this study (QEQ, IIEF and RAND-36) concerned the month previous to the survey.

IIEF

The IIEF was originally developed in English and validated for the assessment of the degree of severity of erectile dysfunction. It is made up of 15 items. It was translated to Portuguese (17) and validated in Brazil in 2013 (18) and is also available in another 32 languages (19). The questionnaire comprises five domains: erectile function, orgasm, sexual desire, sexual satisfaction and general satisfaction. The IIEF score is compartmentalized and ranges from 1 to 75 points.

The erectile function domain classifies the patients into five categories depending on the degree of severity of ED. Between 26 and 30 points, the individual is considered normal or without erectile dysfunction, between 22 and 25 point, as having mild ED, between 17 and 21 points, as having mild/moderate ED, between 11 and 16, with moderate ED, and from 1 to 10 points, with severe ED.

The sensitivity and specificity are adequate but the IIEF is limited by the exclusion of other aspects of male sexuality and the relationship with a partner (19).

QEQ

The QEQ was developed and validated in English and is made up of six items. It focuses on the patients' satisfaction with the quality of their erections. It takes into account the quality of erection, time necessary to achieve an erection and its duration (13-15).

The instrument can be filled out in 3 min and is sensitive in the assessment of changes resulting from effective ED treatments. It has demonstrated high internal consistency and one-dimensional structure. The final score ranges from 0 to 100 points. The higher the score, the better the quality of erection (13-15).

RAND 36-Item Health Survey

The RAND-36 is a general QoL evaluation instrument. It assesses physical aspects, pain, functional capacity, mental health, emotional aspects, social aspects, vitality and general health condition. Its questions are similar to those of the MOS SF-36 (16, 20), but it has a simplified score, developed by the International Resource Center for Health Care. All 36 items are scored from 10 to 100%, the higher the score, the better the health condition.

Statistical analysis

The study sample was profiled according to the investigation variables using frequency tables of categorical variables with absolute frequency (n) and percentage (%) values and descriptive statistics for continuous variables. Categorical variables were compared between groups using the Fisher exact test. Numerical variables were evaluated between two groups using the Mann-Whitney test, and between three or more groups with the Kruskal-Wallis test due to the lack of normal distribution of the variables.

The Spearman correlation coefficient was used to analyze the correlation between numerical variables. The QEQ (Brazil) score temporal stability (test-retest) was assessed with intra-class correlation (ICC), and the internal consistency of the translated version, with Cronbach's alpha coefficient. The statistical significance level for the tests was 5% ($p<0.05$).

RESULTS

Of the 197 respondents, most were white, 167 self-reported ED, were aged between 23 and 82 years, with a mean age of 57 and median of 58.5 years. The time elapsed before ED complaint varied from 0.3 to 25 years, with a mean of 4.9 years. 30 of the men without ED were under medical follow-up for infertility, age range of 23-61, mean age of 34 and median of 33 years.

Two of the men with self-reported ED declined to participate in the study and three were excluded because they used IPDE-5 between the test and the retest. Patients with infertility complaint

Table 1 - Caracteristics of patients with erectile dysfunction.

Variable	QEQ Test - Retest (n=101)	QEQ No Retest (n=61)	p
Age (mean)	58 (23-82)	55.08 (23-78)	0.260
Sexual frequency (per month)	6.37 (0-28)	4.88 (0-28)	0.340
Time from the beginning of symptoms (Years)	4.72 (0.3-20)	5.13 (0.3-25)	0.480
Use of PDE-5 inhibitor	33 (32.67%)	22 (36.07%)	0.660
Race			
White	90 (89.11%)	43 (70.5%)	
Black	4 (3.96%)	10 (16.39%)	0.007
"Brown" (Black/White)	7 (6.93%)	8 (13.11%)	
Age (decades)			
<50 years	24 (23.76%)	18 (29.51%)	
50-59 years	29 (28.71%)	16 (26.23%)	0.850
60-69 years	32 (31.68%)	19 (31.15%)	
≥ 70 years	16 (15.84%)	8 (13.11%)	
Familiar income per month*			
≤ 300	19 (18.81%)	20 (32.79%)	
600	33 (32.67%)	21 (34.43%)	0.094
900	44 (43.56%)	16 (26.23%)	
≥ 1200	5 (4.95%)	4 (6.56%)	
Literacy			
Literate	70 (69.30%)	51 (83.61%)	
High school	25 (24.75%)	6 (9.84%)	0.130
More than high school	6 (5.94%)	4 (6.56%)	
Co-morbidities			
Diabetes	36 (35.64%)	16 (26.23%)	0.210
Hypertension	54 (53.47%)	29 (47.54%)	0.460
Hypercolesterolemia	18 (17.82%)	20 (32.79%)	0.020
Hormonal treatment	10 (9.9%)	1 (1.64%)	0.054
Radiotherapy	6 (5.94%)	4 (6.56%)	1
Radical prostatectomy	6 (5.94%)	5 (8.2%)	0.710
Alcoholism	23 (22.77%)	15 (24,6%)	0.790
Smoking	10 (9.9%)	12 (19,67%)	0.080
Sedentarism	56 (55%)	30 (49%)	0.430

PDE-5 = phosphodiesterase type 5 / ** in American dollars (calculated by the authors using currency date 29/11/2012)

Table 2 - Caracteristics of patients without erectile dysfunction.

Variables	n=30
Age (mean)	34 (23-61)
Sexual frequency (per month)	11 (2-28)
Race	
White	29(97%)
Black	1(3%)
"Brown" (Black/White)	0
Familiar income per month*	
≤ 300	1(3%)
600	10(33%)
900	12(40%)
≥1200	7(23.33%)
Literacy	
Literate	4(13%)
High school	18(60%)
More than high school	8(27%)
Co-morbidities	
Diabetes	2(7%)
Hypertension	2(7%)
Hypercolesterolemia	0
Hormonal treatment	0
Radiotherapy	0
Radical prostatectomia	0
Etilism	1(3%)
Smoking	2(7%)
Sedentarism	19(63%)

*In American dollars (calculated by the authors using currency date 29/11/2012)

and without ED were intentionally included in this study for evaluation of equivalence of the questionnaires in the absence of ED. Age distribution and social and ethnic characteristics are detailed in Tables 1 and 2. The scores of men with self-reported ED are given in Table-3.

Some of the patients with ED (n=61) did not participate in the retest. However, the group of ED patients who did not come for or interrupted the retest was considered statistically homogeneous and were considered as a single group, the only significant difference being a greater number of hypercholesterolemia (Table-1).

The Portuguese version of the QEQ had high internal consistency (α Cronbach 0.93), high stability between test and retest (ICC 0.83, with IC 95%: 0.76, 0.88, p<0.001) and a Spearman correlation coefficient r=0.82 (p<0.001), which confirmed the high correlation between the values. No floor or ceiling effects were observed for ED patients that might compromise the reliability of the questionnaire translated into Portuguese, QEQ 0% in 15.43% and QEQ 100% in 4.32%.

The IIEF and QEQ scores of the population as a whole, including both ED and non-ED patients, were correlated. The strongest correlations were found between QEQ and total IIEF (r=0.73, p<0.001), between QEQ and Erectile Function (r=0.71, p<0.001) and between QEQ and the general sexual satisfaction domain (r=0.73, p<0.001). The correlation values are given in Table-4.

When the sample was stratified according to ED severity, as measured by the IIEF erectile function domain, significant differences were also observed between QEQ scores of non-ED and mild-to-severe ED men. The mean QEQ score difference for ED severity was 16.8 points. All values are given in Table-5.

The correlation between the QEQ and RAND-36 scores was r=0.40, p<0.0001; the domain details are given in Table 4. The comparison of the scores of the respondents within the same ED severity range according to the IIEF erectile function domain score revealed a difference between non-ED (mean total RAND-36 score 85.96%) and ED patients (mean total RAND-36 score 64.86%) for p<0.001 (Table-6). Additionally, there were differences between the RAND-36 general health perception of mild ED and moderate ED patients and between the scores of mild Ed and severe ED patients for p<0.0001. No statistical difference was found between the other ED patient groups (mild to severe).

Regarding the age of the respondents, the QEQ score was inversely proportional to age (r=-0.32 p<0.0001). The reported frequency of sexual intercourse correlated with the QEQ scores (r=0.45, p<0.0001).

Table 3 – Scores of IIEF, QEQ and RAND 36-Itens for patients with erection dysfunction.

SCORES	N	Mean	Median	Min-Max.	SD
International Index of Erectile Function					
Total	162	34.99	33.5	5-75	17.33
Subdomains					
Erectile function	162	13.12	12	1-48	8.51
Orgasmic function	162	5.38	5	0-10	3.57
Sexual desire	162	6.36	6.5	0-10	2.48
Intercourse satisfaction	162	5.65	5.5	0-15	4.19
Overall satisfaction	162	4.68	4	0-10	2.69
Quality of Erections Questionnaire					
Test	162	41.74%	37.50%	0-100%	31.89
Retest	101	38.66%	41.66%	0-100%	33.04
RAND 36-Item Health Survey					
Total	**162**	**64.36%**	**67.78%**	**8.75-95%**	**20.74**
Physical functioning	162	69.79%	80%	0-100%	28.67
Role limitations due physical problems	162	57.41%	50%	0-100%	39.79
Role limitations due emotional problems	162	60.90%	66.67%	0-100%	40.63
Vitality	162	61.55%	65%	0-100%	23.69
General mental health	162	65.39%	68%	0-100%	24.5
Social Functioning	162	70.68%	75%	0-100%	28.46
Bodily pain	162	64.46%	67.50%	0-100%	27.84
General health perceptions	162	57.16%	61.25%	12.5-100%	21.56

DISCUSSION

The use of questionnaires in ED research and evaluation is supported by arguments such as better ED symptom evaluation and treatment response (9, 17), greater rate of detection when compared to isolated questions (19) and improvement of communication between health professionals and patients about a subject still surrounded by "taboos", like impotency (21).

However, their supporters and critics are as many as the varied options of questionnaires. In clinical studies, the IIEF remains the gold standard (10, 11) despite its limitations: length and non-specificity to sexual performance, since it does not distinguish ED from premature ejaculation or alterations in sexual desire (11). The IIEF-5 complies with the health consensus guidelines regarding the evaluation of sexual performance in the previous 6 months (22). However, studies indicate a high ceiling effect, that is, a maximal score in 50% of the sample that impairs clinical assessment (12, 23). They also point out is use being limited to clinical practice because of the time period it covers (11).

The study sample was similar to those of other epidemiological studies, with a mean age of 53.3 years and association of ED with chronic diseases (1, 6, 24). In agreement with Araújo et al., 2004 (25), we also observed poorer erection with aging. Regarding ethnicity, white race predominated (p=0.007), which agrees with the general population of Southeast Brazil (26), where most of the population self-reported to be white or of European ancestry.

Table 4 - Spearman Correlation (QEQ Versus IIEF, QEQ Versus RAND 36-Item Health Survey, QEQ Versus Aging and QEQ Versus Sexual Intercourse Frequency).

Quality of Erections Questionnaires versus		
International Index of Erectile Function SCORE		
Total		**r=0.73 p<0.0001**
	Erectile Function	r=0.71 p<0.0001
	Orgasmic Function	r=0.51 p<0.0001
	Sexual Desire	r=0.36 p<0.0001
	Intercourse Satisfaction	r=0.64 p<0.001
	Overall Satisfaction	r=0.73 p<0.0001
RAND 36-Item Health Survey Score		
Total		**r=0.40 p<0.0001**
	Physical Functioning	r=0.37 p<0.0001
	Role Limitations Due Physical Problems	r=0.34 p<0.0001
	Role Limitations Due Emotional Problems	r=0.20 p=0.0042
	Vitality	r=0.23 p=0.0010
	General Mental Health	r=0.23 p=0.0012
	Social Functioning	r=0.19 p=0.0059
	Bodily Pain	r=0.14 p=0.0430
	General Health Perceptions	r=0.38 p<0.0001
Participants Age		
QEQ score		r=-0.32 p<0.0001
Sexual Intercourse Frequency		
QEQ score		r=0.45 p<0.0001

Non self-reported ED male infertility out-patients were intentionally included in the study to fill the patient gap in the QEQ development and validation in English. Only 1.25% of the patients studied by Porst et al. 2007 did not present ED or presented mild ED according to the IIEF classification (13).

The Portuguese version of the QEQ filled in this gap, since we obtained good correlations both in IIEF mild ED patients as well as non-ED patients. Additionally, the Portuguese QEQ version yielded psychometric properties similar to those of the original English version, with high internal consistency and high stability between test and retest.

An ED patient subgroup was absent in the retest. To better understand this fact, we investigated the causes of absence. Our hypotheses included lack of financial means and/or low education level that might have made access to a retest difficult, neither of which was confirmed by statistical analysis. Statistical significance was observed only for self-reported hypercholesterolemia between groups, which was interpreted as a random result without any clinical correlation.

The use of the QEQ Portuguese version is recommended for the evaluation of the response of Brazilian men to ED treatment based on its excellent psychometric properties and its easy and rapid application. On responding the QEQ, the patients do not need to recall each of the aspects involved in sexual intercourse, but rather the quality and satisfaction with their erections in the previous month (11, 13).

Table 5 - Correlation between Quality of Erections Questionnaires Score and Erectile Dysfunction (ED) degree.

Grade	Score	N	Mean QEQ	Median QEQ	Min-Max	SD	p
Normal	26-30	38	91.12	95.82	58.33-100	11.22	
Mild ED	22-25	22	69.12	68.75	29.16-100	18.92	
Mild-To-Moderate ED	17-21	23	59.42	62.50	8.33-100	25.35	<0.001
Moderate ED	11-16	38	39.03	37.50	0-100	24.13	
Severe ED	1-10	71	23.88	12.50	0-100	28.61	

Table 6 - Correlation between RAND 36-Items Health Survey (RAND) and Erectile Dysfunction (ED) Grade According International Index of Erectile Function (IIEF).

Grade	Score	N	Mean RAND	Median RAND	Min-Max	SD	P
IIEF Normal	26-30	38	85.96%	88.27%	60.71-98.19%	8.66	<0.001
IIEF Mild ED	22-25	22	73.12%	76.60%	35-94.03%	14.51	ns
IIEF Mild-to-Moderate ED	17-21	23	62.09%	66.67%	16.81-93.43%	20.58	ns
IIEF Moderate ED	11-16	38	62.81%	66.67%	29.72-90.83%	18.21	ns
IIEF Severe ED	1-10	71	61.42%	62.92%	8.75-92.92%	22.61	ns

ns = non significant.

The current version of the QEQ deals with the patients' perspective by including physical, psychological and social wishes (10, 11, 14, 27, 28) and sexual satisfaction. Patients with mild ED according to the IIEF classification may be rather dissatisfied while patients with severe ED may not be dissatisfied. The QEQ has the power to discriminate patients dissatisfied with their erection and thus driven to follow the proposed treatment (13, 15).

The impact of sexual dysfunction on QoL has been demonstrated by various studies (29-34). The expectation of a significant correlation between QoL and ED severity has not been confirmed. A significant difference in QoL was observed only in self-reported ED men, followed by non-ED infertile men. Only the general health perception subdomain of the RAND-36 presented significant difference between mild ED and moderate ED and between mild ED and severe ED patients.

In our sample, this correlation may have been influenced by the global evaluation of the patients. We point out that other factors besides ED may have affected the QoL of the studied population such as urinary incontinence, aches and osteoarticular pains. Additionally, at the time of evaluation, the mean ED length of time before complaint was 4.9 years (min 0.3 and max. 25 years) and the mean age of ED respondents was 57 years old.

The questionnaire scores correlated with the effects on QoL only in ED patients in comparison to non-ED patients, which was expected considering that non-ED patients presented fewer comorbidities such as diabetes, dyslipidemia and hypertension ($p<0.001$) and lower rates of alcoholism ($p=0.01$). However, the comparison of the QoL of mild-to-severe ED patients, according to the IIEF, gave similar and non significant values in relation to QoL measured with the RAND-36. We attributed this fact to the time elapsed since the beginning of the symptoms and the moment of evaluation and the patients' "adaptation" to their condition.

Studies have demonstrated the existence of psychological mechanisms that affords a well-being feeling to individuals even in adverse conditions. Generally, after three months, the individuals can interpret negative events such as the permanence of ED in a way that allows them to overcome it and minimize its impact on their QoL. This psychological transformation occurs unconsciously and automatically. Evidence shows that around the age of 60, negative events are overcome and even reconstructed even faster probably as a result of emotional learning over the years of life (35).

In fact, it has been described that only a small number of ED patients seek treatment spontaneously (36-38). In Brazil, only 21% of men with some form of sexual dysfunction seek specialized counseling and treatment (39), among which 30-57% of those who start treatment stop using ED medication (40-42).

The patients' lack of initiative to seek treatment is justified by a lack of perception of the severity of the disease and also because they consider ED a minor problem (37,39). We believe that these justifications agree with the action of

a psychological mechanism that minimizes the impact of ED on the QoL.

Van Damme-Ostapowicz, 2012 (43) reported a significant correlation between disease acceptance and better QoL indexes measured with specific questionnaires. Gades, 2009 (44) found evidence that despite the greater incidence of ED and greater functional loss with aging, the perception of ED as a problem tends to be minimized and despite the loss of QoL, dissatisfaction is little reported. Datta, 1989 (45) reported similar results in chronic diseases when the time elapsed allowed the patients to adapt to the loss of specific functions.

A study by Lindau et al., 2010 (46) revealed a correlation between better general health scores with sexual satisfaction in men and women and proposed using this correlation to improve treatment adherence and the modification of hazardous habits such as smoking.

While in men the erectile function and sexual satisfaction are affected by cardiovascular diseases, diabetes and prostate cancer, in women sexual satisfaction is situational and depends on the partner. Elderly men are more sexually active than women of similar age. In the 57-64 age group, 76.7% of the men and only 35.9% of the women reported interest in sex.

The general QoL questionnaire used in this study, RAND-36, has questions similar to those of the SF-36, which has already been translated to Portuguese and validated in Brazil (47), but has a simpler score developed by the International Resource Center for Health Care. The RAND-36 properties and design have good reproducibility, validity and susceptibility to alterations (16).

CONCLUSIONS

The Portuguese version of the QEQ presented high internal consistency and excellent stability between test and retest (r=0.82), in addition to good psychometric properties. It also presented strong correlations with the IIEF ED severity classification in the erectile function domain, which stimulates its use in further studies of the Brazilian population.

Differences in QoL as measured with the RAND-36 were observed only among patients with normal erectile function and those who complained about ED. Our study did not demonstrate a statistically significant association between ED severity and QoL worsening.

CONFLICT OF INTEREST

None declared.

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SURGICAL TECHNIQUE

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Single-port retroperitoneal renal biopsy using standard urological instruments

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ABSTRACT

Objective: To describe the surgical technique and initial experience with a single-port retroperitoneal renal biopsy (SPRRB).
Materials and Methods: Between January and April 2013, five children underwent SPRRB in our hospital. A single 1.5 cm incision was performed under the 12th rib at mid-axillary line, and an 11 mm trocar was inserted. A nephroscope was used to identify the kidney and dissect the perirenal fat. After lower pole exposure, a laparoscopic biopsy forceps was introduced through the nephroscope working channel to collect a renal tissue sample.
Results: SPRRB was successfully performed in five children. The mean operative time was 32 minutes, and mean estimated blood loss was less than 10 mL. The hospital stay of all patients was two days because they were discharged in the second postoperative day, after remaining at strict bed rest for 24 hours after the procedure. The average number of glomeruli present in the specimen was 31.
Conclusion: SPRRB is a simple, safe and reliable alternative to open and videolaparoscopic approaches to surgical renal biopsy.

ARTICLE INFO

Key words:
Kidney; Biopsy; Retroperitoneal Space; Surgical Procedures, Operative; Minimally Invasive Surgical Procedures; Laparoscopy

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INTRODUCTION

Image-guided percutaneous renal biopsy is the most widely used method to sample renal parenchyma for the evaluation of malignancy or diffuse renal disease. The risks of this procedure are minimal and the overall success rate of all renal biopsies varies from 70 to 100% (1). Its major indications rest on diagnosis and follow-up of several systemic and nephrological conditions that lead to glomerular damage and renal function impairment, providing useful data for treatment and prognosis. It may also be used for evaluation of solid renal masses and cystic renal lesions (1).

However, this method has absolute and relative contraindications that may hamper or preclude it, such as the presence of a solitary kidney, uncontrolled arterial hypertension, coagulation disorders, renal artery aneurysm, previous percutaneous needle biopsy failure and obesity. Bleeding and inadequate amounts of renal tissue for diagnosis are not infrequent, and constitute potential disadvantages of the procedure. In addition, children may be unable to cooperate, requiring general anesthesia.

In these settings, open and laparoscopic approaches are well-established alternatives and should be considered, although with a higher level

of invasiveness and complexity. In search for an alternative that could minimize surgical aggressiveness of these procedures and hence spread its use, we outlined a renal biopsy technique through a single retroperitoneal laparoscopic access using standard urological instruments. The aim of this paper is to describe the technique now standardized in our institution and our initial experience with the Single Port Retroperitoneal Renal Biopsy (SPRRB).

SURGICAL TECHNIQUE

After receiving general anaesthesia, orogastric and bladder catheterization, the patient is usually positioned in the left flank position, as the kidney is more easily accessible at the right side due to its lower position. Standard preparation of the surgical field is performed. A 1.5 cm incision is carried out just below the tip of the 12th rib, at the mid-axillary line, and is followed by blunt access to the retroperitoneum space. An initial digital dissection is done aiming to identify the lower renal pole, while also displacing the peritoneum anteriorly. During this step, care must be taken in order to avoid peritoneal tearing, as the pneumoperitoneum resulting from gas insufflation would hamper the maintenance of adequate retroperitoneal working space. Next, a rubber balloon is positioned between the kidney and the posterior abdominal wall, and is filled with 300-400 cc of saline, creating a virtual cavity. The saline is drained after a few minutes, to achieve hemostasis, and the balloon is then removed. An 11 mm trocar is inserted and carbon dioxide is used to maintain pneumoretroperitoneum at 12 to 15mmHg. Retroperitoneal inspection and identification of the psoas muscle and the lower pole of the kidney are now performed with a standard 26 French nephroscope, as shown in Figure-1. It is frequently possible to expose the renal surface bluntly, by using gentle movements of the tip of the scope to drag the perirenal fat away from the intended site of biopsy. Alternatively, standard laparoscopic surgical aspirator, scissors or hooks can be inserted through the working channel of the nephroscope, and then be used to dissect, cut and coagulate nearby structures, allowing a clear renal surface to be assessed. Once the biopsy site is cleared from fat, one or two samples are taken with the aid of a toothed biopsy forceps, also through the nephroscope (Figure-2). Bleeding is expected to be negligible, as the injury caused by the forceps is shallow (Figure-3), but the parenchyma can be coagulated with the same instruments, and a cellulose hemostatic bolster can be applied, if needed. Finally, the pneumoretroperitoneum is evacuated and, if no bleeding is observed, the trocar is removed and the access port is closed.

Figure 1 - Positioning of trocar and use of nephroscope for retroperitoneoscopy.

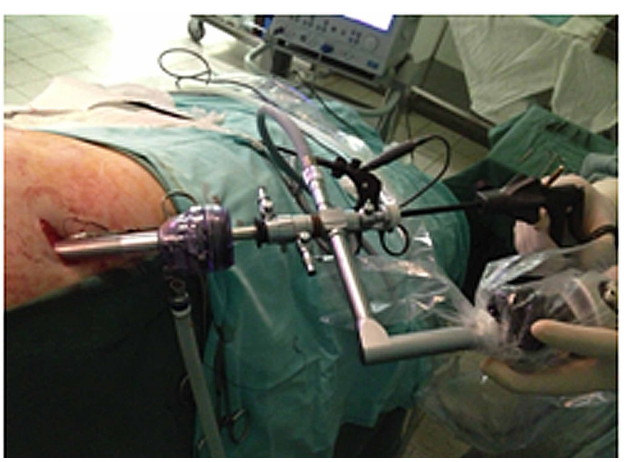


Figure 2 - Sampling renal parenchyma with a toothed biopsy forceps, through the nephroscope working channel.

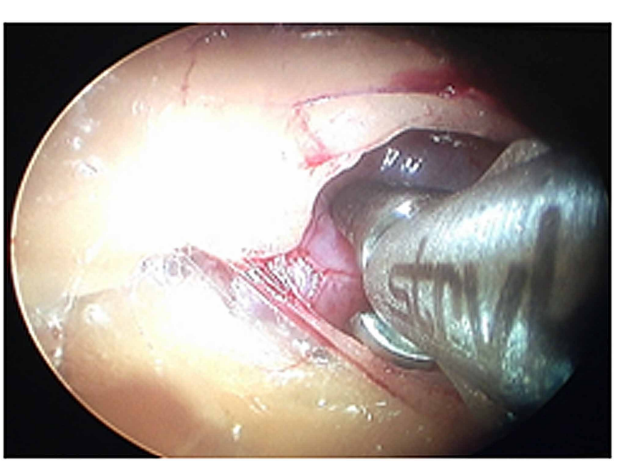
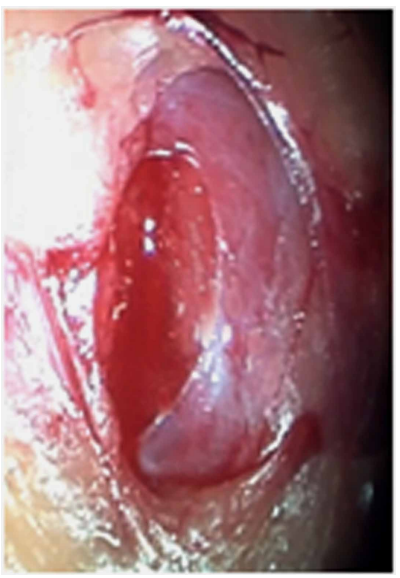


Figure 3 - Aspect of kidney surface after a tissue sample was taken, with only minimal bleeding.



COMMENTS

At our institution, laparoscopic retroperitoneal renal biopsy is currently often performed for pediatric patients with nephrological conditions (2). As the surgical team's experience progressed and the procedure was standardized, however, we felt that it should be even less invasive, especially for this very young population. Additionally, in order to spread and popularize its execution, we devised how to use instruments that are already present in a regular urological operating room, such as the nephroscope and laparoscopic scissors and forceps, in a different fashion. A similar approach has been described previously, in pediatric surgery, for appendectomies and varicocelectomies, but with only one case of renal biopsy (3).

Between January and April/2013, five children underwent SPRRB in our hospital, referred from the Nephrology Clinic for renal biopsy. Informed consent was previously obtained from parents, respecting our institution's Ethics Committee recommendations and approval. Clinical characteristics of these patients are summarized in Table-1. In all cases, the procedure was successfully performed with the technique above described, by a supervised resident in-training. The overall mean operative time was 32 minutes, and mean estimated blood loss was less than 10 mL. No open conversion was needed. The hospital stay of all patients was two days because they were kept in absolute bed rest for 24 hours after the procedure, before being discharged home. Pain and analgesics use were low, and there were no significant detected complications. Regarding the obtained samples, the average number of glomeruli present in the specimens was 31, and the histopathological findings showed focal proliferative lupus glomerulonephritis in two cases, diffuse mesangial proliferative glomerulonephritis in another two, and nephritis related to Henoch-Schönlein purpura in one child. These results are comparable to those previously shown by us, with laparoscopic renal biopsy in children, regarding operative time, blood loss, hospital stay and success in obtaining adequate samples (2).

Although it is likely that the same approach could be used in adult patients as well. Our experience with this very initial group was composed entirely of children, and SPRRB has been shown to be a very simple, safe and reliable alternative to other laparoscopic approaches. The use of a nephroscope, instead of a regular laparoscope, obviates the need to place an additional trocar for using an auxiliary instrument to dissect the perirenal fat, as is the standard practice (4, 5). Its working channel finely substitutes that, sparing one incision, the cost of another trocar and also surgical time to place it. Because a second trocar traditionally would be only 5 mm wide, it may seem that the benefit here is not strongly relevant in terms of postoperative pain or cosmetic results, but it is our understanding that no technical difficulty was added whatsoever, by using only one access. Moreover, especially children could benefit the most even of a small effect, and coincidently they constitute the majority of patients requiring a surgical renal biopsy in our hospital. Mini-perc nephroscopes are not available at our institution at this time, but its use could be a step forward, in this regard, and further decrease the required size of the access port incision. Additionally, the ease for urologists in using regular urological equipment, and the possibility that the surgeon simultaneously

Table 1 - Clinical features of patients submitted to Single-port retroperitoneal renal biopsy.

Patient	Gender	Age (years)	BMI (Kg/m^2)	OT (min.)	BL (mL)	GN	Diagnosis	Complications
1	M	07	23.6	25	4	23	Diffuse mesangial proliferative glomerulonephritis	None
2	F	09	24.5	37	13	38	Nephritis related to Henoch-Schönlein purpura	None
3	F	11	21.8	27	5	30	Focal proliferative lupus glomerulonephritis	None
4	M	10	24.0	40	17	43	Diffuse mesangial proliferative glomerulonephritis	Small skin ecchymosis
5	F	12	32.0	31	6	21	Focal proliferative lupus glomerulonephritis	None
Average	-	9.8	25.18	32	9	31	-	-

BMI = Body mass index (kg/m^2); **OT =** Operative time (minutes); **BL =** Blood loss (milliliters); **GN =** Number of glomeruli per biopsy.

controls both the camera and laparoscopic scissor/biopsy forceps, are other advantages of this alternative method.

In our hospital, retroperitoneal laparoscopy is the procedure of choice for renal biopsy in children and the SPRRB is an even less invasive option for these patients, performed through a single incision and with very satisfactory results and only minor pain.

ABBREVIATIONS

SPRRB = Single Port Retroperitoneal Renal Biopsy

CONFLICT OF INTEREST

None declared.

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Nephron-sparing surgery for treatment of reninoma: a rare renin secreting tumor causing secondary hypertension

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ABSTRACT

Main findings: A 25-year-old hypertensive female patient was referred to our institution. Initial workup exams demonstrated a 2.8 cm cortical lower pole tumor in the right kidney. She underwent laparoscopic partial nephrectomy without complications. Histopathologic examination revealed a rare juxtaglomerular cell tumor known as reninoma. After surgery, she recovered uneventfully and all medications were withdrawn.
Case hypothesis: Secondary arterial hypertension is a matter of great interest to urologists and nephrologists. Renovascular hypertension, primary hyperadosteronism and pheocromocytoma are potential diagnosis that must not be forgotten and should be excluded. Although rare, chronic pyelonephritis and renal tumors as rennin-producing tumors, nephroblastoma, hypernephroma, and renal cell carcinoma might also induce hypertension and should be in the diagnostic list of clinicians.
Promising future implications: Approximately 5% of patients with high blood pressure have specific causes and medical investigation may usually identify such patients. Furthermore, these patients can be successfully treated and cured, most times by minimally invasive techniques. This interesting case might expand knowledge of physicians and aid better diagnostic care in future medical practice.

ARTICLE INFO

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INTRODUCTION

Approximately 5% of patients with hypertension have specific secondary causes, which may be identified after meticulous medical history, physical examination, laboratory tests, and image workup. Secondary hypertension might be caused by several conditions affecting the kidneys, heart, arteries, or the endocrine system. Proper treatment addresses the underlying condition and tends to normalize blood pressure, reducing the risk of severe heart, kidney and brain complications.

The purpose of this article is to report and illustrate an interesting case where radiological investigation discovered a renal tumor as a possible cause of hypertension.

Cases hypothesis and rational

A 25-year-old female patient was referred for examination at our institution because of severe hypertension. She presented with daily mild headache for one year. When she arrived to our office, she was already taking propanolol, hydrochlorotyazide and spironolactone for blood pressure control. Physical examination was essentially normal except for persistent high blood pressure (Systemic Blood Pressure = 150x100 mmHg). She had no family history of hypertension.

Laboratory screening included serum sodium, calcium, potassium, aldosterone, renin, cortisol, catecholamines, and urinary metanephrines. Initial work-up revealed mild hypokalemia (3.4 mEq/L) and increased renin levels (7.7 ng/mL/h) with normal aldosterone (22 ng/dL). Other hormone levels were within normality. Doppler ultrasound did not reveal any abnormality in renal vessels flow. However, a 2.5 cm hypoecogenic mass was found in the right kidney. Contrast-enhanced computed tomography of the abdomen demonstrated a 2.8 cm, well circumscribed, solid, hypoenhancing cortical lower pole lesion in the right kidney with 100 Hounsfield Units (Figure-1). The patient was counseled on options regarding radical nephrectomy and nephron-sparing surgery, as well as alternative for open or laparoscopic intervention. She decided for laparoscopic partial nephrectomy and the procedure was accomplished without intra-operative complications. Total surgical time was 120 minutes and renal hilum clamping time was 14 minutes. Bleeding was negligible. The patient had an uneventful recovery and was discharge home in postoperative day one. Histopathologic examination revealed a rare juxtaglomerular cell tumor known as reninoma (Figure-2) after minucious immunohistochemical analysis, which was negative for Cytokeratin 35BH11, EMA, CD 34, CD 56, S-100, Chromogranin A, HMB-45, WT-1, and CD 31; and positive for AML (areas), vimentin (focally), ACTIN HHF35 (rare cels), and CD 117 (focally). Patient's blood pressure normalized within 2 months of surgery (Systemic Blood Pressure < 120x90 mmHg), allowing withdrawn of all medications.

DISCUSSION AND FUTURE PERSPECTIVES

Secondary hypertension is a topic of particular interest for urologists worldwide, mainly because it has potential causes that may be recognized and definitively treated by their specialty. Patients with severe or refractory hypertension, sudden onset of hypertension, high blood pressure before 20 year-old or after 50 year-old, spontaneous hypokalemia, and unexplained renal dysfunction are situations in which complete workup for secondary hypertension and its related pathologies should be performed. Renovascular hypertension, primary hyperadosteronism, and pheocromocytoma are among those causes and should always be ruled out (1-4). Although

Figure 1 - Contrast-enhanced computed tomography reveals a 2.8 cm, well circumscribed, solid, hypoenhancing cortical lower pole mass in the right kidney with 100 Hounsfield Units (axial and coronal view).

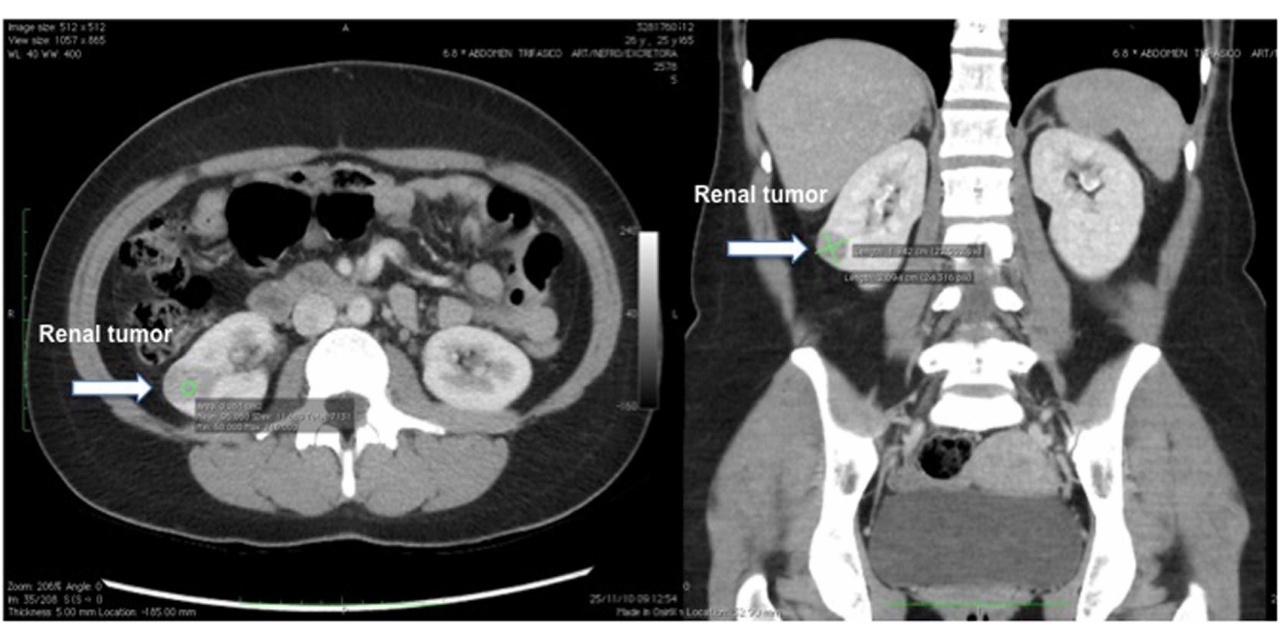
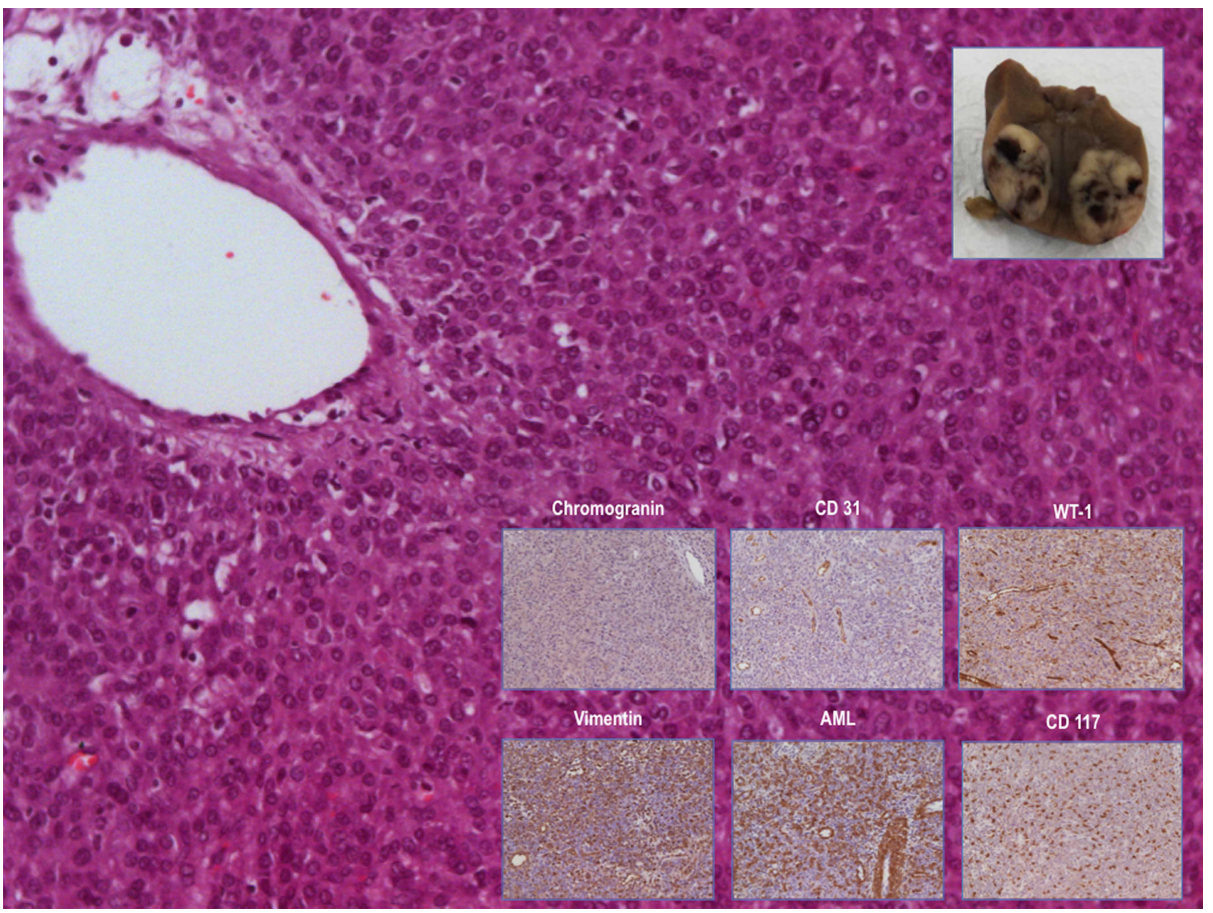


Figure 2 - Histological examination showing microscopic characteristics of juxtaglomerular tumor cells (Eosin and Hematoxylin): tumor cells with mild nuclear atypia, inconspicuous nucleoli and pale ill-defined cytoplasm; Immunohistochemical study negative for Chromogranin A, WT-1, and CD 31; positive for AML (areas), vimentin (focally), and CD 117 (focally).



rare, chronic pyelonephritis and renal tumors as renin-producing tumors, nephroblastoma, hypernephroma, and renal cell carcinoma might also induce hypertension by different mechanisms and should be a part of the clinician diagnostic list. The purpose of this article was to report and illustrate an interesting case where radiological investigation discovered a renal tumor as a possible cause of hypertension. Partial nephrectomy and pathological examination confirmed a juxtaglomerular cell tumor known as reninoma. The rationale is to provide the better care for patients with reversible causes of hypertension, diminishing their need for medications and cardiovascular risks.

In our case, a young female patient presented with severe hypertension. The above-mentioned diagnoses must be remembered so that appropriate investigation can be started. Renovascular hypertension is a condition in which patients have unilateral or bilateral renal artery stenosis and become normotensive when the vessel constriction is treated by angioplasty or surgery (1). The two main etiologies are fibromuscular dysplasia and atherosclerotic plaque. Doppler ultrasound is the most cost-effective study to screen renal artery stenosis, but it is dependent on the operator. The following option is nuclear magnetic angiography or computed tomography angiography. Atherosclerotic disease is more common in older patients

and has worse outcomes than fibromuscular dysplasia when treated by angioplasty (5).

This case was very illustrative to remind us that approximately 5% of patients with hypertension have reversible secondary causes (6). Here, we presented a patient with reninoma, an unusual cause of hypertension that mainly affects young individuals (7-9). The patient was successfully treated by minimally invasive laparoscopic nephron-sparing surgery, reducing the risk of loss of renal function and shorting hospital stay. Gottardo el al (8) reported the case of a 16-year-old hypertensive boy who presented with severe hypokalemia and markedly increased plasma renin activity. Abdominal ultrasonography and contrast-enhanced computed tomography revealed a 2 cm well-circumscribed, solid, hypoenhancing cortical lesion in the lower pole of the left kidney. The patient underwent open nephron-sparing surgery. Histopathologic examination revealed a juxtaglomerular cell tumor. In our case, immunohistochemical (IHC) study comprised vascular markers (CD31 and Vimentin), neuroendocrine tumor marker (Cromogranin), Mesothelioma marker (WT1), and hematopietic markers (CD117 and AML). All were negative or focally positive (Vimentin, CD117) and were used to exclude others rare renal tumors. Cases like reninoma do not have a specific pattern and IHC findings are inconsistent in the literature. Our diagnosis was based on microscopic characteristics such as tumor cells with mild nuclear atypia, inconspicuous nucleoli and pale ill-defined cytoplasm (8, 10).

Mete et al (7) reported a similar case in which a 14-year-old boy with hypertension and preoperative diagnosis of reninoma underwent open nephron-sparing surgery for a 2 cm mass in right kidney. The patient became normotensive postoperatively and follow-up intravenous urography showed bilateral normally functioning kidneys. Although image exams may find renal masses that could be associated to secondary arterial hypertension, there are other methods to prove such association. Wong et al (9) demonstrated the utility of both appropriate imaging studies and selective venous catheterization following provocative administration of an ACE-I for diagnosis of reninoma. We do not perform selective venous sampling routinely since it is a more invasive technique. Nevertheless, it may help in cases where all other diagnostic modalities have been performed and doubt regarding the specific cause of secondary hypertension persists.

General physicians, urologists and nephrologists are probably the most prone to seeing these patients in an office basis. We hope that our case may help these and other physicians in their future practice. Laboratory testing and image workup may identify the cause of secondary hypertension and guide therapeutic options as in our case. Untreated secondary hypertension culminates in complications such as heart failure, kidney failure and stroke. The detection of a secondary cause provides an opportunity to convert an incurable disease into a potentially curable one. Moreover, even when cure cannot be achieved, early recognition and management may prevent target organ damage, reduce socioeconomic burden and improve quality of life (11).

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

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Peripyelitis: A risk factor for urinary fistula after tubeless PCNL

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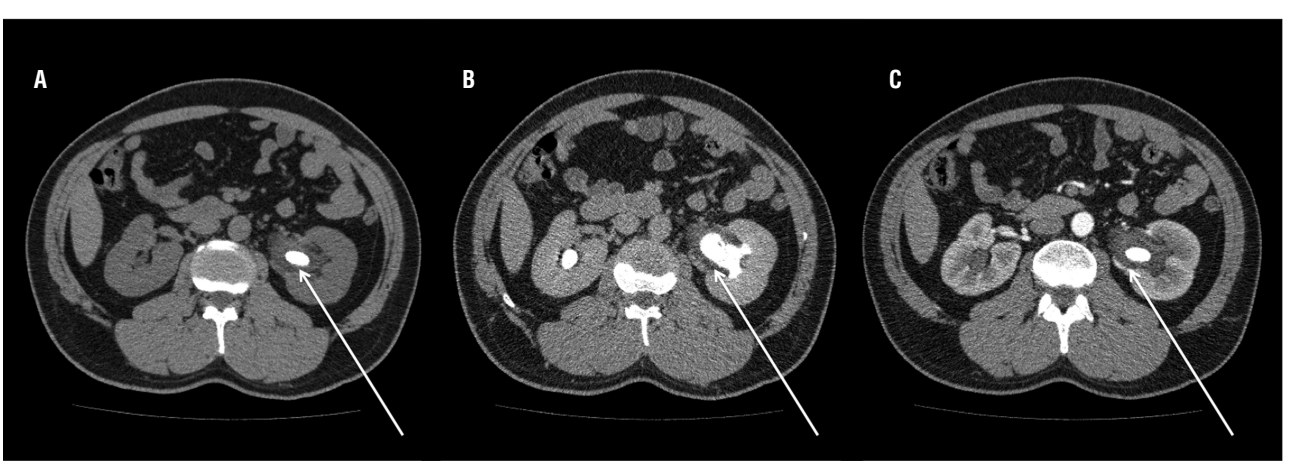
ABSTRACT

A 43 years-old man presented to our stone clinic complaining of back pain for the last 3 months. He had significant past medical history for nephrolithiasis: he had undergone unsuccessful SWL for left renal calculi five years ago and also presented with several episodes of pyelonephritis in the last months, requiring hospitalization for intravenous antibiotics. Initial laboratory work-up revealed normal serum creatinine (0.92 mg/dL) and hemoglobin levels (15.3 g/dL); urine culture was negative. Abdominal computed tomography (CT) revealed a 140 mm² stone in the left renal pelvis with 1500 Hounsfield Units (Figure-1a); thickening of the urothelium surrounding the stone was suspected after contrast infusion (Figure-1b) and confirmed in the excretory phase (Figure-1c).

Nonenhanced CT is the gold standard for detecting urinary calculi in the acute setting with reported sensitivity of 96% and specificity of 98% (1). Nearly all stones are visible on CT and secondary signs of obstruction are easily identified. Contrast-enhanced CT may be indicated if there are findings that suggest renal or other pathology which requires further evaluation (2). Our patient presented with significant edema surrounding the renal stone, fact correctly pointed-out by the radiologist reading the image exam.

The patient underwent a percutaneous nephrolithotripsy (PCNL) in the complete supine position as previously described (3). A single puncture in the middle calyx provided access to the collecting system. Tract dilatation was performed

Figure 1 - Abdominal computed tomography (CT) revealed a 140 mm² stone in the left renal pelvis with 1500 Hounsfield Units (a); thickening of the urothelium surrounding the stone was suspected after contrast infusion (b) and confirmed in the excretory phase (c).

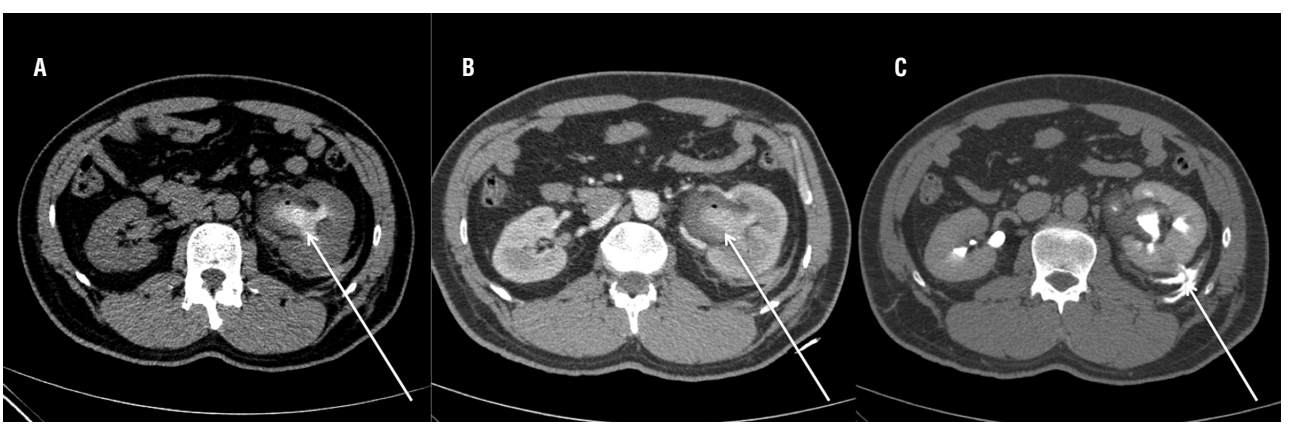


with sequential dilators. An ultrasonic device was used to break and eliminate stone fragments. No significant bleeding occurred and a 6 Fr ureteral catheter was left in place. No nephrostomy tube or double J stent were used. On the first postoperative day, the patient developed severe left flank pain. His serum creatinine was 1.14 mg/dL and hemoglobin 12.8 g/dL. Diagnostic CT scan showed no residual stones (Figure-2a); nonetheless, significant thickening of the urothelium with hyperdense material indicative of blood clots in the collecting system (125 HU; Figure-2b) and urinary extravasation to the retroperitoneal space through the puncture site (Figure-2c) were seen.

The patient underwent retrograde 6 Fr double J placement; left pain resolved after surgery. The ureteral catheter was removed after 4 weeks and the patient had no recurrence of symptoms or fistula.

Our main hypothesis is that bleeding from the collecting system with clot formation occurred due to the severe peripyelitis. Insufficient drainage due to clot obstruction and absence of a double J or nephrostomy tube led to fistula formation. Although based on a single case, an important lesson was learned: when preoperative CT reveals significant inflammation of the urothelium, adequate drainage of the collecting system is advised even when the surgery is uneventful and the patient becomes stone free. In most cases, peripyelitis' diagnosis can only be made with the expertise of an experienced radiologist.

Figure 2 - Diagnostic CT scan showed no residual stones (a); nonetheless, significant thickening of the urothelium with hyperdense material indicative of blood clots in the collecting system (125 HU; b) and urinary extravasation to the retroperitoneal space through the puncture site (c) were seen.



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VIDEO SECTION

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Robotic transmesocolonic Pyelolithotomy of horseshoe kidney

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ABSTRACT

Introduction: The purpose of this video is to demonstrate the use of the robot to perform a transmesocolonic pyelolithotomy of a horseshoe kidney.
Materials and Methods: A 35-year old female presented with vague abdominal pain. CT scan imaging revealed the presence of a left horseshoe kidney with multiple pelvicalyceal stones. The patient was positioned in the supine position. A total of 4 ports were introduced. A 3-arm da Vinci robotic surgical system was docked, and the arms were connected. First, the dilated renal pelvis was identified behind the thin mesocolon. The mesocolon was entered and renal pelvis was dissected completely from the surrounding fat. Then, the renal pelvis was opened after adequate dissection and stones were visualized inside the calyces. By Prograsp forceps, stones were removed from all the calyces under vision and were extracted from the assistant trocar. Finally, the pylotomy incision was closed using 4 0 Maxon in a continuous fashion and the mesocolon was closed using 3 0 PDS interrupted sutures. A JP drain was placed.
Result: Operative time was forty-five minutes, blood loss was 100 ml. The patient was discharged after 48 hours with no immediate complications.
Conclusion: The utilization of minimal invasive surgery using the robot to extract multiple pelvicalyceal stones from a horseshoe kidney without reflecting the mesocolon proved to be a feasible and novel way in the management of complex stone disease improving the outcome with minimal morbidity.

ARTICLE INFO

Available at: www.brazjurol.com.br/videos/january_february_2015/Rajih_179_180video.htm

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EDITORIAL COMMENT

In this video Rajih and colleagues nicely detail the transmesocolic approach for robot-assisted laparoscopic pyelolithotomy. Their patient had a significant stone in a horseshoe kidney. In select patients, laparoscopy can facilitate the removal of large stones. Flexible endoscopes can also be deployed through the laparoscopic trocars in order to ensure complete stone removal (1). With a transmesocolic approach, mobilization of the colon is not necessary. The renal pelvis can be directly accessed after incision of the mesocolon. This approach is best suited for patients with a thin mesentery when extensive mobilization of the kidney is not required (2). Robotic technology can also help with concomitant repair of a ureteropelvic junction obstruction if present (3).

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LETTER TO THE EDITOR

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RE: Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination

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Int Braz J Urol. 2014; 40: 443-53

To the editor,

Dr. Sandro Esteves and collegues, from Brazil, performed on page xx at this issue of the International Braz J Urol an elegant review that discuss how the new World Health Organization (WHO) criteria for seminal parameters could affect the clinical management of men presenting with male infertility. The authors emphasized the factors that limit the use of seminal parameters as a surrogate for male fertility and also propose a template to be used for semen analysis reports to allow a better interpretation for clinicians.

Biological proof of male sterility is only present in cases of azoospermia or in the presence of a complete lack of sperm motility. Since such cases of male sterility are uncommon, clinicians presume to obtain a clear indication of a man's fertilizing potential from semen analysis. That would be finding a cutoff value in order to determine which number of sperm count, motility or morphology could better differentiate fertile patients from subfertile patients. The precise statistical test to find this "magical" number would be through a generation of a receiver operating characteristic curve which examined various cutoff values to determine one with high sensitivity, specificity and accuracy that would be superior in differentiating both populations. Unfortunately, the application of this test may be relevant in relation to certain clinical tests including levels of sodium or potassium in serum, but are unsuitable for seminal parameters because there is a significant overlapping distribution in the sperm characteristics between fertile and subfertile populations (1, 2).

The definition of "normal" semen quality has changed over time (3, 4). The 2010 WHO guidelines have reduced the reference limits for seminal parameters, in the sense that the 'normal' reference range was defined as the one that covers 95% of a population (5). The current suggested reference values fail to satisfy clinical and statistical standards and pose the risk of misclassifying a subject's true fertility status (2). Moreover, the introduction of these new values to the clinical practice is likely to result in a reclassification of many infertile couples (6). As an example, those couples previously classified as having male factor infertility with sperm parameters greater than the new reference limits, but less than the previous values, probably, will now be diagnosed as having unexplained infertility. Moreover, as the newest lower reference limits are even lower than the previous reference values, clinicians will likely be faced with an increased number of men presenting with treatable causes of infertility, as varicocele, and semen parameters within the "normal reference" values. Since the recommendation for varicocele treatment has been based on the results of routine seminal parameters, an important question has now risen: Should we perform a varicocele repair for an infertile

men presenting with clinical varicocele and sperm concentration of 16 million/ml? According to the current guidelines for varicocele management, treatment should be offered to men with clinical varicocele in the presence of abnormal semen analyses. The application of the new reference values might consider ineligible for treatment many men previous submitted to varicocelectomy, as many previous abnormal semen analysis will now be considered "normal". Therefore, these patients will not only be left without treatment but also will not even be referred for male infertility evaluation.

It is tempting to suggest that the lower reference limits of semen parameters, as proposed by the most recently WHO manual, are part of gradual declines in sperm count extensively reported over the past decades, and that these changes might be responsible for a possible decline in the fertility rates in the industrialized world (7). The stated drop in semen quality is a matter of great interest since it has been associated with an adverse trend for an increased incidence of other urologic male disorders including testis cancer and undescended testis. The observed effects have been linked to lifestyle and environmental exposures to endocrine disrupters. However, currently, there is no scientific truth of a causative role for endocrine disruptors in the temporal decline of sperm production as well as there is no enough evidence to confirm a worldwide decline in sperm counts or other semen parameters (8). As a result, one must exercise caution when concluding that the newly proposed lowered WHO reference values can be justified by the suggested decline in global sperm quality, because it is more probable that such differences are instead related to a methodological bias created by different ways of generating reference values (6).

The 2010 WHO manual still retains the nomenclature that is regularly applied by some to describe deviations from reference semen values. The use of words rather than numbers such as oligozoospermia, asthenozoospermia and teratozoospermia, do not allowed for an exactly knowledge were the result is according to the complete reference interval. I perfectly agree with the authors that such terminology should be abandoned. Seminal parameters results should be reported only numerically to allow an appropriate individual interpretation. In addition, the proposal of a new template for seminal analysis report including the full reference interval is an excellent suggestion allowing a better understanding for clinicians as well as patients when interpreting seminal parameters numbers by comparing the specimen results with the entire reference group distribution.

In conclusion, the current WHO guidelines for normal semen quality should be used with caution. We must keep in mind that the interpretation of the reference ranges for semen parameters requires an understanding that seminal parameters within the 95% reference interval do not guarantee fertility nor do values outside those limits necessarily indicate male infertility (5). Although, the 2010 WHO manual aimed to provide evidence-based thresholds that would aid clinicians in estimating the relative fertility of a given patient, seminal parameters absolutely do not allow the definitive classification of patients into fertile or infertile.

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LETTER TO THE EDITOR

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RE: Minimal Hydrocelectomy with the aid of scrotoscope: a ten-year experience

Yan Bin, Wei Yong-Bao, Yin Zhuo, Yang Jin-Rui

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Int Braz J Urol 2014; 40:384-9

To the editor,

Dear editor, we would like to discuss on the article on "Minimal hydrocelectomy with the aid of scrotoscope (1)". Bin et al. concluded that "the combination of minimal hydrocelectomy and scrotoscopy seems to be an encouraging technique (1)". This result can support the previous observation that minimally invasive hydrocelectomy is safe and requires a short operative time (2). It is agreeable that the technique can be useful but the case selection is the important prerequisite. As noted by Bin et al., some cases (such as those with thickening) still required open surgery (1). Focusing on scrotoscope, it is a useful tool for assessment of scrotal contents (3). However, it is still considered as an invasive technique. According to our experience from China, the use of B-ultrasonography, which is totally non invasive, can give no different ability to assess scrotal contents (4).

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REPLY BY THE AUTHORS

Dear editor,

Thanks for the discussion on our article "Minimal hydrocelectomy with the aid of scrotoscope" (1). It is undeniable that sccrotoscope is an invasive technique and B-ultrasonography is an predominant diagnostic technique in scrotal lesions. However, in our previous study comparing the diagnostic preciseness of scrotoscope and B-ultrasonography on scrotal lesions, the results demonstrated that scrotoscope has an higher effectiveness rate, especially in distinguishing a benign lump from a tumor (2). As a result, scrotoscope remains to be valuable in scrotal diseases and it is worth be to developed.

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The authors

LETTER TO THE EDITOR

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RE: Proximal bulbar periurethral abscess

Sarah D. Blaschko, Dana A. Weiss, Anobel Y. Odisho, Kirsten L. Greene, Matthew R. Cooperberg

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Int Braz J Urol. 2013;39:137-8

To the editor,

We read the article by Dr. Blaschko et al. with interest (1). They reported a 67 year-old diabetic male with persistent leukocytosis despite appropriate antibiotic treatment for pneumonia. After computed tomography (CT) evaluation, a 3.5 centimeter rim enhancing fluid collection at the level of his bulbar urethra was noticed. In the next step, under the guidance of transrectal ultrasonography, they performed transrectal ultrasound-guided needle aspiration and, pus was aspirated from the lesion. The abscess fluid culture was negative. Accordingly, we presented a 63-year-old male admitted with the complaints of dysuria, difficulty in urination, pain and hyperemia in ventral side of the penile shaft for 3 months. One month later, his complaints were increased and he consulted an urologist. Under local anesthesia, the urologist treated the patient by small penile shaft incision and drained pus. As in the case reported by Dr. Blaschko et al., our patient completed a two-week antibiotic course per infectious disease recommendations. The abscess culture was also negative in our case. However, during follow-up, the complaints did not resolve. We decided to re-operate the patient. We incised the skin and obtained a biopsy from the floor of the abscess cavity. Histopathological examination showed moderately differentiated squamous cell carcinoma (SCC). The patient was a heavy smoker and circumcised at the age of 7 years. There was no previous history of genital warts and urethral discharge. During last visit, on physical examination, destruction of the urethra and possible invasion into corpus spongiosum was suspected. Partial penectomy was performed (Figures 1a and b). Histopathological examination confirmed the diagnosis of SCC (moderately differentiated) with 1.8 cm tumor free resected margins. In addition, corpus spongiosum invasion was also reported. An (18)F-FDG PET/CT exploration showed hypermetabolic lymphadenopathies in bilateral inguinal lymph nodes (SUV max=2.3). Bilateral modified radical inguinal lymphadenectomy was performed. Histopathological examination revealed reactive lymph nodes without tumoral infiltration. For today, the patient feels good without any complaints.

We think that, in suspected cases, after drainage of the abscess, the scrapings from the abscess wall or a part of any non-healing ulcer must be sent to pathological or cytological examination. In certain cases ultrasound guided biopsy can also be done. In case reported by Dr. Blaschko et al., as the patient had subsequent rapid clinical improvement after the aspiration of abscess confirmed by radiological imaging, they did not send any specimen for cytological or histological examination. But, we must keep in mind that, resistant abscess formations or non-healing ulcers especially in genital regions should be evaluated for neoplasia. Because, as we see in our case, SCC can masquerade as a periurethral abscess.

Another important point we need to mention is about the etiologic factors related to SCC of penis. As we all know, the risk factors for developing SCC on the penis include lack of circumcision,

Figure 1a - During partial penectomy, after degloving of the penis inner wall of the previously drained periurethral abscess was exposed (arrowhead).

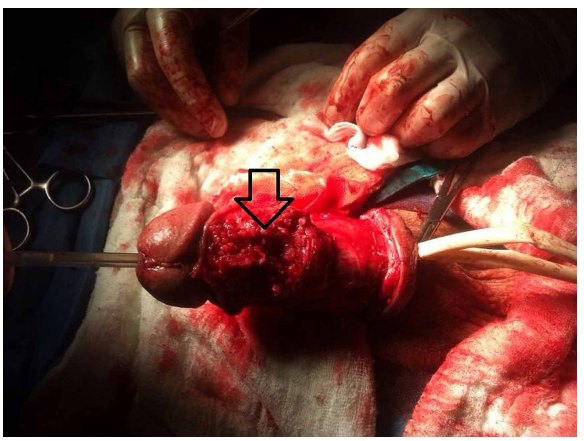
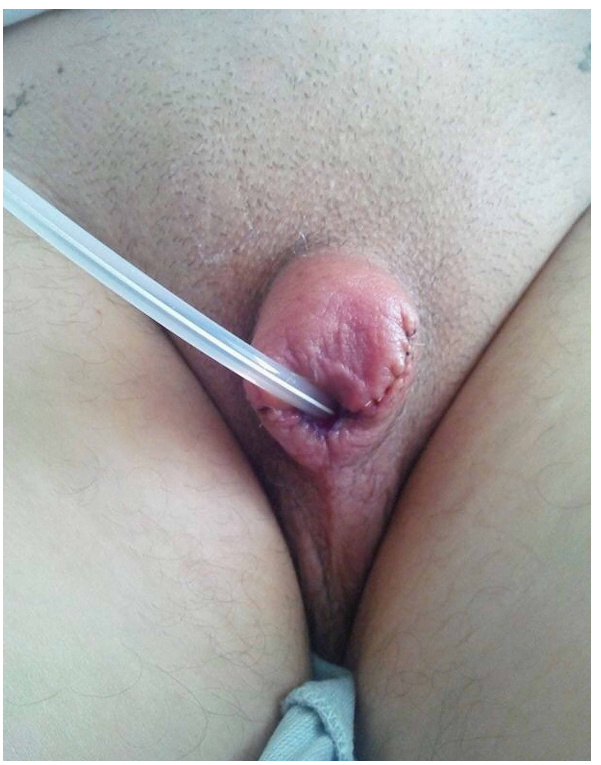


Figure 1b - Appearance of the penis 2 days after the operation.



HPV infection, chronic balanitis, smoking and phimosis. The only risk factor documented in our patient was cigarette smoking. So, smoking may have a greater impact on the development of penile SCC in populations ritual circumcision in early childhood period is common as in our country.

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Books:
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