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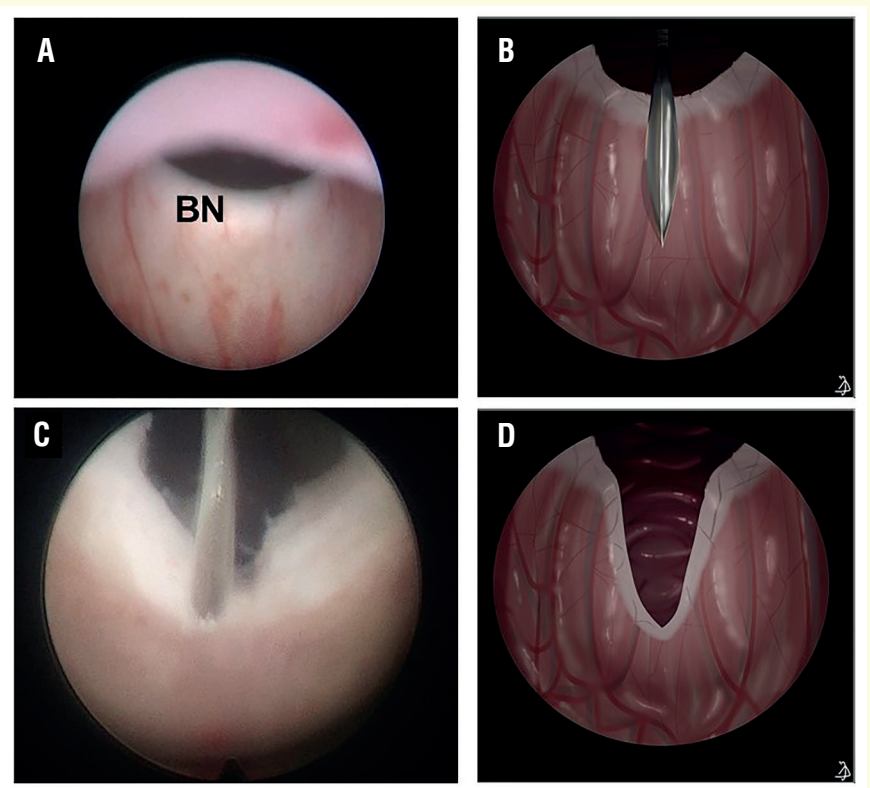

A) before the incision, the posterior lip of the bladder neck (BN) is elevated, making it difficult to visualize the bladder lumen while the tip of the scope at the level of the verumontanum. Also, the tip of the scope has to be aggressively deflected upwards to gain access to the bladder, B) schematic drawing of elevated BN with the cold knife in place, C) a single incision is performed using the sickle-shaped cold knife at 6 o'clock until the bladder can be accessed easily without the need to significantly deflect the scope, D) schematic drawing of figure C. (page 487)

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EDITORIAL
IN THIS ISSUE

Upper tract urothelial carcinoma and bladder cancer in review in this number of International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

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The May-June number of Int Braz J Urol, the 16th under my supervision, presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Male Infertility, Overactive Bladder, Bladder Cancer, Upper urothelial carcinoma, renal stones, sexual dysfunction, PUV, Dysfunctional voiding and Uroanatomy. The papers came from many different countries such as Brazil, USA, Canada China, Italy, India, Denmark, Belgium and Egypt, and as usual the editor´s comment highlights some of them.

In the present issue we present two important reviews about upper urothelial carcinoma (UUC) and bladder cancer. The paper about UUC of the group of Dr. Sharma from India in page 406 shows a very complete systematic review about the topic (1). The authors shows that the tumor grade, stage, presence of lymphovascular invasion, lymph node metastasis, hydronephrosis, variant histology, sessile architecture, margin positivity and multifocality were associated with poor recurrence free survival (RFS), cancer-specific survival (CSS) and overall survival (OS). Presence of carcinoma in situ was associated with poor RFS and CSS but not OS. Tumor necrosis was associated with worst CSS and OS but not RFS. Tumor location was not a predictor of any of the survival parameters. Dr. Korkes and colleagues from Brazil and USA in page 397 (2) in a interesting narrative review about bladder cancer shows that patients with low-grade-non-muscle-invasive bladder cancer that TURBTs, chemoablation, BCG immunoablation, partial cystectomy, radical cystectomy, radiotherapy, and chemotherapy are attractive modalities to treat them effectively and proposes an algorithm to overcome these challenges. The editor in chief would like to highlight the following works too:

Dr. Mazzucchi and colleagues from Brazil and Canada, presented in page 456 (3) a nice review about the single use flexible ureteroscopes and concluded that these ureteroscopes are lighter and have superior quality of image when compared to fiberoptic ones and that there are no definite data showing a higher stone-free rate or less complications with the use of single-use flexible ureteroscopes.

Dr. Sobrinho and colleagues from the Urogenital Research Unit from Brazil performed in page 561 (4) a interesting translational study about the lower pole anatomy in anomalous kidneys and concluded that the knowledge of spatial anatomy of lower pole is of utmost importance during endourologic procedures in patients with kidney anomalies. The horseshoe kidneys had more restrictive anatomic factors in lower pole than the complete ureteral duplication.

Dr. Laursen and colleagues from Denmark and Brazil performed in page 471 (5) a nice study about the recombinant gonadotropin therapy to improve spermatogenesis in nonobstructive azoospermic patients and concluded that hormonal therapy with recombinant gonadotropins could be considered in infertile men with nonobstructive azoospermy as an alternative to sperm donation. Large-scale studies are needed to substantiate hormone stimulation therapy with recombinant gonadotropins in routine clinical practice for this severe form of male infertility.

Dr. Abdelhalim and colleagues from Egypt performed in page 485 the paper that is the cover in this edition (6). In this paper the authors assess the effect of bladder neck morphology and its incision (BNI) in patients with posterior urethral valve (PUV) on early reintervention rate and concluded that in morphologically high bladder neck associated PUV, concomitant BNI with posterior valve ablation doesn't reduce early re-intervention rate.

Dr. Schulze and colleagues from Brazil performed in page 493 an important report about robotic surgery (7). The authors evaluated whether criteria exist to guide election between the use the three- or four-arm technique in robotic partial nephrectomy (RPN) instead of just the surgeon's preference and concluded that the two robotic partial nephrectomy techniques had similar oncological and postoperative outcomes, with minimal perioperative complications. The three-arm technique is safe and feasible regardless of the complexity and size of the tumor. Additionally, the use of the three-arm technique reduced surgery costs by US$ 413.00 per patient.

The Editor-in-chief expects everyone to enjoy reading.

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REVIEW ARTICLE

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Incontinence after laparoscopic radical prostatectomy: a reverse systematic review

Wilmar Azal Neto [1], Diego M. Capibaribe [1], Luciana S. B. Dal Col [2], Danilo L. Andrade [1], Tomas B. C. Moretti [2], Leonardo O. Reis [1,2]

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ABSTRACT

Purpose: To report the prevalence of the definitions used to identify post-prostatectomy incontinence (PPI) after laparoscopic radical prostatectomy (LRP), and to compare the rates of PPI over time under different criteria.

Materials and Methods: In the period from January 1, 2000, until December 31, 2017, we used a recently described methodology to perform evidence acquisition called reverse systematic review (RSR). The continence definition and rates were evaluated and compared at 1, 3, 6, 12, and >18 months post-operative. Moreover, the RSR showed the "natural history" of PPI after LRP.

Results: We identified 353 review articles in the systematized search, 137 studies about PPI were selected for data collection, and finally were included 203 reports (nr) with 51.436 patients. The most used criterion of continence was No pad (nr=121; 59.6%), the second one was Safety pad (nr=57; 28.1%). A statistically significant difference between continence criteria was identified only at >18 months (p=0.044). From 2013 until the end of our analysis, the Safety pad and Others became the most reported.

Conclusion: RSR revealed the "natural history" of PPI after the LRP technique, and showed that through time the Safety pad concept was mainly used. However, paradoxically, we demonstrated that the two most utilized criteria, Safety pad and No pad, had similar PPI outcomes. Further effort should be made to standardize the PPI denomination to evaluate, compare and discuss the urinary post-operatory function.

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INTRODUCTION

The rate of prostate cancer (PCa) detection is currently increasing, and so is the rate of radical prostatectomy (RP). Urinary incontinence is a potential adverse event after RP for PCa, which leads to a significant worsening of quality of life (1).

Nevertheless, there is no international consensus on the optimal way to define, assess and grade post-prostatectomy incontinence (PPI). This heterogeneity in evaluating this aspect potentially explains the different prevalence rates reported, detains ideal comparison, and delays enlightenment of the question. The most common definitions of continence when evaluating PPI are based on the use of pads; however, they exclude patients who report any leakage - with no pad use-, which is the definition of incontinence promoted by the International Continence Society (ICS) (2, 3). Also, widely used criteria are

the "no leak", "no pad" or "safety pad", while some are still grading PPI through a validated symptom scale of objective and subjective experience (4).

Our primary objective was to report the prevalence of the definitions used to identify PPI after laparoscopic radical prostatectomy (LRP), and secondly, to compare the rates of PPI overtime under these different criteria. To reach this propose we used a novel methodology described by our group, which can delineate the "natural history" of an issue reported along its timeline, called reverse systematic review (RSR). In the RSR, clinical evidence starts from general information, in this case, LRP, to then is filtered until it reaches a specific knowledge, such as PPI, through a wide search criterion (5).

MATERIALS AND METHODS

Since reverse systematic review (RSR) is a novel methodology, it is not possible to register in international database of prospectively registered systematic reviews such as PROSPERO.

Systematized research for evidence acquisition for the RSR was carried out in January 2018 and we searched systematic reviews (SR) articles, with or without meta-analysis, that approached the topic LRP. We did not study papers in 2019 and 2020 because there were very few SR about LRP in this period, since robotic assisted laparoscopic prostatectomy predominates more recently. The databases used were: PubMed, Web of Science, Cochrane Library, Embase, ProQuest, CINAHL (The Cumulative Index to Nursing and Allied Health Literature), BVS/Bireme, and Scopus. Only papers in English were considered for our search, in a period within January 1, 2000, until December 31, 2017. Reviews without a clear and systematized search methodology, integrative methodology, expert consensus, and abstracts or summaries were excluded.

After we identified the two most used criteria of continence when assessing PPI (No pad and Safety pad), results were divided into three groups: No pad, Safety pad, and Others (No leak, any score, no precise information). The continence rates were evaluated at 1, 3, 6, 12, and >18 months post-operative. Finally, we compared the respective criteria of continence reported and their rates at the different post-operative moments.

Descriptive and arithmetic methods were used to describe the samples (mean and median) and dispersion (standard deviation, standard error of the mean, and confidence interval). Parametric distributions were compared through one-way ANOVA and post-hoc analysis with Bonferroni's correction. Otherwise, non-parametric distributions were compared with the Kruskal-Wallis test. In all analyses, a significance level of 5% ($p < 0.05$) was used for 2-tailed interpretation. Calculations were performed with the IBM SPSS Statistics v.24.

RESULTS

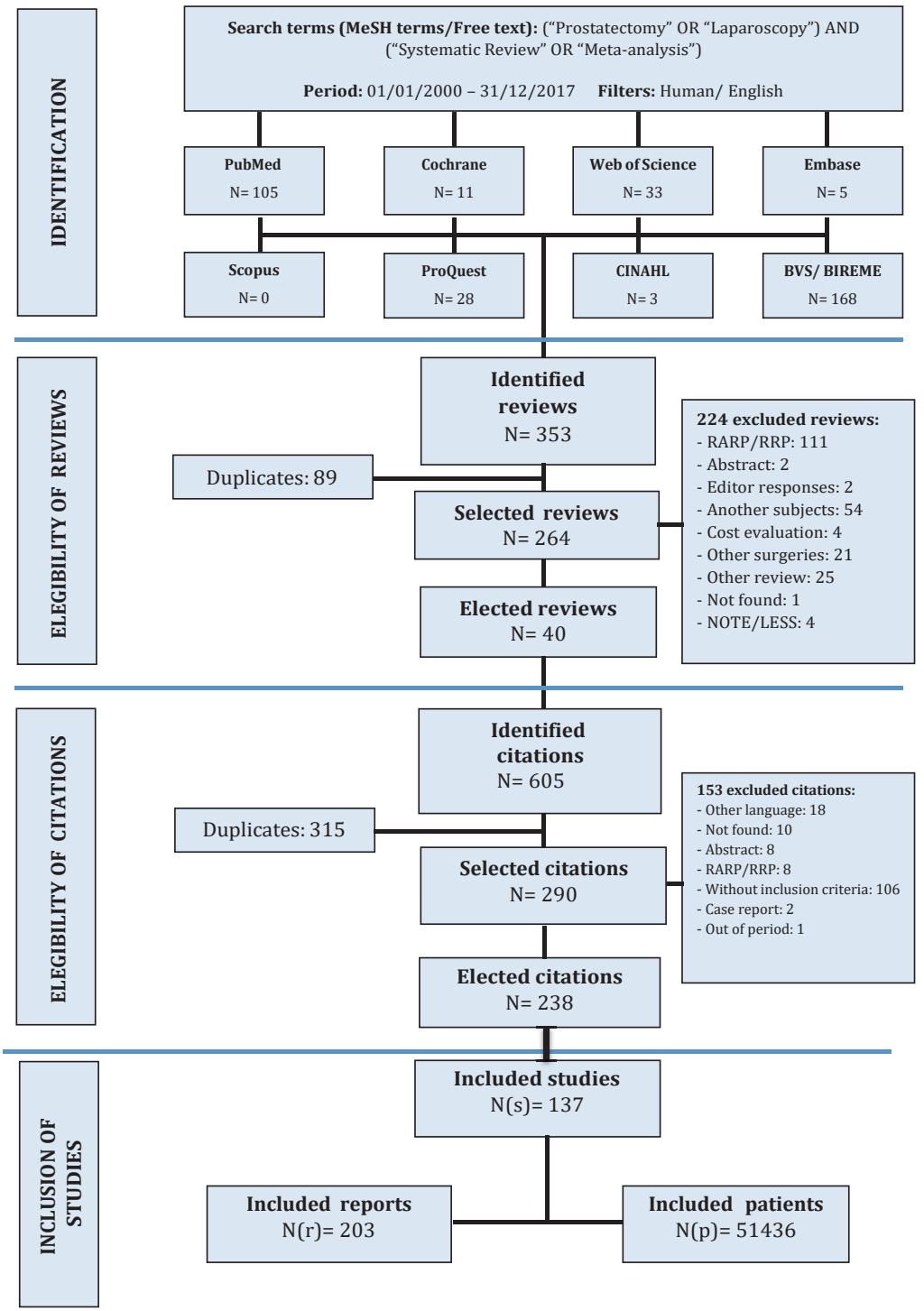
We identified 353 review articles in the systematized search. After the exclusion of duplications and filters by the inclusion and exclusion criteria, 40 reviews were chosen, which cited 605 articles about LRP. After exclusion of doubling and eligibility criteria, 137 studies about PPI were selected for data collection, finally including 203 reports (nr) and 51.436 patients (Figure-1).

In all the post-operative timeframes, the most used criterion of continence was No pad (nr=121; 59.6%), the second one was Safety pad (nr=57; 28.1%), followed then by a small number of other classifications (nr=25; 12.3%). Accordingly, results were divided into three groups: No pad, Safety pad, and Others.

The PPI after LRP was evaluated in each of these three continence criteria in each specific post-operative period. A statistically significant difference between criteria was identified only at >18 months ($p=0.044$). The post-hoc analysis at this timeframe showed that there was no difference between No pad vs. Safety pad ($p=0.699$), but there was statistical significance between No pad vs. Others ($p=0.023$) and Safety pad vs Others ($p=0.015$), Table-1, Figures 2A-D and 3A.

Regarding the evaluation of the continence criteria used along the manuscript year of publication, there is a significant difference among No pad (median=2007) and the other two criteria, Safety pad (median=2013) and Others (median=2013), with $p < 0.001$. It was observed that until 2007 the No pad criteria predominated. From 2013 until the end of our analysis, the Safety pad and Others were the most reported, Figure-3B.

Figure 1 - This figure shows the design of the search strategy by a flowchart, which illustrates the eligibility process of systematic reviews and primary studies to compose the final database.



n_r = number of reports; n_s = number of studies; n_p = number of patients.

Table 1 - Continence rate over time in each criterion.

Continence criteria	1 month		3 months		6 months		12 months		> 18 months	
	n_R	%Mean, SE	n_R	%Mean, SE	n_R	%Mean, SE	n_R	%Mean, SE	n_R	%Mean, SE
No PAD	34	33.9 (3.6)	75	61.8 (2.4)	75	76.9 (1.6)	95	84.4 (1.2)	19	88.4 (2.9)
Safety PAD	16	40.7 (6.1)	36	65.1 (3.1)	21	78.6 (3.8)	32	88.8 (1.2)	14	90.0 (1.5)
Others	3	47.2 (12.8)	7	69.6 (11.7)	3	84.8 (10.5)	5	81.1 (4.9)	4	72.5 (11.7)*
Total	53	36.7 (3.0)	118	63.3 (1.9)	99	77.6 (1.4)	132	85.3 (0.9)	37	87.3 (2.1)
p		0.418		0.529		0.570		0.089		0.044*

n_R = number of reports; SE = standart error of the mean; *$p < 0.05$

Figure 2 A-D - The figures show the continence rate (% mean and SE with 95% CI) after LRP over time, at 1 (A), 3 (B), 6 (C) and 12 (D) months, stratified by three continence criteria (No PAD; Safety PAD; Others).

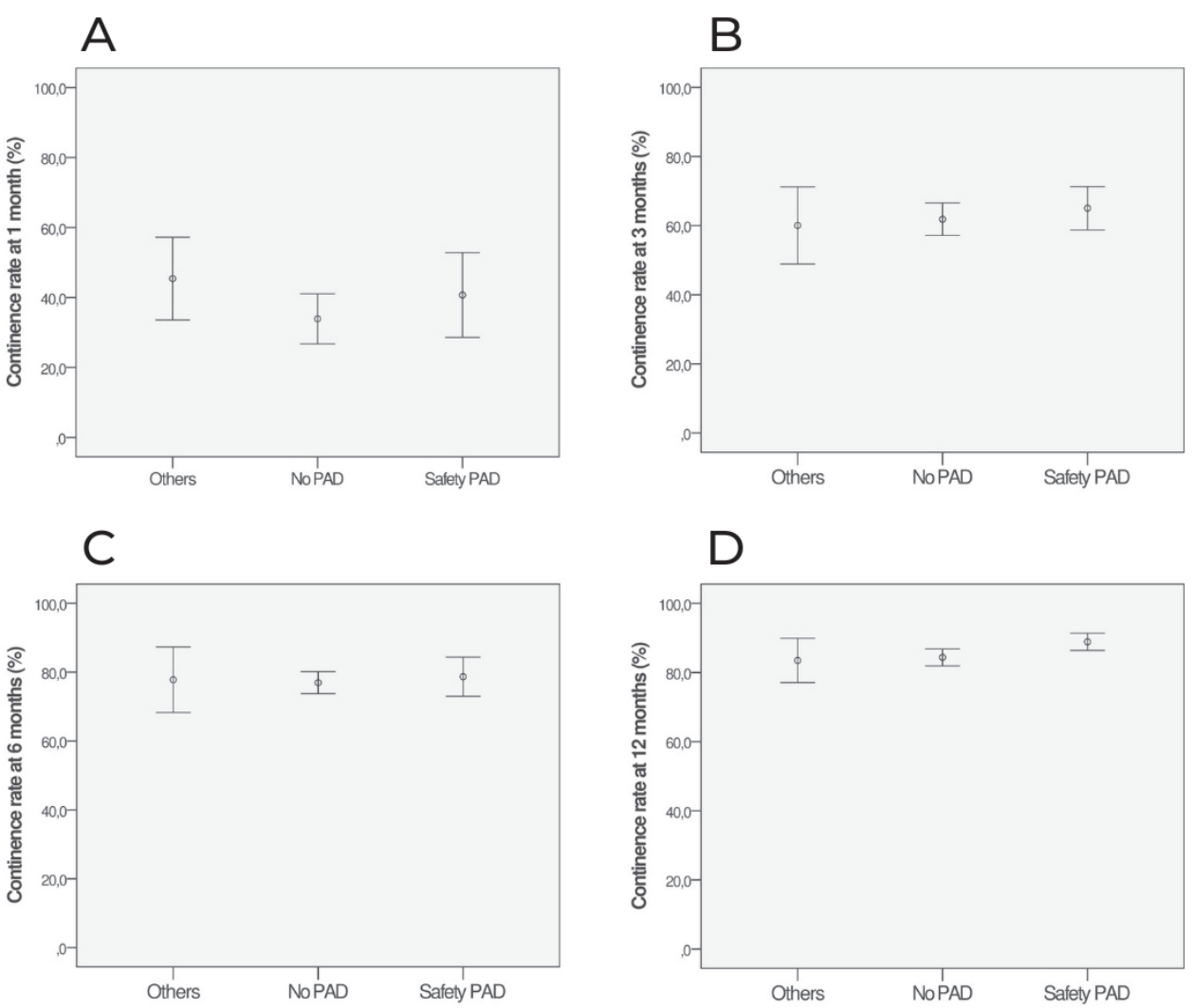
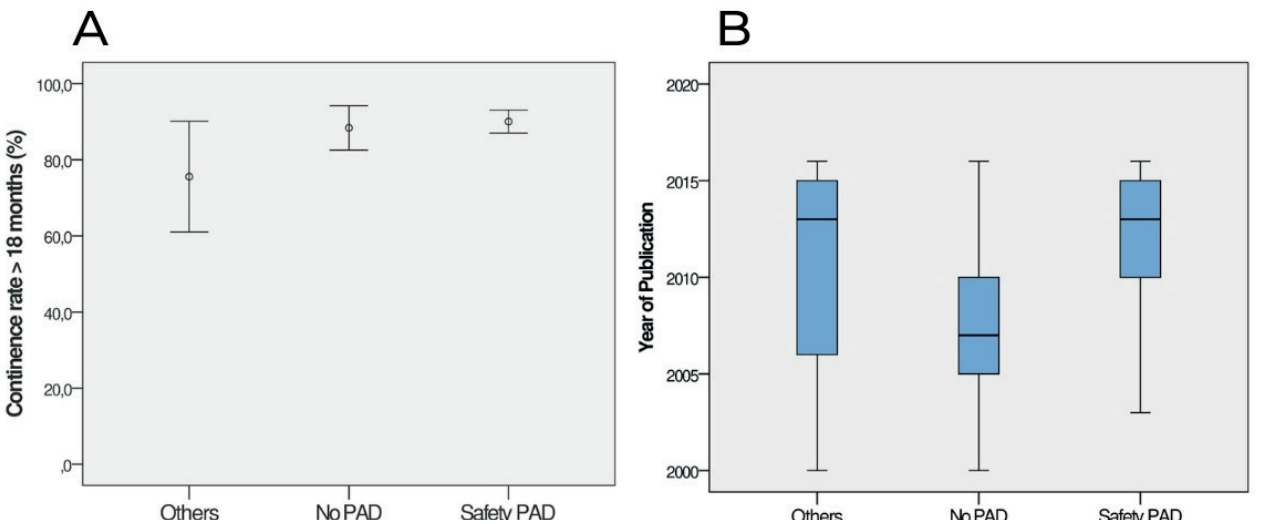


Figure 3 A-B - The figure A shows the continence rate (% mean and SE with 95% CI) after LRP at >18 months. The figure B shows the boxplot distribution of year of publication of the studies, stratified by three continence criteria (No PAD; Safety PAD; Others) with median comparisons by Kruskal-Wallis test (p<0.001).



DISCUSSION

Urinary incontinence is still today one of the main concerns after RP for PCa treatment, despite the improvement in technique and technology, afflicting up to 74% of patients undergoing this surgery in the short term (3, 6). Various factors have been hypothesized to contribute to this undesired outcome. Potential preoperative variables might be age, body mass index, prostate size, oncological factors, preoperative urinary and sexual dysfunction, prior transurethral resection of the prostate, membranous urethral length before surgery (7-9).

In addition to that, hypothetic intraoperative factors that could influence PPI include puboprostatic ligament sparing, surgical neuro-vascular bundle approach, preservation of the endopelvic fascia, selective suturing of dorsal venous complex, size of the urethral stump, bladder neck preservation, posterior or anterior reconstruction supports, and others (7, 8, 10, 11).

Moreover, cultural differences in the way the patient reports urinary leakage and pad use could also interfere in the analyzed outcomes (12). PPI has been the topic of studies ever since the first patient came back for a follow-up after surgery and urologists have been comparing notes and studies to find a better way of avoiding this complication. Urinary continence is known to be a strong determinant of quality of life; however, how much incontinence is "too much"? How much incontinence is incontinence and how to compare this outcome? Studies show very heterogenous PPI results, ranging from 3 to 74% (5, 6, 11).

Surgeons may operate the same surgery, with the same intent, similar cases, but they are different and might have different results. It is imperative to find a pattern to graduate PPI, to compare the outcomes obtained in clinical practice. Loughlin and Prasad described methodological instruments and definitions used for PPI: pads use/number, pad weight, urodynamics assessment, validated questionnaire, institutional questionnaire, phone or face-to-face interview (8). Still, there is a need to homogenize the approach to the same concept or question to be able to evolve in the right direction. This study tries to demonstrate the prevalence of the definitions used to identify PPI after LRP as time goes by and to compare the PPI rates overtime under these different terminologies.

We used a new methodology to perform our evidence acquisition: reverse systematic review (RSR). Conceptually, a standard systematic review (SR) allows the selection of eligible primary studies

to answer a specific clinical question, and this method inherently eliminates multiple secondary variables. In the RSR, clinical evidence starts from general information, in this case, LRP, to then be filtered until it reaches a specific knowledge, such as PPI. It follows the opposite path of an SR, going from the specific data of the systematic revisions and then back to its primary studies. Also, the RSR has a wide search criterion, heterogeneous eligibility, and an intention of studying the development through temporal correlation (5).

We found the main criteria used for classifying PPI after LRP: No pad and Safety pad. Yet, most publications have been using "pads" to measure the degree of incontinence, and although trying to be quantitative, they are still subjective (13). Moreover, as referred above, some investigators proposed to weigh the pads, since some patients only use them for safety (14). Scores are acceptable to evaluate continence, as seen in many cases (3, 5), but validation, translation, comprehension by patients and doctors sometimes are yet challenging barriers to overcome.

Many authors studied this topic and even tried to propose a new standardization. Ellison et al. in 2013 (4) propounded a stratification of the Expanded Prostate Cancer Index Composite - Short Form Urinary Domain (EPIC-UIN) (which contains 3 questions related to urinary function and 2 to urinary bother) to simplify the results in a "meaningful fashion": mild, moderate and severe incontinence. These levels are already used by another classification, the Incontinence Severity Index (ISI) (which contains 3 questions about urinary stress incontinence, 3 about urinary urge incontinence, and 2 related to pad number and type). Even though they stated that this system would aid physicians and doctors to interpret the PPI status, as they found an agreement of 74.1% when comparing both instruments, when observing publications afterward, it is seen that this stratification did not become a standard.

In this manner, Holm et al. in a prospective study, concluded that PPI varied considerably according to the definition applied, and any leakage is incontinence. The authors also stated that "further effort should be made to reach consensus on PPI severity grading" (3). Considering the finding related to the two most used criteria, one should think that the simpler the PPI described, the better it is. However, both continence criteria came with their theories for limitations. Could a more restrictive classification such as No pad diminish continence ratios to a grimmer scenario? Could the Safety pad concept for characterizing a patient as a continent lower the bar enough to rate as continent people that are suffering from significant leakage? What is the real difference between these two parameters?

The RSR responded to the last one. It proved to be useful in demonstrating the "natural history" of the evolution of PPI after LRP, which is not captured by a standard SR. Its reverse methodology was able to demonstrate the stability of the population sample obtained even in different scenarios, allowing a comparison of the main criteria used for this purpose along the timeline. This stability, from a statistical point of view, is proven by the substantial sample size and reduced standard error of the mean, since incorporating any additional value in the analysis would hardly change the overall mean.

Interestingly, this study reported that not only there are no differences in continence ratios in the two main criteria at 1, 3, 6, and 12 months after surgery, but also there is no difference when comparing other denominations used for PPI in some publications (which we labeled "Others"). The mean continence rates at these periods, respectively, were: 36.7%, 63.3%, 77.6%, and 85.3%. Statistically, a significant value was only seen at 18 months post-operative ($p=0.044$). However, at this time frame we have the fewest total number of studies (nr=37), mainly due to the minimum clinical improvement after 12 months of RP (15), -and our results corroborate with this data, with an improvement rate of 2.0% when comparing 12 vs. 18 months post-operative (85.3 ± 0.9 vs. 87.3 ± 2.1%). Moreover, further analysis at this latest period showed no difference between No pad vs. Safety pad ($p=0.699$) and only observed statistical significance between No pad vs. Others ($p=0.023$) and Safety pad vs. Others ($p=0.015$).

The fact that there was no significant difference in the result's rates in any post-operative period between both PPI main denominations may indicate that they measure the same thing in a very similar way. The subtle difference between groups may point to a need to investigate other parameters affecting the quality of life that may differ between these patients. The Safety pad offers real benefits, or is it just

like safety wheels after you have already learned how to ride a bike? Eventually, a better conversation with the patient as to the usefulness of this "Security pad" might end in a more incisive recommendation by the urologist to just do not use it at all.

Time frame analysis of publications (Figure--3B) documented the already mentioned "natural history" of the use of these PPI criteria, which is another peculiar aspect of the RSR. It depictured that most authors preferred to use the Safety pad terminology after 2011, probably in pursuit of better continence outcomes. Likely, many other authors then followed the same path from that point on, inferring in a herd mentality, which resulted in a wave swooping after previous publications in which prevailed other criteria. Very interestingly, we verified that this attempt to raise continence percentages by allowing the Safety pad parameter to enter the "continent group" did not impact continence rates in most scenarios, and only lead to a false sensation of better outcomes in PPI.

This study is not free of limitations. The composition of a heterogeneous sample allows the temporal analysis but prevents the defragmentation of variables to analyze specific outcomes, a characteristic of SRs with meta-analysis. The presence of correlations with reduced coefficients of determination limits the statistical strength despite being a common feature in heterogeneous population samples. Further multivariate analysis, such as stratification by other variables that may influence continence after surgery, may reduce such interference.

In addition, even if the isolated samples show asymmetric distributions, they are small enough to contribute a significant weight alone, and the overall size is high enough to minimize or even avoid such bias. Finally, the results found in this study must be evaluated with caution regarding biases when comparing continence rates after LRP before and after 2011, especially if one is inclined to compare them to open radical prostatectomy and robotic-assisted radical prostatectomy (RALP) rates. This novel methodology of RSR also allows for PPI measurement criteria and their rates to be compared in future studies, including RALP, which is the main RP technique currently (16-18). Its strength is beyond scientometrics, adding to the evidence-based medicine by temporally analyzing the surgical complication in question, allowing possible projections for the future, and exposing significant bias neglected by SRs.

CONCLUSION

Reverse Systematic Review revealed the "natural history" of PPI after the LRP technique. Beyond that, the study analyzed the criteria used to evaluate PPI and showed that through time, with the presumable objective of reaching better continence results, the Safety pad concept was mainly used. However, paradoxically, we demonstrated that the two main criteria utilized, Safety pad and No pad, had similar PPI outcomes. Further effort should be accomplished to reach an international consensus on a clear and objective concept for PPI so that a more accurate comparison between studies and techniques of RP can be achieved.

Compliance with Ethical Standards

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Challenging dilemmas of low grade, non-invasive bladder cancer: a narrative review

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ABSTRACT

Purpose: To describe the current scientific knowledge and clinical experience in low-grade-non-muscle-invasive bladder cancer (LG-NMIBC) patients in challenging scenarios.
Materials and Methods: Medline, Embase, Google Scholar, and Cochrane Central were searched until March 2021.
Results: A total of 841 studies were identified, and abstracts were analyzed. Twenty-one relevant studies were then identified and reviewed. After all, information was gathered from 16 studies, the authors discussed the specific topics, and expert opinions were also included in the discussion. There have been some studies that can help us to have some insights on how to manage these patients. Very distinctive strategies have been reported in the literature, mainly anecdotally or in small randomized studies. Some of these treatments outlined in the present manuscript include repeated TURBTs, chemoablation, BCG immunoablation, partial cystectomy, radical cystectomy, radiotherapy, chemotherapy, and future perspectives. In the current manuscript, we have combined these strategies in a proposed algorithm.
Conclusion: For those LG-NMIBC patients in challenging scenarios, we have found repeated TURBTs, chemoablation, BCG immunoablation, partial cystectomy, radical cystectomy, radiotherapy, and chemotherapy are attractive modalities to treat them effectively. Also, the current manuscript proposes an algorithm to overcome these challenges.

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INTRODUCTION

Bladder cancer is the sixth most common cancer in the US and represents 4.6% of all new cancer diagnoses, equivalent to 80.470 new cases and 17.670 deaths in the US during 2019 (1). It also has significantly elevated expenses and perhaps the highest lifetime treatment costs per patient (2).

In high-risk non-muscle-invasive bladder tumors (NMIBC), radical progression and metastasis are significant concerns. The standard treatment of these patients is TURBT and BCG installations. Nonetheless, a radical cystectomy is a good

option (3). On the other side, for muscle-invasive bladder cancer (MIBC), the last one is the standard intervention. However, nowadays, there is increasing evidence that trimodal therapy (complete TURBT, chemotherapy, and radiotherapy) might be an essential and acceptable intervention for selected cases (low-volume T2, absence of CIS, no hydronephrosis) (4).

Non-muscle invasive bladder cancer (NMIBC) is commonly treated and cured through transurethral resection of the bladder tumor (TURBT). Low-grade, non-invasive tumors rarely metastasize, the high recurrence rates and progression risk are avoided through adjuvant measures and an extensive follow-up program (5). Even though TURBT is a standard procedure mastered by most urologists, there are certain challenging situations. Sometimes the urologist faces a TURBT with an NMIBC located in an inaccessible position, a large prostate / urethral stricture precluding the resectoscope introduction or an extensive low-grade Ta lesion that cannot be endoscopically resected. Accordingly, large-volume, multifocal cancers can usually be managed with conservative techniques with a good prognosis (6).

We aimed to describe the current scientific knowledge and clinical experience LG-NMIBC patients challenging scenarios. An international panel of experts on bladder cancer treatment performed a review and identified alternatives in complex TURBT cases for LG NMIBC.

MATERIALS AND METHODS

We conducted this comprehensive review following Joanna Briggs Institute recommendations (7).

Eligibility criteria: Studies including alternative interventions for patients over 18 years of age with a Ta NMIBC diagnosis and considered complex TURBT.

Information sources: We carried out the literature search in the MEDLINE (OVID), EMBASE, Google Scholar, and CENTRAL databases from inception to March 2021. We performed a structured search using terms and synonyms related to the condition of interest.

DATA COLLECTION

Two researchers identified each reference by title and abstract. Subsequently, we reviewed the full texts of relevant studies and applied pre-specified inclusion and exclusion criteria. Using a standardized form, the reviewers independently extracted the following information from each article.

Data synthesis: We showed each clinical trial result descriptively, trying to respond to the proposed objective.

RESULTS

Study selection

We identified 841documents from the search strategy. Finally, we included sixteen studies that were eligible for our review. (Figure-1)

Characteristics of included studies

We found multiple design studies, including primary studies, reviews, and commentaries. They were all published in worldwide journals as the primary purpose of this study is to present the strategies, as a way to standardize alternative interventions in complex cases, we go ahead to present them.

Specific strategies

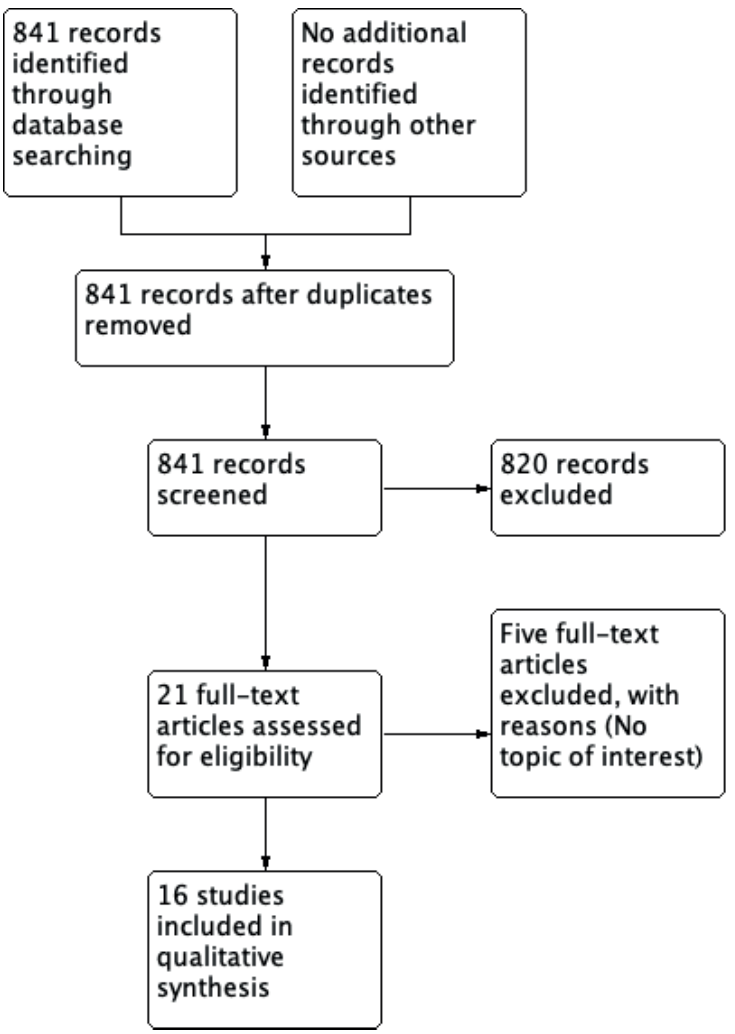
Strategies to access the tumor

Difficult-to-reach tumors

At times, urologists have to deal with challenging situations at the TURBT, such as large prostates, large-distended bladders, severe urethral strictures or stenosis, and often obese patients making access to the bladder tumor foci quite prohibitive (Table-1). Additionally, tumors located at the bladder dome and anterior bladder wall can pose additional difficulties. In these cases, conventional maneuvers as emptying the bladder, suprapubic pressure, or Trendelenburg position are not helpful tips.

Correspondingly, the cystoscope or even the ureteroscope might be valuable tools to perform this procedure. It is possible to perform a cold-cup biopsy and Bugbee cauterization of some LG lesions through the cystoscope. Also, laser

Figure 1 - Flowchart for study selection.



ablation or en-bloc resection with the resecoscope might be possible and accessible.

An extra-long resectoscope may be another tool to use in these challenging situations. If not readily available, the procedure can be postponed. Also, an old but exciting technique is a perineal urethrostomy, which can also be used as an access route in challenging cases (8, 9).

Extensive tumors

In multiple LG-NMIBC tumors with almost no normal urothelium, the surgical resection might be difficult and dangerous. It is crucial to ensure a good visualization throughout the procedure, controlling significant hematuria, cauterizing bleeders throughout the resection, and evacuating clots with an Ellik or some other means of effective evacuation. For extensive tumors, incomplete resection may be unavoidable sometimes, and staged procedures are the safest approach. Even though there are no current formal recommendations for such cases, adjuvant treatment strategies, as mentioned below, can be of value.

Treatment strategies

Staged procedures

For extensive tumors, incomplete resection may be unavoidable sometimes, and staged procedures can be the safest approach (6). In such cases, we suggest a complete tumor resection in one

area, providing meticulous hemostasis. A second procedure can be scheduled between two to four weeks to complete the procedure.

Also, for patients with a huge prostate or a huge median lobe that precludes access to a bladder tumor, benign prostatic hyperplasia can be initially treated, and the TURBT can be performed as a staged procedure.

Alternatively, if there is a high-volume prostate, it can be resected as a first-step procedure, and then a delayed TURBT in 6-8 weeks.

Chemoablation of NMIBC

A few studies describing chemoresection or chemoablation as an alternative to TURBT have been published during the last decade. Bono et al. (10) evaluated mitomycin C (MMC) and epirubicin in two EORTC trials. They observed 57% and 67% complete response rates, respectively.

Similarly, in a prospective trial, Lindgren et al. (11) treated 120 patients with Ta-NMIBC (LG or HG), with intravesical MMC with 40mg/40mL/2 hours, three times a week for two weeks. They found 57% complete tumor response at four weeks. Interestingly, adverse events were less common after chemoablation than after TURBT plus MMC or BCG.

Colombo et al. (12) included 54 small-LG--Ta NMIBC patients. Patients received a weekly MMC instillation/6 weeks or three instillations/ week for two weeks. They found a 70.4% complete response after 14 days. Contrarily, Mostafied et al. (13) evaluated 82 small LG-Ta-NMIBC patients. They only found 37% complete responses after four MMC instillations for one week.

It seems that a more intense (3x / week) and more extended period (two weeks) chemoablation with MMC might be more effective. Nonetheless, this is low-quality evidence, and we need high-quality clinical trials for decision--making. Other chemotherapies have not been tested in this setting.

Gemcitabine has also been studied in incomplete resection settings (14). A 6x / weekly gemcitabine reached a 23% complete response. An escalated dose of 2.000mg achieved a better complete response (33.3%). Another study found a similar 31% complete response in this setting (15).

BCG ablation

BCG is currently recommended as an adjuvant measure to reduce NMIBC recurrence after TURBT in high-risk patients. Nonetheless, it has been tested as a neoadjuvant treatment strategy in only one study (16) (They also previously reported their outcomes with almost the same results (17)). Akaza et al. applied 80mg weekly BCG for eight weeks in 125 Ta, T1, or CIS patients before TURBT. There was a complete response in 66.4% of the papillary tumors. For Cis, there was an 84% complete response (16). It is noteworthy that this approach has been tested in a very controlled trial setting and needs more evidence to extrapolate its results. For larger tumors, persistent hematuria might delay treatment and require emergency treatments. It should therefore be considered very cautiously. To our knowledge, there are no other studies for this intervention.

Partial Cystectomy

Partial cystectomy (PC) is considered a treatment only for exceptional cases of urothelial bladder carcinoma. Even though there is no consensus regarding this intervention, the main indications are single tumors in diverticula or T2--small-single tumor with good bladder capacity in a favorable position and without extensive CIS.

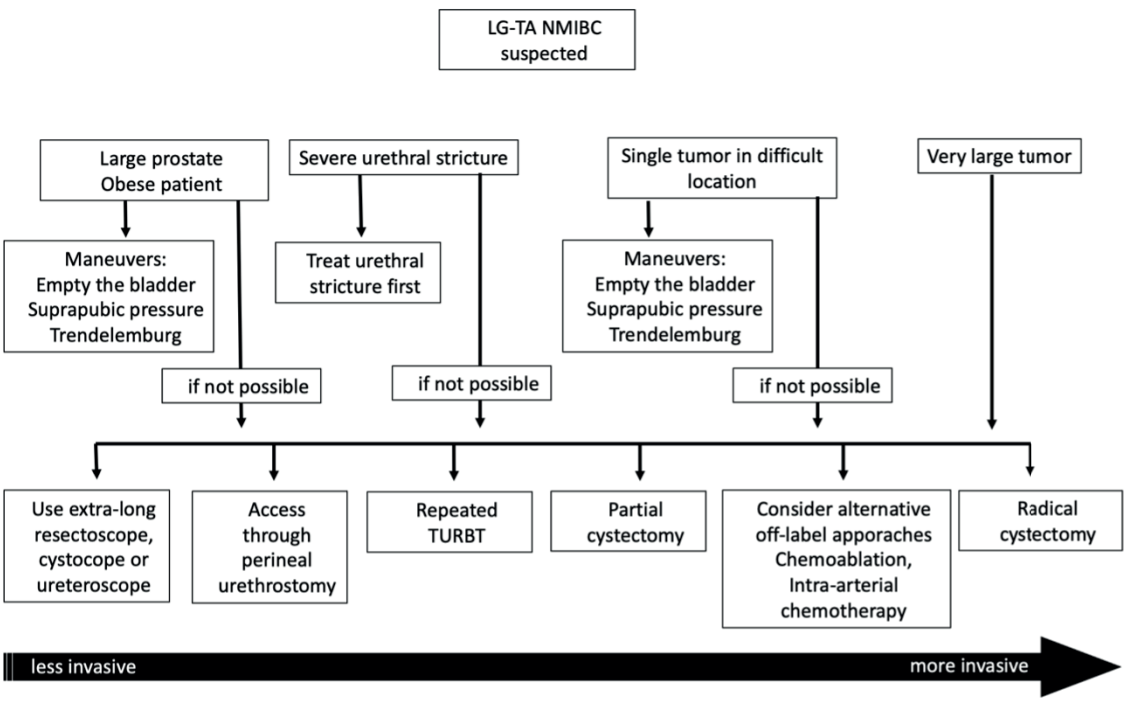
One of the most extensive available series about this intervention in this setting is published by Capitanio et al. (18). They analyzed the SEER database and observed that 23.3% of all 1.753 PC were performed for Ta tumors. There was no recurrence nor other oncological outcomes report.

This situation is not widely mentioned in the literature and guidelines; however, there might be some room for PC in NMIBC. For instance, single large LG/Ta tumors, close to the bladder neck and not easily accessible by TURBT (Figures 2a and 2b).

Radiotherapy

Urothelial carcinoma is a radio-sensitive tumor. Radiotherapy may not be considered as monotherapy for treating MIBC. Instead, combined with chemotherapy and TURBT (Trimodal therapy) has essential effects in oncological outcomes of selected patients, even with fiducial markers as new tools for improving effectiveness (4, 19).

Figure 2 - Algorithm for challenging LG-NMIBC management.



Rodel and Akcetin tried radiotherapy and radiochemotherapy in high-risk T1 bladder cancer. They found an 83-90% complete remission after TURBT. Also, overall survival of 75% at five years and 50% at ten years (20, 21).

Weiss et al. reported radiotherapy or chemoradiotherapy as an alternative for high-risk T1 bladder cancer (22). They found 88% complete response, 30% progression at ten years, and disease-specific survival of 73% at ten years. However, there are no high-quality studies to confirm this data. We did not find any information for low--grade or large volume Ta tumors.

Neoadjuvant arterial chemotherapy

We found a single report of such treatment for an extensively large papillary NMIBC patient who was not amenable to endoscopic resection. This 50-year-old man underwent an arterial infusion of cisplatin (100mg/body) into the superior vesical artery twice, with a 5-week interval. A ten-time fold reduction in tumor volume was observed, and the low-grade-Ta tumor was rendered amenable to TURBT (23).

This use of single-agent intra-arterial chemotherapy seems to be an exciting strategy to be considered in low-grade large-volume NMIBC, where bladder preservation is intended.

Radical Cystectomy

Radical Cystectomy (RC) is currently considered the gold-standard treatment for patients with MIBC (24). In NMIBC patients, RC is an option, mainly considered after BCG failure, especially for high-risk or very high-risk patients, unreachable T1 tumors, residual T1 tumors after resection, or high-grade tumors with CIS and lymphovascular invasion (3). RC is not an option for intermediate-risk tumors.

EAU, NCCN, or AUA guidelines do not mention the specific treatment of a low-grade, extensive Ta tumor, not exposed to BCG treatment, and not amenable to endoscopic resection. The AUA guideline states that for a Ta low- or intermediate-risk patient, the clinician should not perform an RC until bladder-sparing modalities (sta-

ged TURBT, intravesical therapies) fail. We only found one reference (case series) supporting this statement for RC in such tumors (25).

Although a multifocal or very large LG NMIBC represents a rare situation, RC might be effective and considered in these cases where repeated endoscopic resections fail to succeed (Figure 2c, 2d and 2e).

DISCUSSION

Non-muscle invasive bladder cancer (NMIBC) is a disease that can commonly be cured through transurethral resection of the bladder tumor (TURBT). The high recurrence rates and progression risk are avoided through adjuvant measures and an extensive follow-up program (3).

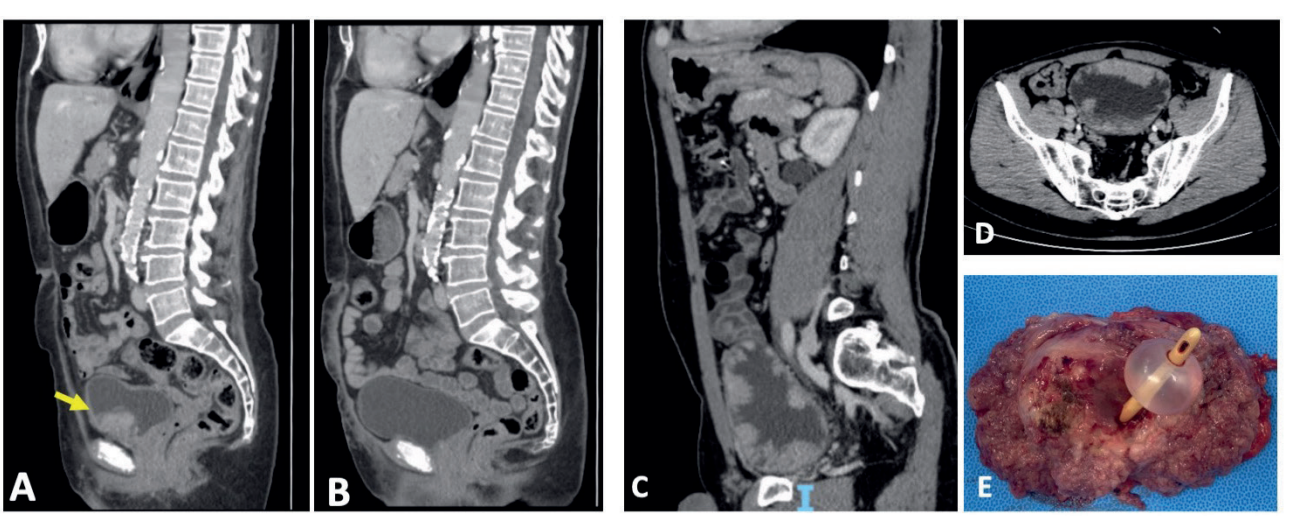
Although TURBT is a standard procedure mastered by most urologists, there are certain challenging situations to discuss. Sometimes urologists face an unreachable NMIBC, a high--volume prostate, or a urethral stricture that precludes the resectoscope introduction, or an extensive low-grade Ta tumor that cannot be endoscopically resected.

In this review, we have found some studies helping to have some insights on how to manage these patients, although those are low-quality evidence. Very distinctive strategies have been reported in the literature, mainly descriptive, anecdotally, or small randomized studies.

Some of these treatments outlined in the present manuscript include repeated TURBTs, chemoablation, BCG immunoablation, partial cystectomy, radical cystectomy, radiotherapy, and chemotherapy. In summary, we have combined these strategies into a proposed algorithm to be considered in this situation (Figure-3).

Another vital consideration for decision-making is prognostic factors and how to improve the outcomes with a more invasive procedure. Regarding the first one, we need to identify high-risk recurrence and progression patients with algorithms, artificial intelligence, or laboratory tools. To predict oncological outcomes and optimal, tailored therapeutic decision-making, we have found that a high neutrophil-to lymphocyte ratio (NLR) was already consistently associated with locally advanced disease. Also, it represents an independent prognostic factor of recurrence and progression in NMIBC patients (26). For the second issue, the Enhanced recovery after surgery (ERAS) program has been described as an alternative to reduce the perioperative morbidity and mortality in patients undergoing a radical cystectomy

Figure 3 - Computed Tomography (CT) scan of a patient who underwent a partial cystectomy for an anterior bladder neck LG-NMIBC (yellow arrow) could not be adequately resected endoscopically.



A) preoperative image. B) After 22 months of follow-up. Radical cystectomy was performed for an extensive LG Ta NMIBC. C) and D) CT scans demonstrating extensive LG-Ta lesion. E) surgical aspect of the bladder after radical cystectomy.

Table 1 - Frequent situations associated with LG-NMIBC challenges.

Challenging situations to treat LG-Ta NMIBC*:
1 - Large prostates
1 - Obese patients
2 - Large distended Bladder (not highly compressible)
3 - Severe urethral stricture(s) or stenosis/small urethral caliber
4 - Difficult location (inaccessible bladder dome/anterior bladder wall)
5 - Difficult location (bladder neck)
6 - Extensive LG-Ta (probably the most frequent scenario)

* low grade non muscle-invasive bladder cancer (LG-Ta NMIBC)

(27, 28). Therefore, we may counsel every urologist to follow these recommendations when deciding to perform an RC in these settings.

From a future perspective, the landscape of new drugs for the treatment of bladder cancer has widely improved in the last decade. The pathophysiology knowledge and genomic profile of such tumors have also been increasing rapidly (29). In such a context, we might have a near-future further option for these uncommon situations of challenging LG-Ta NMIBC. Immuno-oncology and targeted therapies have already been used for specific situations of NMIBC.

Some new drug trials evaluate oncolytic virus regimen, recombinant fusion proteins, immune modulation, cytotoxic therapies, and targeted small molecule kinase inhibitors. As research improves, we are likely to see an increase in the number of options for such patients.

CONCLUSIONS

For those patients with an unreachable LG-NMIBC, a high-volume prostate, an urethral stricture that precludes the resectoscope introduction, or an extensive low-grade Ta tumor, we have found that repeated TURBTs, chemoablation, BCG immunoablation, partial cystectomy, radical cystectomy, radiotherapy, and chemotherapy are attractive modalities to treat them effectively. Also, the current manuscript proposes an algorithm to overcome these challenges. We also consider that there is a wide gap to fill in with high-quality evidence.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Impact of pathological factors on survival in patients with upper tract urothelial carcinoma: a systematic review and meta-analysis

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ABSTRACT

Introduction: There is an ongoing need to identify various pathological factors that can predict various survival parameters in patients with upper tract urothelial carcinoma (UTUC). With this review, we aim to scrutinize the impact of several pathological factors on recurrence free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) in patients with UTUC.

Materials and Methods: Systematic electronic literature search of various databases was conducted for this review. Studies providing multivariate hazard ratios (HR) for various pathological factors such as tumor margin, necrosis, stage, grade, location, architecture, lymph node status, lymphovascular invasion (LVI), carcinoma in situ (CIS), multifocality and variant histology as predictor of survival parameters were included and pooled analysis of HR was performed.

Results: In this review, 63 studies with 35.714 patients were included. For RFS, all except tumor location (HR 0.94, p=0.60) and necrosis (HR 1.00, p=0.98) were associated with worst survival. All the pathological variables except tumor location (HR 0.95, p=0.66) were associated with worst CSS. For OS, only presence of CIS (HR 1.03, p=0.73) and tumor location (HR 1.05, p=0.74) were not predictor of survival.

Conclusions: We noted tumor grade, stage, presence of LVI, lymph node metastasis, hydronephrosis, variant histology, sessile architecture, margin positivity and multifocality were associated with poor RFS, CSS and OS. Presence of CIS was associated with poor RFS and CSS but not OS. Tumor necrosis was associated with worst CSS and OS but not RFS. Tumor location was not a predictor of any of the survival parameters.

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INTRODUCTION

Upper tract urothelial carcinomas (UTUCs) are rare but aggressive malignancies, accounting for about 5-10% of all urothelial cancers (1). They have an estimated incidence of around 2 cases per 100.000 person-year in the United States (1, 2). Radical nephroureterectomy with bladder cuff excision with or without lymph node dissection is the cornerstone for the management of these cases (3). Until recently, data on the use of systemic chemotherapy either in the adjuvant or neoadjuvant setting was based on small retrospective studies (4). Only in a recently reported phase III randomi-

zed controlled trial (RCT), definite survival advantage with adjuvant chemotherapy has been shown (5). Multiple prognostic factors have been implicated with survival outcomes in patients with UTUCs. These prognostic factors have been conveniently divided into clinical, surgical and pathological factors (3, 6). Besides, several molecular markers have been associated with prognosis in UTUCs in various single or multicenter studies (6, 7). The purpose of these prognostic markers is to identify patients with aggressive disease and institute prompt adjuvant therapy.

Some of the pathological factors such as tumor stage, lymph node metastasis, tumor grade, lymphovascular invasion (LVI) have been consistently reported as predictors of all the survival outcomes i.e. recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) (6). The literature on the other pathological factors such as the presence of tumor necrosis (8, 9), carcinoma in situ (CIS) (10-12), variant histology (13-19) and multifocality (20-22) as prognostic factors for survival in UTUC is still conflicting concerning for different survival outcomes. Data for these pathological factors have been mostly derived from retrospective observational studies. Some of these pathological variables have been individually evaluated in systematic reviews as a predictor of survival parameters (23-25). However, these studies had multiple limitations (including data from overlapping patient population studies, limited search) and were not methodologically adequate (24, 25). Furthermore, there has been only one review that assessed various clinical-pathological factors associated with intravesical recurrence in patients with UTUC (26). To the best of our knowledge, there hasn't been a systematic review examining all the pathological variables for all the clinically essential survival outcomes i.e. CSS, RFS and OS following surgical management for patients with UTUC. Thus, this systematic review aimed to scrutinize the survival predictability of various pathological variables (such as tumor necrosis) for which literature is still conflicting and generate pooled hazard ratios (HR) for other pathological factors for all the relevant survival parameters (OS, CSS and RFS) in a single study.

MATERIALS AND METHODS

Study Design

With this study, we comprehensively explored all the available literature regarding various pathological factors implicated in the survival of patients with UTUCs. We included all the studies where data on multivariable analysis predicting various survival outcomes such as CSS, OS and RFS were available. From each of these studies, HR for different pathological variables was extracted for quantitative analysis. While conducting this review standard preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (27) were followed. The study protocol was registered with PROSPERO (CRD42020184885).

Search Strategy and selection criteria

The literature search for this review was conducted by two review authors independently (GS & TP). Multiple electronic databases such as Pubmed/Medline, Scopus, Embase, CENTRAL and Web of Science were used for conducting the literature search. The literature search was conducted from the date of inception of these databases till the last search on 29th March 2020. Following filters were applied [Species--Humans] and [Language-English]. Additional articles were sought from the articles selected for the full-text review.

We followed the PICO (patient/population, intervention, control, outcome) methodology to design our search strategy.

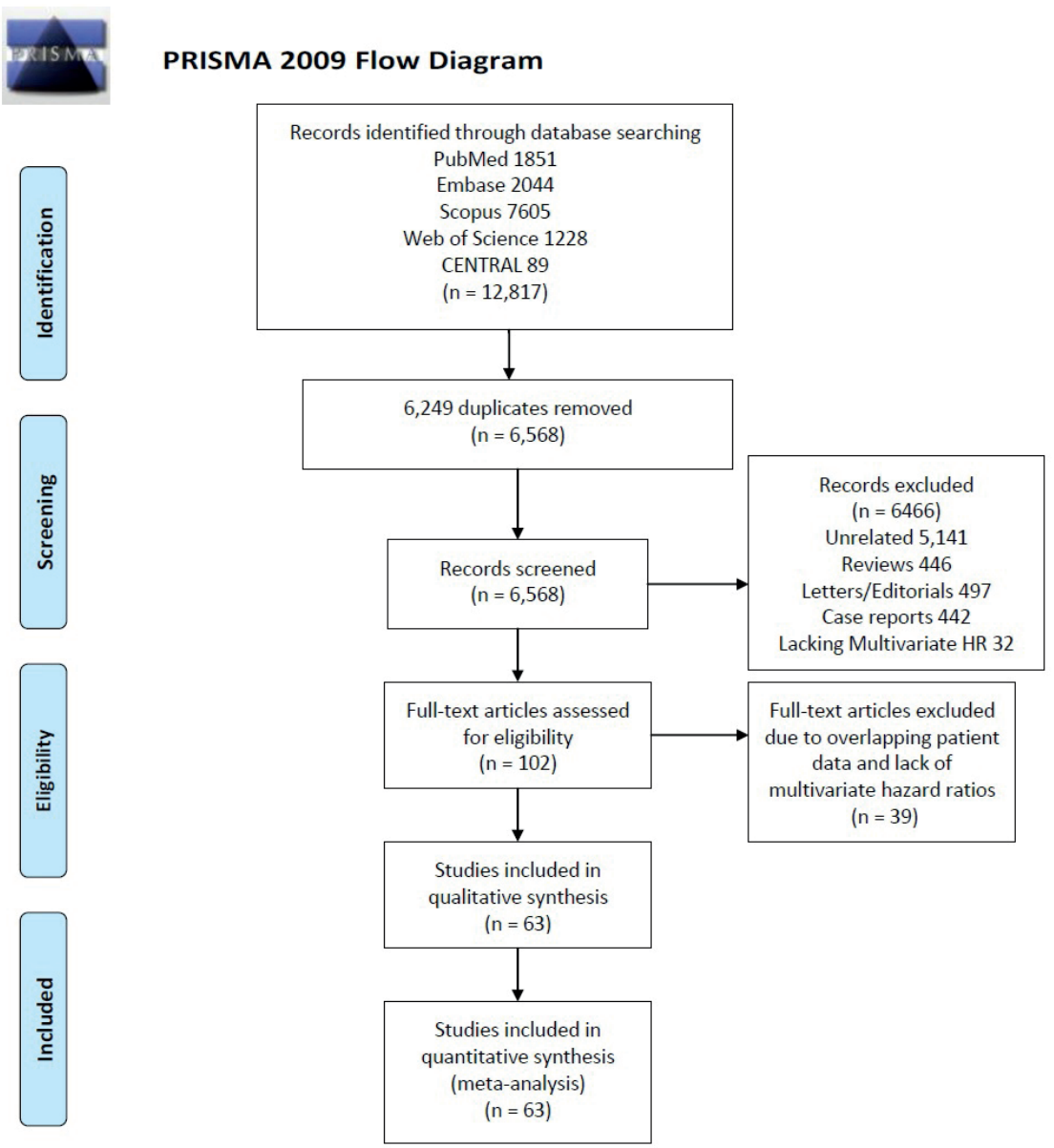
Patient/population: Upper tract urothelial carcinoma, upper tract urothelial cancer, UTUC

Control/Intervention: stage, grade, lymphovascular invasion, LVI, tumor necrosis, margin, tumor margin, carcinoma in situ, CIS, multifocality, architecture, sessile, pathology, pathological, variant histology, tumor location.

Outcome: prognosis, prognostic, survival.

Both key words and meshed terms were used to develop the search strategy. Key words used for this study were "upper tract urothelial carcinoma" OR "upper tract urothelial cancer" OR "UTUC" AND "stage" OR "grade" OR "lymphovascular invasion" OR "LVI OR "tumor

Figure 1 - PRISMA flow-chart depicting search strategy used for conducting this review.



necrosis" OR "margin" OR "tumor margin" OR "carcinoma in situ" OR "CIS" OR "multifocality" OR "architecture" OR "sessile" OR "pathology" OR "pathological" OR "variant histology" OR "location" AND "prognosis" OR "prognostic" OR "survival" OR "outcome".

The search strategy used for PubMed has been provided in supplementary file S1 (Appendix-1).

Statistical Analysis

Forest plots were used to perform quantitative analysis of multivariate HR and generate pooled HR to describe relation between a particular pathological variable and survival parameters (CSS, OS and RFS). For T- stage of the tumor we performed a pooled analysis of HR of those studies that only compared stage T_3 and T_4 stages against

T_{is}, T_1 and T_2. For assessment of grade, we used HR describing the relation between high grade and low-grade tumor for survival outcomes. Similarly, pooled HRs was generated for variant histology (absence or presence), tumor necrosis (absence or presence), LVI (absence or presence), multifocality (absence or presence), CIS (absence or presence), margin status (negative or positive), tumor architecture (papillary or sessile), tumor location (ureter vs. renal pelvis), and lymph node metastasis (absence or presence) in relation to various survival parameters (CSS, OS and RFS). Statistical analysis was performed using the Cochrane Collaboration review manager software RevMan 5.2™ (the Cochrane Collaboration, Copenhagen, Denmark). Chi^2 and I^2 tests were used to assess heterogeneity across each variable in the quantitative analysis. A p-value <0.10 was used to indicate significant heterogeneity and in such a case Random effect model was used. Whereas, p-value was >0.10 signifies absence of statistical heterogeneity and in such a case fixed-effects model (Mantel-Haenszel method) was used. A p-value of <0.05 was considered statistically significant.

Outcomes

Survival parameters (CSS, OS & RFS) were assessed according to various pathological factors such as stage (T_{is}, T_A, T_1 & T_2 vs. T_3 & T_4), tumor grade (low versus high), variant histology (absence vs. presence), tumor necrosis (absence vs. presence), LVI (absence vs. presence), multifocality (absence vs. presence), tumor location (ureter vs. renal pelvis), CIS (absence vs. presence) and margin status (negative vs. positive), tumor architecture (papillary vs. sessile) and lymph node metastasis (absence vs. presence). Recurrence-free survival was defined as the absence of extraluminal metastasis (local surgical site recurrence, distant metastasis, local and distant metastatic lymph nodes). Studies including only bladder or contralateral upper urinary tract were not included in recurrences free survival calculations. We initially also planned to study tumor size variable, however pooled analysis was not possible due to lack of consistent data for this parameter. Some studies had reported tumor size as a continuous variable and others as a categorical variable with variable cut-offs. Impact of other clinical parameters such as mode of surgery (open or minimally invasive) or chemotherapy (adjuvant and neoadjuvant) were not a part of this study.

Quality assessment

We used the Newcastle-Ottawa quality assessment scale (NOS) for the quality assessment of the studies included in this review. Using this scale quality assessment of non-randomized studies was done based upon selection and comparability of study groups and ascertainment of the primary outcome in the two groups. A study can be awarded a maximum of 9 stars, studies with >5 stars are considered to be of good quality. Quality assessment was performed by two review authors (GS & TP) independently and the help of other authors was sought in case of discrepancy of results (AKR & PMK).

RESULTS

Search strategy and study selection

Using various electronic databases mentioned above, a total of 12.817 articles were extracted of which 6.249 duplicate citations were removed. A total of 6.568 articles underwent initial title and abstract screening of which 6.466 articles were excluded for not meeting the inclusion criteria. Full-text reviews of 102 articles were performed of which 39 articles were removed due to overlapping patient data and lack of multivariate HR. For the final analysis, 63 studies were included in this meta-analysis (supplementary file S2 – Appendix-1).

Study characteristics and quality assessment

A total of 63 studies were included in the final analysis with 35.714 patients. All the included studies were retrospective in nature and 30 were multicenter. The duration of follow-up and variables adjusted in multivariate analysis were variable in all the studies (Supplementary Table-2). Further details on age, stage, LVI, tumor necrosis, factors controlled in multivariate analysis and survival parameters studies across the studies have been provided in supplementary Table-S3 (Appendix-1). Quality assessment as performed

using NOS revealed stars ranging from 6-8, with 26, 34 and 3 studies being awarded 6, 7 and 8 stars respectively.

Pooled analysis

Tumor location (Ureter versus renal pelvis)

Multivariate HRs for tumor location concerning to RFS, CSS and OS were available from 3, 5 and 3 studies respectively. Pooled HR for the RFS, CSS and OS were 0.94 (0.75, 1.18), 0.95 (0.78, 1.17) and 1.05 (0.80, 1.36) respectively. There was no statistically significant difference for the pooled HR for any of the survival outcomes.

Stage of the tumor

Of all the studies, data comparing T3 and T4 to lower stages of the tumor was available from 14, 22 and 16 studies for RFS, CSS and OS respectively. Higher tumor stage was significant predictor of recurrence (HR 2.43, 95% CI (1.86, 3.17), p <0.00001), poor CSS (HR 2.69, 95% CI (2.28, 3.18), p <0.00001) and poor OS (HR 2.45, 95% CI (2.19, 2.73), p <0.00001).

Grade of the tumor

Data on comparison for the high-grade to the low-grade tumor was available for RFS, CSS and OS from 22, 38 and 23 studies respectively. Higher tumor grade was associated with poor survival outcomes with significantly higher HRs i.e. RFS (HR 1.39, 95% CI (1.17, 1.65), p <0.00001), CSS (HR 1.69, 95% CI (1.45, 1.98), p <0.00001) and OS (HR 1.60, 95% CI (1.44, 1.77), p <0.00001) (Appendix-2).

LVI and positive lymph nodes

The presence or absence of LVI for RFS, CSS and OS were noted in 27, 36 and 21 studies respectively, whereas data on the positivity of lymph nodes was available from 23, 36 and 21 studies for RFS, CSS and OS respectively. Both presence of LVI and lymph node positivity were associated with significantly higher HRs for all three survival parameters. Pooled HRs for LVI and positive lymph nodes were 1.73 (95% CI (1.47, 2.03) and 2.22 (95% CI (1.88, 2.62) respectively for RFS. Pooled HRs for CSS was 2.03 (95% CI (1.74, 2.36) and 2.24 (95% CI (1.99, 2.52) for LVI and lymph node positivity. For OS pooled HRs were 1.60 (95% CI (1.37, 1.87) for LVI and 2.02 (95% CI (1.72, 2.39) for positive lymph nodes (Appendix-2).

Architecture of the tumor (papillary versus sessile)

Quantitative data on multivariate HR for tumor architecture was available from 12, 12 and 8 studies for RFS, CSS and OS respectively. Sessile tumor architecture was associated with significantly higher HR for RFS (1.48 (95% CI (1.20, 1.83)), CSS (1.47 (95% CI (1.22, 1.76)) and OS (1.58 (95% CI (1.26, 1.99)) (Appendix-2).

Multifocality and presence of CIS

The presence of multiple tumors and CIS were associated with significantly higher HR for all the survival parameters except for one (CIS for OS). For RFS pooled HR was 1.14 (95% CI (1.02, 1.29) for CIS and 1.52 (95% CI (1.13, 2.04) for multifocality, for CSS pooled HR were 1.21 (95% CI (1.06, 1.38) for CIS and 1.33 (95% CI (1.12, 1.59) for multifocality, for OS pooled HR were 1.05 (95% CI (0.87, 1.25) for CIS and 1.50 (95% CI (1.28, 1.76) for multifocality (Appendix-2).

Tumor margin positivity and necrosis

From the pooled analysis of all the studies with available data on surgical margin status, we noted positive surgical margin was associated with the worst RFS (HR 1.38, 95%CI (1.20, 1.59), p <0.00001), CSS (HR 1.59, 95% CI (1.36, 1.87), p <0.00001) and OS (HR 1.71, 95% CI (1.34, 2.19), p <0.0001). Presence of tumor necrosis was significant predictor of poor CSS (HR 1.47, 95% CI (1.08, 1.99), p=0.01) and OS (HR 1.77, 95% CI (1.05, 2.95), p=0.03) but not RFS (HR 1.00, 95% CI (0.86, 1.16), p=0.98).

Variant histology

As previously mentioned, some studies have described specifically the subtype of variant histology whereas others have not. The presence of variant histology was associated with significantly worst survival parameters i.e. RFS (HR 1.48, 95% CI (1.31, 1.66), p <0.00001), CSS (HR 1.86, 95% CI (1.51, 2.30), p <0.00001) and OS (HR 1.74, 95% CI (1.47-2.05), p <0.00001) (Appendix-2).

DISCUSSION

UTUCs are considered to be one of the most aggressive urological malignancies, around 60% of cases have muscle invasion compared to 15-25% of the bladder tumors at diagnosis (28, 29). One of the vexing issues associated with their management is the high rates of the bladder (22-47%) and contralateral upper tract (2-6%) recurrences following treatment (30-32). To prognosticate and intensify the treatment regimens according to the patient-specific risk factors, a risk-adapted classification has been provided in the European Association of Urology (EAU) guidelines (3). Many pathological factors are considered important prognostic factors and guidelines recommend explicit reporting of such elements in the final pathology. As previously noted, the role of some of the pathological factors as an independent predictor is not clear as the data are conflicting. In a previous meta-analysis by Seisen et al. (26), assessing risk for intravesical recurrence for various clinic-pathological factors; the authors noted ureter tumor location, multifocality, pathological T stage, tumor necrosis and positive surgical margin were independent predictors of intravesical recurrence and, LVI, concomitant CIS, tumor grade, and positive lymph node status were not identified as independent predictors of intravesical recurrence. The above mentioned-review despite being exhaustive and methodologically sound was limited by the fact that they only studied the risk factors for intravesical recurrence. Thus, the clinical relevance of this review becomes more as no previously conducted review has examined all the pathological factors at the same time for all the survival outcomes.

In this large systematic review, a total of 63 studies with 35.714 patients were included. Most of the studies included in this review were multicenter and retrospective case series. Quality assessment performed using NOS and all the studies scored more than 6 on this scale implying that all the studies were of adequate quality. However, caution should be exerted while interpreting the results of this review as the results have been pooled from retrospective case series which are inherently at risk of bias. With the paucity of properly conducted prospective studies, this study remains the best evidence available so far in the literature.

In this study, pooled analysis for survival outcomes (RFS, CSS and OS) for 11 pathological variables was performed (Table-1). For RFS, all the pathological variables except tumor location and necrosis were associated with significantly higher pooled HRs. Thus, for RFS tumor location and necrosis were not predictors of survival. For CSS, all the variables except tumor location were identified as independent predictors and for OS all but tumor location and presence of CIS were independent predictors. In a previous meta-analysis by Ku et al. (33), authors noted LVI to be a predictor of RFS and CSS but not OS, on the contrary, we noted LVI to be a predictor of all the survival parameters (CSS, OS, RFS). Compared to the study by Ku et al. (33) our study is much larger and most updated. In another meta-analysis, Fan et al. (24) noted sessile tumor architecture to be associated with worst the RFS and CSS, however, authors did not include OS in the analysis. Regarding presence of CIS, our findings are similar to a previous meta--analysis by Gao et al. (25), who also noted CIS to be associated with poor RFS and CSS but not OS. These two previously mentioned meta-analysis by Fan et al. (24) and Gao et al. (25) were of limited methodological quality as they contained studies with overlapping patient populations. For the presence of variant histology (23), our findings are similar to a previously reported meta-analysis on the topic by Mori et al. Another important point noted in our study is that tumor location is not an independent predictor of survival which is contrary to few individual studies (34, 35) in which ureter location was identified as an independent predictor of poor survival outcomes. However, we acknowledge that the pooled analysis for the location was derived from a handful number of studies which can be its limitation. Literature regarding tumor necrosis as an independent prognostic factor is controversial (8, 9). From our pooled analysis, we noted tumor necrosis to be associated with the worst CSS and OS but not RFS. Even after an exhaustive literature search, we could not find any systematic review reporting data on grade,

Table 1 - Survival analysis for various pathological factors with their pooled analysis.

Recurrence free survival								
S.no.	Variable	Number of studies	Chi^2	I^2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	3	2.99	33%	IV Fixed	0.94	0.75,1.18	0.60
2	T stage	14	60.11	78%	Random	2.43	1.86-3.17	<0.00001
3	Grade	22	46.86	55%	IV, Random	1.39	1.17, 1.65	0.0002
4	LVI	27	121.1	79%	IV, Random	1.73	1.47, 2.03	<0.00001
5	LN positivity	23	62.29	65%	IV, Random	2.22	1.88, 2.62	<0.00001
6	Architecture	12	43.27	75%	IV, Random	1.48	1.20, 1.83	0.0002
7	CIS	9	6.24	0%	IV Fixed	1.14	1.02, 1.29	0.02
8	Multifocality	7	22.39	73%	IV, Random	1.52	1.13, 2.04	0.006
9	Margin	9	7.93	0%	IV Fixed	1.38	1.20, 1.59	<0.00001
10	Necrosis	4	5.35	44%	IV, Random	1.00	0.86, 1.16	0.98
11	Variant Histology	11	16.27	26%	Fixed	1.48	1.31-1.66	<0.00001
Cancer specific survival								
S.no.	Variable	Number of studies	Chi^2	I^2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	5	3.66	0%	IV, Fixed	0.95	0.78,1.17	0.66
2	T stage	22	34.07	38%	Random	2.69	2.28-3.18	<0.00001
3	Grade	38	81.55	55%	IV, Random	1.69	1.45, 1.98	<0.00001
4	LVI	36	117.1	70%	IV, Random	2.03	1.74, 2.36	<0.00001
5	LN positivity	36	52.69	35%	IV, Random	2.24	1.99, 2.52	<0.00001
6	Architecture	12	22.9	52%	IV, Random	1.47	1.22, 1.76	<0.0001
7	CIS	17	14.31	0%	IV, Fixed	1.21	1.06, 1.38	0.004
8	Multifocality	14	27.7	53%	IV, Random	1.33	1.12, 1.59	0.001
9	Margin	12	13.53	19%	IV, Fixed	1.59	1.36, 1.87	<0.00001
10	Necrosis	8	20.14	65%	IV, Random	1.47	1.08, 1.99	0.01
11	Variant Histology	20	60.66	64%	IV, Random	1.86	1.51-2.30	<0.00001
Overall survival								
S.no.	Variable	Number of studies	Chi2	I2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	3	2.63	24%	IV, Fixed	1.05	0.80,1.36	0.74
2	T stage	16	10.86	0%	IV, Fixed	2.45	2.19-2.73	<0.00001
3	Grade	23	14.28	0%	IV, Fixed	1.60	1.44, 1.77	<0.00001
4	LVI	21	60.48	67%	IV, Random	1.60	1.37, 1.87	<0.00001
5	LN positivity	21	38.46	48%	IV, Random	2.02	1.72, 2.39	<0.00001
6	Architecture	8	19.73	65%	IV, Random	1.58	1.26, 1.99	<0.0001
7	CIS	8	2.8	0%	IV, Fixed	1.05	0.87, 1.25	0.63
8	Multifocality	10	8.75	0%	IV, Fixed	1.50	1.28, 1.76	<0.00001
9	Margin	10	21.07	57%	IV, Random	1.71	1.34, 2.19	<0.0001
10	Necrosis	5	8.5	53%	IV, Random	1.77	1.05, 2.95	0.03
11	Variant Histology	13	21.01	43%	IV, Random	1.74	1.47-2.05	<0.00001

HR= Hazard ratio; **CIS**= carcinoma in situ, **LN** = lymph node; **LVI**= lymphovascular invasion; **IV**= Inverse variance

stage, lymph node status, tumor location, tumor necrosis and margin status as predictors of survival in patients with UTUCs. Thus, our study is the first systematic review to provide pooled analysis for the above-mentioned pathological variables.

LIMITATIONS

There are multiple limitations of this study that needs to be highlighted. We acknowledge that the studies included in this study were observational studies that have inherent selection bias. Furthermore, the likelihood of reporting bias cannot be completely ruled out as negative trials have lower chances of publication. We also noted significant heterogeneity in the analysis of some pathological factors for survival parameters. For accounting for heterogeneity in the model we used the random-effects model. Since our review focused only on the impact of various pathological factors on oncological outcomes, we were not able to control for other multiple confounding factors. Firstly, different types of surgical methods have been employed for the treatment (open or laparoscopic or segmental ureterectomy). Secondly, lymph node dissection was performed in some and not in others. Thirdly, some studies had included patients with prior history of bladder cancer, a group associated with the poor prognosis. Lastly, the use of chemotherapy in an adjuvant or neoadjuvant setting could also influence the outcomes. Subgroup analysis, according to a number of adverse pathological factors was also not possible due to lack of data. We were also not able to perform pooled analyses for tumor size as it was reported differently in different studies. Some studies had reported it as a continuous variable and others had reported it as a dichotomous variable with different cut-offs. Most of the studies in this review lack a central review of pathological specimens and have been based on the interpretation of a single pathologist. Furthermore, many of the studies did not properly define various pathological characteristics such as LVI, site of margin positivity, percentage of tumor necrosis and percentage of variant histology in the tumor.

CONCLUSION

From this review, we noted tumor grade, stage, presence of LVI, lymph node metastasis, hydronephrosis, variant histology, sessile tumors, margin positivity and multifocality were associated with poor RFS, CSS and OS. The presence of CIS was associated with poor RFS and CSS but not OS. Tumor necrosis was associated with the worst CSS and OS but not RFS. Tumor location was not a predictor of any of the survival parameters.

CONFLICT OF INTEREST

None declared.

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APPENDIX 1

Supplementary Table 1 - Pubmed search with search query, search details and results

Query	Search Details	Results
((((Upper tract urothelial carcinoma) OR (Upper tract urothelial cancer)) OR (UTUC)) AND (((((((((((((location)) OR (variant histology)) OR (pathological)) OR (pathology)) OR (multifocality)) OR (sessile)) OR (architecture)) OR (CIS)) OR (carcinoma insitu)) OR (tumor margin)) OR (margin)) OR (tumor necrosis)) OR (LVI)) OR (lymphovascular invasion)) OR (grade)) OR (stage))) AND ((((outcome) OR (survival)) OR (prognostic)) OR (prognosis))	(((((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])) OR (("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields])))) OR "UTUC"[All Fields]) AND (((((((((("locate"[All Fields] OR "located"[All Fields]) OR "locater"[All Fields]) OR "locates"[All Fields]) OR "locating"[All Fields]) OR "location"[All Fields]) OR "locational"[All Fields]) OR "locations"[All Fields]) OR "locator"[All Fields]) OR "locators"[All Fields])) OR ((("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])))) OR (((((("pathologic"[All Fields] OR "pathologically"[All Fields]) OR "pathologics"[All Fields]) OR "pathology"[MeSH Terms]) OR "pathology"[All Fields]) OR "pathological"[All Fields])) OR ((("pathology"[MeSH Terms] OR "pathology"[All Fields]) OR "pathologies"[All Fields]) OR "pathology"[MeSH Subheading])) OR ((("multifocal"[All Fields] OR "multifocality"[All Fields]) OR "multifocally"[All Fields]) OR "multifocals"[All Fields])) OR "sessile"[All Fields]) OR ((((((("architectural"[All Fields] OR "architecturally"[All Fields]) OR "architecture"[MeSH Terms]) OR "architecture"[All Fields]) OR "architecture s"[All Fields]) OR "architectured"[All Fields]) OR "architectures"[All Fields])) OR "CIS"[All Fields]) OR ((((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])))) OR (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All	1,851

	Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasms"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumors"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields])))) OR "LVI"[All Fields]) OR ("lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields]))) OR ((((("grade"[All Fields] OR "graded"[All Fields]) OR "grades"[All Fields]) OR "grading"[All Fields]) OR "gradings"[All Fields])) OR ((((("stage"[All Fields] OR "staged"[All Fields]) OR "stages"[All Fields]) OR "staging"[All Fields]) OR "stagings"[All Fields])))) AND ((((("outcome"[All Fields] OR "outcomes"[All Fields]) OR ((((((((("mortality"[MeSH Subheading] OR "mortality"[All Fields]) OR "survival"[All Fields]) OR "survival"[MeSH Terms]) OR "survivability"[All Fields]) OR "survivable"[All Fields]) OR "survivals"[All Fields]) OR "survive"[All Fields]) OR "survived"[All Fields]) OR "survives"[All Fields]) OR "surviving"[All Fields])))) OR ((((((((((("prognostic"[All Fields] OR "prognostical"[All Fields]) OR "prognostically"[All Fields]) OR "prognosticate"[All Fields]) OR "prognosticated"[All Fields]) OR "prognosticates"[All Fields]) OR "prognosticating"[All Fields]) OR "prognostication"[All Fields]) OR "prognostications"[All Fields]) OR "prognosticator"[All Fields]) OR "prognosticators"[All Fields]) OR "prognostics"[All Fields])))) OR (("prognosis"[MeSH Terms] OR "prognosis"[All Fields]) OR "prognoses"[All Fields]))	
((Upper tract urothelial carcinoma) OR (Upper tract urothelial cancer)) OR (UTUC)	((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])) OR ((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields]))) OR "UTUC"[All Fields]	3,368
((((((((((((((((location)) OR (variant histology)) OR (pathological)) OR (pathology)) OR (multifocality)) OR (sessile)) OR (architecture)) OR (CIS)) OR (carcinoma insitu)) OR (tumor margin)) OR (margin)) OR (tumor necrosis)) OR (LVI)) OR (lymphovascular invasion)) OR (grade)) OR (stage)	(((((((((("locate"[All Fields] OR "located"[All Fields]) OR "locater"[All Fields]) OR "locates"[All Fields]) OR "locating"[All Fields]) OR "location"[All Fields]) OR "locational"[All Fields]) OR "locations"[All Fields]) OR "locator"[All Fields]) OR "locators"[All Fields])) OR ((("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])))) OR (((((("pathologic"[All Fields] OR "pathologically"[All Fields]) OR "pathologics"[All Fields]) OR "pathology"[MeSH Terms]) OR "pathology"[All Fields]) OR "pathological"[All Fields])) OR ((("pathology"[MeSH Terms] OR "pathology"[All Fields]) OR	6,005,790

	"pathologies"[All Fields]) OR "pathology"[MeSH Subheading])) OR ((("multifocal"[All Fields] OR "multifocality"[All Fields]) OR "multifocally"[All Fields]) OR "multifocals"[All Fields])) OR "sessile"[All Fields]) OR ((((((("architectural"[All Fields] OR "architecturally"[All Fields]) OR "architecture"[MeSH Terms]) OR "architecture"[All Fields]) OR "architecture s"[All Fields]) OR "architectured"[All Fields]) OR "architectures"[All Fields])) OR "CIS"[All Fields]) OR ((((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields]))) OR (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields]))) OR "LVI"[All Fields]) OR ("lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields]))) OR ((((("grade"[All Fields] OR "graded"[All Fields]) OR "grades"[All Fields]) OR "grading"[All Fields]) OR "gradings"[All Fields])) OR ((((("stage"[All Fields] OR "staged"[All Fields]) OR "stages"[All Fields]) OR "staging"[All Fields]) OR "stagings"[All Fields])	
(((outcome) OR (survival)) OR (prognostic)) OR (prognosis)	"outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields] OR "prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields] OR "prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]	4,432,884

outcome	"outcome"[All Fields] OR "outcomes"[All Fields]	2,461,422
survival	"mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]	2,086,064
prognostic	"prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields]	301,748
prognosis	"prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]	1,823,869
location	"locate"[All Fields] OR "located"[All Fields] OR "locater"[All Fields] OR "locates"[All Fields] OR "locating"[All Fields] OR "location"[All Fields] OR "locational"[All Fields] OR "locations"[All Fields] OR "locator"[All Fields] OR "locators"[All Fields]	771,575
variant histology	(("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])	74,389
pathological	"pathologic"[All Fields] OR "pathologically"[All Fields] OR "pathologics"[All Fields] OR "pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathological"[All Fields]	3,795,533
pathology	"pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathologies"[All Fields] OR "pathology"[MeSH Subheading]	3,554,131
multifocality	"multifocal"[All Fields] OR "multifocality"[All Fields] OR "multifocally"[All Fields] OR "multifocals"[All Fields]	33,181
Sessile	"sessile"[All Fields]	7,165
architecture	"architectural"[All Fields] OR "architecturally"[All Fields] OR "architecture"[MeSH Terms] OR "architecture"[All Fields] OR "architecture s"[All Fields] OR "architectured"[All Fields] OR "architectures"[All Fields]	171,172
CIS	"CIS"[All Fields]	123,073
carcinoma insitu	((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields]	1,315
tumor margin	((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])	63,557
Margin	(((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields])	159,816

	OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields]	
tumor necrosis	((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields])	254,227
LVI	"LVI"[All Fields]	1,509
lymphovascular invasion	"lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields])	5,770
Grade	"grade"[All Fields] OR "graded"[All Fields] OR "grades"[All Fields] OR "grading"[All Fields] OR "gradings"[All Fields]	451,054
Stage	"stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]	1,203,520
UTUC	"UTUC"[All Fields]	869
Upper tract urothelial cancer	("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields])	2,343
Upper tract urothelial carcinoma	("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])	3,098

Supplementary File S2: List of studies included in the review.

1. Abe T, Kondo T, Harabayashi T, Takada N, Matsumoto R, Osawa T, et al. Comparative study of lymph node dissection, and oncological outcomes of laparoscopic and open radical nephroureterectomy for patients with urothelial carcinoma of the upper urinary tract undergoing regional lymph node dissection. Jpn J Clin Oncol. 2018;48:1001-11. Epub 2018/10/03.

2. Akao J, Matsuyama H, Yamamoto Y, Hara T, Kawai Y, Sakano S, et al. Clinical significance of lymphovascular invasion in upper urinary tract urothelial cancer. BJU Int. 2008;102:572-5. Epub 2008/05/20.

3. Aydin AM, Singla N, Panwar V, Woldu SL, Freifeld Y, Wood CG, et al. Prognostic significance of BAP1 expression in high-grade upper tract urothelial carcinoma: a multi-institutional study. World J Urol. 2019;37:2419-27. Epub 2019/02/14.

4. Aziz A, Rink M, Gakis G, Kluth LA, Dechet C, Miller F, et al. Preoperative C-reactive protein in the serum: a prognostic biomarker for upper urinary tract urothelial carcinoma treated with radical nephroureterectomy. Urol Int. 2014;93:352-60. Epub 2014/08/21.

5. Bolenz C, Shariat SF, Fernandez MI, Margulis V, Lotan Y, Karakiewicz P, et al. Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. BJU Int. 2009;103:302-6. Epub 2008/11/08.

6. Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2012;61:818-25. Epub 2012/01/31.

7. Cho YH, Hwang JE, Chung HS, Kim MS, Hwang EC, Jung SI, et al. The De Ritis (aspartate transaminase/alanine transaminase) ratio as a predictor of oncological outcomes in patients after surgery for upper urinary tract urothelial carcinoma. Int Urol Nephrol. 2017;49:1383-90. Epub 2017/05/10.

8. Chromecki TF, Cha EK, Fajkovic H, Margulis V, Novara G, Scherr DS, et al. The impact of tumor multifocality on outcomes in patients treated with radical nephroureterectomy. Eur Urol. 2012;61:245-53. Epub 2011/10/07.

9. Chung HS, Hwang EC, Kim MS, Yu SH, Jung SI, Kang TW, et al. Effects of Variant Histology on the Oncologic Outcomes of Patients With Upper Urinary Tract Carcinoma After Radical Nephroureterectomy: A Propensity Score-Matched Analysis. Clin Genitourin Cancer. 2019;17:e394-e407. Epub 2019/02/21.

10. Dalpiaz O, Pichler M, Mannweiler S, Martin Hernandez JM, Stojakovic T, Pummer K, et al. Validation of the pretreatment derived neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. Br J Cancer. 2014;110:2531-6. Epub 2014/04/03.

11. Ekmekci S, Kucuk U, Dere Y, Cakir E, Sayar HC, Ergani B, et al. 8-armed octopus: Evaluation of clinicopathologic prognostic factors of urothelial carcinoma of the upper urinary system. Turk J Med Sci. 2019;49:153-61. Epub 2019/02/16.

12. Elawdy MM, Taha DE, Elbaset MA, Abouelkheir RT, Osman Y. Histopathologic Characteristics of Upper Tract Urothelial Carcinoma With an Emphasis on Their Effect on Cancer Survival: A Single-Institute Experience With 305 Patients With Long-Term Follow-Up. Clin Genitourin Cancer. 2016;14:e609-e15. Epub 2016/06/06.

13. Fairey AS, Kassouf W, Estey E, Tanguay S, Rendon R, Bell D, et al. Comparison of oncological outcomes for open and laparoscopic radical nephroureterectomy: results from the Canadian Upper Tract Collaboration. BJU Int. 2013;112:791-7. Epub 2012/11/15.

14. Fang D, He S, Xiong G, Singla N, Cao Z, Zhang L, et al. Comparison of clinicopathologic characteristics, epigenetic biomarkers and prognosis between renal pelvic and ureteral tumors in upper tract urothelial carcinoma. BMC Urol. 2018;18:22. Epub 2018/03/29.

15. Gao X, Chen W, Zhang R, Wu C, Li Y, Zhu H, et al. Preoperative AST/ALT ratio predicts long-term survival after radical nephroureterectomy in patients with upper tract urothelial carcinoma. Internaional Journal of Clinical and Experimental Medicine. 2017;10:8.

16. Godfrey MS, Badalato GM, Hruby GW, Razmjoo M, McKiernan JM. Prognostic indicators for upper tract urothelial carcinoma after radical nephroureterectomy: the impact of lymphovascular invasion. BJU Int. 2012;110:798-803. Epub 2012/02/09.

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Supplementary File S3 - Characteristics of included studies.

S. no	Author Year Country	Number of patients	Study type	Multi-centre (Yes/No)	Age (Mean/Median (range)	Male/Female	Surgery (O/L)	L. Node Dissection	Pathological Stage (pTa-is/pT1/pT2/pT3/pT4)	LVI (PRESENT)	No. of Patient with Necrosis	Definition of necrosis	Tumor Site	Tumor Grade (1,2/3/unknown)	Adjuvant Chemotherapy (Yes/No)	Variant Histology (%)	Duration of Follow up	Parameters controlled in multivariate analysis	Survival outcomes assessed	NOS
1.	Hayakawa 2017 Japan	181	R	N	73(36-93)	140/41	NA	N	<T2-78 >T2-103	79	NA	NA	P-101 U-70 Both-10	LG-52 HG-129	NA	30	53(1-253)	-LVI -PD-1 expression in tumor nest	CSS PFS	6
2.	Hong 2005 Korea	73	R	N	59.1	NA	NA	Y-37	Ta-15 T1-18 T2-9 T3-27 T4-4	18	NA	NA	P-40 U-33	G1-6 G2-35 G3-32	13	NA	42.3	-LVI - grade -stage	DSS RFS	6
3.	Hsieh 2015 Taiwan	206	R	N	63(22-84)	138/68	NA	NA	NA	NA	NA	NA	Upper urinary tract-119 Bladder-84 Both-3		206	53	134.5	-Histopathological Variant -Renal function -Visceral metastasis	OS PFS OS	6
4.	Hurel 2013 France	551	R	Y	69.4(61.8-76.4)	365/186	O-551	Y	Ta/Tis-142 T1-124 T2-53 T3-193 T4-39	163	NA	NA	P-302 U-169 Both-80	G1-80 G2-251 G3-415	79	NA	26.8(10.3-48.7)	-Multifocal -pT3 stage -LVI -positive surgical margin(MFS)	CSS RFS MFS	6
5.	Ichimura 2014 Japan	171	R	N	70	119/52	NA	Y	Ta/Tis-44 T1-31 T2-18 T3-69 T4-9	74	NA	NA	P-103 U-68	LG-19 HG-152	NA	NA	56	-High CD204^{+} -LVI -LN Mets	RFS MFS CSS	6
6.	Ikeda 2017 Japan	441	R	Y	69(62-75)	319/122	O-247 L-194	Y	Ta/Tis-86 T1-92 T2-81 T3-158 T4-24	156	NA	NA	P-245 U-196	G1/2-305 G3-130	100	37	35.7	-T stage - Lymph node status -Grade3 -LVI -positive STSM	DFS CSS	7
7.	Kang 2015 Korea	440	R	Y	NA	305/135	NA	Y	Ta/Tis-31 T1-135 T2-101 T3-155 T4-8	76	NA	NA	P-159 U-219 Both-62	LG-110 HG-330	78	NA	31(15-57)	-Locally advanced stage -Node positive status -LVI -Margin status	OS DSS	8
8.	Kim DS 2010 Korea	238	R	N	64.1(25-91)	164/74	NA	Y	Ta-T2-131 T3-107	31	NA	NA	P-134 U-104	LG-95 HG-143	NA	24	53.4(3-240)	-Tumor architecture -squamous differentiation -LVI -Tumor grade	RFS CSS	7
9.	Kim JK 2017 Korea	452	R	N	64±10.2	347/105	O-332 L-120	Y	T0/a/is/1-187 T2-75 T3/4-188	99	NA	NA	P-223 U-165 Both-64	LG-59 HG-81	110	41	67.8(0-254)	-Age -T stage - multifocality -Positive STSM -tumor location -variant histology -LVI	OS CSS	7
10.	Kim SH 2015	371	R	N	64.7(57.7)	287/84	O-271	Y	pT0/a/is/1-162	71	NA	NA	P-183 U-140	LG-125 HG-246	85	28	50.8	-LRUN - stage	OS CSS	7

	Korea						L-100		pT2-63 pT3/4- 146				Both-48					-grade		
11.	Lee Sang 2006 Korea	119	R	N	62(36- 90)	92/27	NA	Y	Ta/T1-38 pT2-4-81	30	19	>1 0% ma cro sc opi c ne cro sis	P-54 U-65	G1/2-76 G3-43	40	NA	41(2- 164)	-T stage -LVI -Tumor necrosis	DSS	7
12.	Lee Young 2014 Korea	341	R	N	63.1(5 6.4- 70.5)	301/4 0	NA	Y	Ta/Tis-54 T1-81 T2-58 T3-144 T4-4	70	NA	NA	NA	G1-39 G2-206 G3-96	86	27	66.8(30- 95.3)	-Age -T stage -LVI -positive STSM -Nodal metastasis -Histological variant	CSS OS	7
13.	Lee Hsiang 2014 Taiwan	250	R	N	68	108/1 42	O- 166 L-84	Y	Ta/Tis-40 T1-53 T2-73 T3-70 T4-14	60	NA	NA	P-128 U-122	LG-55 HG-195	42	NA	41	-T stage - Lymph node involvement -LVI -Concomitant bladder tumor(RFS)	CSS MFS RFS	7
14.	Li Tao 2019 China	704	R	N	66±11. 4	401/3 03	O- 474 L-230	Y	</=T2- 359 >/=T3- 345	107	NA	NA	P-375 U-202 Both- 127	LG-185 HG-519	286	162	39(3 4-43)	-Low lymphocyte to monocyte ratio -Tumor size >/=3cm -High tumor grade -Advance tumor stage(>/=T3) -Lymph node invasion -Tumor architecture -Concomitant variant histology -Albumin to globulin ratio	CSS RFS OS	7
15.	Li Yifan 2019 China	602	R	N	66.77± 9.90	285/3 17	NA	Y	Ta-6 T1-322 T2- 2956T3- 238 T4-24	46	114	NA	P-310 U-292	G1-15 G2-342 G3-245	NA	105	6138 -102)	-High AST/ALT -T stage -N stage -Age -Gender -Tumor location -Tumor size -Glandular	CSS OS RFS	7

																		differentiation		
16.	Liu 2013 China	421	R	Y	62(51-70)	285/136	O-364 L-57	Y	Ta/Tis/T1-157 T2-91 T3-144 T4-29	101	NA	NA	P-225 U-196	G1-87 G2-128 G3-206	88	NA	NA	-Female gender -LVI -Tumor grade -Tumor stage - N stage	CSS	6
17.	Masson 2013 France	519	R	Y	68.4(61.2-76.5)	342/177	O-519	Y	Ta/is/1-246 pT2/3/4-273	361	NA	NA	P-289 U-154 Both-76	G1-46 G2-167 G3-306	80	39	27(10.2-48.7)	-T stage -LVI -margin status -Adjuvant chemotherapy	CSS MFS	6
18.	Matsumoto 2011 Japan	2163	R	Y	69(61-76)	1478/685	O-1790 L-373	Y	T0-10 Ta-450 Tis-36 T1-488 T2-401 T3-667 T4-111	481	496	NA	NA	LG-655 HG-1508	224	NA	36(15.3-71.1)	-Age - T stage -Tumor grade -LVI -Tumor architecture - N stage	RFS CSS	7
19.	Nakagawa 2017 Japan	109	R	Y	71(64-77)	67/42	NA	Y	T3-104 T4-5	78	NA	NA	P-50 U-23 Both-36	G1-0 G2-40 G3-69	43	NA	46.5(23.2-76.7)	-Adjuvant chemotherapy -lower nuclear grade -absence of hydronephrosis	RFS CSS	8
20.	Ouzzane 2012 France	714	R	Y	70(60-75)	484/228	NA	Y	Ta/Tis-131 T1-216 T2-124 T3-205 T4-40	157	NA	NA	P-388 U-236 Both-90	G1-71 G2-244 G3-399	NA	NA	27(10-50)	-Age -T stage - surgical margin	CSS MFS OS	6
21.	Qin 2017 China	346	R	N	66.61±9.897	206/140	NA	N	Ta/is/1-258 pT2/3/4-88	NA	18	NA	P-175 U-171	LG-59 HG-287	169	50	21(10-36)	-T stage -Tumor grade -variant histology -adjuvant chemotherapy	RFS CSS OS	6
22.	Kikuchi 2009 japan	1453	R	Y	69.7(27-97)	986/467	NA	Y	Ta-295 Tis-28 T1-317 T2-269 T3-475 T4-69	349	387	NA	P-958 U-495	LG-516 HG-937	169	NA	NA	-T stage -Tumor grade -N stage -LVI	CSS RFS	6
23.	Kawashima 2011 Japan	93	R	Y	NA	68/25	NA	Y	>T3-93	54	NA	NA	P-55 U-38	G1-6 G2-31 G3-56	38	11	NA	-Adjuvant chemotherapy -Tumor grade -LVI -Sex -Histology	CSS RFS	6
24.	Kim TH 2019 South Korea	1521	R	Y	65(57-72)	1127/394	O-906 L-615	Y	Ta/Tis-235 T1-404 T2-255	332	NA	NA	P-682 U-565 Both-274	LG-485 HG-993 Missing-43	340	NA	54.9(32.7-89.7)	-Previous bladder Tumor -Concomitant bladder tumor	IVRFS PFS CSS OS	6

									T3-592 T4-35									-Age -T stage -Tumor grade -LVI -Concomitant CIS -N stage		
25.	Kohada 2018 Japan	148	R	N	71(64-78)	112/36	NA	Y	Ta/1/2-82 T3/4-66	55	NA	NA	P-82 U-66	G1/2-60 G3-88	25	NA	35.5(12-66)	-Elevated pre-op Neutrophil-lymphocytes ratio -Hydronephrosis -LVI	CSS RFS	7
26.	Morizane 2015 Japan	345	R	Y	74(38-95)	234/111	O-244 L-101	Y	<T3-188 >/=T3-152	102	NA	NA	P-140 U-205	Non G3-222 G3-109	80(23.2%)	29	39.9(6.1-160)	-ECOG performance status -Number of tumor foci -Serum HB -eGFR -T stage -Histological variant -Tumor grade -Positive LN -INF -LVI -Positive margin	CSS	6
27.	Makise 2015 Japan	140	R	N	NA	101/39	NA	Y	Ta/Tis-36 T1-25 T2-11 T3-60 T4-8	61	NA	NA	P-89 U-51	G1/2-63 G3-77	42	23	NA	5 -T stage -N stage -LVI -Tumor grade -Age	MFS CSS OS	7
28.	Zhang 2016 China	184	R	N	70(60-74)	84/100	O-125 L-59	Y	Ta/1-73 T2/3/4-111	28	30	NA	P-99 U-85	G1/2-117 G3-67	NA	NA	78(34-92)	-preoperative plasma fibrinogen level -Gender -T stage -Age>70 -Preoperative CKD4/5	OS CSS	7
29.	Su 2016 China	687	R	N	<3cm-69(20-90) >3cm-68(29-86)	306/381	O-220 L-467	Y	Ta/is/1-129 T2-242 T3-197 T4-19	NA	79	NA	P-380 U-307	G1-21 G2-368 G3-298	NA	81	65(3-144)	-Older age -Male -presence of hydronephrosis -Advance T stage -Positive LN -preoperative ureteroscopy -Lower tumor grade -N0 status -Tumor multifocality	CSS RFS	7

30.	Huang 2016 China	481	R	N	65.8±11.1	311/170	O-318 L-163	Y	Ta/1-248 T2/3/4-233	76	NA	NA	P-232 U-160 Multifocal-89	LG-163 HG-318	96	NA	40(24-64)	-F-PLR score -Age >65 -Tumor multifocality -T stage -Higher grade -LVI Higher pN stage	OS CSS	6
31.	Abe 2018 Japan	214	R	Y	70.5 (35-93)	151/63	0-100 L-114	Y 214	42/48/41/75/8	96	NA	NA	P-127 U-82 Both-5	100/113/1	14/200	NA	15	-T stage -LVI -- Tumor number	RFS CSF OS	7
32.	Akao 2008 Japan	90	R	N	NA	57/33	NA	NA	0/3/24/14/43/6	34	NA	NA	P-51 U-39	4/56/29	24/61	NA	42(2-179)	-LVI - pT - pN - Tumor grade -Adjuvant therpy	DSS	6
33.	Aydin 2019 USA	348	R	Y	70(64-77)	163/185	NA	Yes (n=86)	31/103/57/129/28	98	62	NA	P-267 U-81	NA	NA	NA	36	-T stage - LVI -Necrosis- Architecture	RFS CSS OS	7
34.	Aziz 2014 Germany	265	R	Y	67.7 ± 9.85; 69.8 ± 8.85	169/96	NA	Yes (n=59)	106(Ta-T1)/49/102/8	52	NA	NA	P- 57 U- 33 Both-26	43/60/162	46/219	NA	37(9-48)	-ECOG -Tumor multifocality -LN involvement -LVI	RFS DSS ACS	6
35.	Bolenz 2008 Germany	116	R	N	NA	80/36	0-107 L-09	Y 27	9/3/23/28/42/11/20	36	17	10 %	P-84 U-32	12/58/46	NA	NA	38	-LVI -Pathological stage	DSS	7
36.	Cha 2012 USA	2244	R	Y	69 (61.6-76.0)	1502/742	NA	Y-129 N-540 X-1575	516/46/537/444/606/80	484	NA	NA	P- 1449 U- 795	HG-1838 LG- 406	NA	NA	45	-T stage -LN status -LVI -Architecture -CIS	RFS CSM CSS	7
37.	Cho 2017 Korea	1049	R	Y	68.5 (60.5-74.3)	759/290	NA	505	106/316/201/403/23	202	NA	NA	P-489 U-306 Both-92	HG- 745 LG- 304	Y-300	NA	40 (18.4 - 64.8)	-T stage -N1 disease -Hydronephrosis -De Retis Ratio	RFS CSS OS	8
38.	Chromecki 2011 USA	1169	R	Y	69 (30-92)	785/384	O-1014 L-155	Y 398	285/20/274/231/318/53	259	287	NA	P-742 U-427	LG-179 HG- 982	Y- 78	NA	37 (1-197)	-Age -Stage -Grade -Architecture -Necrosis -LVI	CSD OS	7
39.	Chung 2019 Korea	1173	R	Y	68.8 (61-74.6)	849/324	NA	540	Tis/Ta/T1-460 T2-230 T3/T4-483	236	NA	NA	P-542 U-537 Both-94	LG-343 HG-830	Y-357	93 (7.9%)	NA	-Preoperative anemia -HDN -LVI -VH	RFS CSS OS	7

40.	Dalpiaz 2014 Austria	171	R	N	69 +/- 10.1	107/ 64	NA	NA	T1-79 T2-4=92	NA	21	NA	P-95 U-76	G1-2=92 G3-4=79	NA	NA	31 (13-69)	-p stage -Grade pHistological - Tumor necrosis	CSS OS	7
41.	Ekmekci 2019 Turkey	74	R	Y	63.3 (40-84)	60/ 14	NA	64	pTa-16 13/ 04/ 28/ 13	25	29	NA	P-38 U-7 Both-29	NA	NA	22 (39.2 %)	43.5 +/- 48.7	-Tumor necrosis -Tumor differentiation -LN metastasis	DFS OS	7
42.	Elawddy 2016 Osman	305	R	N	59+/- 11	262/ 43	O-268 L-24 Renal sparing-13	NA	T0-3 Ta,is.1-196 T2-44 T3-61 T4-1	NA	NA	NA	P-183 U-182	G0-3 G1-16 G2-195 G3-100	NA	NA	34 (6-300)	-Tumor stage -Micropapillary variant	CSS OS	7
43.	Fairey 2012 Canada	849	R	Y	70.5		O-403 L-446	245	<=T1-186 T2-66 T3-89 T4-22	NA	NA	NA	NA	HG-274 LG-123	Y-94	NA	2.2 (0.6-5.0)	-T stage -Surgical approach -LN stage -Grade -Surgical margin	OS DSS RFS	6
44.	Fang 2018 China	612	R	N	Pelvis-65.29 +/- 11.11 Ureter-68.07+/ -10.20	340/ 272	NA	41	pTa-1=206 pT2-4= 406	NA	75	NA	P-341 U-271	G1-19 G2-334 G3-259	NA	NA	64	-Necrosis -LN status -Architecture -Grade -CIS	OS CSS	7
45.	Gao 2017 China	259	R	N	67.53	187/ 179	O-80 L-179	24	<=pT2-171 >=pT3-88	212	NA	NA	NA	G1-59 G2-3= 200	NA	23(8.8%)	33.3 (15.5-64.2)	-AST/ALT -Stage -Grade -HIstology -Sarcomatoid differentiation	OS PFS CSS Bladder recurrence free survival	7
46.	Godfrey 2012 USA	211	R	N	70 (11.4)	124/ 87	O-121 L-90	59	Ta-Tis=78 T1-41 T2-18 T3-71 T4-3	68	NA	NA	P-170 U-41	HG-134 LG-77	NA	NA	27 (11-65.5)	-Race -LVI -High nuclear grade	OS OSS	6
47.	Hara 2015 Japan	1172	R	Y	NA	806/ 366	O-750 L-421 Missing data-1	1138	Ta-125 Tis-29 T1-344 T2-302 T3-240 T4-21 Tx-111	423	NA	NA	P-593 U-546 Both-32 Missing data-1	G0-1 G1-71 G2-528 G3-558 Missing data-14	179	NA	55.8	-Age -Stage -LN -Metastasis -LVI -Infiltrative growth pattern	OS RFS	7
48.	Inamoto 2011 Japan	103	R	N	68.6 ±10.05	71/32	NA	Y	Tis/Ta/T1 - 43 T2- 13 T3/T4- 47	32	Nil	NA	-	G1-20 G2-28 G3-55	-	11	29 (14-63)	-C reactive protein -BMI -Focality -Lymph.Node	OS CSS RFS	6
49.	Saito	189	R	N	NA	94/41	NA	Y	≤T2 –	57	Nil	NA	59/76	LG-81	30	-	55	-Age	CSS	6

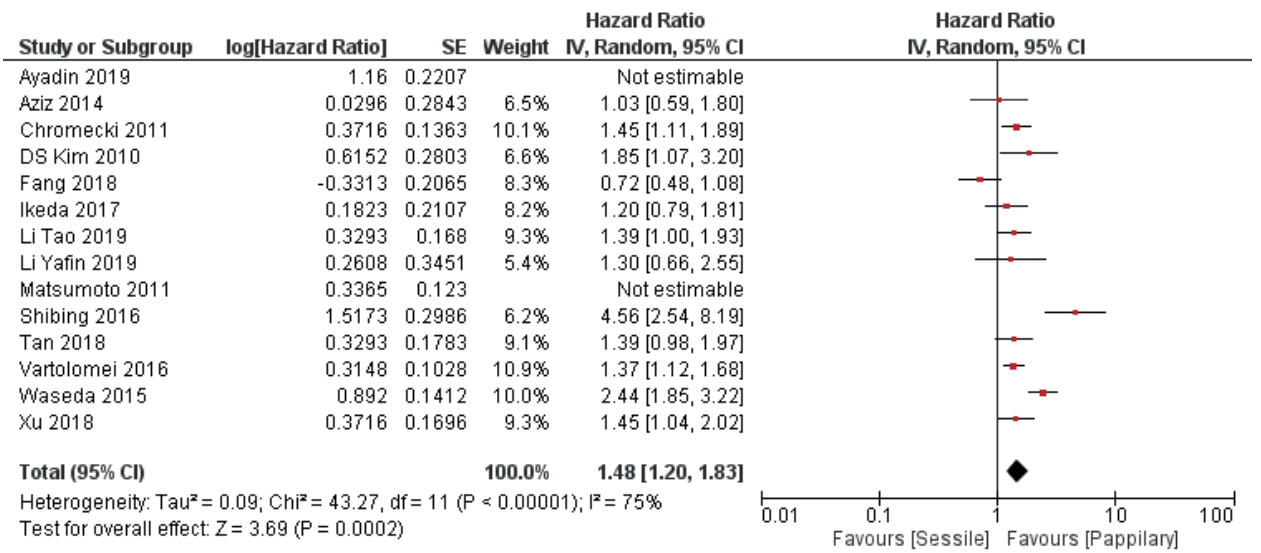
	2007 Japan								73 T3 – 62					HG- 54			(3-232)	-pT -LVI	RFS	
50.	Sakano 2014 Japan	502	R	Y	72 (32-93)	344/158	NA	Y	<3 – 290 ≥3-212	166	Nil	NA	221/232	LG-257 HG-233	144	60	41.4 (3-200)	-pT -Grade -LVI -Variant Histology	CSS	7
51.	Shibing 2015 China	417	R	N	67 (26-86)	246/171	NA	Y	Tis/Ta/T1 - 118 T2-79 T3-168 T4-52	74	Nil	NA	271/110	LG-100 HG-317	78	90	26 (12-54)	-pT -Grade -L.Nodes -Tumor Size -SurgicalMargins	OS CSS RFS	7
52.	Song 2019 Korea	453	R	N	69 (52-80)	320/133	O-164 L-143 Robotic-146	Y	Ta-6 T1-127 T2-147 T3-145 T4-23	132	Nil	NA	161/201	G1-2 G2-225 G3-222	-	-	23.2 (0-172)	-BMI -pT -LVI -L.Node -HDN -HTN	OS CSS RFS	7
53.	Sung 2014 Korea	386	R	N	64 (56-71)	293/93	NA	Y	Ta/Tis-78 T1-85 T2-56 T3/T4-167	-	Nil	NA	175/166	G1-20 G2-193 G3-161	-	7	39 (21.1 - 70.6)	-Age -Gender -Location -Grade -pT	RFS CSS	7
54.	Tai 2015 Taiwan	503	R	N	68 (60-74.8)	249/254	NA	Y	Ta/Tis/T1 -144 T2-31 T3-101 T4-4	49	Nil	NA	280/184	LG-135 HG-142	8	-	52 (23-77)	-Grade -pT -LVI -Location	OS RFS CSS	6
55.	Tan 2018 China	668	R	Y	65.8 (54.4-77.2)	380/288	NA	Y	≤ pT2-338 ≥pT3-330	99	Nil	NA	353/196	LG-173 HG-495	281	-	45 (21-74)	-Focality -pT -L.Nodes -LVI -LDH	CSS OS RFS MFS	7
56.	Tanaka 2012 Japan	218	R	Y	69 (38-92)	160/58	O-155 L-63	Y	Ta-T1-75 T2-27 T3-107 T4-9	84	Nil	NA	130/88	LG-59 HG-159	42	-	38 (3-187)	-Plasma Fibrinogen -pT -LVI	CSS RFS	7
57.	Tanaka 2015 Japan	394	R	Y	70 (63-77)	289/105	NA	Y	Ta/T1-125 T2-57 T3-201 T4-11	170	Nil	NA	232/162	LG-128 HG-266	88	-	30 (15-63)	-pT -LVI -Plasma Fibrinogen	CSS RFS ACM	7
58.	Tang 2015 China	687	R	N	68 (20-90)	306/381	NA	Y	T1-216 T2-217 T3-160 T4-13		Nil	NA	339/267	G1-20 G2-354 G3-232	-	81	65 (3-144)	-Gender -pT -Variant Histology -Pre op -HDN	RFS CSS	7
59.	Vartolomei 2015 Multicentre	2274	R	Y	69 (61-76)	1527/747	NA	Y	Ta-497 Tis-48 T1-532	499	516	-	1448/826	LG- 367 HG-1907	-	-	40 (20-76)	-pT -Grade -LVI	RFS CSS	7

									T2-441 T3-671 T4-85									-NLR -L.Node -Gender		
60.	Waseda 2015 Japan	1068	R	Y	70 (62-76)	758/310	NA	Y	Ta-127 Tis-34 T1-186 T2-164 T3-518 T4-39	446	Nil	NA	198/181	LG-751 HG-317	-	-	40 (17-77)	-Age -LVI -pT -pN -Location	RFS CSS	6
61.	Xu 2018 China	662	R	N	67 (59-74)	376/286	O-430 L-232	Y	≤pT2-338 ≥pT3-324	100	Nil	NA	349/193	LG-169 HG-493	279	149	42 (19-72)	-Grade -pT -L.Node -Variant Histology -CONUT score	OS RFS CSS	6
62.	Shibing 2016 China	795	R	Y	NA	462/333	O-588 L-207	Y	Tls/Ta/T1-149 T2-241 T3-313 T4-92	169	Nil	NA	497/187	LG-212 HG-583	202	162	32 (17-60)	-Grade -pT -LVI -Variant Histology -Size -Lymph.Node	OS CSS RFS	7
63.	Zamboni 2019 Multicentre	1610	R	Y	69 (61-76)	1096/512	O-999 L-489	Y	T0/Ta/Tis-401 T1-330 T2—227 T3-521 T4-110	344	235	NA	NA	HG-1058	233	150	42	-micropapillary variant -T3-4 stage -Sarcomatoid variant	RFS CSM	6
		35714																		

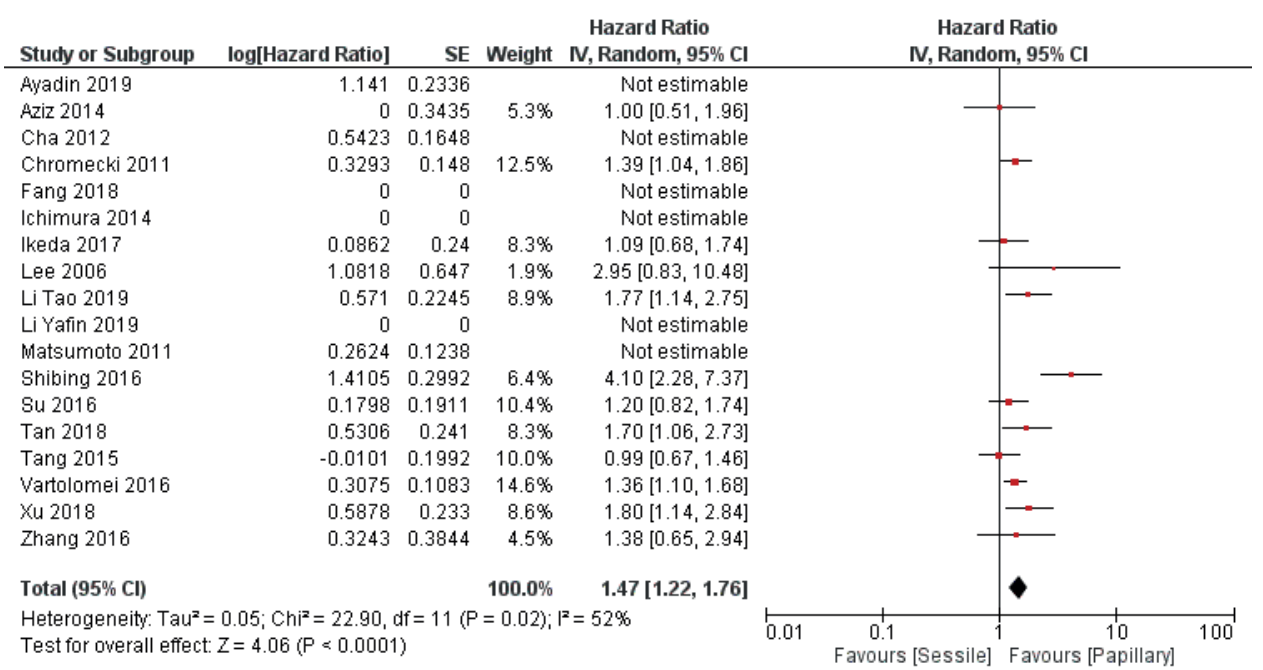
R-Retrospective, U- ureter, P-Renal Pelvis, O- Open, L- Laparoscopic, R- retrospective , LG- low grade, HG- high Grade, G-grade , LVI-Lymphovascular invasion, STSM- soft tissue surgical margin, T stage- pathological T stage, INF- interferon, O –Open, L= Laparoscopic, X= not known, LN- Lymph node, AST- aspartate transaminase, ALT-alanine transminase, CSS- cancer specific survival, RFS- Recurrence free survival, OS- overall survival, MFS-metastasis free survival, ECOG- Eastern co-operative oncology group, HB- hemoglobin, GFR- Glomerular filtration rate, CIS- carcinoma in situ.

APPENDIX 2

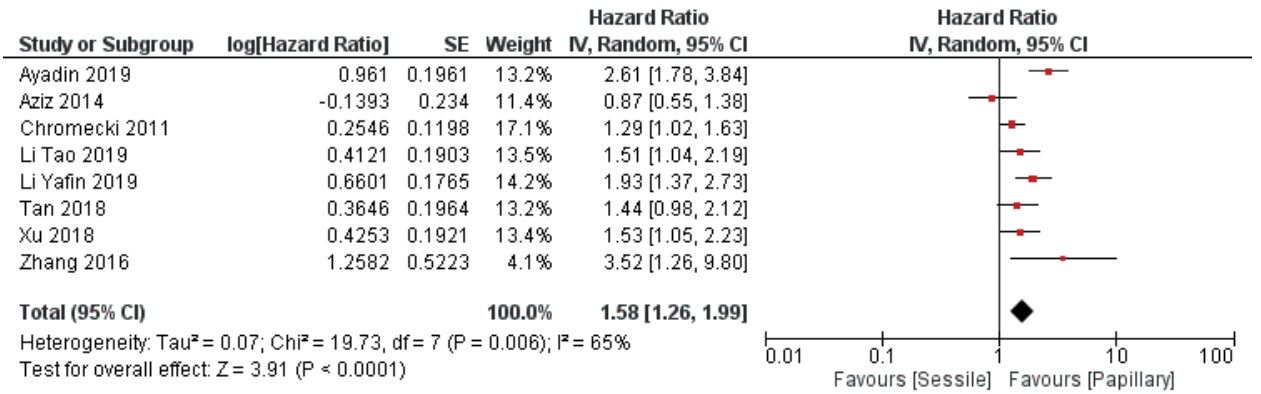
Supplementary Figure 1 - Forest plot depicting RFS for architecture



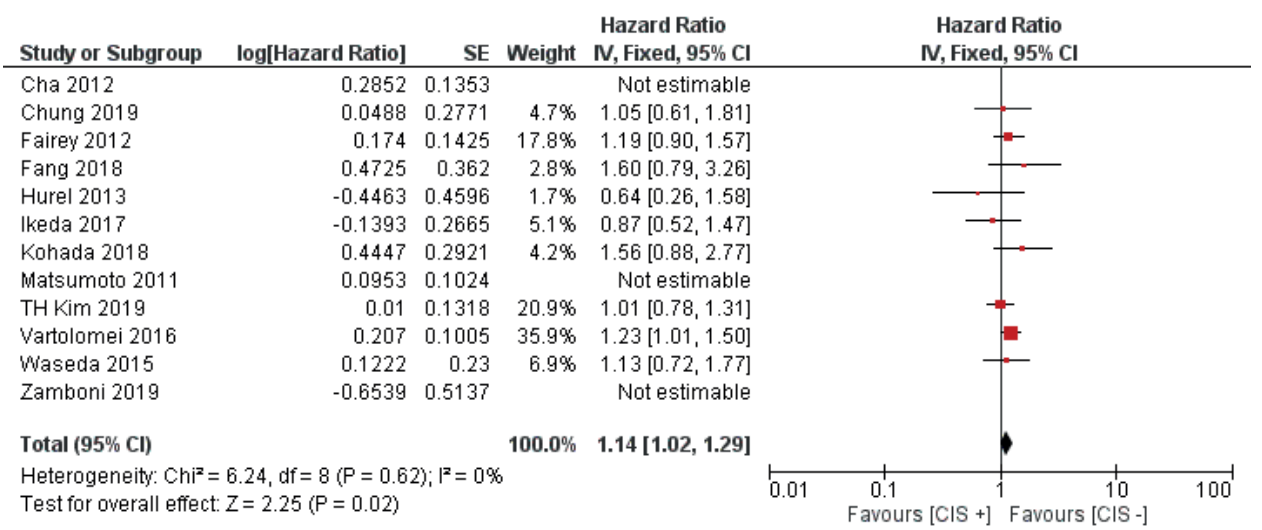
Supplementary Figure 2: Forest plot depicting CSS for architecture.



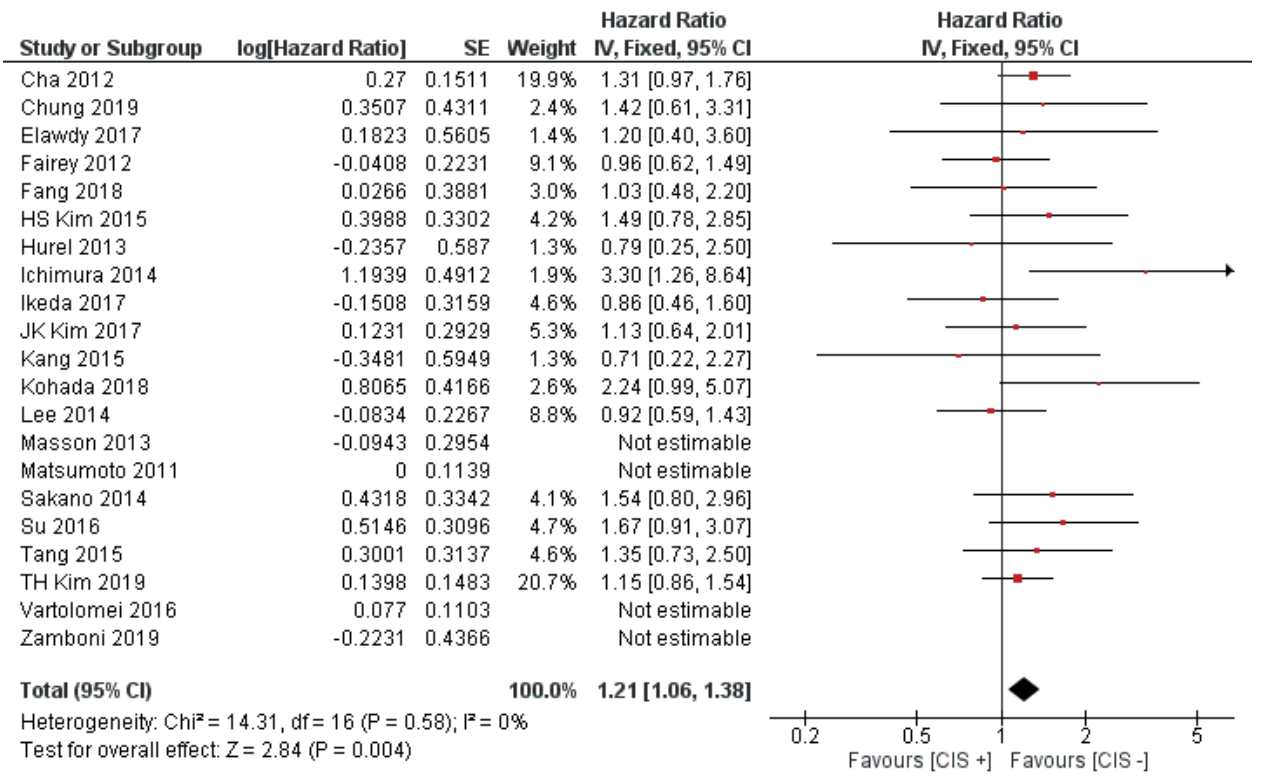
Supplementary Figure 3: Forest plot depicting OS for architecture.



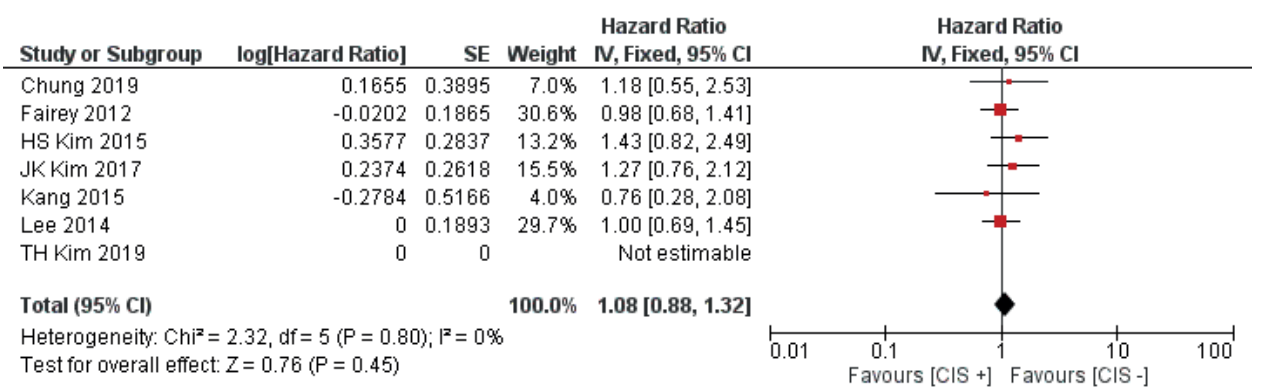
Supplementary Figure 4: Forest plot depicting RFS for carcinoma in situ.



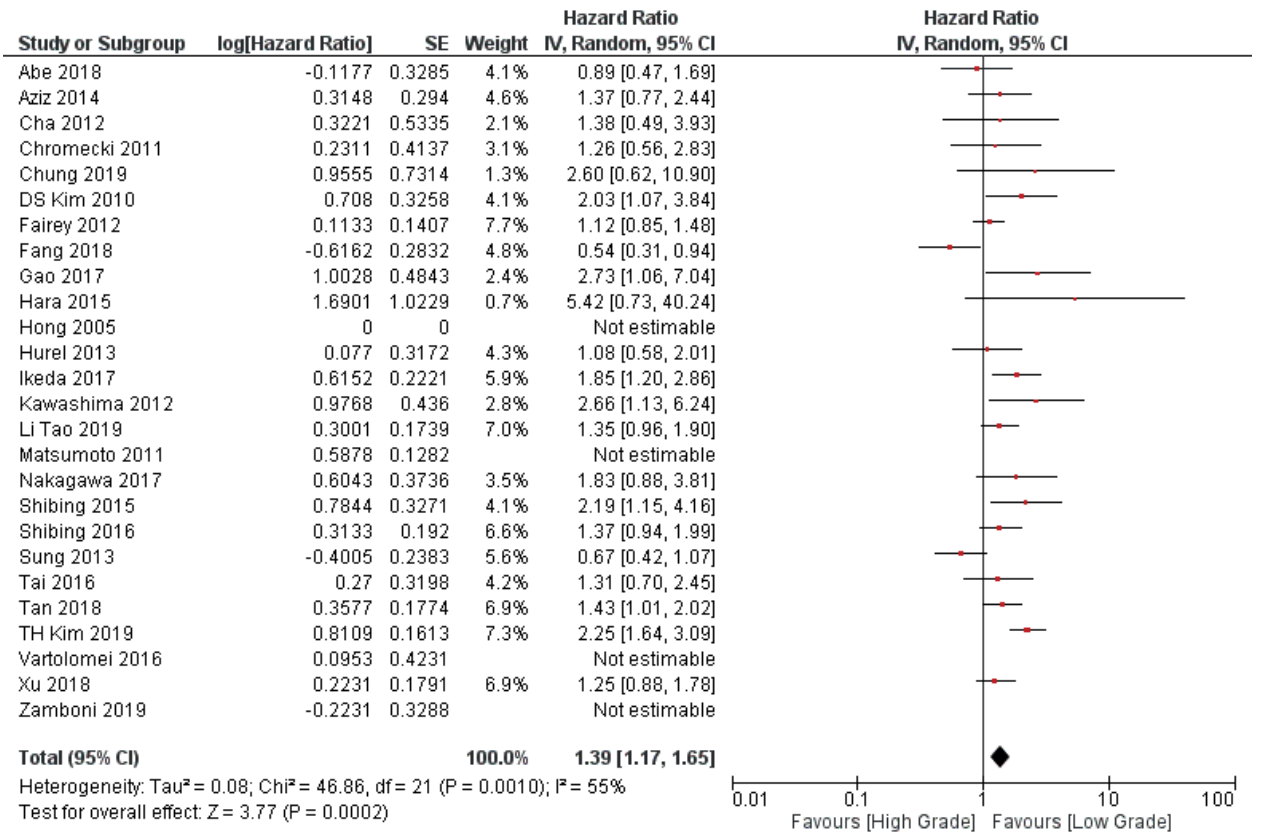
Supplementary Figure 5: Forest plot depicting CSS for carcinoma in situ.



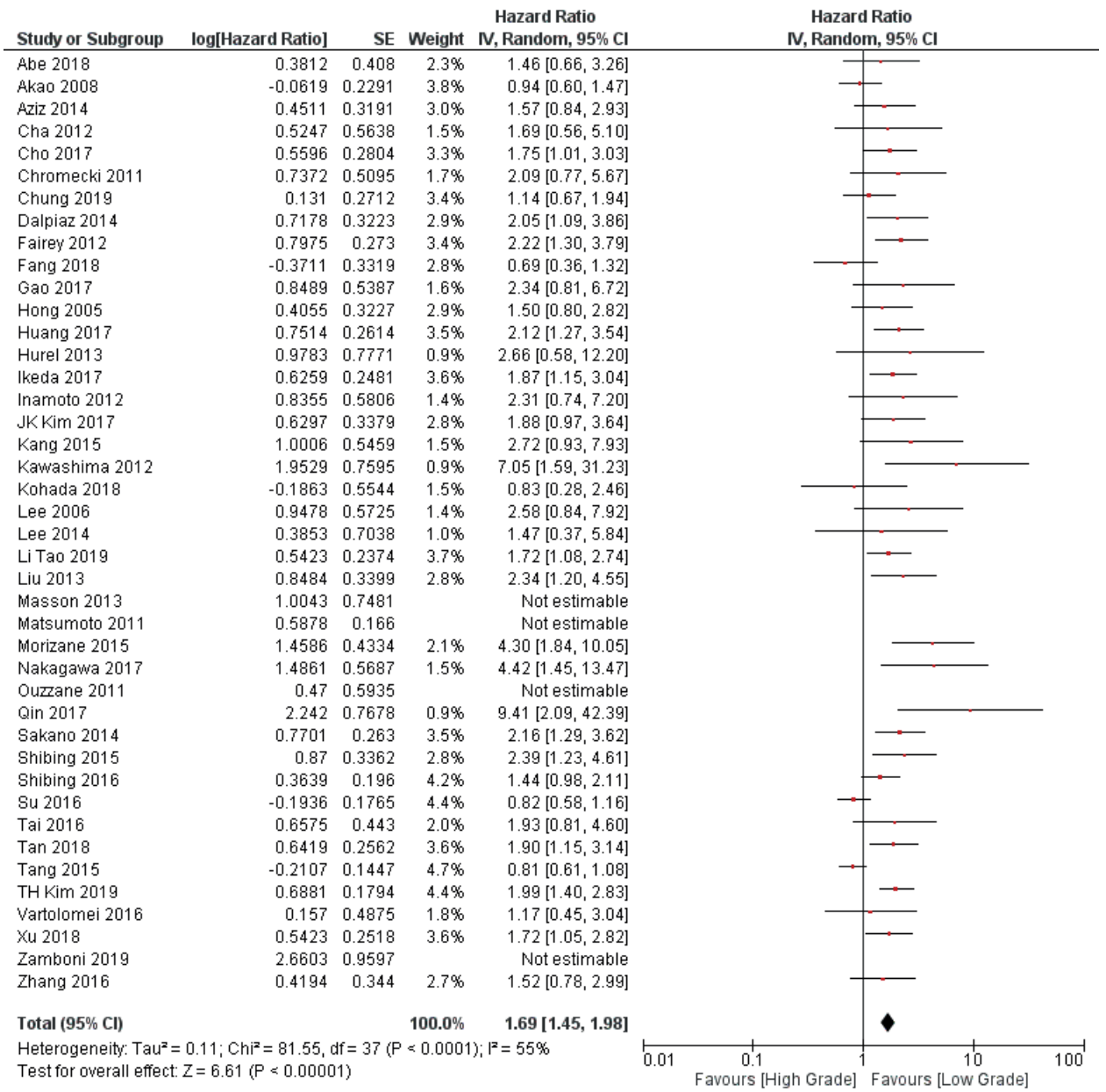
Supplementary Figure 6: Forest plot depicting OS for carcinoma in situ.



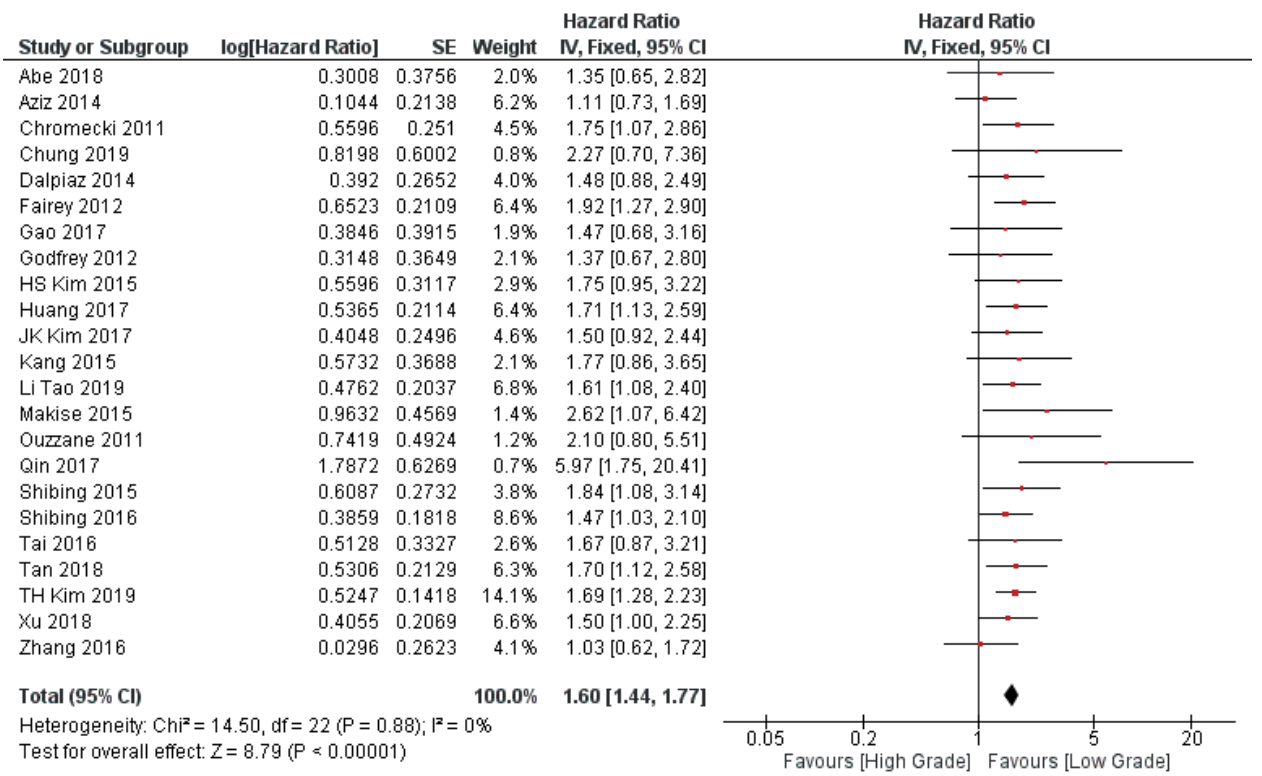
Supplementary Figure 7: Forest plot depicting RFS for grade.



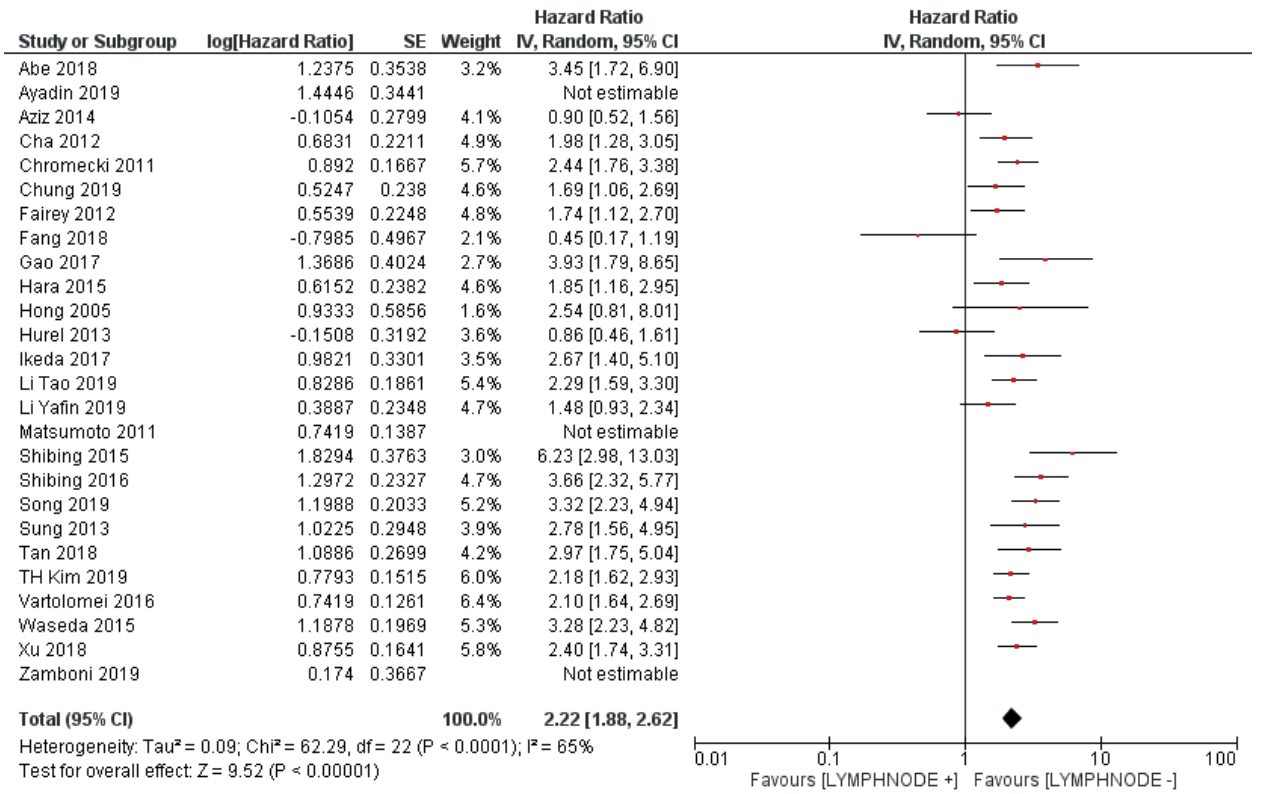
Supplementary Figure 8: Forest plot depicting CSS for grade.



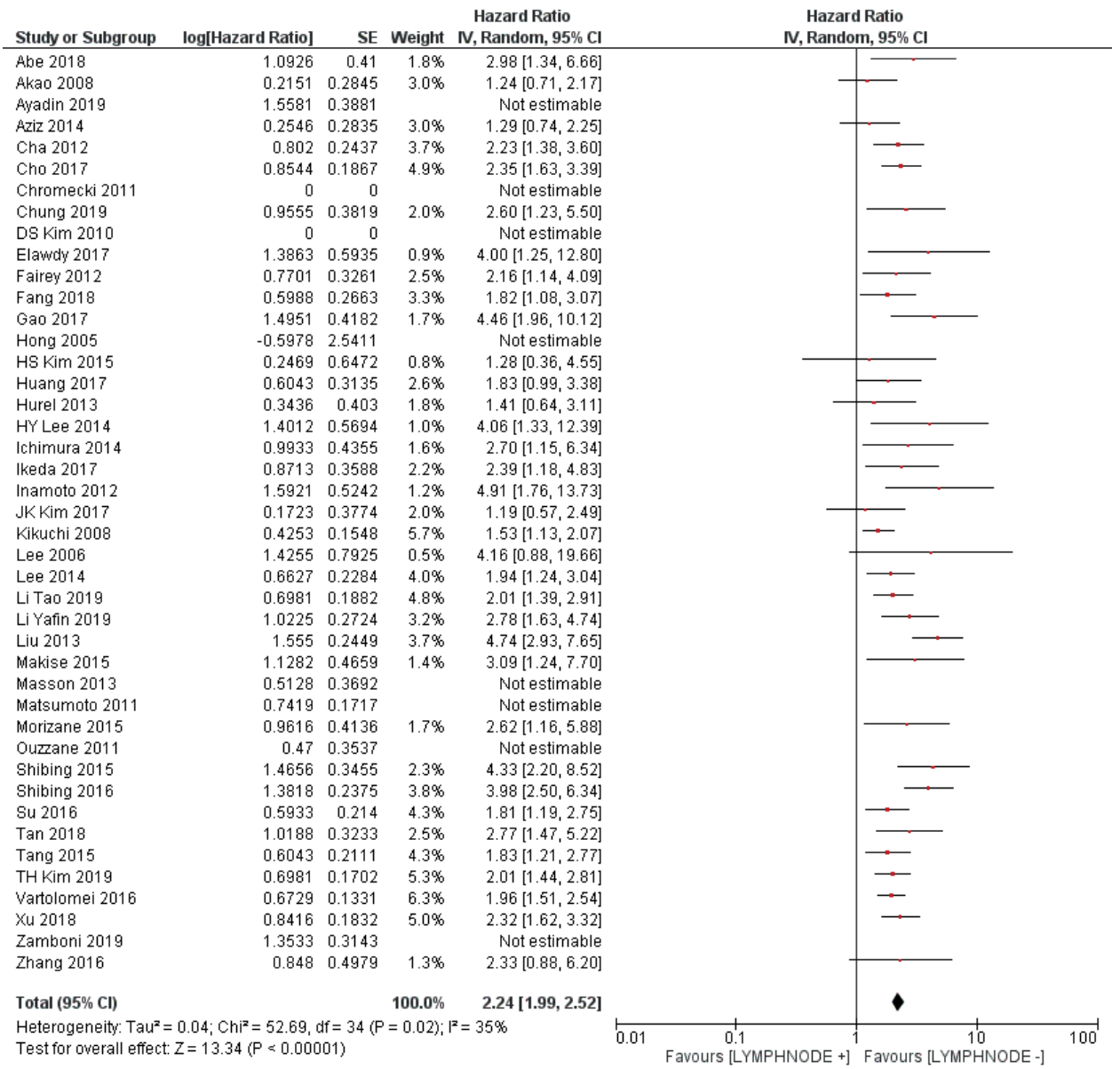
Supplementary Figure 9: Forest plot depicting OS for grade.



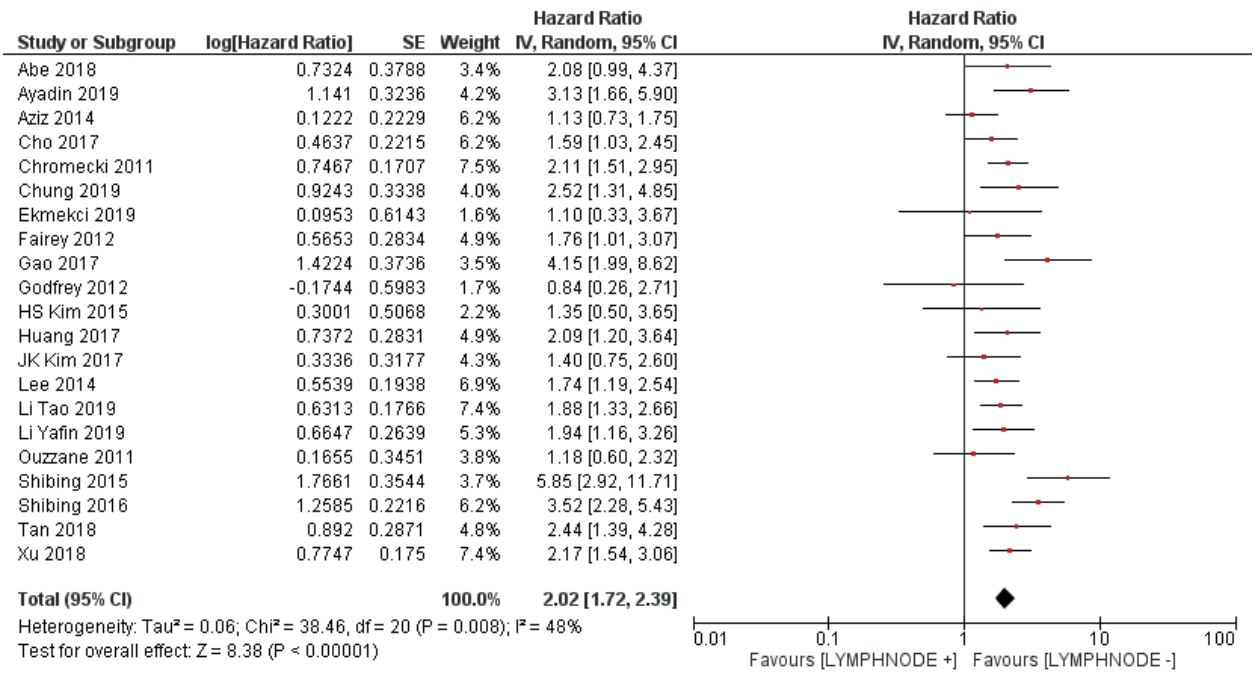
Supplementary Figure 10: Forest plot depicting RFS for lymph node positivity.



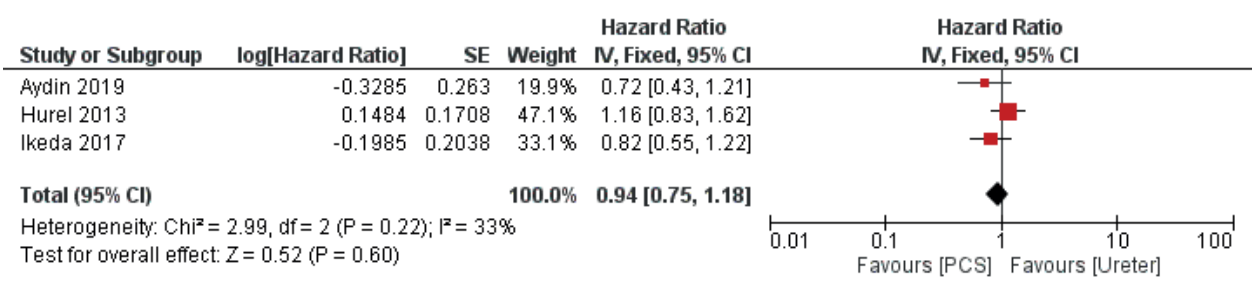
Supplementary Figure 11: Forest plot depicting CSS for lymph node positivity.



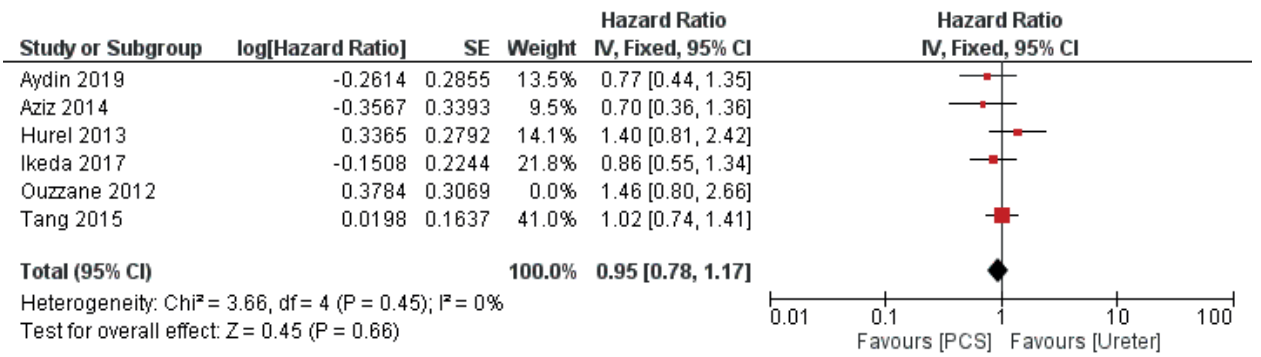
Supplementary Figure 12: Forest plot depicting OS for lymph node positivity.



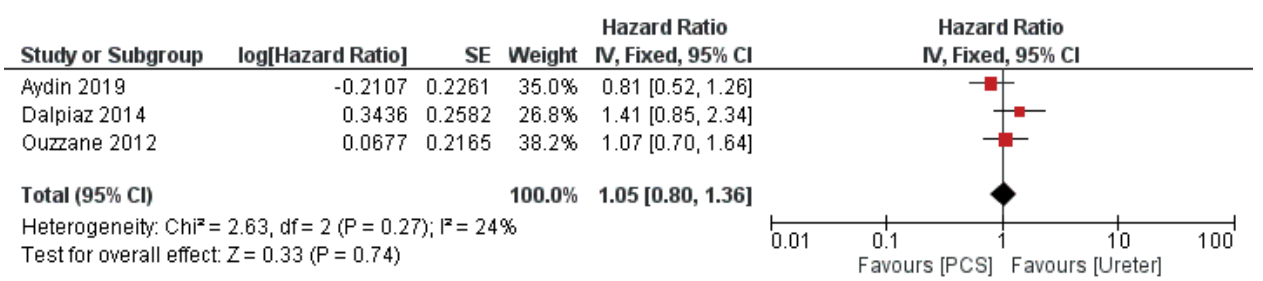
Supplementary Figure 13: Forest plot depicting RFS for location of tumor.



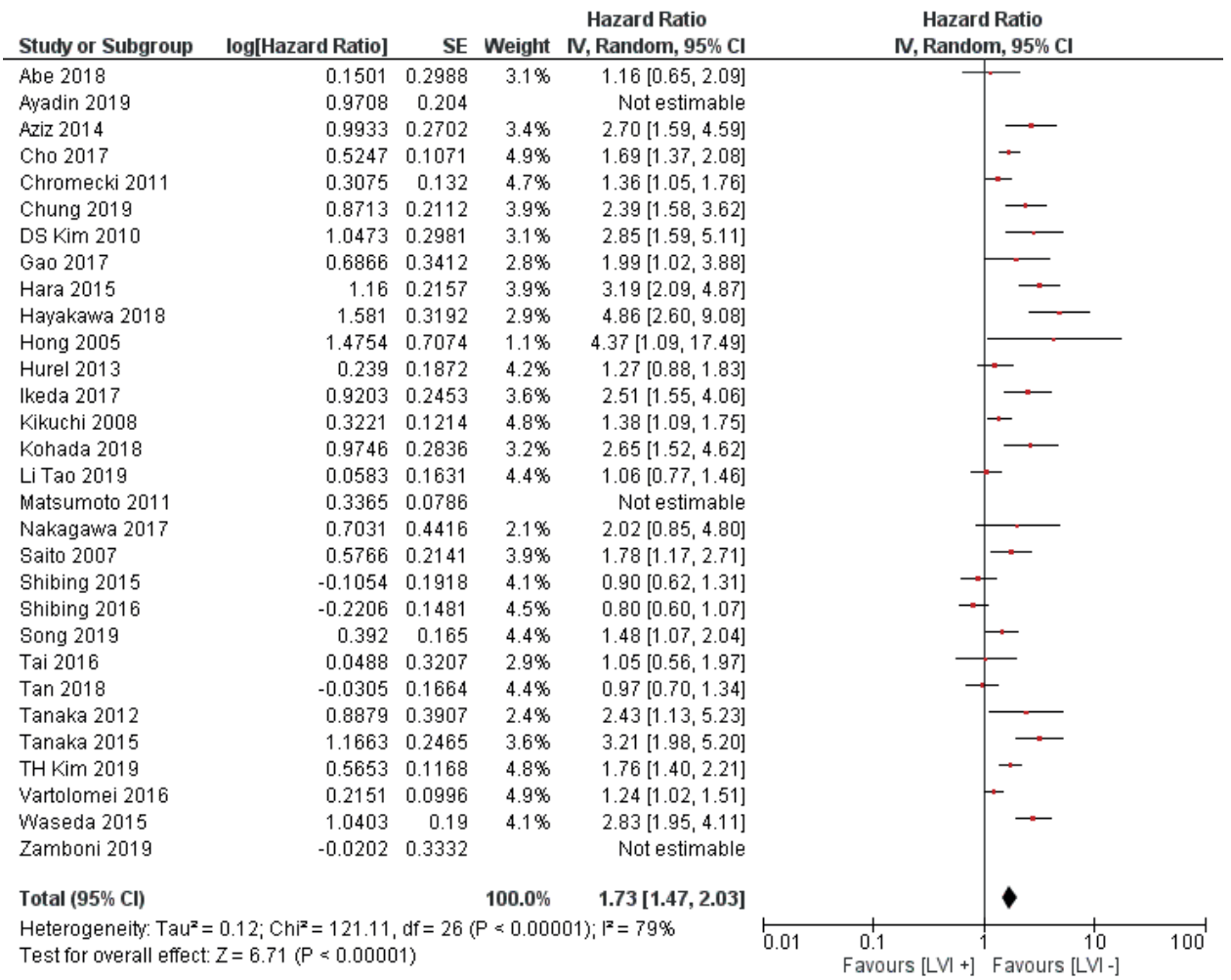
Supplementary Figure 14: Forest plot depicting CSS for location of tumor.



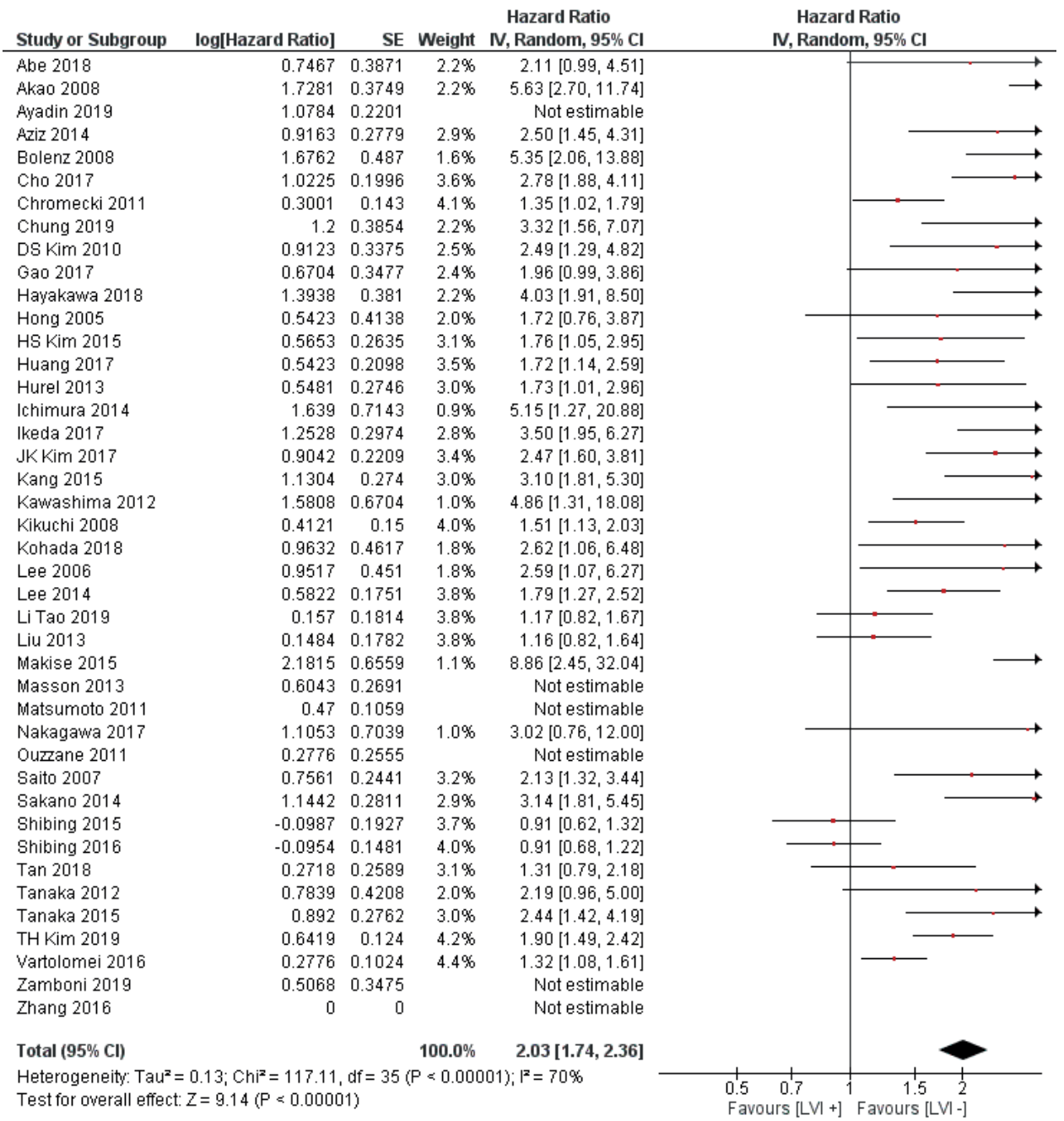
Supplementary Figure 15: Forest plot depicting OS for location of tumor.



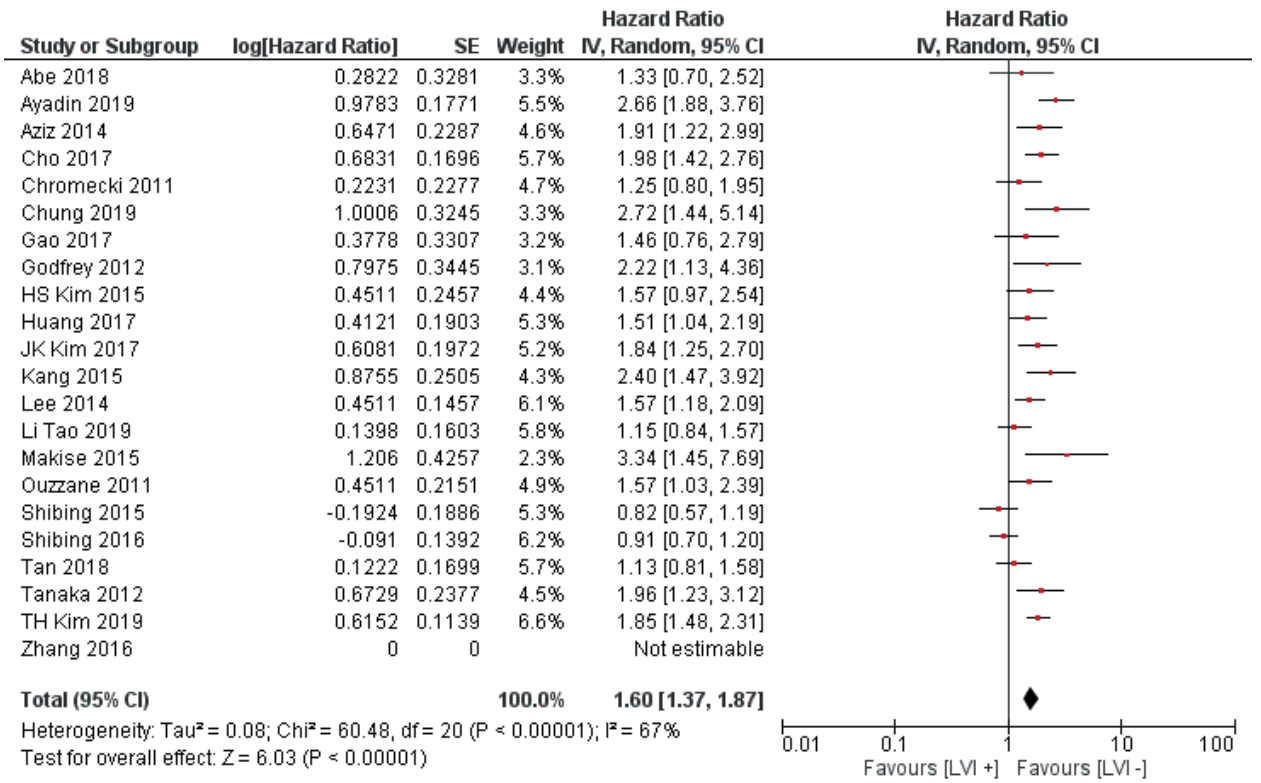
Supplementary Figure 16: Forest plot depicting RFS for lymphovascular invasion.



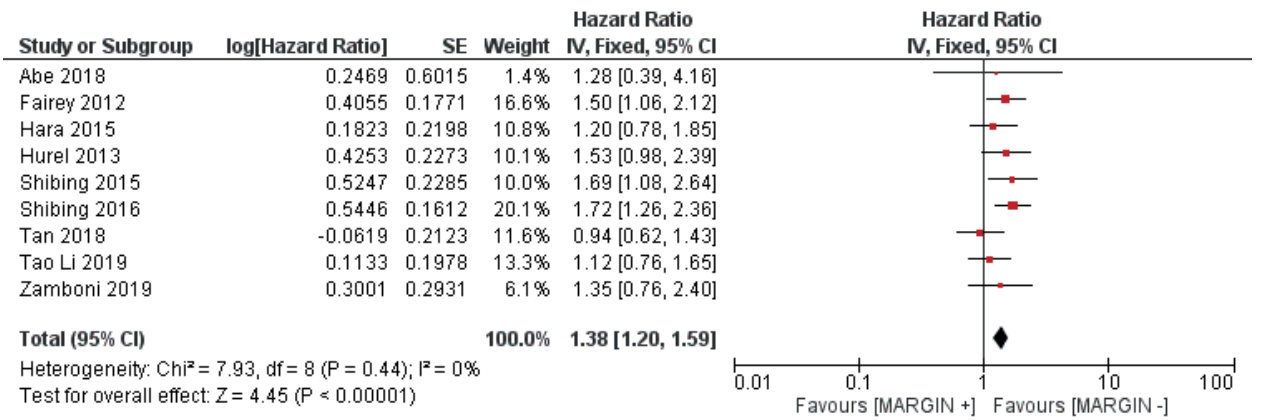
Supplementary Figure 17: Forest plot depicting CSS for lymphovascular invasion.



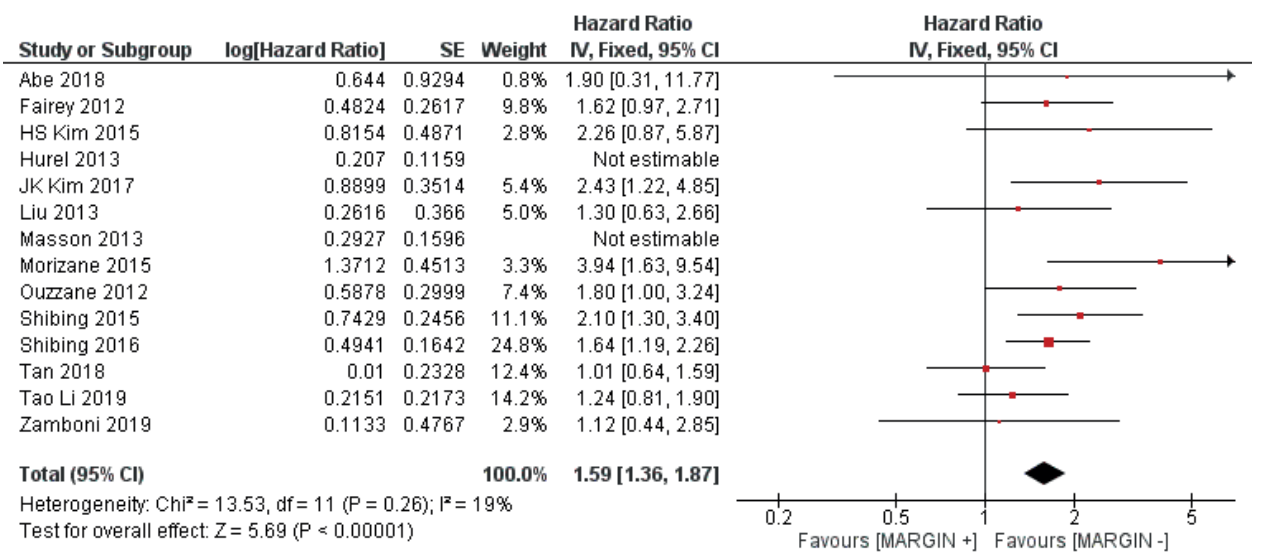
Supplementary Figure 18: Forest plot depicting OS for lymphovascular invasion.



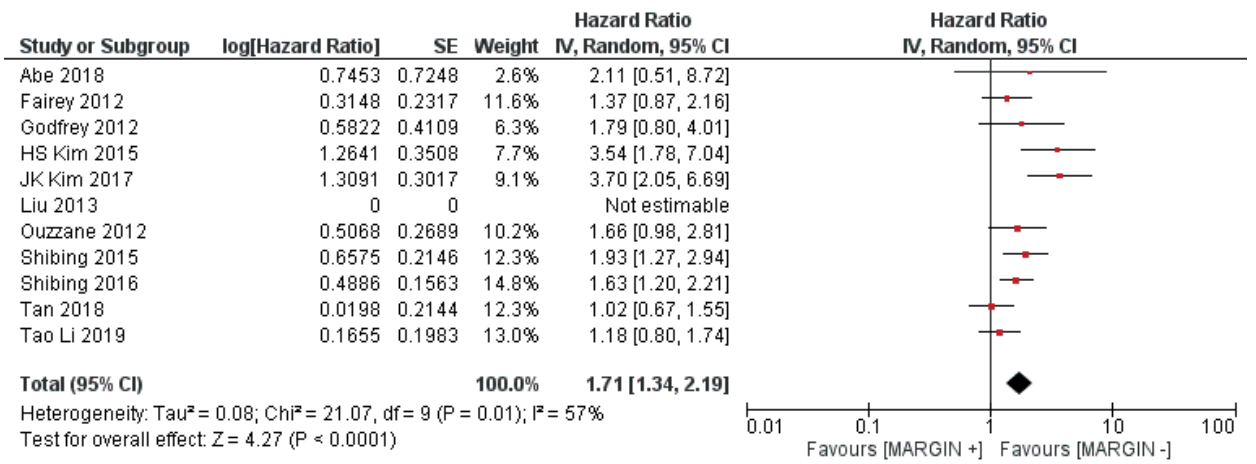
Supplementary Figure 19: Forest plot depicting RFS for margin positivity.



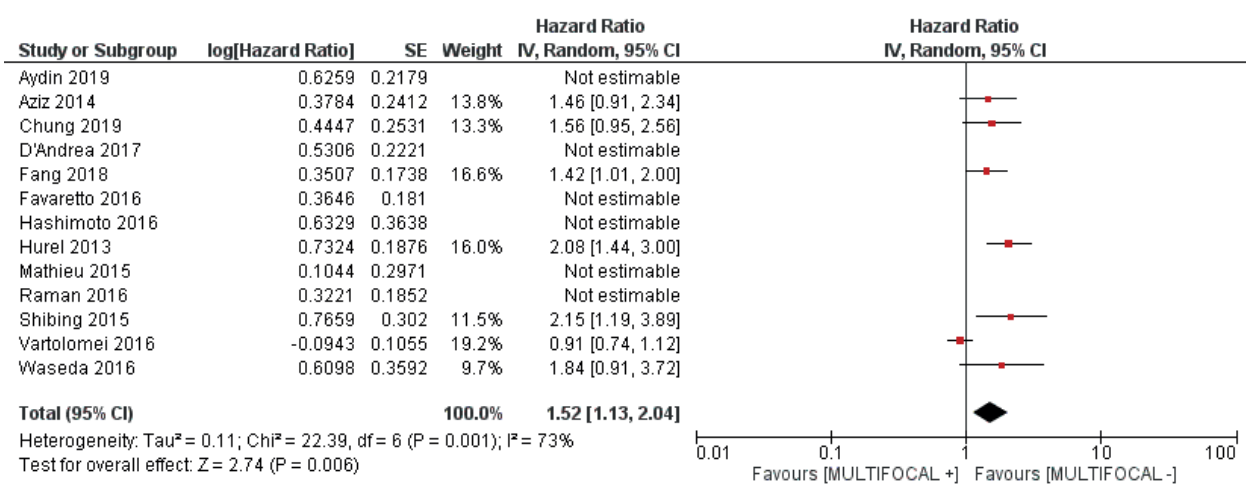
Supplementary Figure 20: Forest plot depicting CSS for margin positivity.



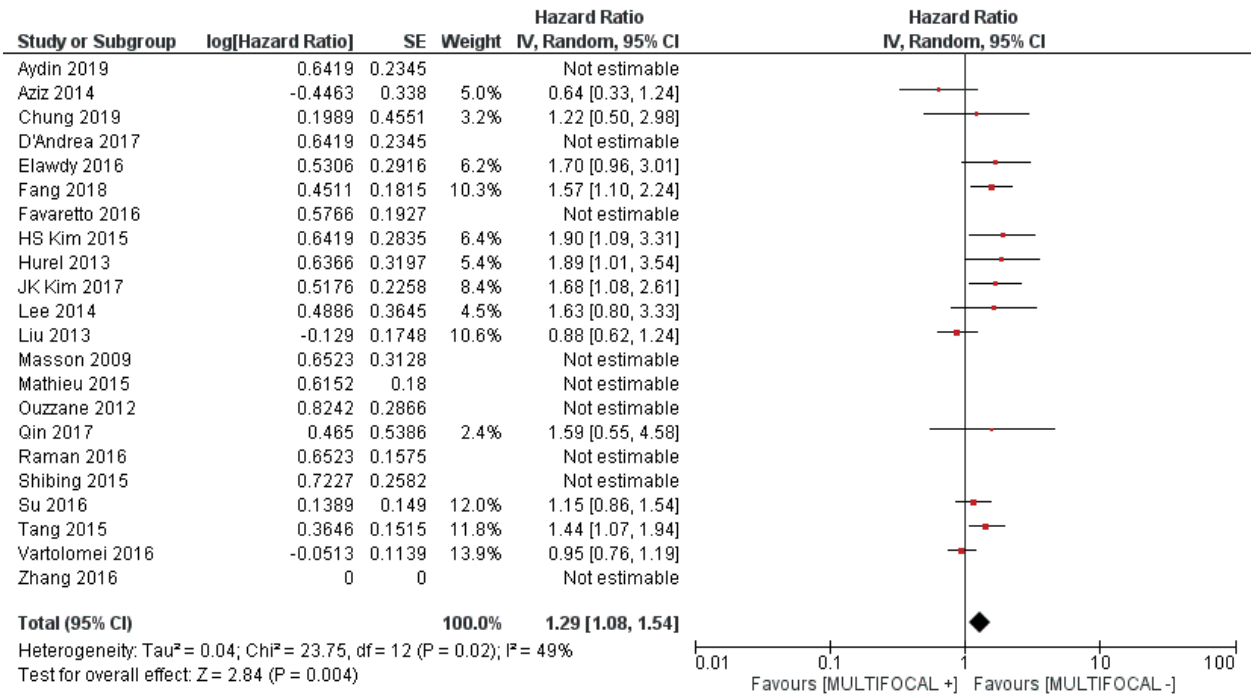
Supplementary Figure 21: Forest plot depicting OS for margin positivity.



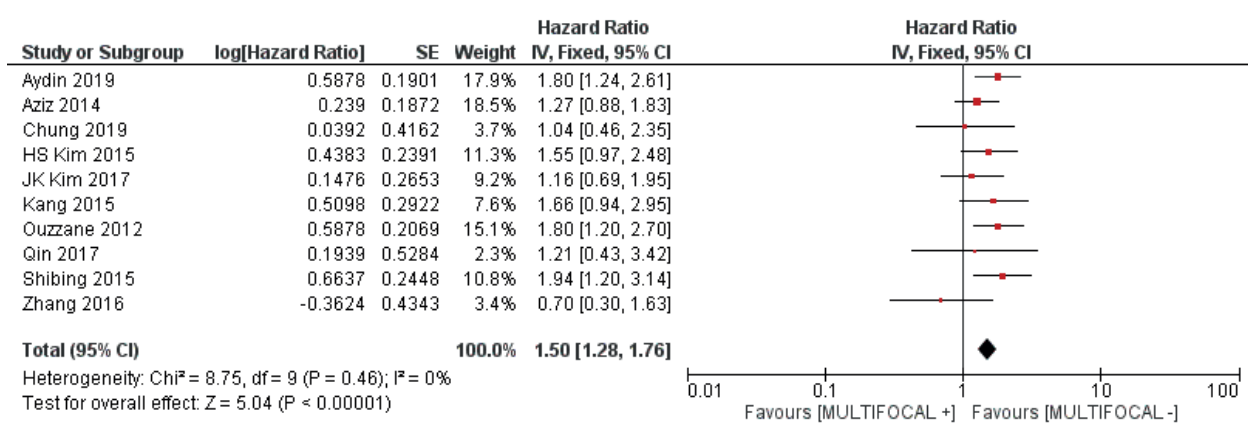
Supplementary Figure 22: Forest plot depicting RFS for multifocality.



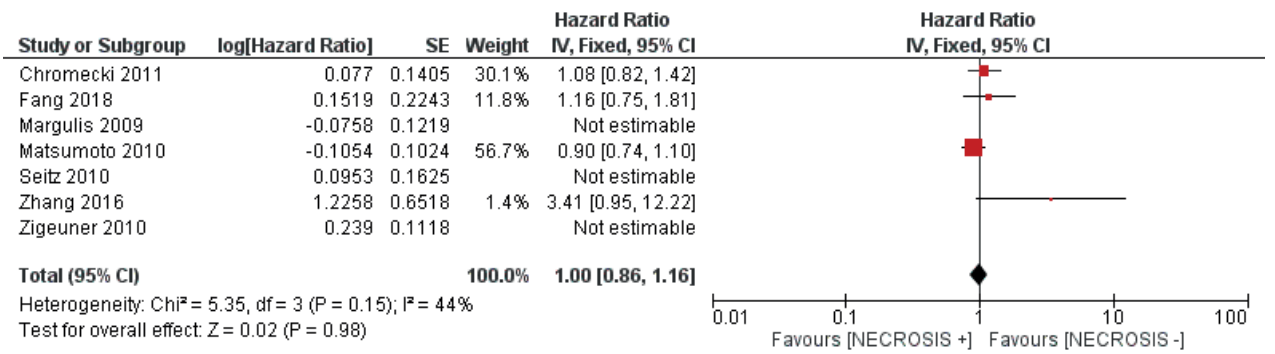
Supplementary Figure 23: Forest plot depicting CSS for multifocality.



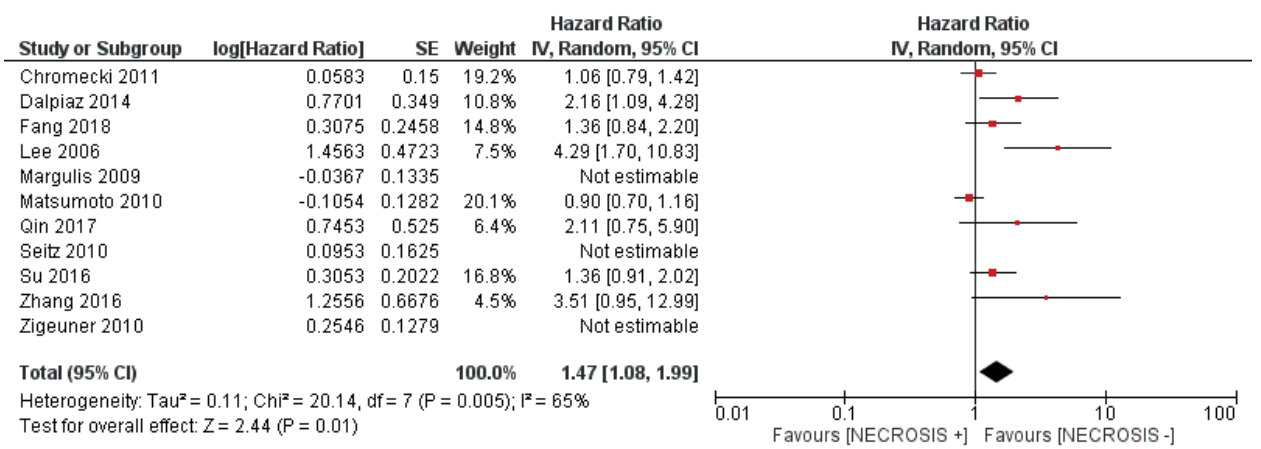
Supplementary Figure 24: Forest plot depicting OS for multifocality.



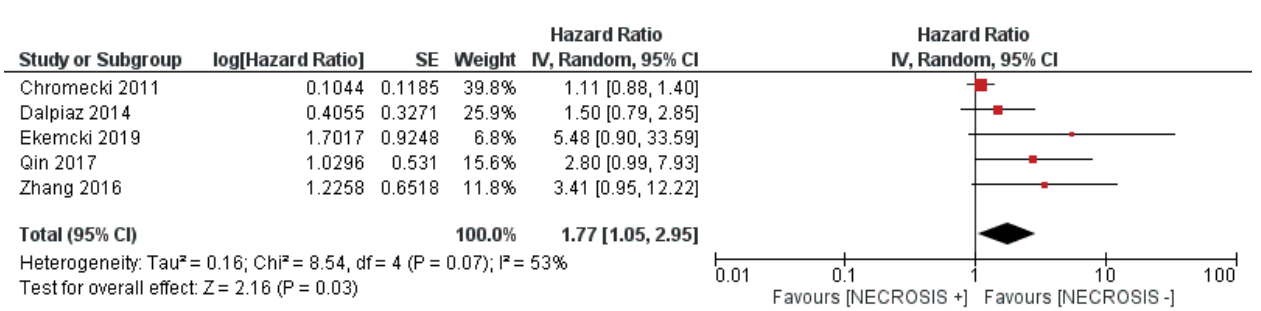
Supplementary Figure 25: Forest plot depicting RFS for necrosis.



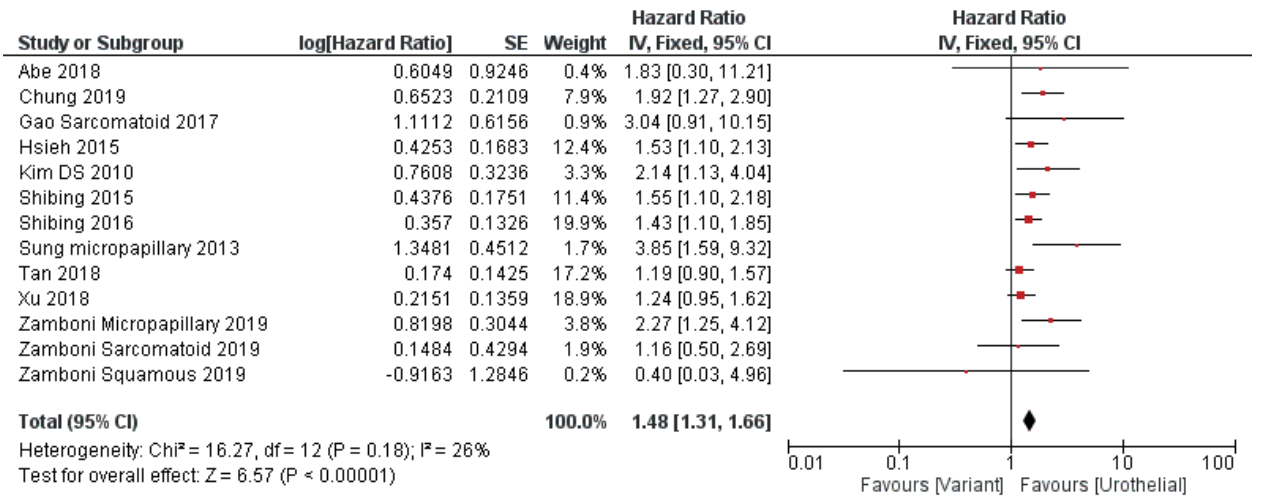
Supplementary Figure 26: Forest plot depicting CSS for necrosis.



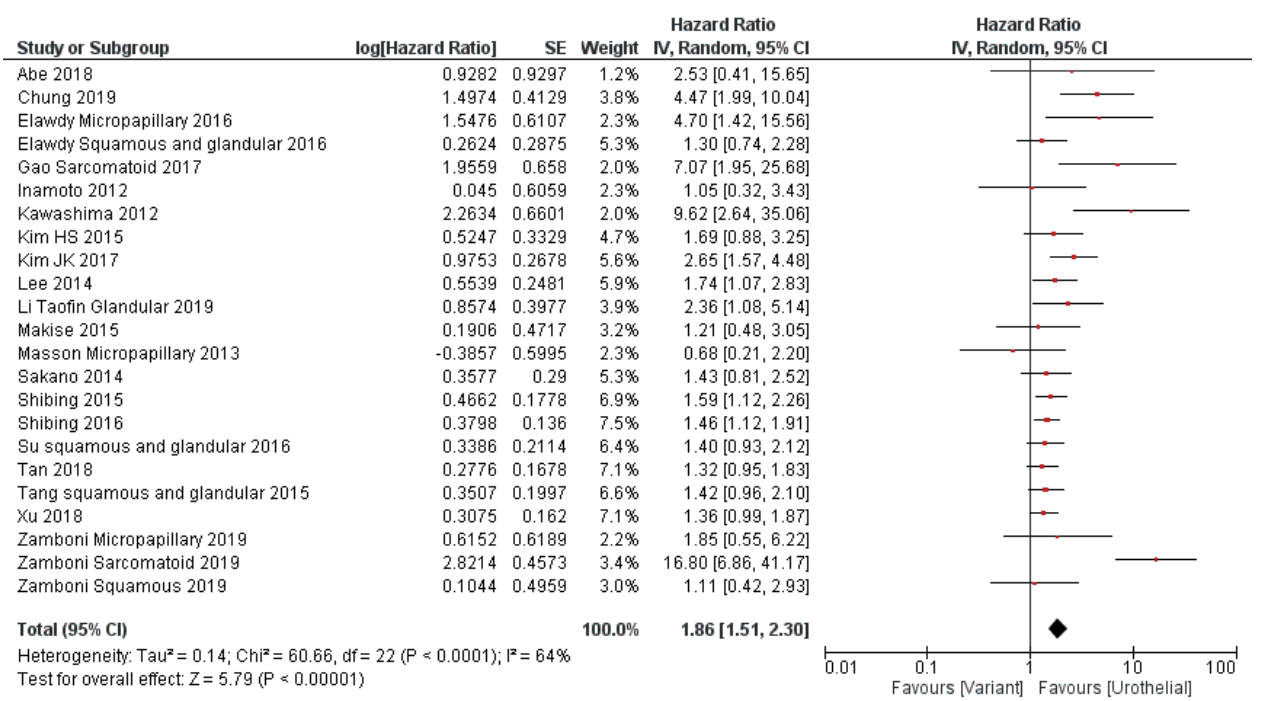
Supplementary Figure 27: Forest plot depicting OS for necrosis.



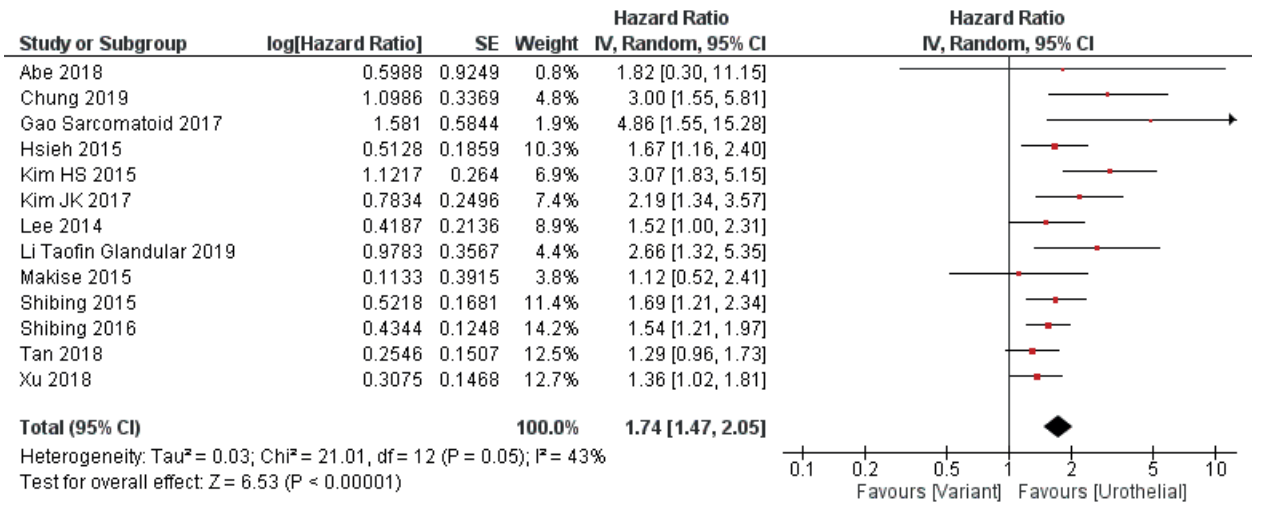
Supplementary Figure 28: Forest plot depicting RFS for variant histology.



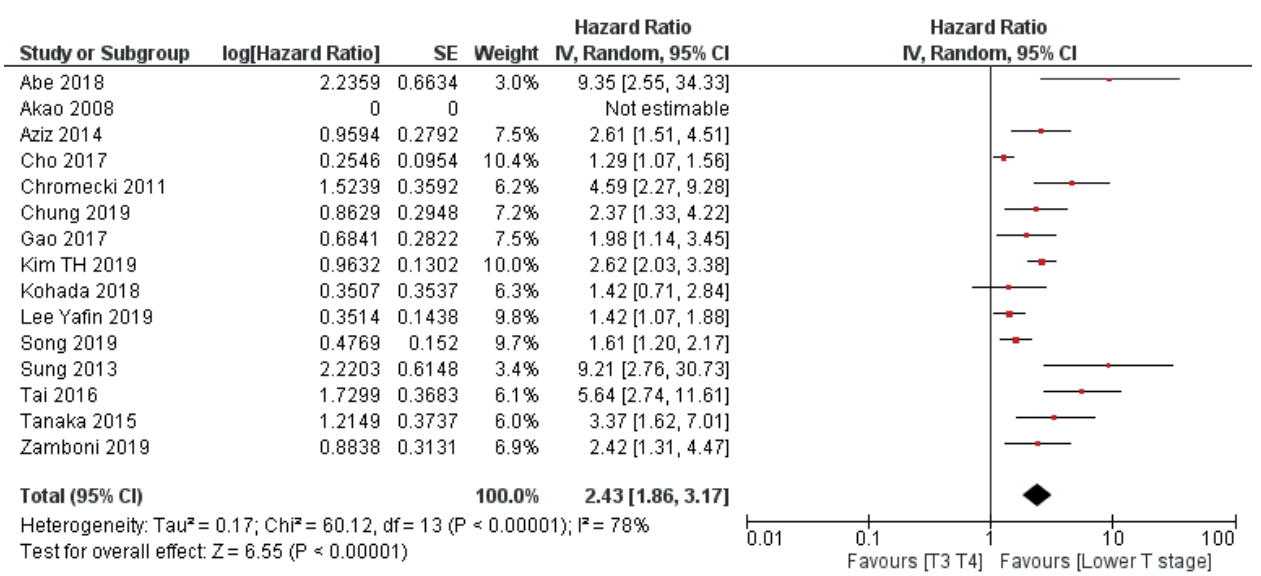
Supplementary Figure 29: Forest plot depicting CSS for variant histology.



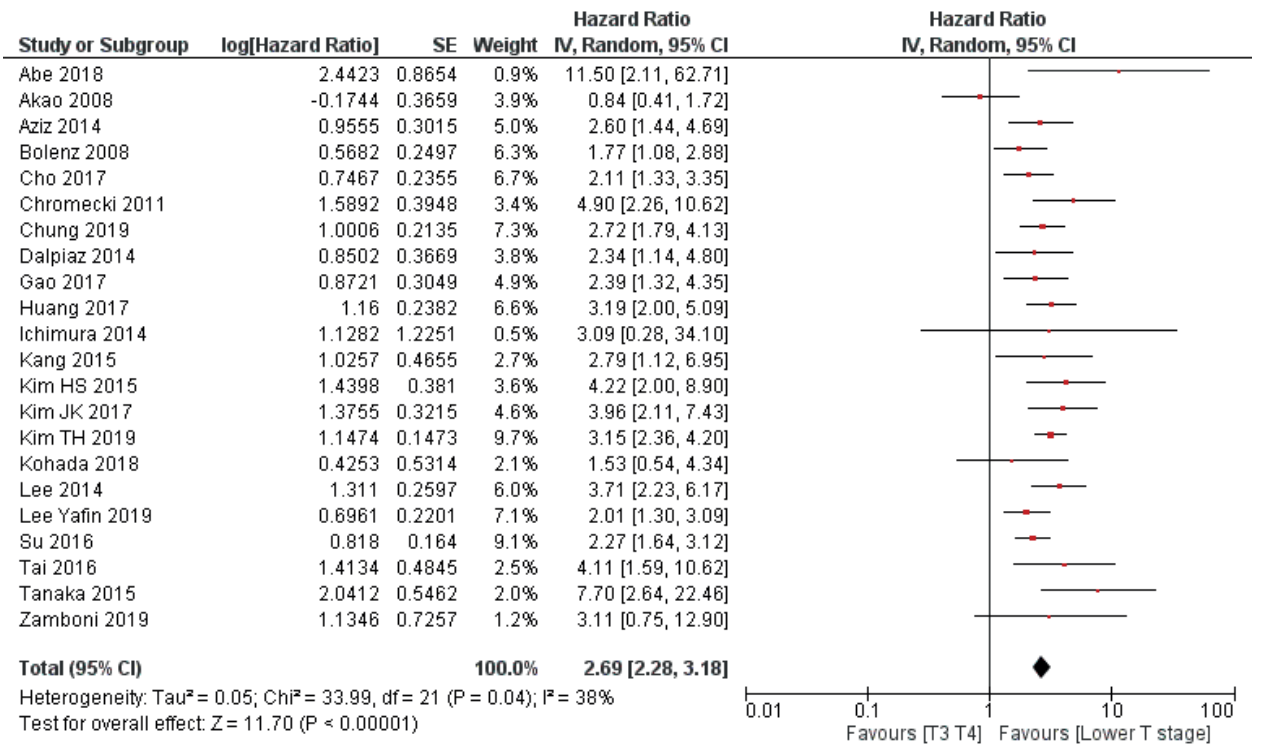
Supplementary Figure 30: Forest plot depicting OS for variant histology.



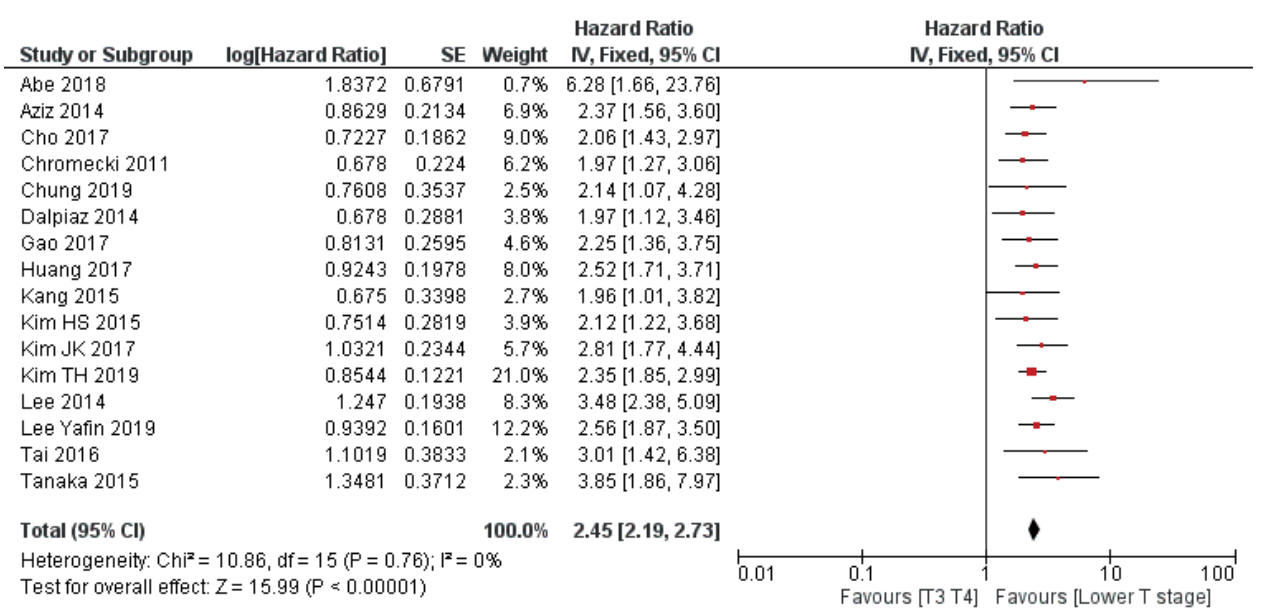
Supplementary Figure 31: Forest plot depicting RFS for stage.



Supplementary Figure 32: Forest plot depicting CSS for stage.



Supplementary Figure 33: Forest plot depicting OS for stage.



REVIEW ARTICLE

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Single-use flexible ureteroscopes: update and perspective in developing countries. A narrative review

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ABSTRACT

Flexible ureteroscopy is a well-established method for treatment of urinary stones but flexible ureteroscopes are expensive and fragile devices with a very limited lifetime. Since 2006 with the advent of digital flexible ureteroscopes a great evolution has occurred. The first single-use flexible ureteroscope was launched in 2011 and new models are coming to the market. The aim of this article is to review the characteristics of these devices, compare their results with the reusable devices and evaluate the cost-benefits of adopting single-use flexible ureteroscopes in developing countries.

Materials and Methods: an extensive review of articles listed at PubMed and published between 2000 and 2021 was performed.

Results: Single-use flexible ureteroscopes have a shaft with 65 to 68cm length and weight between 119 and 277g. Their deflection goes up to 300 degrees. Their stone-free rates vary between 60 and 95% which is comparable to reusable scopes and operative times ranges from 54 to 86 minutes which are lower when compared to reusable flexible scopes. Their costs vary between 800 and 3180 US dollars.

Conclusion: single-use flexible ureteroscopes are lighter and have superior quality of image when compared to fiberoptic ones. There are no definite data showing a higher stone-free rate or less complications with the use of single-use flexible ureteroscopes. Each institution must perform a cost-benefit analysis before making the decision of adopting or not such devices depending on the local circumstances.

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INTRODUCTION

Flexible ureterorenoscopy is a well-established procedure for renal and ureteral stone management and reusable flexible ureteroscopes have been the standard device used for such procedures (1-3). A flexible ureteroscope (fURS) should be able to produce a good image, access the entire collecting system, have a good irrigation flow despite having a device in the working channel and be durable at a reasonable cost. These are simple requirements in theory, although they are not easy to achieve in daily practice, even with a variety of devices available in the market. Enormous progress in flexible ureteroscope

technology has occurred in recent years, but problems with durability and costs persist. Considering these facts and aiming to mitigate these issues, manufacturers have launched single-use ureteroscopes. Currently, there are several single-use models in the market, and they have advantages and disadvantages over the reusable models.

Historically, the first ureteroscopy was described by Young in 1912 and, in 1964, the first ureteroscope was introduced by Marshall (4, 5). The clinical application of early devices was limited and allowed only diagnostic procedures as they lacked active deflection and a working channel. In 1987, Bagley introduced the flexible ureteroscope with a working channel, transforming ureteroscopy from a diagnostic to an interventional procedure (6). Another milestone in the flexible ureteroscope development was the introduction of digital technology in 2006 by Olympus - Gyrus - ACMI which greatly improved overall imaging quality (7). In the recent years, other technological advances, such as reductions in the scope's caliber and improvement in the active deflection allowed for better surgical outcomes and a decrease in morbidity and surgical times (8). The most recent advancement in ureteroscope technology was the introduction, in 2011, of the first single-use ureteroscope (Polyscope™) by Lumenis which utilized a reusable fiberoptic bundle that could be attached to disposable flexible catheters (9). The model was not widely adopted due to its low efficacy especially for lower pole stones owing to limited deflection capabilities reaching a 69% success rate in such cases (10). In January 2016, Boston Scientific introduced the first digital single-use ureteroscope, the LithoVue™ (11). This opened a new era for the development of new single-use devices transforming flexible ureteroscopy and retrograde intra renal surgery (RIRS).

The aim of this article is to review the current literature on single-use flexible ureteroscopes, including advantages and disadvantages over reusable ureteroscopes and analyze their cost-benefit in the context of developing countries.

MATERIALS AND METHODS

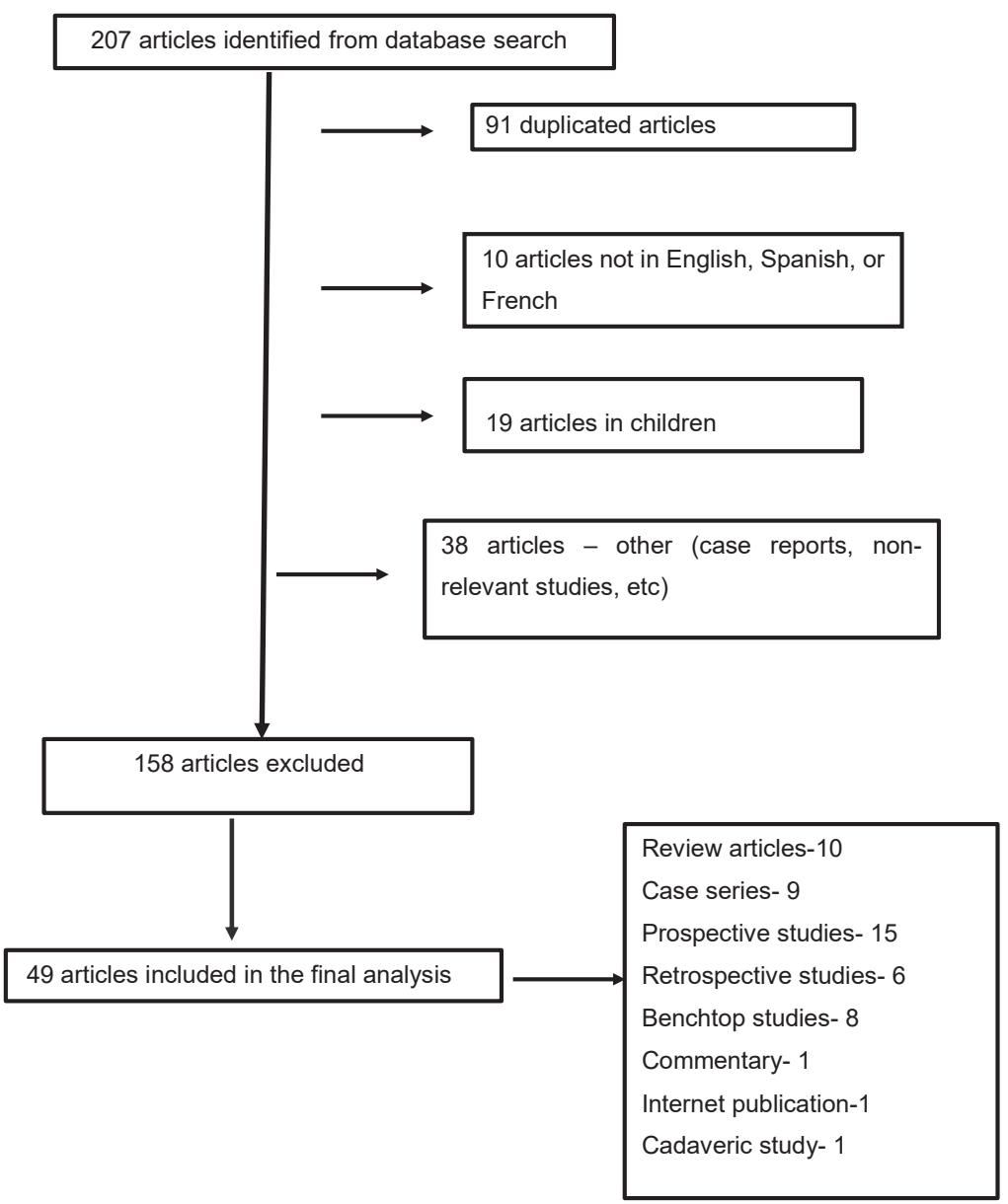
A PubMed database search was conducted in January-February 2021 using the following Medical Subject Heading (MeSH) terms in several combinations: single-use flexible ureteroscope, disposable flexible ureteroscope, cost of flexible ureteroscopy, cost of single-use ureteroscope, durability of reusable flexible ureteroscopes, ureteroscopy, ureteropyeloscopy, ureterorenoscopy. We included original articles published between January 2000 and January 2021, in English, French or Spanish languages. Additionally, web pages from manufacturers were included. Studies involving children and case reports were not included. Initially, 208 articles were reviewed, 158 studies were excluded due to reasons shown in the flowchart. Therefore, in our final analysis, 51 articles were included. The flowchart is shown in Figure-1.

Potential advantages of single-use ureteroscopes

Single-use flexible ureteroscopes have advantages and disadvantages when compared to reusable ureteroscopes. Reusable ureteroscopes are expensive devices requiring a high initial investment which includes the purchase of light source, camera, image processor, monitors, and cables, among others. Also, processing the instruments after each use requires specialized personnel and facilities and involves cleaning, decontamination, drying, testing, sterilizing, and packing. This procedure is time and financially consuming. According to Isaacson et al., the processing of a ureteroscope after surgery takes an average of 229 minutes while the mean case duration of flexible ureteroscopy for treating a renal stone is, on average, 64 minutes at the same hospital (12). Processing a single flexible ureteroscope costs 96 US dollars, with the cost of a single Sterrad™ sterilization cassette being responsible by 25% of the total cost (12). Of course, these costs were calculated in a single North American Institution and may vary in the different countries around the World. Another issue is the breakage of flexible scopes either during surgeries or processing after surgery. It is common sense that instruments manipulated by many surgeons and/or by inexperienced urologists have a higher chance of damage, especially if not properly supervised (13). Mishandling during reprocessing and out of the operating room can be responsible for 7.7% to 22% of damage to flexible ureteroscopes (14, 15). Repairing flexible ureteroscopes is difficult, and at times almost impossible in developing countries. The durability of a flexible ureteroscope varies significantly according

to multiple factors such as the complexity of the cases treated, the number of surgeons that manipulate the scope, the sterilization method, and the presence of specialized personnel for handling the instrumentation. When handled by a single surgeon, a reusable scope can reach up to 159 procedures (16). According to the literature, a fiberoptic scope needed repair after a mean of 21 cases, and a digital scope after 10 to 21 cases with a mean cost of 848 US dollars per repair (17-19) with eleven days being the mean time for repairing the scopes. The time for repairs can vary widely depending on the region/country involved (17-19).The durability of refurbished flexible ureteroscopes though, is inferior when compared to a new device with a mean life of only seven procedures (20). None of these issues are relevant for single-use ureteroscopes and surgeons have the additional advantage of always using a brand-new device.

Figure 1- Flow diagram of evidence acquisition in a review on single-use and reusable flexible ureteroscopy.



Another discussion point is regarding infection. The occurrence of acute pyelonephritis following ureteroscopy is 2.4%, which is low, but not negligible (21). A study published in 2017 by Ofstead et al., showed the presence of bacteria, hemoglobin and protein inside reusable ureteroscopes after manual cleaning and sterilization by hydrogen peroxide gas but there are no clinical data proving the influence of these findings in the occurrence of post-operative infections following ureteroscopy (22). Despite these data, single-use ureteroscopes did not decrease the occurrence of infectious complications after ureteroscopy according to a recently published study showing that the scope is probably not the main source of post-operative infections in ureteroscopy cases (23).

Another point refers to a potential higher success and stone-free rate with single-use scopes, especially when dealing with difficult cases such as acute-angle lower pole stones and abnormal kidneys such as horseshoe and pelvic kidneys. The literature is still scarce and fails to show any significant difference between reusable versus disposable instruments (24). Many studies have examined that kidneys with a steep lower pole angle represent a risk factor for ureteroscope damage and unfavorable results encouraging the use of single-use flexible ureteroscopes in such cases (25, 26). This can be especially true when working with an extensively used scope where deflection and vision are already impaired, which is common in developing countries.

Operative time should also be considered when discussing the choice for a flexible ureteroscope, since longer operative times impact directly in costs. Both reusable and disposable digital flexible ureteroscopes present a 20% shorter operative time when compared to fiberoptic scopes (13). In a series published by Somani et al., the cases performed with the Olympus URF-V™ had an operative time nine minutes shorter than the cases where an Olympus URF-P5™ was used (27). Similar results were observed by Usawachintachit et al. comparing the LithoVue™ with reusable flexible ureteroscopes in stone cases (57.3±5.1 vs. 70.3±36.9 minutes, p <0.005) (28).

Single-use flexible ureteroscopes: technical characteristics

Generally, single-use flexible ureteroscopes have similar physical characteristics (Figure-2). The shaft length varies between 64.5 and 68cm; the shaft size ranges 9.0 to 9.5Fr with the tip diameter between 7.4 and 9.5Fr. The working channel is commonly 3.6Fr. The illumination is by LED (light-emitting diode) and the camera sensor type, which is an electronic chip that converts photons to electrons for digital processing, is CMOS (complementary metal oxide semiconductor) in the majority of devices. Deflection is dual, reaching 280 degrees up and downward. They are lighter when compared to reusable scopes: LithoVue™ weighs 277g against 344g for the Storz Flex X2™ and 942g for the Olympus URFV 2™ (29). One of the new models, the Neoflex™ (Neoscope™) has an advantage regarding portability. The scope can be connected by an attached USB 2.0 cable directly to any high definition (HD)-compatible video monitor or personal computer. This way, the ureteroscope does not require a separate processor or light source. This connectivity feature enables Neoflex™ to be completely portable compared with other single-use flexible ureteroscopes that require an endoscopic video tower to function. Its portability is a major advance as this ureteroscope can be used in diverse environments, including remote and developing areas of the World (30) (Figure-2). The Axis™ single-use ureteroscope showed a 300-degree deflection in an in vitro study performed by Whelan et al. and this deflection was reduced by only 2% after 200 deflections, proving its high level of resistance which can be useful in demanding cases (31).

Data on technical characteristics of several single-use flexible ureteroscopes are summarized in Table-1.

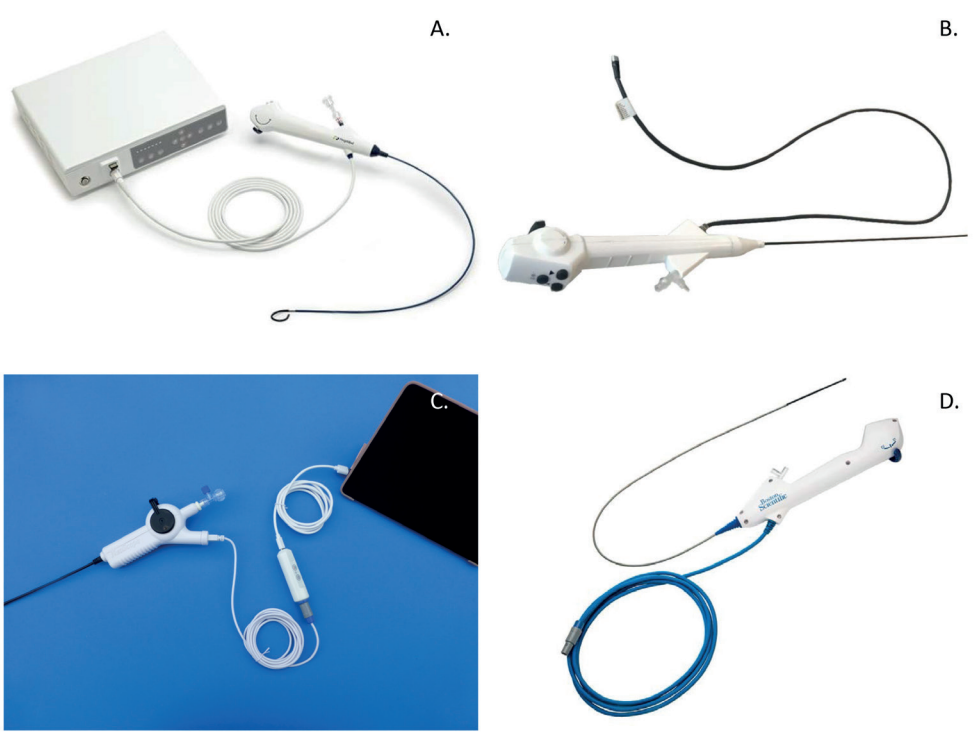
In vitro and clinical comparisons between reusable and single-use flexible ureteroscopes

Somani et al. compared the clinical results between fiberoptic and digital reusable flexible ureteroscopes for the treatment of renal stones. The stone-free rates were 86% and 88% (p-value not significant) for fiberoptic and digital ureteroscopes, respectively and the complication rates were 1% and 0.9% for both ureteroscopes. The operative time was significantly shorter for digital flexible ureteroscopes (44 min vs. 54 min for fiberoptic scopes, p <0.05) (27). More recently some studies comparing the various characteristics of

Table 1- Shows the comparison of the physical (weight, shaft length, working channel) and functional(deflection, irrigation flow) characteristics of the single-use flexible ureteroscopes currently disponible in the market (modified from Scotland et al. (7), Proietti et al. (28), Whelan et al. (30) and Dragos et al. (31).

	LithoVue™	Uscope UE3022™	Neoflex™	Dornier - Axis™	WiScope™
Shaft length (cm)	68	65	68	66	67
Tip outer diameter (Fr)	9.5	9.0	9.0	8.5	7.4
Deflection up/down (degree)	270	270	280	275	275
Working channel (Fr)	3.6	3.6	3.6	3.6	3.6
Irrigation flow empty channel (mL/min)	42	52	40	NA	49
Illumination	LED	Fiberoptic fiber	LED	LED	LED
Imager technology	CMOS	CMOS	CMOS	CMOS	CMOS
Weight (g)	277	147	119	160	200
Connector type	Round and 8 pins	Flat	USB	USB	Round

Figure 2 - shows the different types of single-use flexible ureteroscopes.



A - Pulsen; **B** - Wiscope; **C** - Neoflex; **D** - Lithovue

reusable and single-use scopes in vitro and in vivo have been published.

Irrigation is of utmost importance in flexible ureteroscopy to facilitate adequate vision of the operating field. Two studies compared irrigation parameters between reusable and single-use scopes. In the first, Marchini et al. compared the LithoVue™ and Pusen™ with the Storz Flex X2™, a fiberoptic reusable flexible ureteroscope immensely popular in developing countries. The irrigation flow was superior in the single-use scopes when compared to the reusable scopes with the working channel empty or when instruments such as a 200µm laser fiber or a 1.3Fr basket were inserted (32). In a similar study, the Neoscope™ showed better irrigation in all situations (empty channel, 200µm laser fiber and 1.9Fr basket inserted) when compared with digital reusable Storz Flex XC™ and fiberoptic Wolf Cobra™ (32). These data were confirmed by another study conducted by Dragos et al. who compared the irrigation flow between four single-use and four reusable flexible ureteroscopes. The only exception was the Wolf Cobra which has two working channels (one 3.6Fr and another 2.4Fr) and it is not affected by the insertion of instruments (33).

Imaging quality was evaluated by Talso et al. who conducted an in vitro study comparing the fiberoptic flexible ureteroscopes (Olympus P6™, Storz Flex X2™) and digital (Olympus URF-V™ and URFV2™, Storz Flex XC™, Wolf Cobra vision™) reusable devices with the LithoVue™. Two of the reusable digital scopes (Storz Flex XC™ and Olympus URFV™) provided better images than the LithoVue™. The LithoVue™ imaging quality though, was superior to Olympus URFV2™ and Wolf Cobra vision™. All of them were significantly better than the fiberoptic flexible scopes in the different settings of the evaluation (34). In another in vitro study comparing LithoVue™ with the Storz Flex XC™ and the Wolf Cobra fiberoptic scope™, the authors concluded that the image resolution was similar in the Flex XC™ and in the LithoVue™ and it was 40% better than in the Cobra reusable scope™ (34). In a third study, conducted by Dragos et al., four single-use flexible scopes (LithoVue™- Boston Scientific, Uscope™- Pusen, Neoscope™- Neoflex™ and Shao GangTM- You Care) were compared to four reusable flexible ureteroscopes (Flex XC™- Storz, URFV2™- Olympus, Cobra™ and Boa vision™- Richard Wolf). The authors concluded that the field of view was slightly better in the LithoVue™ but the depth of view, resolution and color reproducibility were better for the reusable scopes tested (33). In conclusion, it seems clear that all digital scopes (single-use or reusable) provide better imaging quality when compared to fiberoptic scopes. In the same study by Dragos et al., deflection was compared among the eight scopes. A 200µm laser fiber had the least impact on deflection (2.198 degrees) for the single-use flexible ureteroscope, and the 1.5Fr retrieval basket (1.971 degrees) for the reusable scopes. The PTFE coated guidewire determined the highest impairment on deflection for all flexible ureteroscopes (31). In almost all settings, the single-use scopes had better deflection than their reusable counterparts, but reusable flexible ureteroscopes achieved superior deflection compared to the single-use scopes when larger caliber instruments were inserted through the working channel (365µm laser fiber or guide wires - both PTFE and nitinol). After the tests, almost all of the single-use flexible ureteroscopes had some deflection loss but none of the reusable scopes presented with deflection impairment (33).

Some of these in vitro findings were confirmed in a fresh-cadaver study performed by Proietti et al. In this study, LithoVue™ was compared with the Olympus P5™ fiberoptic scope and the URFV™ digital scope in four renal units of fresh female cadavers regarding accessibility to the kidney and navigation of the entire collecting system with and without ureteral access sheath (UAS). Access to the lower pole was measured evaluating the deflection of the ureteroscope with an empty working channel and with the presence of different baskets and laser fibers. LithoVue™ performed similar to the two reusable devices regarding maneuverability, navigation of the entire collecting system, and angle of deflection in the lower pole with or without devices inside the working channel (35).

Usawachintachit et al., prospectively compared the stone-free rate (in this case the complete absence of residual fragments), the occurrence of insignificant residual fragments (≤2mm), and the

presence of significant fragments (>2mm) between the fiberoptic device Olympus P6™ and the LithoVue™. The results were 60.0%, 12.5%, 27.5% for LithoVue™, and 44.7%, 13.2%, 42.1% for URF-P6™ (p=0.36), with a tendency towards better outcomes with the single-use scope. The complication rate was lower in the LithoVue™ group (5.4%) compared to 18% in the URF-P6™ group (p <0.05) (28).

Mager et al., in another clinical study, evaluated two groups of 68 patients. In the first group, surgery was performed using reusable flexible ureteroscopes from Storz (models Flex X2S™ and Flex XC™) while the second group was treated using the LithoVue™. The stone-free rates were 82% and 85% for reusable and single-use scopes, respectively. There were no differences in operative time and fluoroscopy time. Patients treated using the single-use device LithoVue™ though, had a higher complication rate compared to those operated with the reusable scopes (17% vs. 7%, p=0.06) (36).

Salvadó et al. reported the results of 71 procedures for upper ureteral and renal stones with a mean size of 11.4mm using the Uscope - Pusen 3022™ (37). The mean operative time was 57min and the stone-free rates were 98% for stones smaller than 10mm, 95% for stones 10-20mm and 78% for stones larger than 20mm. The complication rate was 9% and complications were all minor according to the Clavien-Dindo classification (38, 39). Average fluoroscopy time was 74 seconds. These numbers are comparable to those published by the Clinical Research Office of the Endourological Society (CROES) study in the predisposable era (39). The same author compared the stone-free rates of the Pusen 3022™ with the Wolff Cobra™ reusable scope for treatment of lower pole stones and found no significant differences (95% for the Pusen™ and 88.2% for the Cobra™, p=0.1). The operative and the fluoroscopy times were both significantly shorter for the single-use ureteroscope (56.1±34.8 and 77±37.4 minutes, p=0.01 and 66.1±60.9 and 83.4±44.9 seconds, p=0.02 for the Pusen™ and Cobra™, respectively). There were no surgical complications reported in this study (40).

In a more recent study, Kam et al. conducted a prospective and randomized comparison among the LithoVue™, the Pusen 3022™, and the Olympus URFV2™ reusable digital scopes in 150 patients. Scope failure occurred in 14 of 150 procedures (9%) and was similar among scopes: three failures with the LithoVue™ (5%), six failures for the Pusen™ (10%) and five for the Olympus URFV2™ (8%) (41). Visibility and maneuverability were better for the Olympus URFV2™ when compared to both single-use flexible ureteroscopes. Despite these technical differences there were no differences regarding operative time, complications and necessity for a second-look procedure demonstrating that all scopes performed satisfactorily in the clinical setting (40). Results of flexible ureteroscopy for treatment of renal stones with single-use and reusable flexible ureteroscopes are summarized in Table-2.

The treatment of urothelial tumors should also be taken into consideration when comparing advantages and disadvantages of single-use flexible ureteroscopes. According to what we have shown above, digital ureteroscopes achieve better quality of image when compared to fiberoptic scopes and this is a fact of significant importance for the endoscopic treatment of such tumors (42, 43). Reusable digital scopes have image enhancement technologies like the NBI (Narrow Band Image) from Olympus and Image 1-S™ technology from Karl Storz. NBI is basically a color filtering of the light emitted by the ureteroscope which enhances the visibility of highly vascularized tissues. Compared to white-light ureteroscopy, real-time NBI technology increases tumor detection rate by 22% (44, 45). NBI is a trademark from Olympus and requires an NBI-able light source and a corresponding NBI-able ureteroscope capable of digital reprocessing. NBI is currently solely integrated to the Olympus URF-V™, URF-V1™ and URF-V2™.

The Image 1-S™ technology (formerly SPIES) involves re-processing of the image captured by the digital image sensor and, on the contrary of NBI, does not rely on a modified light source spectrum. Image 1-S™ technology offers enhanced contrasting of digitalized images providing better imaging quality. With this technology any light source can be used. The Image 1-S™ technology allows five re-processing modes, of which the "Clara+Chroma" mode has been shown to reach the highest quality of image. Whether this improvement impacts on tumor detection rate during ureteroscopy has not been evaluated in any study to date. The Image 1-S™ technology is currently solely integrated to the Storz Flex XC™ but theoretically, may be applied to any fiberoptic urete-

Table 2 - shows the comparison of results (stone-free rates, complications and operative time) of renal stone treatment with single-use and reusable flexible ureteroscopes.

	Stone-free rates (%)		
	Single-use	Reusable	p
Usawachintachit et al., 2017 (28)	60	44.7	0.36
Mager et al., 2018 (36)	82	85	0.8
Salvadó et al., 2019 (40)	95	88.2	0.1
Kam et al., 2019* (41)	87	90	ns
	Complication rates (%)		
Usawachintachit et al., 2017 (28)	5.4	18	< 0.05
Mager et al., 2018 (36)	17	7	0.06
Kam et al., 2019 (41)	29	19	ns
	Operative times (min)		
Usawachintachit et al., 2017 (28)	54.1 ± 25.7	64.5 ± 37.0	< 0.05
Mager et al.,2018 (36)	76.2	76.8	0.9
Salvadó et al., 2019 (40)	56.1	77	<0.01
Kam et al., 2019 (41)	86.1	72.3	ns

*Stone-free rate calculated based on the need for a second look pyeloscopy.

roscope when an Image 1-S™ camera is appended at the instrument's eyepiece (45, 46).

In conclusion, for stone treatment, the data currently available in the literature demonstrate that single-use flexible ureteroscopes have similar performance to the reusable scopes in the majority of the studied parameters with some advantage in terms of quality of image for the digital reusable scopes and advantages regarding irrigation flow and deflection for the single-use instruments. To date there are no definite clinical data proving advantages of one or another in terms of better clinical results (higher stone-free rates, lower complication rate, less fluoroscopy time, less related infection) but the idea of always using a new device during surgery and having less concerns regarding the quality of image, deflection, and breakage during or after procedures seems very attractive. On the other hand, according to the current literature one can conclude that reusable digital flexible ureteroscopes present some advantages in the treatment of urothelial tumors thanks to technologies that enhance visibility and increase tumor detection, but this has not yet been proven.

Cost analysis of single-use ureteroscopes

As discussed previously, there are no significant differences among single-use and reusable digital flexible ureteroscopes regarding the stone-free rates, but the operative time is significantly reduced according to the current literature as showed above. Nonetheless, there are significant differences in terms of costs according to the device's mode of usage across different countries.

Flexible ureteroscopes are recognized as fragile and expensive devices. It is important to keep in mind that beyond the cost of the ureteroscope per se, there are other expenses for building an endourological operating room like the light source, camera, image processor, monitors, and cables, among others. Although these apparatuses are much more durable, they require a high initial investment from hospitals which can reach prohibitive values especially in lower income countries.

On the other hand, the cost of the single-use flexible ureteroscope comprises only the cost of the scope once the processor/image unit is provided by the manufacturer or its representative. For reusable scopes, a simplified equation was created to estimate its cost:

Cost of a reusable scope=(original purchasing cost of reusable fURS) + [(repair cost per case/average number of cases before failure) (x)] + [(reprocessing cost per case) (x)] + [(cost of labor per case) (x)], where x=the number of cases (17).

It must be acknowledged that in most developing countries there is limited availability and capacity for repair of reusable flexible ureteroscopes. The final cost will be the initial cost for purchase divided by the number of cases per scope plus the total costs of reprocessing the instrument during its lifetime. As a result, surgeons and paramedical staff must be extremely committed to the correct use and processing of scopes otherwise, many hospitals will not be able to afford these procedures. Complete reprocessing of a scope after a procedure involves cleaning and decontaminating the instrument itself and its storage case with appropriate detergents, drying, performing a leak test, and sterilizing in the Sterrad™ before sending it to storage or to another procedure as mentioned earlier in this article. In Germany, a study analyzed the costs of 423 diagnostic and therapeutic ureteroscopies during a four-year period comparing reusable scopes (Storz Flex - X2™ and Olympus URFV™) with the LithoVue™. Each procedure performed with reusable scopes cost 503 euros while those performed with single-use devices resulted in 1000 euros expense (47). Conversely, an US study compared the Olympus P6™ with the LithoVue™ in a one-week trial that included all costs of reprocessing the scopes. The authors reported a cost of 2.799 US dollars for each procedure performed with the Olympus P6™ and 2.852 US dollars for those performed with the LithoVue™ (48). In a third study, also from the United States, the authors evaluated the costs of 160 procedures performed with the Storz Flex XC™ and compared with the potential costs of surgeries performed with the LithoVue™. The cost of each procedure with the Flex XC™, excluding the costs of purchasing, was 848 US dollars. The authors concluded that, in their center, single-use scopes were cost-effective only if less than 99 procedures were performed each year and recommended single-use devices for low-volume centers (17).

The acquisition cost of each ureteroscope varies throughout the World. Moreover, high volume hospitals can negotiate better capital purchase pricing which can include repairing or substitution of damaged scopes at no cost or lower prices. The same rationale can be applied to single-use devices where manufacturers or representatives charge lower prices for a higher volume of devices. Temporary variations of costs are also observed according to the model of the scope. Single-use flexible ureteroscopes costs range from 800 to 3.180 US dollars and reusable scopes from 13.000 to 85.000 US dollars (49).

Based on the above, one can conclude that the decision of adopting the use of single-use or reusable scopes, or a hybrid model will depend on the conditions of purchase between the hospital and the manufacturer or its representative and the volume of cases in each institution. Basically, there are three models of cost-analysis for adopting single-use scopes. The first is in high-volume centers where the high number of scopes used leads to a more attractive arrangement with the supplier and a reduction in the scopes processing time resulting in a final gain to the institution. The second model is for hospitals with a very low volume of surgeries where the initial investment and maintenance costs of the facilities where a flexible ureteroscopy could be performed is not cost--effective. The third model is the adoption of a hybrid system where single-use scopes are used in those cases where the chance of breakage of a reusable scope is higher (examples: a steep angle between the ureter and the inferior calyx, anomalous kidneys like horseshoe or pelvic kidneys, stones larger than 2cm) (17, 26, 48, 49). Again, the adoption of each model will depend on each country, its health care system, and institutional models.

In conclusion, the current established concepts are that single-use flexible ureteroscopes are lighter, have excellent deflection and irrigation parameters. They have superior quality of image when compared to fiberoptic scopes but are inferior to reusable digital instruments. Additionally, single-use flexible ureteroscopes do not have enhancement image technologies present in reu-

sable digital scopes that can make difference in the treatment of urothelial tumors. There are no definite data regarding a higher stone-free rate or less complications with the use of single-use flexible ureteroscopes, but the operative times are shorter when compared to reusable ureteroscopes. Furthermore, they can be of great value in difficult cases where the chance of instrument damage is higher, especially in lower pole stones. Regarding costs, each institution must perform a cost-benefit analysis before making the decision of adopting or not such devices depending on the local circumstances.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Single-use flexible ureteroscopes: update and perspective in developing countries. A narrative review

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COMMENT

The article by Mazzucchi et al. presents an excellent review of the characteristics of flexible, optical or digital ureteroscopes, single-use or not, in addition to describing the advantages and disadvantages of each. As an additional objective, this article contains a benefit-cost analysis between the different devices (1).

When analyzing the costs of devices and procedures in developing countries, one needs to keep in mind the availability of resources, sometimes present only in larger cities, and the real advantage of opting for the higher-cost alternative, such as digital single-use ureteroscopes.

In Brazil, there are two distinct realities: private practice medicine and public health medicine. In public health settings, the cost of disposable or reusable ureteroscopes from a single institution can be accounted for by the institution, even though the public system often cannot afford adequate equipment maintenance programs. Conversely, in private hospitals, where several providers and health insurance companies are involved in the process, a cost-benefit analysis becomes more difficult. Reusable ureteroscopes are often owned by the supplier of disposable materials, such as fiber lasers, baskets, and catheters. The cost to the health insurance company will be higher in case of surgery where the disposable ureteroscope is used in addition to other devices, as the company does not need to pay for the reusable ureteroscopes.

Regarding the performance of ureteroscopes, there is no sufficient technical data that is consistent to determine that disposable devices are superior to reusable ureteroscopes. In general, optical reusable ureteroscopes display a smaller outer diameter of the insertion tube than the digital ones. An example relies on the most used ureteroscopes, the Storz FlexX2, with 7.5 Fr, whereas the digital ones have around 9.0 Fr (8.7 to 9.9 Fr). This may cause difficulties in thinner ureters or in those subjects without the previous presence of double j catheter (2).

Complex stones, especially in the lower pole, require greater deflection of the ureteroscope. A previous study investigated the access to the most caudal calyx of the lower caliceal group with the optical ureteroscope and showed that, depending on the anatomy of the collecting system, the access rate varies between 64 and 85% of cases (3). In these cases, when there is a greater risk of damage to the device due to forced deflection, the adoption of a single-use ureteroscope is indicated.

Previous evidence showed that surgery time is reduced by up to 30% when disposable devices are used (4-6). We can infer that the use of these devices can be advantageous for large stones (> 2 cm in the largest diameter) as the stone mass will require more time to be fragmented, and surgeries with operative time longer than 90 min significantly increase the risk of infection (7).

The stone-free rates are higher or similar when using the disposable ureteroscope according to several authors (6, 8) but not all authors report the same conclusion. Mager et al. compared the use of disposable and reusable ureteroscopes and reported similar stone-free rate, operative time and fluoroscopy time, and a higher rate of complications when using the single-use device (9).

In their article, Mazzucchi et al. perfectly show different situations where we observe advantages and disadvantages of using each type of device and the different results found by different authors (1).

The use of the material by several surgeons, especially those with less experience, is known to increase the frequency of damage to the devices, thereby increasing the associated costs. In hospital units where there is medical residency, these occurrences must be anticipated and included in the expected costs per procedure. After the learning curve, however, it is expected that the surgeon's experience will result in better clinical outcomes, with shorter operative time and hospital stay, lower complication rates and higher stone-free rates.

When initially marketed in the 1990s, the Holmium-Yag laser was expensive and hardly available in both public and even in private hospitals, as its authorization by health insurance companies was quite restricted. Currently, usage of laser is already a reality in many health services. As we monitor the evolution of laser usage, we believe that the cost of single-use ureteroscopes will decrease over time and that they will be more readily available for use in health settings.

CONFLICT OF INTEREST

None declared.

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Recombinant gonadotropin therapy to improve spermatogenesis in nonobstructive azoospermic patients – A proof of concept study

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ABSTRACT

Purpose: Nonobstructive azoospermia (NOA) associated with primary spermatogenic failure is a common cause of male infertility usually considered untreatable; however, some reports have suggested that hormonal stimulation to boost the intra-testicular testosterone level and spermatogenesis might increase the chance of achieving pregnancy using homologous sperm.

Materials and Methods: We report a series of eight NOA males who received long-term treatment with recombinant human chorionic gonadotropin twice a week for spermatogenesis stimulation. Six males received additional recombinant follicle-stimulating hormone (FSH) supplementation 150-225 IU twice weekly.

Results: After recombinant gonadotropin therapy, viable spermatozoa were retrieved from the ejaculate in two patients and by testicular sperm aspiration (TESA) in another two subjects. Singleton spermatozoon retrieved from testes were frozen by vitrification on Cell-Sleeper devices. Two live births were obtained after intracytoplasmic sperm injection with ejaculated spermatozoa and one live birth and an ongoing pregnancy using thawed spermatozoa from TESA.

Conclusion: Our proof-of-concept study indicates that hormonal therapy with recombinant gonadotropins could be considered in infertile men with NOA as an alternative to sperm donation. Large-scale studies are needed to substantiate hormone stimulation therapy with recombinant gonadotropins in routine clinical practice for this severe form of male infertility.

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INTRODUCTION

Azoospermia is defined as the absence of spermatozoa in the ejaculate following centrifugation (1). It is a common reason for infertility, affecting about 10-15% of infertile males (1, 2). Approximately 60% of all azoospermia cases are related to impaired spermatogenesis, known as nonobstructive azoospermia (NOA). In contrast, in ~40% of cases, azoospermia is caused by blockage of the ductal system (i.e., obstructive azoospermia) (2, 3). NOA is challenging for couples seeking parenthood who wish to use their own gametes, especially in countries with strong cultural and religious beliefs (4). Notably, the absence of sperm in the ejaculate does not always reflect a complete lack of spermatogenesis because, in some males, it is possible to identify residual sperm production in the testicular tissue (2, 5). The most effective surgical technique to retrieve sperm from these focal areas is microdissection testicular sperm extraction (micro--TESE), after which they can be used either immediately for intracytoplasmic sperm injection (ICSI) or cryopreserved for future use (2, 5, 6).

Non-obstructive azoospermia is typically considered untreatable; however, recent reports have shown that sperm maturation might be boosted by selective estrogen-receptor modulators and exogenous urinary gonadotropins (5, 7-11). The reasons why some individuals respond to treatment whereas others do not are largely unknown but might be related to the fact that in some patients, spermatogenesis is arrested during the early or later stages. Yet, until now, there is minimal evidence concerning the effectiveness of gonadotropin therapy for males with NOA.

The use of recombinant gonadotropins in preference over urinary counterparts might be advantageous due to their increased efficacy, safety, and patient-centeredness profile (12). However, only two case reports explored the combined use of recombinant human chorionic gonadotropin (hCG) and recombinant follicle-stimulating hormone (FSH) to treat this condition (10, 11). Importantly, the knowledge about side effects, risks, and reproductive outcomes after hormonal stimulation with urinary or recombinant gonadotropins in NOA males is scanty.

The primary aim of this study was to evaluate the role of recombinant gonadotropin therapy for spermatogenesis stimulation in patients with NOA due to spermatogenic failure. Secondary aims were to report the clinical outcomes of treatment and possible side effects.

MATERIALS AND METHODS

A total of eight patients with NOA admitted to a public fertility clinic in Denmark received gonadotropin therapy with recombinant drugs for spermatogenesis stimulation since December 2016. Before treatment, all patients had a diagnostic testicular sperm aspiration (TESA) showing either no sperm or only few non-viable sperm. Patients were informed that recombinant gonadotropin therapy for their condition was off-label and that evidence concerning its effectiveness and safety was minimal.

The standard evaluation included medical history, physical examination, repeated semen analyses with the examination of pelleted semen, ultrasound of testes, basic hormone evaluation, and genetic studies, as previously described (10). In all patients, NOA was confirmed by testicular histopathology of specimens taken by TESA. Most patients had an unremarkable history explaining NOA, although one patient reported cryptorchidism. Notably, one patient reported a history of long-term anabolic steroid use. Although such a case would best fit in the category of NOA due to hypogonadotropic hypogonadism (10), this particular patient had an atypical clinical presentation. Specifically, baseline endogenous FSH and LH levels were markedly elevated, and azoospermia was found in repeated semen analyses even though the patient had stopped using steroids for several years (Table-1). Another patient had a history of anejaculation due to spinal cord injury, and again, an atypical presentation as azoospermia was noticed on examination of specimens obtained by electroejaculation.

Three cases were histologically diagnosed as early maturation arrest, three cases as hypospermatogenesis, one case as a late maturation arrest, and one case as Sertoli-cell only (Table-1). All patients had a normal karyotype, no Y chromosome microdeletions, or cystic fibrosis pathogenic variants. Furthermore, none of the males had clinically significant varicoceles.

Table 1 - Baseline patient characteristics.

Case No.	Age (years)	Medical history	Testis size (mL) L/R	Baseline hormonal serum levels				Testicular histopathology
				FSH IU/l	LH IU/l	E2 pmol/l	T nmol/l	
1	28	Cryptorchidism	8/8	11.6	8.0	111.0	18.2	Hypospermatogenesis [2]
2	30	Unremarkable	10/8	8.3	6.4	82.8	14.1	Early maturation arrest [1]
3	38	Left inguinal hernia repair	8/12	37.0	11.9	<18.0	9.2	Early maturation arrest[1]
4	45	Unremarkable	10/10	15.1	6.5	44.7	6.2	Sertoli cell only [1]
5	33	Unremarkable	12/12	48.0	14.9	<18.0	11.5	Early maturation arrest [1]
6	34	Long-term anabolic steroid abuse	15/15	34.0	14.0	30.0	11.5	Late maturation arrest [1]
7	40	Unremarkable	4/4	8.3	9.4	23.5	3.1	Hypospermatogenesis [2]
8	42	Tetraplegia; anejaculation *	10/10	7.5	2.7	31.9	6.3	Hypospermatogenesis [2]

[1] No sperm observed on diagnostic testicular sperm aspiration
[2] Rare nonmotile and morphologically abnormal sperm observed on diagnostic testicular sperm aspiration
*Azoospermia on examination of specimen obtained by electroejaculation
L = left; R = right; **IU** = International units

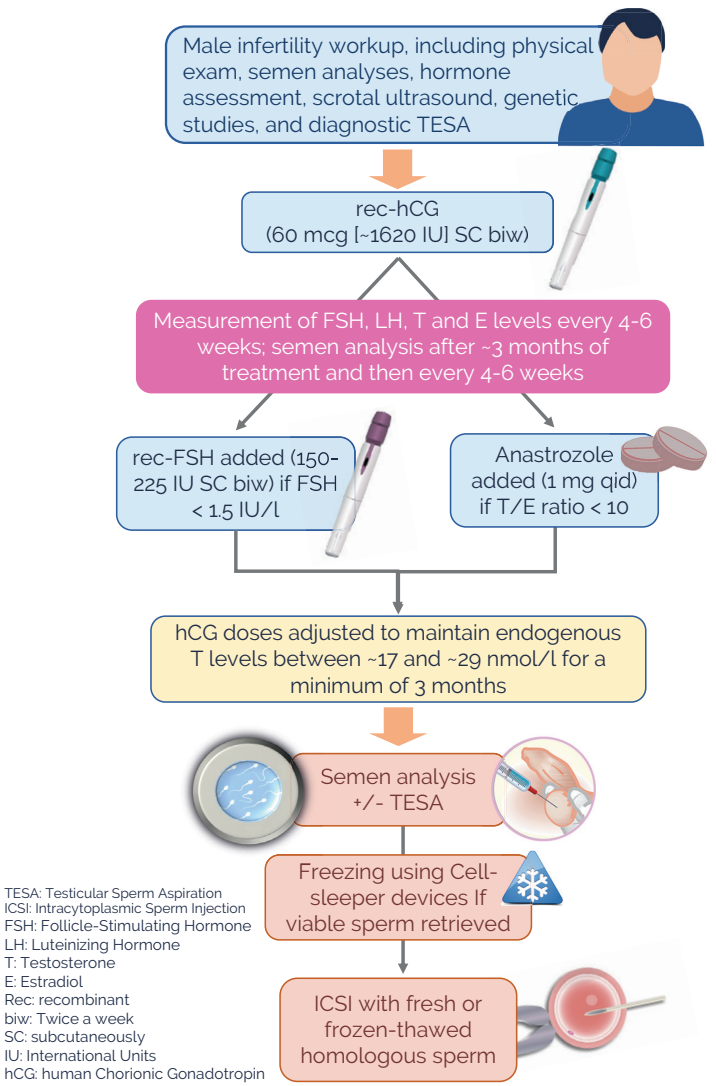
Hormonal Treatment

After signed informed consent, the patients started treatment with human chorionic gonadotropin (rec-hCG; choriogonadotropin alfa, Ovitrelle 250 micrograms/0.5 mL prefilled pen ready for injection, Merck) 60 mcg, subcutaneously, twice weekly. The 60-mcg dose corresponds to approximately 1620 IU of the drug, and the medication was self-administered using a pen device. A doctor or a nurse taught patients how to set the dose and administer the medication. To set the amount, patients were instructed to gently rotate the setting knob of the pen device clockwise until six audible 'clicks' were reached. We estimated that each audible click corresponded to approximately ten micrograms (mcg) of rec-hCG (~270 IU), considering that the pen contains 250 mcg of rec-hCG and the setting knob has 25 audible clicks when rotated until the end. Notably, information about the bioequivalence of the fractioned dose was not available in the technical or patient user's manual as the pen is intended for single-use in women undergoing infertility treatment.

Six patients received additional subcutaneous injections of recombinant follicle-stimulating hormone (rec-FSH; follitropin alfa, Gonal-f 300 IU/0.5 mL, prefilled multidose pen ready for injection, Merck) 150-225 IU, subcutaneously, twice weekly. Figure-1 depicts the treatment algorithm, and Table-1 details the characteristics of the treated patients. The mean baseline FSH level was 21.2 IU/l (range 7.5-48), and the serum testosterone (T) level was 10 IU/l (range 3.1-18.2) before initiation of treatment.

During treatment, semen analyses and hormone testing were performed periodically. Specifically, serum FSH, luteinizing hormone (LH), estradiol, and T levels were monitored every three to four weeks. Notably, the blood sampling was standardized to 48-50 hours after the last hCG injection and before 10 a.m. to minimize the influence of circadian variation (13). Semen analysis

Figure 1 - Illustration depicting the hormonal treatment algorithm.



was carried out three months after treatment commencement and then periodically every four to 6 weeks.

The rec-hCG dosing was adjusted to maintain the T level between 17 and 29 nmol/l, and when and if the serum FSH level dropped below 1.5 IU/l, supplementation with rec-FSH (150-225 IU) twice weekly commenced and continued for at least three months. Moreover, if the T to estradiol ratio turned <10 (ng/dL:pg/mL), an aromatase inhibitor (anastrozole, 1mg daily) was added and continued as needed. The computation above was made after converting T and estradiol levels as follows: Testosterone: 1 ng/dL = 28.818 nmol/L; Estradiol: pg/mL = 0.272 pmol/L.

RESULTS

The mean age of the males was 36.3 years. All patients received long-term treatment with rec-hCG for spermatogenesis stimulation for a mean of 10 months (range: 8 to 15 months). After recombinant gonadotropin therapy, viable spermatozoa were seen in the ejaculate in

Table 2 - Treatment characteristics and outcomes.

Case No.	Treatment regimen			Treatment duration (months)	Sperm retrieved post-treatment	Sperm freezing	Pregnancy by ICSI using homologous sperm
	hCG dose (IU) (initial/final)	FSH dose (IU) (initial/final)	IA added				
1	1620/1080	150/225	No	9	Ejaculate	Yes	Yes; Live birth
2	1620/1080	150/150	No	8	No	-	-
3	1620/1080	150/150	No	10	No	-	-
4	1620/2700	150/150	Yes	10	No	-	-
5	1620/1620	150/150	No	9	No	-	-
6	1620/810	NA	No	8	Ejaculate	Yes	Yes; Live birth
7	1620/3240	NA	No	14	TESA	Yes	Yes; Live birth
8	1620/1080	150/200	No	15	TESA	Yes	Yes; Ongoing

TESA = Testicular sperm aspiration; **ICSI** = Intracytoplasmic sperm injection; **IU** = International units; **hCG** = human chorionic gonadotropin; **FSH** = Follicle-stimulating hormone; **AI** = Aromatase inhibitor; **NA** = not applicable

two cases and retrieved by TESA in another two cases (Table-2). The Cell-Sleeper method, previously described by Endo et al. and Coetzee et al. (14, 15), was used for sperm cryopreservation. In four patients, spermatozoa were neither found on the examination of pelleted semen nor obtained by TESA after treatment.

Hormonal treatment with recombinant gonadotropins resulted in two live births after ICSI with ejaculated spermatozoa and one live birth using thawed spermatozoa from TESA. The last couple (patient No. 8) achieved a clinical pregnancy after ICSI using frozen-thawed sperm retrieved by TESA, which is ongoing.

No adverse effects were recorded during the treatment period. However, patient No. 4 exhibited elevated estradiol levels during treatment and required the addition of an aromatase inhibitor to keep the testosterone to estradiol ratio within optimal levels. In this patient, anastrozole was used for nine months. In case No.5, a right-sided testicular seminoma was diagnosed after nine months of treatment. The patient underwent unilateral orchiectomy, and the couple subsequently obtained a pregnancy and live birth after in vitro fertilization using donor sperm.

DISCUSSION

We herein presented a proof-of-concept study based on a case series of eight males with NOA and failed TESA treated with recombinant gonadotropin therapy for spermatogenesis stimulation. After treatment, viable sperm were obtained in four cases, resulting in three healthy children and one ongoing pregnancy by ICSI.

Stimulation of spermatogenesis with exogenous gonadotropins

Outside the context of NOA, it has been suggested that 58-80% of men with idiopathic infertility might be sensitive to exogenous FSH stimulation since these patients have FSH receptor gene polymorphisms (16, 17) and, thus, could benefit from an increase in their circulating FSH level. It has been estimated that a total of 10-18 males with idiopathic infertility need to undergo medical treatment with exogenous gonadotropins to achieve one additional pregnancy (18). As gonadotropin therapy is costly and the evidence concerning its effectiveness is limited, it is debated whether FSH as a standard treatment for males should be recommended (19). Despite that, recently, gonadotropin therapy was approved to treat idiopathic male infertility in Italy for patients with a serum FSH level of less than 8 IU/L. Interestingly, Santi et al. reported an increase in sperm concentration and morphology in about half of the treated

males and, importantly, without any adverse events during treatment (20). Furthermore, two small meta-analyses evaluating natural conception rates after gonadotropin therapy reported an odds ratio (OR) of 4.94 (CI:2.13-11.44) and 4.5 (CI:2.17-9.33) in favor of treatment (18, 21). Despite these promising results in men with idiopathic infertility, there is no consensus on using gonadotropins in NOA males with spermatogenic failure (22), and treatment is not routinely recommended (23, 24).

Moreover, data about the clinical utility of recombinant gonadotropins in the context of NOA is minimal. To our knowledge, only two case reports by our group have been published (10, 11). In one report, a full-term delivery of a healthy child was obtained with the aid of ICSI using ejaculated sperm in an infertile couple whose male partner had NOA due to cryptorchidism (patient No. 1 in the current series) (10). The patient received long-term hormonal stimulation with combined use of rec-hCG and rec-FSH, cryopreservation of ejaculated spermatozoa using the cell sleeper method, and subsequently ICSI. In another report, two NOA patients with testis biopsy revealing maturation arrest were treated similarly (11). In one case, the patient remained azoospermic. A micro-TESE, carried out six months after treatment, successfully harvested sperm; the couple achieved a live birth delivery by ICSI using testicular sperm. The second case was more challenging, as only morphologically abnormal (mainly globozoospermic sperm) were retrieved by micro-TESE after one year of therapy. Despite two ICSI trials and transfer of apparently healthy embryos to the uterine cavity, the couple remained childless as no implantation occurred.

Clinical Interpretation

A crucial step in the sperm maturation process is maintaining a physiological intra-testicular T level (ITT), which is 50-100-fold higher than the levels in circulation (25). HCG stimulates LH-receptors on Leydig cells resulting in an increased T production, which in synergy with Sertoli cell stimulation by FSH further promotes spermatogenesis (2, 7-9). Indeed, a positive relationship exists between a normal serum T level (vs. a low T level) and a higher chance of sperm retrieval (OR 1.63, 95% CI 1.08-2.45, p=0.02) (24). However, no data support a clear threshold of serum T levels facilitating optimal spermatogenesis.

In humans, spermatogenesis is stimulated by FSH and T in synergy; FSH mainly stimulates the first stages of spermatogenesis (FSH-dependent phase), including determination of Sertoli cell number, spermatogonial proliferation, stimulation of meiotic progression until spermatid stage, and transport of nutritive substances to germ cells. In contrast, T supports the post-meiotic advancement of round spermatids to mature sperm (testosterone dependent phase) (19). The combined action of the two gonadotropins in cases of NOA associated with hypergonadotropic hypogonadism could either induce or increase spermatogenesis and thus, enhance the chances of obtaining sperm for biological offspring through ART.

It is generally believed that empirical hormonal therapy with FSH for NOA males with primary testicular failure is ineffective because baseline serum gonadotropin levels are already elevated. However, it has been shown that excessive circulating FSH levels might induce FSH receptors down-regulation on the Sertoli cell (26-30). Interestingly, hCG treatment decreases circulating FSH levels (7, 10, 11), which are typically elevated in most NOA patients. Thus, an FSH reset to normal levels might reduce Sertoli cell desensitization caused by excessive circulating FSH and enhance Sertoli cell function (31, 32). However, in some NOA men treated with hCG, FSH levels are profoundly suppressed (e.g., below 1.5 IU/L) (7, 10, 11). These patients need exogenous FSH supplementation to optimally stimulate the Sertoli cells and spermatogonia proliferation (2, 7-11, 31).

The mean duration of therapy for the present case series was ten months. In contrast, most studies, including those using gonadotropin therapy for idiopathic male infertility, reported outcomes after only three months of treatment (8-10, 20, 33). Our case series focused on achieving optimal T and FSH levels before starting fertility treatment, and therapy continued during the subsequent IVF treatment. If a pregnancy was achieved, treatment continued until at least the seventh week of pregnancy.

Sperm Retrieval

There is no agreement on whether a diagnostic testicular biopsy should be performed before stimulation with exogenous gonadotropins. NOA patients with hypergonadotropic hypogonadism have an increased number of interstitial testicular lesions

(containing no Leydig cells) and fibrosis compared with obstructive azoospermia patients (32). Interestingly, Oka et al. (32) observed an association between hCG use, decreased interstitial lesions, and Leydig cell hypertrophy, which might increase the sperm retrieval rate.

As regards the retrieval method, higher sperm retrieval rates have been reported using micro-TESE than TESA or conventional TESE in the general NOA population (2, 6, 34-37). However, data on sperm retrieval after gonadotropin therapy is minimal. In two studies by the same authors, a 10-21% sperm retrieval rate by micro-TESE was reported in a group of males stimulated with gonadotropins after failed sperm retrieval (7, 38). Yet, micro-TESE is an advanced procedure, requiring a fully equipped operating theatre and a trained microsurgeon, which is unavailable in our Unit.

Collectively, we were able to harvest sperm from 50% of patients, considering both TESA and ejaculated specimens. Although our results are higher than that reported in the literature, it should be noted that our population comprises patients with a good prognosis for sperm retrieval. In our series, a single patient had Sertoli-cell only on testis biopsy, whereas the remaining patients had either maturation arrest or hypospermatogenesis. Previously, only NOA males with late maturation arrest and hypospermatogenesis have been shown to benefit from gonadotropin therapy in terms of the highest chance of sperm retrieval (39), which is in line with our data. Hypospermatogenesis and maturation arrest are typical findings in NOA males. In a 2021 study including 918 patients with NOA, testis biopsy specimens taken during micro-TESE showed hypospermatogenesis (either pure or mixed) in 16.6% and maturation arrest (either pure or mixed) in 30.6% of individuals (40).

In the present study, all couples whose partners had sperm harvested succeeded in achieving a pregnancy. Despite favorable, this finding should not be perceived as indicative of a high pregnancy rate in NOA cases. In a recent systematic review of studies evaluating pregnancy outcomes by ICSI using testicular sperm retrieved from NOA males by micro-TESE, the pooled clinical pregnancy rate was 39% (range 12.2–72.4%), and live birth delivery was achieved in 24% of couples (range 11.8–62.1%) (35). Interestingly, in our series, the pregnancies were achieved in subjects with late maturation arrest and hypospermatogenesis but not in cases with early maturation arrest. However, due to a limited number of patients included, no conclusive recommendation can be made on the ideal candidates for treatment.

Sperm Cryopreservation

Freezing of few spermatozoa is a time-consuming procedure that requires skilled laboratory staff. In the present series, the Cell-Sleeper method was used. This technique was initially described by Endo et al. (14) and Coetzee et al. (15), who reported a sperm recovery rate of 83% and 88%, respectively, which is in line with our experience.

Sperm cryopreservation after gonadotropin therapy is highly recommended as it will allow repeat ICSI cycles, thus enhancing the likelihood of achieving biological parenthood. The method used in our study allows the preservation of 10-15 spermatozoa per device, which optimized the sperm usage for ICSI as in most cases, the number of oocytes collected does not surpass that number.

Adverse Effects of Gonadotropins Therapy

In general, gonadotropins are considered safe for stimulating spermatogenesis in the context of idiopathic infertility and hypogonadotropic hypogonadism (17, 19, 33, 41). Only a few side effects like gynecomastia and temporary mastalgia were reported in patients with excessive endogenous T and estradiol levels (33). In our series, no such adverse effects were reported. However, one patient was diagnosed with testicular cancer after nine months of therapy. We speculate that the diagnosis of testicular cancer was likely coincidental as it is well established that NOA patients have an increased risk of developing testicular cancer (hazard ratio: 3.3, 95% confidence interval [CI] 1.6–6.9) (42, 43).

Nevertheless, a previous case report described the development of a seminoma after prolonged FSH and hCG therapy (44). This report concerned a 43-year-old patient with oligozoospermia, normal serum gonadotropins, and an unremarkable ultrasound testicular examination, treated with exogenous FSH for one year. The patient presented with bilateral testicular tumors two years later, and histology revealed a bilateral seminoma.

Although it is currently unknown if gonado-

tropin therapy might stimulate a pre-existing carcinoma in situ to develop into a testicular tumor, considering the above, our recommendation is to perform repeated testicular ultrasound scans: before initiating therapy, six months later, and at the end of treatment. Moreover, the patient should be encouraged to perform testicular self-examination and contact the handling clinic if any abnormality is detected during or after treatment.

Patient Counselling

Currently, it has still to be determined which patients could benefit from gonadotropin therapy in a clinical setting. Due to the high cost and long duration of treatment and the uncertainties of sperm acquisition, it is critical to thoroughly discuss the pros and cons of hormonal therapy. Notably, an evaluation of the chance of obtaining a pregnancy should be considered, accounting for the female partner's age. A diagnostic testicular biopsy providing the dominant histological pattern of the testes before initiating therapy could help in patient selection.

The chances of achieving a pregnancy through sperm retrieval and ICSI without gonadotropin therapy need to be weighed against the cost of treatment and potential side effects. Moreover, introducing this new male treatment regimen raises essential questions about the most optimal treatment plan, sperm retrieval method, and cryopreservation technique when a minimal number of spermatozoa are present. Lastly, the monitoring process during treatment, possible side effects, and the future need for exogenous T supplementation in low-level T males after sperm retrieval must be considered.

Notwithstanding the above considerations, recombinant technology has fulfilled the need for a more reliable source of FSH and hCG, particularly in female infertility treatment (12, 45). While urine-derived gonadotropins require large amounts of human urine as a primary source for manufacturing, the production and purification of recombinant gonadotropins are subjected to continuous quality control assessments, ensuring a pure, consistent, and high-quality product (45). The manufacturing process typically utilizes genes coding for the human FSH and hCG, which are incorporated into the nuclear DNA of a host cell via a plasmid vector, using spliced DNA strings containing the gonadotropin gene and segments of bacterial DNA. Recombinant gonadotropins are generally presented as ready-to-use solutions filled in pen devices, increasing treatment compliance as the patient can inject the drug subcutaneously (12, 45).

Strengths and Limitations

Our study has several limitations related to the nature of a proof-of-concept study based on a small case series. Despite that, to our knowledge, this is the first series reporting the combined use of recombinant gonadotropins to stimulate spermatogenesis in men affected by NOA. To enhance the appeal of our article, we discussed the current evidence associated with the use of gonadotropin therapy in men affected by this severe form of male infertility. Our literature review only found studies using urinary gonadotropins. Therefore, our study adds to the current literature as recombinant drugs have potential advantages over urinary products.

Another limitation relates to the heterogeneous characteristics of treated patients. Of note, two patients (No. 6 and No. 8) do not perfectly fit in the NOA-spermatogenic failure classification. Patient No. 6, despite reporting a history of anabolic steroid abuse, remained azoospermic even after stopping the drugs for several years. Notably, his baseline endogenous FSH and LH levels were found to be remarkably elevated, thus not fulfilling the classic hypogonadotropic hypogonadism profile that would be expected in such a case. We speculate that this patient had some degree of primary testicular impairment unrelated to the use of anabolic steroids, exacerbated after its prolonged use. Patient No. 8 was primarily characterized as having anejaculation due to spinal cord injury. Still, he produced azoospermic ejaculates after electroejaculation, his testes were hypotrophic, and the hormone profile suggested a primary testicular deficiency. Notwithstanding these observations, all patients fulfilled the criteria of NOA due to primary testicular deficiency based on the clinical picture and unequivocal testis histopa-

thology findings. Importantly, none of them fulfilled the criteria of NOA due to hypogonadotropic hypogonadism, as their baseline hormone levels were either markedly elevated or within normal ranges.

CONCLUSIONS

Recombinant gonadotropin therapy for males with NOA and spermatogenic failure seems to be a valuable strategy to overcome infertility. In our case series of eight patients, hormonal treatment provided satisfactory results overall with no apparent side effects. It resulted in the retrieval of viable spermatozoa for ICSI in four cases, resulting in three live births and one ongoing pregnancy. Our findings suggest that hormonal stimulation with recombinant gonadotropins could be considered for selected infertile men with NOA as an alternative to sperm donation. Nevertheless, the evidence supporting its use remains minimal and, therefore, large-scale studies are warranted to determine its efficacy and safety.

Data availability

All data regarding this case series have been reported in the manuscript. Further details can be obtained by contacting the corresponding author.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Hormonal treatment for men with Non-obstructive Azoospermia: too many rationales, too little data

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COMMENT

Non-obstructive azoospermia (NOA) is the most severe form of male infertility, and despite all the research efforts, the last (and only) breakthrough in the management of NOA , the development of testicular sperm extraction techniques and intracytoplasmic sperm injection (ICSI), happened three decades ago and only benefit approximately half of the affected men (1). Because an etiological diagnosis is not possible in most cases, more often than not, men with NOA are managed using a "syndromic" approach that usually ends in a testicular sperm extraction procedure. The most challenging cases are those men that failed a testicular sperm extraction procedure, which are often offered sperm donation or adoption

In the current paper, Laursen et al. (2) described the first case series of men with NOA that failed a diagnostic testicular sperm extraction and underwent hormonal stimulation with recombinant gonadotropins. The participants were treated with recombinant human chorionic gonadotropin (hCG) and recombinant follicle-stimulating gonadotropin (FSH). The goal was to increase testosterone to the upper limit levels while keeping FSH in the normal range. After treatment for a mean duration of 10 months, the authors reported that 25% of the participants had viable sperm in the ejaculate and another 25% had viable sperm in a second testicular sperm retrieval. Despite the limitations of such small case series, the authors should be commended to have published their results, since this topic is frequently discussed among male infertility specialists, but rarely addressed via scientific publications.

Recombinant gonadotropins have been shown to have less batch-to-batch variation and contaminants when compared to preparations from purified urine (3). In addition, these medications are marketed in prefilled pens that allow dose adjustment and are easier to use. However, from female studies, it still unclear if these advantages translate into better reproductive outcomes (4). Thus, studies assessing the efficacy and safety of these preparations in the management of male infertility are welcomed. Conversely, the exciting results reported by the authors may be derived from the high proportion of men with hypospermatogenesis and late maturation arrest included in the study. It is known that these two histological patterns cofer good prognosis for both hormonal stimulation and salvage sperm retrieval (5, 6). Not surprisingly, only men with these histological patterns benefited from the treatment in the current study. Moreover, the long duration of the treatment may also explain the good results. However, the duration and the costs of the recombinant medications may restrict the applicability this hormonal stimulation protocol.

Due to the still suboptimal results of testicular sperm extraction procedures, male infertility specialists often try to improve any residual spermatogenesis using several medical treatments such as antioxidants, vitamins, and "optimizing" the sexual hormones levels. Nevertheless, the evidence level

for most of these treatments are low (7). Besides, it is still unclear what are the optimal levels of such hormones for sperm production, and most cut-offs found in the literature are arbitrary (8). More confusion is added by the large heterogeneity of phenotypes displayed by men with NOA, thus, it is obvious that different patients will require different levels of sexual hormones, a classic example of "one size does not fit all"

Several protocols of "hormonal stimulation" have been proposed for use in this scenario. Some of these protocols include gonadotropins to increase testosterone above a certain cut-off levels, others consist in increasing FSH to supra-physiologic levels, whereas some even advocate the combined use of GnRH antagonists or testosterone with gonadotropins to bring FSH to "normal" levels in those men with high baseline FSH (6, 9, 10). However, most of the studies included a small number of participants and the results had disputable clinical significance. Furthermore, if these protocols are used in men with NOA before their first attempt of sperm retrieval, without knowing their predominant testicular histological pattern, we risk disturbing their endogenous hormonal milieu that might be responsible to sustain small foci of active spermatogenesis or prescribing a futile treatment.

Therefore, before the widespread use of "hormonal stimulation" in NOA cases, there are several questions yet to be answered: What are the optimal sexual hormone levels for spermatogenesis in a specific individual? Is it necessary to achieve these levels before the first attempt of sperm retrieval? What medications and how long should them be used? To clarify this topic, well designed randomized controlled trials are urgently needed as well as large observational real-life studies.

CONFLICT OF INTEREST

None declared.

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Can concomitant bladder neck incision and primary valve ablation reduce early re-admission rate and secondary intervention?

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ABSTRACT

Objective: To assess the effect of bladder neck morphology and its incision (BNI) in patients with posterior urethral valve (PUV) on early reintervention rate.
Patients and methods: Infants undergoing PUV ablation (PVA) before 24 months of age and had at least 18 months of follow-up, were categorized into three groups according to the bladder neck appearance on baseline radiological and endoscopic examination: group 1; normal bladder neck underwent PVA, group 2; high bladder neck underwent PVA plus BNI, group 3; high bladder neck underwent PVA only. Early reintervention was defined as the need for check cystoscopy because of persistent renal function deterioration, worsening hydronephrosis and/or unsatisfactory VCUG improvement during the 1st six months post primary PVA.
Results: Between 2000 and 2017, a total of 114 patients underwent PVA and met the study criteria with a median follow-up of 58 (18-230) months. For group 1, 16 (22.9%) patients needed readmission. Check cystoscopy was free and no further intervention was performed in 5(7.5%) and re-ablation was performed in 11(15.7%) patients. For group 2, 3(14.3%) patients needed reintervention. Re-ablation and re-ablation plus BNI were performed in 1(4.8%) and 2(9.5%), respectively. For group 3, cystoscopy was free in 1(4.3%), re-ablation and re-ablation plus BNI were performed 2(8.7%) and 1(4.3%), respectively. There were no significant differences in the re-admission and re-intervention rates among the three study groups (p=0.65 and p=0.50, respectively).
Conclusion: In morphologically high bladder neck associated PUV, concomitant BNI with PVA doesn't reduce early re-intervention rate.

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INTRODUCTION

Endoscopic ablation (PVA) remains the gold standard treatment of posterior urethral valves (PUV). However, bladder dysfunction persists in 75-80% of the affected boys even after successful PVA (1). A significant proportion of boys treated for PUV have high riding bladder neck (BN) that could potentially result in secondary bladder neck obstruction, obstructive voiding pattern, gradual detrusor decompensation and eventually myogenic failure, despite early and adequate valve ablation (2).

The diagnosis of BN obstruction in children with PUV is not straightforward. Waterhouse reported that the BN is usually not narrow, but it only has a "pseudo-narrow" appearance; as it lies between the bladder and the dilated proximal urethra (3). Glassberg and Combs believed that the diagnosis of secondary BN obstruction should be based on videourodynamics with elevated voiding pressure, obstructed uroflow pattern and a silent electromyography. Such a diagnosis should not be solely made based on endoscopic examination or radiological findings (4).

While some authors assume that high riding BN is secondary to PUV obstruction, others believe that concomitant primary BN obstruction could exist in some patients. Even more, long-standing PUV obstruction may result in BN remodelling with subsequent BN obstruction. In that instance, PUV ablation alone my not be sufficient to relieve obstruction. Various treatment options have been proposed to target BN obstruction in PUV patients, including alpha blockers (5-7), bladder neck incision (BNI), BN botulinum toxin injection and clean intermittent catheterization (CIC) (4, 8, 9). Glassberg and Combs favored alpha blocker therapy to BNI; as the effects of alpha blocker treatment are reversible with treatment discontinuation (4). However, data on the safety and efficacy of alpha blockers in children with PUV are lacking. BN botulinum toxin injection failed to improve bladder dynamics or enhance hydronephrosis or vesicoureteral reflux (VUR) resolution in a prospective study by Mokhless et al. (9). Finally, CIC is difficult to establish in boys with PUV owing to sensate urethras and bladder neck hypertrophy that often renders catheterizations challenging.

The outcomes of synchronous PVA and BNI are debatable (8, 10). Kajbafzadeh et al. reported 28% reintervention rate with valve re-ablation and/or BNI when patients were treated with PVA only, versus 0% reintervention rate when BNI was concomitantly performed with PVA. Furthermore, concomitant PVA and BNI decreased the need for anticholinergic therapy and CIC, thereby effectively reducing treatment costs and morbidity (8). It has become clear that unplanned re-admissions and secondary procedures following urologic surgery in children negatively affect the quality of medical care and health care expenses (11). In contrast to Kajbafzadeh's report, Singh et al. reported improved peak flow rates and postvoid residual; but similar compliance, detrusor overactivity, end-filling pressure, maximum Pdet at Qmax and reflux resolution rate in a prospective randomized study comparing PVA alone to concomitant PVA and BNI (12). In this study, we aim to assess the effect of BN status and its incision in PUV patients on the early reintervention rate compared to PVA alone. We believe that bladder neck obstruction in PUV is a secondary phenomenon that would improve after PVA alone. Therefore, adjunctive BNI may not be necessary. Contrary to the conclusion made by Kajbafzadeh et al., we assume that concomitant PVA and BNI does not decrease the need for early reintervention in patients with PUV.

PATIENTS AND METHODS

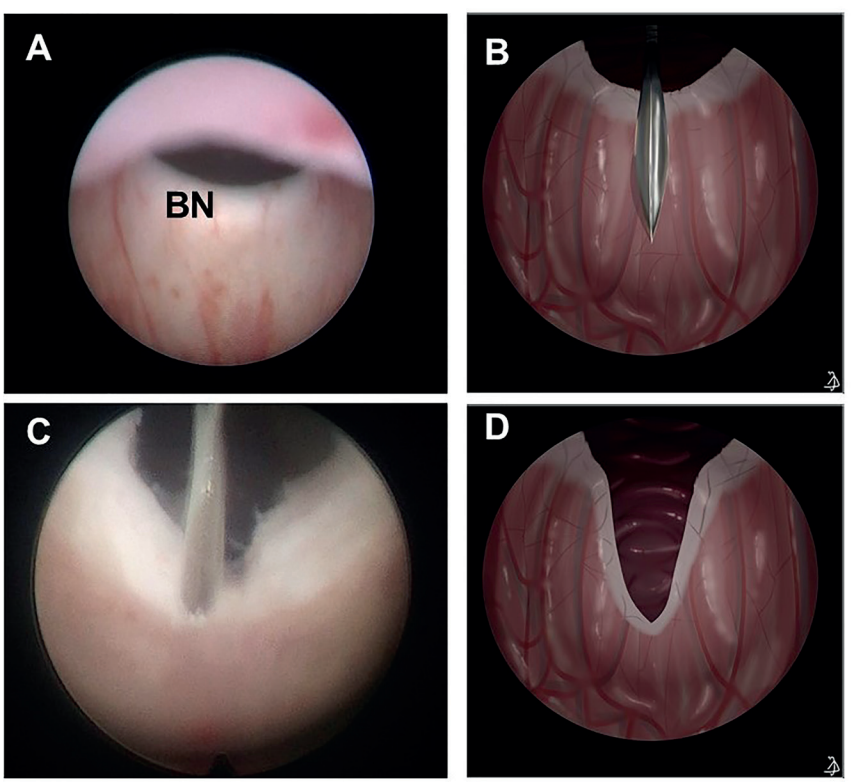
After IRB approval (R.21.07.1384), the database of a tertiary centre was retrospectively reviewed for infants (younger than 2 years of age) diagnosed with and treated for PUV between January 2000 and December 2017. Only patients with at least 18 months of follow-up were included. Patients with other anomalies that could potentially affect the lower urinary tract function and those with history of urinary diversion (e.g., vesicostomy or ureterostomy) were excluded. Patients were categorized into three groups according to the BN appearance on baseline radiological and cystoscopic assessment. High BN was judged at the time of cystourethroscopy by an experienced fellowship-trained pediatric urologist by the need for upward deflection of the scope to access the bladder, with or without the presence of bladder neck shelving on the lateral films of voiding cystourethrogram (VCUG). Group-1 included patients without BN elevation who underwent PVA only. Group-2 included patients with high BN who underwent concomitant PVA and BNI and group-3 included patients with high BN who underwent PVA only.

Preoperative evaluation included history, physical examination, serum creatinine, renal bladder ultrasound and VCUG. After initial bladder decompression using a urethral catheter and correction of any existing electrolyte and acid--base imbalance, cystoscopy and PVA were performed in all patients irrespective of serum cre-

atinine level or imaging findings. Surgeries were performed by one of three experienced pediatric urologists with more than 5 years of experience post fellowship. PVA was routinely performed using cold knife urethrotome at 12, 5 and 7 o'clock. If deemed necessary by the operating surgeon, BNI was carried out with an additional single incision also using cold knife at 6 o'clock position stopping proximal to the verumontanum (Figure-1). Adequacy of BNI was confirmed by the ability to visualize the bladder lumen with the tip of the scope at the level of the verumontanum and the expression of an adequate urine stream with Créde manoeuvre.

Patients were followed up at 6 weeks, 3 and 6 months postoperatively and every 6 months thereafter. Follow-up included serum creatinine, ultrasonography on every visit and VCUG at 3 months. The primary study endpoint was the need for reintervention with check cystoscopy within 6 months postoperatively. Reintervention was indicated if there was repeated urine retention, renal function deterioration, worsening hydronephrosis, persistent or worsening dilation of the posterior urethra, worsening or new onset VUR on VCUG. Secondary endpoints were last follow-up serum creatinine and VUR resolution or downgrading.

Figure 1 - Endoscopic appearance of the hypertrophied bladder neck.



A) before the incision, the posterior lip of the bladder neck (BN) is elevated, making it difficult to visualize the bladder lumen while the tip of the scope at the level of the verumontanum. Also, the tip of the scope has to be aggressively deflected upwards to gain access to the bladder, B) schematic drawing of elevated BN with the cold knife in place, C) a single incision is performed using the sickle-shaped cold knife at 6 o'clock until the bladder can be accessed easily without the need to significantly deflect the scope, D) schematic drawing of figure C.

Statistical analysis

Data were statistically analysed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 20). Qualitative data were described as numbers and percentages.

Quantitative data were described as means±SD or medians (ranges), as appropriate. Chi-square test was used to compare categorical data. In the normally and non-normally distributed variables, one-way ANOVA and Kruskal-Wallis test were respectively used for comparisons. P value <0.05 was considered statistically significant.

RESULTS

Eligible for inclusion were 114 infants who underwent PVA at the study institution at a median age of 7.9 (1-24) months. Median follow-up was 58 (18-230) months. Group-1 (BN not elevated and treated with PVA only) included 70 patients, group-2 (elevated BN treated with concomitant PVA and BNI) included 21 patients, while group-3 (elevated BN treated with PVA only) included 23 patients. Baseline demographics are shown in Table-1. Age at intervention, baseline serum creatinine and baseline VUR were not significantly different between the study groups (p=0.96, 0.95 and 0.42; respectively).

At last follow-up, median serum creatinine was 0.6 (0.3-5.2), 0.5 (0.4-1.4) and 0.5 (0.4-2.4) mg/dL for groups 1, 2 and 3; respectively (p=0.48). Overall, a total of 23 (20.2%) patients required check cystoscopy for repeated urine retention, renal functional deterioration, worsening hydronephrosis or inadequate improvement of VCUG findings. In group-1, 16 (22.9%) patients needed reintervention. Check cystoscopy was unremarkable and no further intervention was required in five (7.5%) cases. Ablation of PUV remnants was performed in 11 (15.7%) patients. In group-2, reintervention was required in three (14.3%) patients: ablation of valve remnants was performed in one patient (4.8%) and BNI was combined with ablation of PUV remnants in two (9.5%) other patients. Reintervention was required in 4 (17.4%) group 3 patients. Of those, check cystoscopy was unremarkable in one patient (4.3%), two patients underwent ablation of PUV remnants (8.7%) and one underwent both BNI and ablation of PUV remnants (4.3%). The reintervention rates and the type of reintervention were not significantly different among the three study groups (p=0.65 and 0.15; respectively). Likewise, follow-up serum creatinine and VUR outcomes were not different among the three study groups. Study results are summarized in Table-2.

DISCUSSION

PUV is the commonest cause of lower urinary tract obstruction in male children (13). Even after successful PVA, the majority of patients will suffer bladder dysfunction. Following PVA, bladder function greatly varies from essentially normal voiding to severe bladder dysfunction with prolonged and weakened urinary stream. Obstructive voiding pattern can be the result of residual valve tissue, urethral stricture particularly if cautery was used for PVA

Table 1 - Baseline patient demographics.

Patient characteristics	Group 1 (BN not elevated and treated with PVA only), N=70	Group 2 (elevated BN treated with concomitant PVA and BNI), N=21	Group 3 (elevated BN treated with PVA only), N=23	P-value
Median age at PVA (range), months	8 (1-24)	7 (1-22)	5.5 (1-24)	0.96
Median follow-up duration (range), months	54 (17 - 230)	44 (18- 136)	49 (22 - 157)	0.14
Median baseline serum creatinine (range), mg/dL	0.5 (0.1-2.2)	0.4 (0.2-1.7)	0.6 (0.2-1.2)	0.95
Baseline VUR, N (%)				0.42
No VUR	42 (60)	11 (52.4)	9 (39.1)	
Non-dilating VUR (grade I-II)	2 (2.9)	0	1 (4.3)	
Dilating VUR (grade III- IV)	26 (37.1)	10 (47.6)	13 (56.5)	

BNI = bladder neck incision; **PVA** = posterior urethral valve ablation; **VUR** = vesicoureteral reflux

Table 2 - Study outcomes.

Study outcome	Group 1 (BN not elevated and treated with PVA only), N=70	Group 2 (elevated BN treated with concomitant PVA and BNI), N=21	Group 3 (elevated BN treated with PVA only), N=23	P-value
Number of patients requiring re-intervention within 6 months postoperatively (%)				0.65
No	54 (77)	18 (85.7)	19 (82.6)	
Yes	16 (22.9)	3 (14.3)	4 (17.4)	
Type of reintervention				0.15
No reintervention	54 (77)	18 (85.7)	19 (82.6)	
Check cystoscopy only	5 (7.5)	0	1 (4.3)	
Ablation of PUV remnants	11 (15.7)	1 (4.8)	2 (8.7)	
Ablation of PUV remnants + BNI	0	2 (9.5)	1 (4.3)	
Median last follow-up serum creatinine (range), mg/dL	0.6 (0.3-5.2)	0.5 (0.4-1.4)	0.5 (0.4-2.4)	0.48
Postoperative VUR, N (%)				
No VUR	46 (65.7)	12 (57.1)	11 (47.8)	
Non-dilating VUR (grade I-II)	3 (4.3)	1 (4.8)	2 (8.7)	0.62
Dilating VUR (grade III- IV)	21 (30)	8 (38.1)	10 (43.5)	
VUR outcome (%)				
Improved	12 (17.1)	4 (19)	5 (21.7)	0.72
Static	55 (78.6)	17 (81)	18 (78.3)	
Worsened	3 (4.3)	0	0	

BNI = bladder neck incision; **PUV** = posterior urethral valve; **PVA** = posterior urethral valve ablation; **VUR** = vesicoureteral reflux

or secondary BN obstruction (14). Radiological and endoscopic examination usually suffice when evaluating valve remnants and urethral stricture. The diagnosis of secondary bladder neck obstruction is, however, more challenging, often requiring videourodynamic assessment (4).

Management of PUV sequelae is dictated by the pattern of bladder dysfunction (15-17). A variety of therapeutic options have been suggested to treat secondary BN obstruction in PUV patients including alpha-blockers, botulinum toxin injection into the BN or BNI (4, 8, 9). For fear of the long-term consequences of BNI on ejaculation and continence, some pediatric urologists favored the use of alpha blockers to relax the BN and treat secondary BN obstruction. In patients with urodynamic diagnosis of secondary BN obstruction, Combs reported decreased mean maximum voiding detrusor pressure (Pdet) from 107.3 to 41.2cm H2O and increased Qmax from 12.5 to 24.7mL/sec following alpha blocker treatment (7). Mokhless et al. injected botulinum toxin into the BN of 10 patients with BN dysfunction following PVA. The authors of that study found no effect of BN botulinum toxin injection on urodynamics, hydronephrosis or VUR resolution 6

months after the procedure (9).

In the 1950s, BNI was commonly performed during PVA to improve voiding. This practice was later abandoned for fear of incontinence and retrograde ejaculation (3). A number of contemporary studies have examined the effect of concomitant BNI and PVA with conflicting results. Kajbafzadeh et al. described, modified BNI at 6 o'clock position through the BN just proximal to the verumontanum cautiously leaving the adventitia untouched to preserve antegrade ejaculation. In this prospective study, 22 patients underwent concomitant PVA and BNI and 24 matched patients underwent PVA only. At baseline, all patients in both groups had hypercontractile bladders and comparable voiding detrusor pressures. After a mean follow-up of 4.5 years, patients who had concomitant PVA and BNI had a mean maximal voiding Pdet of 53±15cm H2O without any bladder hypercontractility or detrusor overactivity. In the PVA group, the mean maximal voiding Pdet was 87±45cm H2O ($p < 0.01$). Nine (37.5%) patients of that group had bladder hypercontractility and six (25%) had detrusor overactivity (8). In another study by Sarin et al., bladder dysfunction and detrusor overactivity rates were similar whether BNI was simultaneously performed with PVA or not. Hypocompliant high-pressure bladder was the predominant cystometric finding in both groups. Although limited by the small number of subjects and short follow-up, this study failed to demonstrate any additional benefits of simultaneous BNI (10). Singh et al. reported improved peak flow rate and PVR, but similar compliance, DO, end-filling pressure, maximum Pdet at Qmax and reflux resolution rate in a prospective randomized study comparing PVA alone to concomitant PVA and BNI (12).

Few studies have examined the effects of BNI performed during childhood on retrograde ejaculation and urinary continence in adulthood. Taskinen et al. reported ejaculation failure in two of 19 adults who had concomitant PVA and BNI during childhood. However, dry ejaculates were also reported in one of 15 patients treated with PVA only indicating that BNI during childhood does not result in retrograde ejaculation (18). Hennus and co-workers reported on the long-term effects on ejaculation and urinary continence in 40 participants who had unilateral superficial BNI at a mean age of 4.5 years. All men had antegrade ejaculation, 10.8% reported possibly reduced ejaculatory volume and 5.8% had moderate urinary incontinence (19). Likewise, Keihani found no effect of BNI on continence, antegrade ejaculation or semen quality in 18 adult patients who had PVA and BNI during childhood (20). These studies provide reassurance that BNI can be safely performed without deleterious effects on continence or ejaculation.

In Kajbafzadeh's study, PVA alone was associated with a 28% reintervention rate versus 0% for patients who underwent concomitant PVA and BNI (8). Without a doubt, reduced readmission risk substantially contributes to improved quality of care and reduced treatment-related costs (11). Furthermore, repeated exposure to general anesthesia during infancy and early childhood has been linked to lower motor and social linguistic skills and poorer school performance (21, 22). Even with questionable benefits to bladder dynamics and upper tract outcomes, reduced risk of readmission and repeated interventions would certainly favor concomitant BNI as long as it does not result in adverse long-term consequences. In contrast to the results of Kajbafzadeh's study, we found that patients treated with concomitant BNI had similar readmission and reintervention rates compared to those treated with PVA only. The re-admission rates were 22.9%, 14.3%, and 17.4% for patients with normal BN, high BN treated with concomitant PVA and BNI and high BN treated with PVA without BNI; respectively. Further, we found no significance difference in re-intervention rates, serum creatinine or VUR outcome among the three study groups. For patients with high BN who underwent concomitant PVA and BNI, re-ablation of valve remnants and re-ablation plus BNI were performed in one (4.8%) and two (9.5%) cases; respectively. For those patients with high BN who had only PVA without BNI, re-ablation of valve remnants was performed in two (8.7%) patients and re-ablation plus BNI were performed in one (4.3%) patient ($p=0.15$).

Our study has several limitations. In addition to its retrospective design, the decision to perform concomitant BNI was not based on a study plan or an institutional protocol, but rather on surgeon's evaluation. In addition, the diagnosis of bladder neck obstruction relied on endoscopic and radiologic findings and not on urodynamic evaluation. The lack of

urodynamic evaluation could be regarded as one of this study limitations. Although urodynamics is the best tool we currently have in hand to assess lower urinary tract functions, it is not without limitations. Urodynamics before PVA would not reliably distinguish whether the obstructive voiding pattern is the result of valves or BN obstruction until valve ablation is carried out. Further, patients with PUV have sensate urethras and hypertrophied BN making catheterization sometimes challenging and resulting in significant patient discomfort and possibly affecting the quality of urodynamic results. Even the smallest urodynamic catheter available (usually 6 French) could be obstructive to the infantile urethra, leading to inaccurate interpretation of voiding cystometry. Likewise, the lowest possible bladder filling rate provided by the current urodynamic machines is probably supra physiologic for infants and young children. Moreover, most PUV patients have VUR, usually of high grade, resulting in inaccurate estimation of the bladder capacity and compliance. Parental separation, catheterization and bladder filling all contribute to patient irritability and discomfort resulting in multiple motion artefacts and frequent urine leaks with subsequent difficulty in interpreting the urodynamic tracing. After all, interpretation of urodynamic results is also subject to inter-rate and intra-rate variability even among experts in this field (23). Despite these limitations of urodynamic studies, they remain fundamental in assessment of bladder dysfunction. Although the follow-up duration is relatively short (median of 58 months with a minimum of 18 months), this duration is quite sufficient to judge the short-term outcomes such as the need for early reintervention.

CONCLUSION

At least in our results, concomitant bladder neck incision with valve ablation in infants with PUV is not associated with reduced early hospital re-admission or re-intervention rates compared to PVA alone. Our results require validation in a larger number of subjects examined in a prospective fashion.

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CONFLICT OF INTEREST

None declared.

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Analysis of surgical and histopathological results of robot-assisted partial nephrectomy with use of three or four robotic arms: an early series results

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ABSTRACT

Objectives: The aim of this study was to evaluate whether criteria exist to guide election between the use the three- or four-arm technique in robotic partial nephrectomy (RPN) instead of just the surgeon's preference.
Material and Methods: We performed a retrospective review of 80 patients submitted to RPN from May 2016 to February 2020. The patients were divided into two groups of 40, the first submitted to the surgical procedure with use of three robotic arms and the second with four arms. The group division was performed independently of the complexity of the cases, age or gender of the patients and laterality of the renal lesions. Peri- and postoperative data were analyzed for comparison between the two groups.
Results: Both techniques had similar oncological outcomes (positive tumor margins), renal function preservation (warm ischemia time) and hemorrhagic complications (estimated blood loss and renal artery pseudoaneurysm), with a small difference in the need for blood transfusion, favoring the technique with three arms.
Conclusions: The two robotic partial nephrectomy techniques had similar oncological and postoperative outcomes, with minimal perioperative complications. The three-arm technique is safe and feasible regardless of the complexity and size of the tumor. Additionally, the use of the three-arm technique reduced surgery costs by US$ 413.00 per patient.

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INTRODUCTION

The early diagnosis of renal masses has increased in recent decades with advances of imaging technology (1). Approximately 60% of renal tumors are diagnosed in stage T1a (≤4 cm). Recent reports have demonstrated the viability of performing partial nephrectomy in tumors at stages T1a and T1b (4-7 cm), making surgery the gold standard for treatment of small renal masses due to the possibility of oncological control with functional preservation and reduction of future cardiovascular risks (2, 3).

Since Gettman et al. described robotic partial nephrectomy (4), the procedure has spread significantly as an option for minimally invasive surgical treatment of small renal masses (5). The learning curve of minimally invasive partial nephrectomy can be reduced with the use of robotic platform as recently published in two series which showed that reasonable 'Trifecta' rates can be achieved even by low volume surgeons (6), and even with surgeons without previously laparoscopic experience (7). Robotic surgery offers all the benefits of minimally invasive procedures: shorter length of stay, less postoperative pain, reduced estimated blood loss and faster recovery (8).

The evolution of robotic surgical techniques has improved peri- and postoperative results of nephron-sparing surgery, such as reduction of warm ischemia time (9,10), lesser conversion into open or radical surgery (11), less severe postoperative complications (12) and better postoperative renal function (11).

There are many articles describing the outcomes of treating renal masses by robot-assisted surgery with use of three or four robotic arms, but the literature lacks studies specifically comparing the results of using three or four arms. Our objective was to evaluate whether criteria exist to determine the best technique to use, other than simple preference of the surgeon and if the three arms procedure is feasible for any case despite of tumor size, location and complexity. For this purpose, we sought to establish what parameters can be used for choosing between these two techniques by comparing the intra- and postoperative results of robot-assisted partial nephrectomy.

MATERIALS AND METHODS

Study design

This study retrospectively reviewed data from May 2016 to February 2020 of 80 patients submitted to robot-assisted partial nephrectomy. The procedures were performed by two surgeons with extensive experience in minimally invasive nephron-sparing surgery. The patients were divided into two groups: 40 consecutive three-arm RPN and 40 consecutive four-arm RPN were reviewed. The option between the two techniques was exclusively based on the surgeon's preference. The group division was performed independently of the complexity of the cases, age or gender of the patients and laterality of the renal lesions. The study design was approved by the ethics committee of the Hospital Universitário Grafree Guinle (No 5258).

Preoperative demographic parameters and tumor characteristics were recorded. Intraoperative details such as operating console time, estimated blood loss, need for blood transfusion and warm ischemia time were recorded. Postoperative variables such as length of hospital stay, postoperative hemorrhage and need of angioembolization were reviewed. Four-arm utilization costs were calculated based on our institution's contracted purchase price from Intuitive Surgical.

Two surgeons (J.M. and V.D.) with extensive experience in minimally invasive renal surgery performed all the surgical procedures. The Da Vinci-Si and Da Vinci-Xi systems (Intuitive Surgical, Sunnyvale, CA, USA) were used.

Surgical technique

Following induction of general anesthesia, an orograstric tube and Foley catheter are placed. The patient is positioned in flank position with the affected side up. Mild table flexion may be applied to increase the space for ports. The ipsilateral arm is positioned to the side. Trocars are positioned after the pneumoperitoneum in direct view. Both techniques use only one 12 mm assistant port for suction, needle exchanges, Hem-o-Lock clipping and specimen bag deployment (see supplementary video).

After colon mobilization and retroperitoneum dissection with identification of the proximal ureter, the kidney is elevated by the fourth robotic arm to place the renal hilar vessels on stretch, enabling the two-handed dissection by the surgeon. When the procedure is performed with only three robotic arms, the assistant plays an important role in elevating the kidney and helping to expose the renal hilum.

The vascular clamping method was not randomized and was used according to the surgeon's preference. Both techniques (three-arm or four-arm) were performed with transperitoneal access, and the renorrhaphy was performed by the sliding-clip technique (13) using V-Loc 3.0 sutures (Covidien). No hemostatic agent or double J catheter was employed.

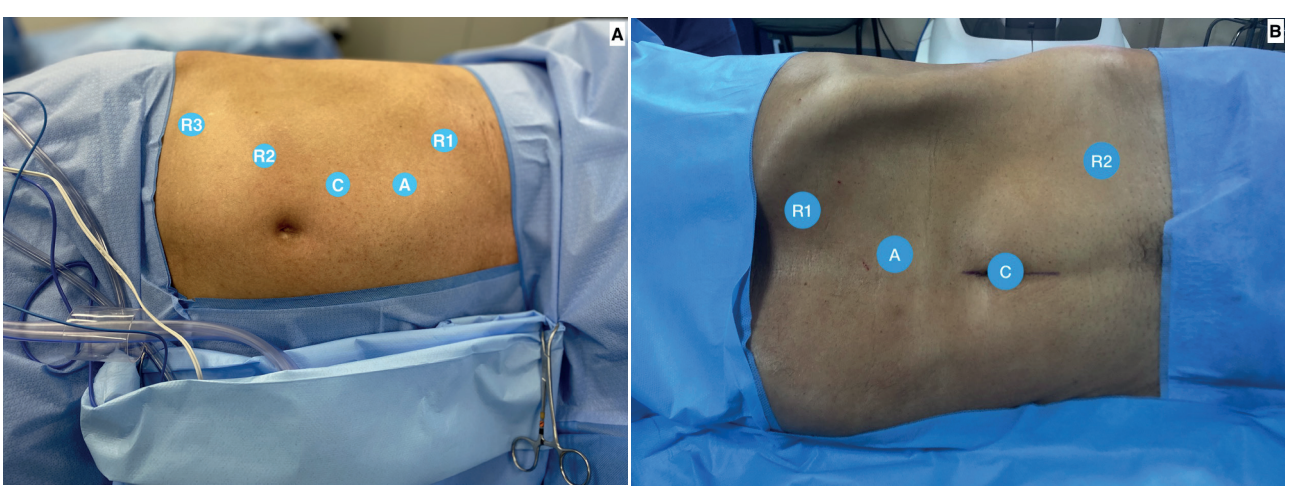
A - Four-arm technique ports placement

The camera trocar is placed above the umbilical scar in the paramedian line. The pattern of port positioning is demonstrated in Figure-1A. The trocar angle can be adjusted slightly cranial or caudal according to tumor location. The 12 mm assistant port is placed cranially in the same line to the camera port at a minimum distance of 5 cm.

B - Three-arm ports placement

The camera trocar is placed at the umbilicus to preserve abdominal aesthetics by using a natural scar. The pattern of port positioning is demonstrated in Figure-1B. The trocar angle can be adjusted slightly cranial or caudal according to tumor location. The 12 mm assistant port is placed cranially in the same line as the camera port at a minimum distance of 5 cm.

Figure 1 - A) Four-arm port placement. Camera port placed medially to the umbilicus (C), midline assistant port (A), right working port (R1), left working port (R2) and third robotic arm (R3). B) Three-arm port placement. Camera port placed in the umbilicus (C), midline assistant port (A), left working port (R1) and right working port (R2).



Statistical analysis

The statistical analysis was carried out by cross-referencing the data of the two groups as a whole, as well as for each variable individually, to ascertain the possible impacts on the final result.

Initially, the data were used to calculate absolute frequencies and percentages (qualitative variables) and to compute descriptive statistics: mean, standard deviation, minimum, median and maximum (quantitative variables). To compare the groups regarding the qualitative variables, and thus to estimate the relative risks (RRs), Poisson regression with robust variance was used with the log-link function. For comparisons involving quantitative variables, linear regression with mixed effects (random and fixed effects) was used. These linear models with mixed effects are used to analyze data in which the responses are grouped (more than one measure for a single individual, since some participants underwent more than one operation), and when the assumption of independence between the observations in each group is not suitable. For comparisons, we used the orthogonal contrast post-test, while to compare the groups regarding the number of days in the hospital we also used Poisson regression with robust variance, but with the identity link function. All the comparisons were adjusted by the patient's age, a possible confounding variable.

RESULTS

A total of 80 patients underwent transperitoneal partial nephrectomy with warm renal ischemia. The patients' demographic characteristics are reported in Table-1. Between the three-arm and four-arm groups, there were no differences in age, gender, tumor laterality, RENAL score nephrometry and tumor size. The average sizes of the tumors in the two groups were 3.82 cm (1.3-10.0) and 3.49 cm (1.0-8.5) for the procedures with three and four arms, respec-

Table 1 - Patients distribution according to age, gender, tumor characteristics and histopathological findings.

VarIABLES	RPN 3 ARMS (n=40)	RPN 4 ARMS (n=40)	p VALUE
Age (years)	57.48 (20-75)	56.63 (34-77)	p=0.78
Gender			
Male	23 (57.5%)	22 (55%)	p=0.82
Female	17 (42.5%)	18 (45%)	
Diameter (cm)	3.82 (1.3-10)	3.49 (1.0-8.5)	p=0.42
Renal Score			
4-6	19 (47.5%)	20 (50%)	p=0.88
7-9	9 (22.5%)	10 (25%)	
≥ 10	12 (30%)	10 (25%)	
Laterality			
Left	22 (55%)	19 (47.5%)	p=0.50
Right	18 (45%)	21 (52.5%)	
Histopatology			
Angiomyolipoma	4 (10%)	4 (10%)	
Oncocytoma	1 (2.5%)	2 (5%)	
Benign cyst	3 (7.5%)	1 (2.5%)	
Papiliferous	2 (5%)	3 (7.5%)	p=0.25
Clear cells	29 (72.5%)	24 (60%)	
Cystic nephroma	1 (2.5%)	0 (0%)	
Chromophobe	0 (0%)	4 (10%)	
Papillary clear cells	0 (0%)	2 (5%)	
Stage			
Pt1a	32 (80%)	28 (70%)	
Pt1b	2 (5%)	9 (22.5%)	p=0.10
Pt2	5 (12.5%)	3 (7.5%)	
Pt3	1 (2.5%)	0 (0%)	

tively. The number of complex cases (RENAL score >10) were similar in both techniques, there were 12 cases (30%) in the three-arm group and 10 (25%) in the four-arm group. The average surgical time for three-arm technique was 81 minutes (29 – 215 minutes), while for the four-arm technique it was 91 minutes (40 – 180 minutes). The mean warm renal ischemia time of the three-arm group was 16.25 minutes (0 – 35 minutes) and of the four-arm group it was 21.78 minutes (0 – 50 minutes). There was no statistical difference in average surgical time between the two groups (RR 0.13 [CI -0.41 to 0.15], *p*= 0.23), as well as in the warm renal ischemia time (RR -5.15 [CI -11.3 to 1.00], *p*= 0.08). There was no statistical difference between the groups in the estimated perioperative blood loss (RR -0.05 [CI -0.67 to 0.57], *p*= 0.81). The average estimated blood loss in the three--arm group was 221 mL (30 – 800 mL), while in the four-arm group it was 325 mL (20 – 2,250 mL). There was a slight advantage in the comparative analysis regarding blood transfusion rate for the patients who underwent three-arm robotic surgery (RR 0.20 [CI 0.05 to 0.77], *p*= 0.02), a finding that might have been less evident with a larger sample size (Table-2).

Both groups presented the same number of positive surgical margins (one case), a rate of only 2.5%. The two groups also had the same number of hemorrhagic complications (renal artery pseudoa-

Table 2 - Per and post-operative data in patients` submitted to partial nephrectomy with three and four arms.

Variables	RPN 3 Arms (n=40)	RPN 4 Arms (n=40)	p Value
Surgical Margins			
Negative	39 (97.5%)	39 (97.5%)	p=0.32
Positive	1 (2.5%)	1 (2.5%)	
Estimated Blood Loss (mL)	221 (30-800)	325 (20-2,250)	p=0.81
Blood Transfusion	1 (2,5%)	3 (7.5%)	p=0.02
Console Time (minutes)	81 (29-215)	91 (40-180)	p=0.23
Warm Ischemia Time (minutes)	16.25 (0-35)	21.78 (0-50)	p=0.08
Renal Artery Pseudoaneurysm	1 (2.5%)	1(2.5%)	p=0.99

RPN = Robotic Partial Nephrectomy

neurism), one in each group. Patients in both groups were submitted to embolization without need of any other surgical approach.

The ProGrasp® (Intuitive Surgical) grasper is commonly used in the fourth arm to dissect the kidney hilum and help during nephrorrhaphy. The unit cost of a ProGrasp® grasper is US$ 3,080.00, and this instrument can be used for 10 cases before expiring, so the per-case cost is US$ 308.00. The disposable canula seal costs US$ 25.20 and the drape utilized for the fourth arm costs US$ 21.00. The fourth arm's sterile plastic cover costs US$ 58.80 per-procedure. The total amount saved with the three-arm technique is US$ 413.00 for each operation.

DISCUSSION

Robotic partial nephrectomy became the preferred surgical technique by allowing treatment of complex renal masses with lower complication rates than traditional laparoscopy and open surgery (14). Both techniques applied to our sample produced similar oncological outcomes (positive surgical margins), renal function preservation (warm ischemia time) and hemorrhagic complications (estimated blood loss and renal artery pseudoaneurism). There was a small difference in the blood transfusion rate, favoring the technique with three robotic arms (RR 0.20 [CI 0.50-0.77], *p*=0.02).

The aesthetic aspects of the three-arms procedure previously described must be taken into consideration. When utilizing the umbilicus for the camera port and using only one 12 mm assistant port there is a significant reduction in postoperative abdominal scars. There was no technical difficulty to access kidney hilum or superior pole tumors by using the umbilical scar to perform a three-arm robotic partial nephrectomy, with the aesthetic benefit of using a natural body scar.

Although both methods are widely used, there are only a few studies comparing the outcomes of the three- and four-arm techniques. Recently, Johnson et al. (15) published a similar cohort study that demonstrated that robotic partial nephrectomy can be safely performed utilizing either 3 or 4 robotic arms, depending on surgeon preference, with slight differences in warm ischemia time and surgical margins between the two methods. We did not find any statistical difference when comparing margins and warm ischemia time between our two groups.

In recent years, the development of robotic surgery has made renal preservation safe and feasible in increasingly challenging cases (10). Moskowitz et al. reported high efficacy, better oncologic outcome, greater overall and cardiovascular survival rate among patients with small renal masses (T1a) when submitted to nephron-sparing surgery (16). In turn, Mir and collaborators conducted a systematic review and reported that partial nephrectomy can be performed safely with similar oncological outcomes in comparison with radical nephrectomy for the treatment of renal tumors up to 7 cm (17). Recent

data also suggest that partial nephrectomy in tumors larger than 7 cm does not increase cancer-specific mortality (18, 19). In this study, the tumor diameter and the RENAL score status were not factors impeding performance of nephron-sparing surgery when technically feasible in both techniques. The average tumor diameter of the patients submitted to robotic surgery with three arms was 3.82 cm while the average size in the group that underwent surgery with four arms was 3.49 cm. Twelve (30%) patients undergoing the three arms procedures had a RENAL score greater than 10. The oncological outcomes were evaluated by the presence of positive surgical margins. There were only two cases, one in each group (2.5%), similar results to those recently reported (20).

Several studies have reported renal artery pseudoaneurysm as the most common and life-threatening complication following partial nephrectomy, regardless of surgical procedure. Scoll et al. described 110 patients that were submitted to robotic partial nephrectomy and showed postoperative blood transfusion rate of 3% and renal artery pseudoaneurysm requiring transfusion of 1% (21). This study's rates of hemorrhagic complications with perioperative transfusion were 2.5% in the three-arm group and 7.5% in the four-arm group, while the rates of renal artery pseudoaneurysm requiring embolization were the same at 2.5%. The hemorrhagic complications were more often observed in this study in larger lesions (>4 cm), hilar renal masses and with collector system violation.

Renal function preservation is extremely important in evaluating the postoperative outcomes of patients submitted to nephron-sparing surgery (22). Recently published data report that warm ischemia time and quality and quantity of preserved kidney are the main factors determining postoperative renal function (23). Warm ischemia time under 25 minutes was the target in this study, which was achieved by 90% of the patients in both groups, with mean times of 16.25 minutes in the three-arm group and 21.78 minutes in the four-arm group. Furukawa and collaborators analyzed data on 130 patients and found that 81 presented warm ischemia time £ 25 minutes (mean of 21 minutes), with low perioperative complications, concluding that partial nephrectomy is safe and feasible even in the presence of hilar tumors (24). In our study, hilar and endophytic tumors (>50%) were associated with greater warm ischemia time but not associated with higher risk of hemorrhagic complications or impaired renal function.

Robotic surgery is more expensive than open and laparoscopic procedures (25). The total amount saved by not using the fourth arm was on average US$ 413.00 per procedure, due to the lower need for surgical supplies such as drapes, ProGrasp® forceps, canula seals and robotic arm sterile plastic covers. The cohort study of Johnson et al. (15) described savings of US$ 280.00 per procedure by avoiding the use of the same supplies. The savings reported in this study are even more significant, probably due to economic disparity between the two countries. This is highly relevant when choosing a surgical technique, by reducing hospital costs and allowing robot use in a larger number of patients. These economic aspects are particularly important in countries with low domestic technology, where universalization of access to robotic surgery depends on imported technology.

This study has several strengths. Both surgeons have extensive experience in minimally invasive renal procedures, with more than 20 years of clinical practice. All bedside assistants are certified robotic surgeons and no procedures were performed by residents or fellows. All patients in each group were treated by the same surgical team. There was no selection bias since a single surgeon was responsible for performing the procedures in each group regardless of tumor characteristics. The study's major limitations are its retrospective nature and its small sample, which can lead to some analysis bias. Due to the complexity of some cases it's is important to suggest that the three arms procedures should be performed by an experienced surgical team. Additionally, in cases of intraoperative necessity, the fourth arm is promptly available for use.

CONCLUSION

The two robotic partial nephrectomy techniques evaluated had similar oncological and postoperative results, with minimal perioperative complications. The three-arm robot-assisted technique had a slight advantage regarding estimated blood loss and need for transfusion. There also was an important aesthetic benefit by utilizing the umbi-

licus for the camera port and using only one 12 mm assistant, with significant reduction in postoperative abdominal scars. Although cost was not the main objective of this study, the three-arm technique was substantially less expensive (US$ 413.00 per patient) due to the lesser cost of inputs, enabling greater use of robotic surgery.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Is biofeedback-assisted pelvic floor muscle training superior to pelvic floor muscle training alone in the treatment of dysfunctional voiding in women? A prospective randomized study

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ABSTRACT

Purpose: To compare the effectiveness of biofeedback-assisted pelvic floor muscle training (PFMT) and PFMT alone on voiding parameters in women with dysfunctional voiding (DV).

Materials and Methods: The patients in group 1 (34 patients) were treated with biofeedback-assisted PFMT, and the patients in group 2 (34 patients) were treated with PFMT alone for 12 weeks. The 24-hour frequency, average voided volume, maximum urine flow rate (Q_{max}), average urine flow rate (Q_{ave}), post-void residual urine volume (PVR), and the validated Turkish Urogenital Distress Inventory (UDI-6) symptom scores were recorded before and after 12 weeks of treatment.

Results: At the end of treatment sessions, the Q_{max} and Q_{ave} values of the patients in group 1 were significantly higher than those in group 2, and the PVR in the patients in group 1 was significantly lower than those in group 2 (p=.026, .043, and .023, respectively). The average UDI-6 symptom scores of the patients in group 1 were significantly lower than those in group 2 (p=.034). Electromyography activity during voiding, in group 1 was significantly lower than in group 2 (41.2 vs. 64.7, respectively, p=.009).

Conclusion: Biofeedback-assisted PFMT is more effective than PFMT alone in improving clinical symptoms, uroflowmetry parameters, and EMG activity during voiding.

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INTRODUCTION

Voiding dysfunction refers to abnormally slow, intermittent voiding and/or incomplete bladder emptying (1). There are two main types of voiding dysfunction: bladder outlet obstruction (BOO) and detrusor underactivity (DU). Functional disorders or structural lesions (mechanical obstruction) may cause the development of BOO. Disorders such as detrusor sphincter dyssynergia and dysfunctional voiding (DV) are among the causes of functional BOO (2). The International Society of Continence defines DV as an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated or levator muscles during voiding in neurolo-

gically normal individuals (1). Simultaneous contraction of the sphincter and detrusor in the presence of a neurological condition is defined as detrusor sphincter dyssynergia (3, 4). The lack of coordination between the detrusor and sphincter is similar in both disorders; however, the etiologies are different, and these two terms cannot be used synonymously (5).

A variety of lower urinary tract symptoms (LUTS) can occur in DV, including storage symptoms (frequency, stress, and urge incontinence) and emptying symptoms (poor or intermittent stream, hesitancy, and feeling of incomplete emptying). It may cause recurrent urinary tract infections and acute or chronic urinary retention (2, 6). The goal of treatment is to normalize the voiding patterns and prevent complications. Despite various treatments that have been tried, there is, unfortunately, no treatment modality that can be recommended with high levels of evidence for DV due to limited data (7).

The muscle groups targeted with pelvic floor muscle training (PFMT) are the levator ani, the external anal sphincter, and the striated urethral sphincter. These exercises aim to increase muscle tone and synchronize contractions (8). The ability to properly contract the pelvic floor muscles is essential for PFMT. Women who are able to contract their pelvic floor muscles correctly are suitable for PFMT (9). The goal of biofeedback is to increase awareness of the function of the pelvic floor muscles and to develop better voluntary control of these muscles and the external urethral sphincter during voiding. Biofeedback is not a therapy by itself but an adjunct to PFMT in measuring the response from the contraction of the pelvic floor muscles (10, 11).

We hypothesized that PFMT may be an effective treatment modality for women with DV, and also that combining PFMT with biofeedback may provide more effective pelvic floor muscle awareness and more successful outcomes than PFMT alone. Therefore, we aimed to compare the effectiveness of biofeedback-assisted PFMT and PFMT alone on the voiding parameters of patients by implementing an effective training program in women with DV.

MATERIALS AND METHODS

This prospective randomized study was approved by the local ethics committee (Approval number: B.30.2.ATA.0.01.00/999).

Participants

Women aged 18-50 years, who presented to our clinic with LUTS between May 2019 and August 2020, were evaluated. Uroflowmetry and post-void residual urine volume (PVR) by ultrasound were performed. Patients with a maximum urine flow rate (Q_{max}) ≤ 15 mL/s and/or PVR > 50 mL in at least two measurements were diagnosed with voiding dysfunction (12). Patients with advanced pelvic organ prolapse (Stage III and IV), diabetes mellitus, neurological disorder (e.g., multiple sclerosis, spinal cord compression, Parkinson's disease, lumbar disc prolapse, or spina bifida), history of lower urinary system surgery or intra-abdominal radiotherapy, active urinary system infection, and urethral stricture/anatomic obstruction were excluded from the study. A 12 Fr Foley catheter was advanced in all patients to exclude urethral stricture or anatomic obstruction. Patients with difficulty advancing the Foley catheter were examined by ureterorenoscope. The remaining patients underwent uroflowmetry with electromyography (EMG). A total of 82 patients with simultaneous detrusor and external sphincter activity during voluntary voiding on EMG were diagnosed with DV. Eight patients refused to participate, and a total of 74 patients were included in the study. The sample size was determined based on the studies on DV in women.

The patients' ability to perform contraction and relaxation and their compliance with PFMT were evaluated with digital palpation by the urotherapist. Patients were randomly assigned using block randomization (a computer-generated list of random numbers) by the researcher (IK) and divided into two groups. The patients in group 1 were treated with biofeedback-assisted PFMT, and the patients in group 2 were treated with PFMT alone for 12 weeks. None of the patients performed PFMT before and had no knowledge of PFMT. The patients in both groups were trained in the clinic by the

same PFMT certified urotherapist. To ensure compliance with the exercise program, the patients were asked to fill in the follow-up chart, and these charts were checked by the urotherapist every week. Comprehensive information was given to the patients, emphasizing the importance of regular and consistent exercise. Six patients were excluded from the study because they did not want to continue. The study was completed with a total of 68 patients: 34 in group 1 and 34 in group 2 (Figure-1).

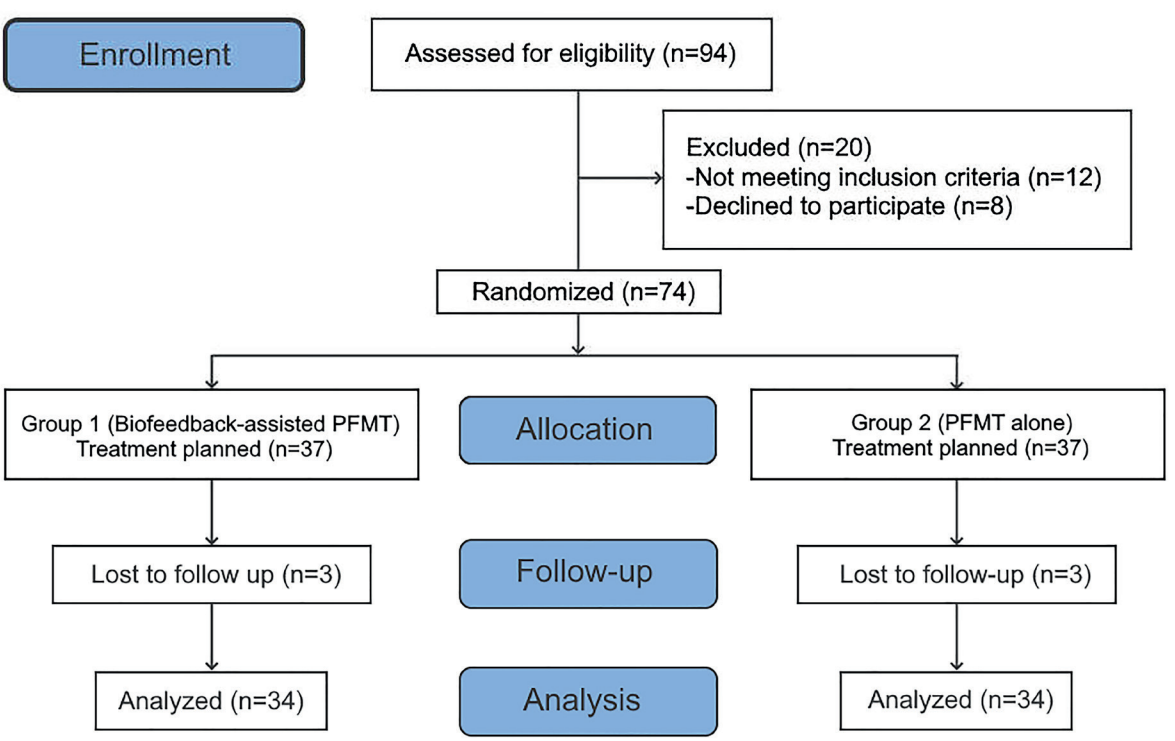
Before and after the 12-week treatment, uroflowmetry (Q_{max}; average urine flow rate: Q_{ave}), bladder diary (24-hour frequency and average voided volume), PVR, the validated Turkish Urogenital Distress Inventory (UDI-6) (13), and EMG activity during voluntary voiding were evaluated in the patients in both groups.

The UDI-6 is a six-item scale developed to evaluate bladder function and the problem-causing symptoms. The first and second questions assess urgency, frequency, and pain; the third and fourth questions assess the stress symptoms; the fifth and sixth questions assess the obstructive/discomfort or symptoms of voiding difficulty.

Primary and Secondary Objectives

The primary objective of our study was to determine whether the 12-week biofeedback-assisted PFMT or PFMT alone is an effective treatment for women with DV. Treatment efficacy was evaluated with the UDI-6 score. The secondary objective was to determine the effects of 12-week biofeedback-assisted PFMT or PFMT alone on bladder diary, uroflowmetry parameters, PVR, and EMG activity during voiding in the treatment of women with DV.

Figure 1 - CONSORT flow diagram. The diagram illustrates the progress of the participants through the enrollment, allocation, follow-up, and analysis phases of the trial.



Biofeedback-Assisted Pelvic Floor Muscle Training

The patients in group 1 were given the necessary anatomical information at the beginning of the biofeedback-assisted PFMT and taught the exercises with one-to-one supervision by a urotherapist. The patients were asked to empty their bladders before the procedure. They were positioned in the supine position with their knees slightly flexed and their heads slightly raised. Surface EMG probes were placed in the three and nine o'clock positions on the perineum, an additional neutral probe was placed on the patella, and the patients were monitored. The patients were asked only to contract their pelvic floor muscles, not their abdominal muscles. They were also asked to follow the contraction and relaxation of their pelvic floor muscles on a monitor and to make sure that they were contracting the correct muscle group; thus, enabling active participation in the education program. By this means, the patients were taught how to identify their pelvic floor muscles and how to use their pelvic floor muscles selectively without using their abdominal muscles. The patients were enrolled in biofeedback-assisted PFMT sessions three times a week (a total of 60 minutes, with each session lasting an average of 20 minutes) for 12 weeks. Moreover, the patients were given an unsupervised standard PFMT program for home practice in which the intensity of 12-week exercise increased gradually and systematically (Supplementary Material – Appendix 1).

Pelvic Floor Muscle Training Alone

The patients in group 2 were given the necessary anatomical information at the beginning of the PFMT and taught the exercises with one-to-one supervision by a urotherapist. The patients were asked to empty their bladders before the procedure. They were asked to lie in the supine position, insert a finger into the vagina, and contract and relax the pelvic floor muscles (not their abdominal muscles), noticing the contraction around the finger. Furthermore, the patients were given an unsupervised standard PFMT program for home practice in which the intensity of 12-week exercise increased gradually and systematically (Supplementary Material – Appendix 1).

Uroflowmetry/EMG

All patients were evaluated with physiologically full bladders. Protocols were carried out by the same urologist using the Itri Pro system (Aymed Medical Technology, Istanbul, Turkey). EMG probes were placed in the three and nine o'clock positions in the perianal region, the neutral electrode was placed on the patella, and the patients were asked to urinate. During voluntary voiding, the urinary stream pattern and EMG activity were recorded. After the procedure, the PVR volume was measured by ultrasound. After the treatment, the protocol was repeated for both groups (Figure-2).

Statistical Analysis

The summary statistics of the variables were presented as means and standard deviations. The normality of the parameters was assessed with the D'Agostino Pearson test. Continuous variables in paired groups were compared using the paired t--test, whereas continuous variables belonging to different groups were compared using the Student's t-test. A two-tailed p-value of <0.05 was accepted as statistically significant. All statistical evaluations were performed using the R statistical software package (R Studio, Vienna, Austria).

RESULTS

A diagnosis of DV was made in 9.8% of women who presented to the outpatient clinic with LUTS. The mean age of the patients in group 1 was 46.5 ± 9.9 years, and their body mass indexes were calculated as 24.8 ± 2.2 kg/m^2. The mean age of the patients in group 2 was 43.1 ± 7.2 years, and their body mass indexes were calculated as 24.5 ± 2.2 kg/m^2. Before treatment, there was no significant difference between patients in group 1 and group 2 in terms of age ($p = 0.708$), body mass index ($p = 0.896$), 24-hour frequency, average voided volume, Q_{max}, Q_{ave}, PVR, average UDI-6 symptom score, and EMG activity during voluntary voiding (Table-1).

In the patients in group 1, there was no significant difference in the average voided volume and EMG activity during voluntary voiding before and after biofeedback-assisted PFMT, whereas Q_{max},

Figure 2 - Electromyography + Uroflowmetry image of the same patient (a) before treatment and (b) at the end of treatment sessions.

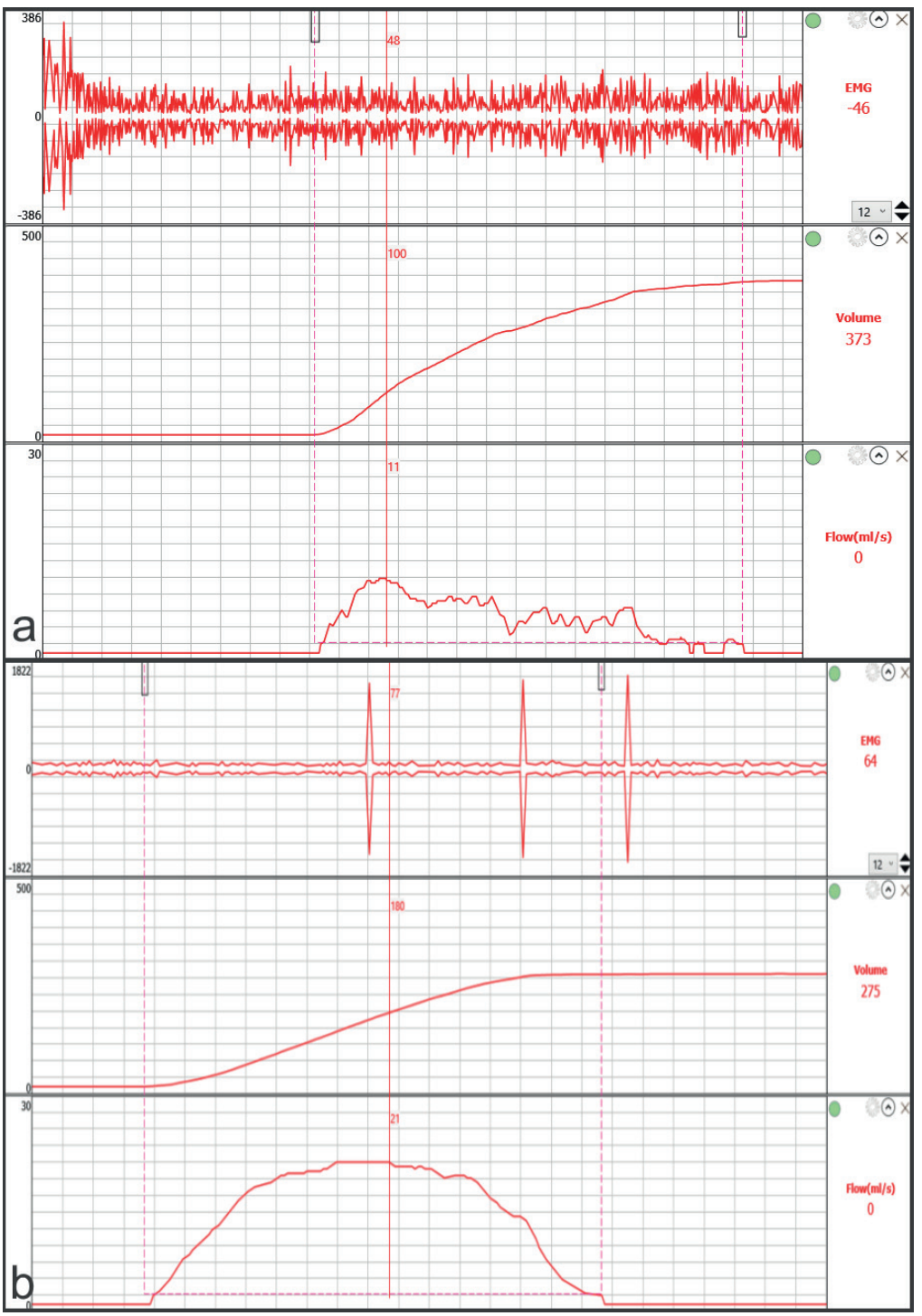


Table 1 - Comparison of groups with each other before treatment.

	Group 1 (n=34)	Group 2 (n=34)	p
Age, years (Mean ± SD)	46.5 ± 9.9	43.1 ± 7.2	0.708†
BMI, kg/m^2 (Mean ± SD)	24.8 ± 2.2	24.5 ± 2.2	0.896†
24-hour frequency (Mean ± SD)	11.2 ± 2.1	11.2 ± 2.0	0.830
Average voided volume, mL (Mean ± SD)	252.2 ± 81.7	261.4 ± 94.4	0.668
Q_{max}, mL/s, (Mean ± SD)	11.0 ± 2.7	11.1 ± 2.6	0.964
Q_{ave}, mL/s (Mean ± SD)	6.0 ± 1.1	6.0 ± 1.1	0.918
PVR, mL (Mean ± SD)	83.2 ± 25.4	82.7 ± 24.8	0.942
UDI-6 score (Median)	13.5	13.5	0.995
EMG activity, n (%)	34 (100)	34 (100)	1††

BMI = Body mass index; **Q_{max}**:maximum urine flow rate; **Q_{ave}** = average urine flow rate; **PVR** = Post-void residual urine volume; **UDI-6** = Urogenital Distress Inventory; **EMG** = electromyography

†Kruskal Wallis †† Intergroup comparison was performed using the Chi-square test

Q_{ave}, PVR, and UDI-6 symptom scores were significantly different. In the patients in group 2, there was no significant difference in the average voided volume and EMG activity during voluntary voiding before and after PFMT, whereas Q_{max}, Q_{ave}, PVR, and the average UDI-6 symptom scores were significantly different (Table-2).

At the end of treatment sessions, there was no significant difference between group 1 and group 2 in the 24-hour frequency and the average voided volume. The Q_{max} and Q_{ave} values of the patients in group 1 were significantly higher than those in group 2 (p = 0.026 and p = 0.043, respectively), and the PVR in the patients in group 1 was significantly lower compared to the patients in group 2 (p = 0.023). Furthermore, the average UDI-6 symptom scores of the patients in group 1 were significantly lower than those in group 2 (p = 0.034). During voluntary voiding, EMG activity continued in 64.7% of the patients in group 2, while this proportion was 41.2% in group 1 (p = 0.009) (Table-3).

DISCUSSION

The majority of DV studies have been conducted in the pediatric population, and the number of studies on women with DV is limited (14). Carlson et al. examined 134 patients who presented with LUTS using video-urodynamics and detected DV in 12% of the patients (15). Furthermore, Nitti et al. found DV to be the cause in 25 (33%) of 76 patients diagnosed with BOO by video-urodynamics (16). We also diagnosed DV in 9.8% of the women who presented to the outpatient clinic with LUTS. These findings show that a significant proportion of the women who present with LUTS have DV. However, in women, DV is likely to be underestimated, and this could lead to the diagnosis of DV being overlooked, thereby causing significant deterioration in the quality of life of women with DV.

It is difficult to determine whether voiding dysfunction is caused by BOO or DU only by looking at the symptoms (17). Therefore, urodynamics is required; however, there is no consensus on urodynamic parameters that provide the most accurate diagnosis of BOO in women. Chassagne et al. reported that it would be reasonable to diagnose BOO in women using the pressure-flow study ($Q_{max} \leq 15$ mL/s and pdet.$Q_{max} > 20$ cmH_2O with 74.3% sensitivity and 91.1% specificity) (18). Nitti et al. suggested that BOO in women should be diagnosed radiologically with

Table 2 - Intra-Group comparisons of voiding parameters before and after treatment.

	Group 1 (n=34)			Group 2 (n=34)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
24-hour frequency (Mean ± SD)	11.2 ± 2.1	7.7 ± 2.9	**<0.001**	11.2 ± 2.0	9.0 ± 3.1	**0.008**
Average voided volume, mL (Mean ± SD)	252.2 ± 81.7	261.7 ± 77.5	0.622	261.4 ± 94.4	258.0 ± 82.0	0.815
Q_{max}, mL/s, (Mean ± SD)	11.0 ± 2.7	14.8 ± 2.6	**0.001**	11.1 ± 2.6	12.8 ± 2.9	**0.005**
Q_{ave}, mL/s (Mean ± SD)	6.0 ± 1.1	8.0 ± 1.0	**0.001**	6.0 ± 1.1	6.7 ± 1.1	**0.007**
PVR, mL (Mean ± SD)	83.2 ± 25.4	54.7 ± 31.5	**<0.001**	82.7 ± 24.8	65.7 ± 24.1	**0.005**
UDI-6 score (Median)	13.5	9	**<0.001**	13.5	12	**0.002**
EMG activity, n (%)	34 (100)	14 (41.2)	0.391†	34 (100)	22 (64.7)	0.122†

Q_{max} = maximum urine flow rate; **Q_{ave}** = average urine flow rate; **PVR** = Post-void residual urine volume; **UDI-6** = Urogenital Distress Inventory; **EMG** = electromyography
† Intergroup comparison was performed using the Chi-square test

Table 3 - Inter-Group comparison of voiding parameters after treatment.

	Group 1 (n=34)	Group 2 (n=34)	p
24-hour frequency (Mean ± SD)	7.7 ± 2.9	9.0 ± 3.1	0.078
Average voided volume, mL (Mean ± SD)	261.7 ± 77.5	258.0 ± 82.0	0.850
Q_{max}, mL/s, (Mean ± SD)	14.8 ± 2.6	12.8 ± 2.9	**0.026**
Q_{ave}, mL/s (Mean ± SD)	8.0 ± 1.0	6.7 ± 1.1	**0.043**
PVR, mL (Mean ± SD)	54.7 ± 31.5	65.7 ± 24.1	**0.023**
UDI-6 score (Median)	9	12	**0.034**
EMG activity, n (%)	14 (41.2)	22 (64.7)	**0.009†**

Q_{max} = maximum urine flow rate; **Q_{ave}** = average urine flow rate; **PVR** = Post-void residual urine volume; **UDI-6** = Urogenital Distress Inventory; **EMG** = electromyography
† Intergroup comparison was performed using the Chi-square test

video-urodynamics. They determined Q_{max} as >15 mL/s in 11.8% and pdet.Q_{max} as <20 cmH_2O in 10.5% of the patients with an obstruction in the radiologic examination, and suggested that pressure-flow studies alone may fail to diagnose obstruction (16). Blaivas and Groutz defined a nomogram for the diagnosis of BOO in women by combining uroflowmetry, pressure-flow study, and voiding cystourethrography (19).

The two most useful screening tests for detecting voiding difficulties, or abnormally slow or incomplete voiding are uroflowmetry and PVR

measurement. Constantini et al. found that uroflowmetry had a high specificity (>70%) and negative predictive value (>79%) for the diagnosis of voiding dysfunction and argued that it was beneficial as the first diagnostic test to exclude voiding difficulty (20). These two tests are both indicative; however, they are not sufficient for the diagnosis of DV and should be combined with EMG (5, 21). The International Children's Continence Society provided a consensus document on the diagnosis of DV by uroflowmetry with EMG or video--urodynamics and declared that the literature on the necessity of invasive studies such as voiding cystourethrography and full urodynamic studies to diagnose DV in children is limited, and there has been a trend toward relying on less invasive studies in recent years (22, 23).

In this study, we evaluated women presenting with LUTS first with uroflowmetry and PVR. We diagnosed voiding dysfunction in patients with abnormal uroflowmetry and/or PVR findings and confirmed the diagnosis of DV by evaluating the EMG activity during voiding in neurologically normal women without anatomical obstruction. Although invasive urodynamics generally gives valuable information in women, its contribution to the diagnosis and management of BOO is not as clear as in men. Therefore, there may be no need to apply invasive urodynamics at first to patients who have not received any therapy yet and will be scheduled for a conservative non-invasive treatment without side effects, such as PFMT. The findings of this study also support our opinion. We believe that our diagnostic algorithm is the most practical, non-invasive, and cost-effective method.

The literature on DV treatment in women is limited. In a prospective randomized study conducted by Minardi et al., biofeedback-assisted PFMT was determined to improve the storage and emptying symptoms, objective urodynamic parameters, PVR, and the incidence of urinary tract infection significantly compared to the control group (24). In a prospective cohort study conducted by Chiang et al., biofeedback-assisted PFMT was effective in more than 80% of 31 women with DV, with significant improvements in clinical symptoms, QoL, and uroflowmetry parameters (25). To the best of our knowledge, this study is the first prospective randomized study comparing biofeedback-assisted PFMT and PFMT alone in women diagnosed with DV. We found that biofeedback-assisted PFMT was superior to PFMT alone in clinical symptoms evaluated with the UDI-6 score, uroflowmetry parameters, PVR, and EMG activity during voiding. This may be due to patients gaining pelvic floor muscle awareness more easily, thanks to biofeedback. Besides, the success of PFMT depends on patients correctly understanding the given tasks and their compatibility with the program. Biofeedback-assisted PFMT can minimize patient-related failures through sessions under the supervision of a urotherapist. Therefore, it would be a more rational approach to recommend biofeedback-assisted PFMT to women with DV.

Our study has some limitations. The fact that there is no consensus on the definitive diagnostic criteria of DV is a significant limitation of the study. Another important limitation is the fact that the patients did not perform invasive urodynamics or video-urodynamics. A clearer differential diagnosis between BOO and DU with invasive urodynamics or video-urodynamics and a comparison of pre- and post-treatment pressure-flow data would have made the study more valuable. Other limitations are the small number of patients and the shortness of the follow-up period.

CONCLUSION

PFMT is a preferable treatment method due to its efficiency in DV management, easy applicability, and absence of side effects. Biofeedback-assisted PFMT is more effective than PFMT alone in improving clinical symptoms, uroflowmetry parameters, and EMG activity during voiding. Large comprehensive prospective randomized studies on this subject are necessary.

ABBREVIATIONS

BOO = bladder outlet obstruction
DU = detrusor underactivity
DV = dysfunctional voiding

LUTS = lower urinary tract symptoms
PFMT = pelvic floor muscle training
PVR = post-void residual urine volume
Q_{max} = maximum urine flow rate
EMG= electromyography
Q_{ave} = average urine flow rate
UDI-6 = the validated Turkish Urogenital Distress Inventory

COMPLIANCE WITH ETHICAL STANDARDS

Prior to this single-center prospective study, approval was obtained from the Ethics Committee of Atatürk University Faculty of Medicine (approval number: B.30.2.ATA.0.01.00 / 999). This study was conducted as per the latest version of the "Helsinki Declaration" and the "Guidelines for Good Clinical Practice". Informed consent was obtained from all patients who participated in the study.

CONFLICT OF INTEREST

None declared.

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APPENDIX 1

Supplementary Material

12 week-Pelvic Floor Muscle Training Protocol

Faucet exercise (F): Repeatedly and strongly contract and release your pelvic floor (like closing-opening a faucet)

Elevator exercise (E): Slowly contract the pelvic floor by counting 5- hold by counting 5- release by counting 5 (like the elevator ascending by counting 5- holding at the top floor by counting 5- descending by counting 5)

Weeks	Exercise intensity per set	Number of sets per day	Total exercise intensity per day
1st and 2nd week	10 F + 10 E	5 sets	50 F + 50 E
3rd and 4th week	12 F + 12 E	5 sets	60 F + 60 E
5th and 6th week	15 F + 15 E	5 sets	75 F + 75 E
7th and 8th week	20 F + 20 E	5 sets	100 F + 100 E
9th and 10th week	25 F + 25 E	5 sets	125 F + 125 E
11th and 12th week	30 F + 30 E	5 sets	150 F + 150 E

P.S = One set was skipped on the days when biofeedback was applied.

ORIGINAL ARTICLE

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Interaction between the impact of the Coronavirus disease 2019 pandemic and demographic characteristics on sexual/erectile dysfunction in Latin America: cross-sectional study

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ABSTRACT

Aim: Our objective was to investigate whether there is an interaction between the COVID-19 pandemic, demographic characteristics and erectile/sexual (E/S) function in individuals from Latin America.

Materials and Methods: Cross-sectional study which included Latin American individuals over 18 years old, recruited through social media and interviewed between July and August 2020 by online surveys (Google Forms) in Portuguese and Spanish languages. The E/S function was evaluated through the following questionnaires: Simplified International Index of Erectile Function (IIEF-5) and Female Sexual Function Index (FSFI); while post-traumatic stress disorder (PTSD) triggered by the COVID-19 pandemic was assessed through the Impact of Event Scale Revised (IES-R). The data was analyzed by T Student, bivariate and multivariate logistic regression, with significance determined by the Wald test ($p<0.05$), using the R software v4.0.

Results: Out of the 2016 individuals that responded to the survey, 1986 were included and 743 of them presented E/S dysfunction. PTSD occurrence was greater among people with E/S dysfunction when compared to those without E/S dysfunction, in the total score (males: IES-R=26.54[±19.17] and females: IES-R=35.92[±19.25]) and also in the three domains. It was found that those who do not live with a partner were 74% more likely to have E/S dysfunction, but living with a partner during the pandemic had a greater impact on E/S function.

Conclusion: A negative interaction between the impact of the COVID-19 pandemic and erectile/sexual function of the Latin American population was observed, with greater implications among the individuals who live with their partners.

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INTRODUCTION

In March 2020, the Coronavirus disease 2019 (COVID-19) pandemic was decreed, starting in Wuhan, China and rapidly affected the whole world, due to its propagation by aerosols and/or droplets (1). Then, governments have adopted social distancing with the intention of diminishing the propagation rate of the disease and raising awareness of its citizens through new health, hygiene, behavioral habits and isolation (2).

According to Schiavi et al. (2020) (2), the COVID-19 pandemic represents a risk factor over individuals mental health. A stressing, traumatic, sudden and extremely unexpected event like the COVID-19 pandemic can cause post-traumatic stress disorder (PTSD) (3), which affects essential characteristics of sexual function, like the sensation of safety, self-efficacy and the capability of connecting with others (4).

The Impact of Event Scale Revised (IES-R) (5) questionnaire has been used to assess the PTSD triggered by COVID-19 pandemic (6). According to Letica-Crepulja et al. (2019) (7), PTSD can be used as a predictor parameter for sexual dysfunction. Because of that we hypothesize that COVID-19 pandemic can have a negative impact on sexual function.

Sexual function is a relevant component that contributes to individuals quality of life, and the negative correlation between psychological state and sexual function are well known (4), but little is known about the COVID-19 pandemic impact over sexual function in Latin American population, a region with peculiar sociocultural characteristics, not only because of its geographical proximity, which has cultural similarities (historical, linguistic, religious and political experiences) (8).

Considering that, the aim of our study was to investigate the interaction between the COVID-19 pandemic, demographic characteristics and erectile/sexual (E/S) function in Latin America.

MATERIALS AND METHODS

Study design, setting and participants

Cross-sectional study based on an anonymous web survey, through the Google Forms platform, provided in Portuguese and Spanish languages for the Latin American population (See supplementary Appendix-1).

The research was conducted from July to September 2020, proposed by the UroPhysiotherapy Laboratory researchers from the Post-graduate Program in Rehabilitation Science of the Federal University of Alfenas, after approval from the Institutional Review Board (IRB) of the university's ethics and research committee (IRB number 34056120.7.0000.5142, Approval number 4128647), following the ethical precepts regulated by Resolution n. 466/12 of the National Health Council and the Helsinki Declaration requirements.

The research was released to the public with an invitation to fill the Google Forms survey through social media (WhatsApp, Facebook, Instagram), UNIFAL-MG communication websites, local newspapers, national and international symposia; reaching for individuals over 18 years old, sexually active, and available to fill the survey through a cell phone, computer or tablet. The Informed Consent Form was made available in the same Google Forms page.

The sample was composed by volunteers who answered the questions, recruited by convenience. The exclusion criteria were individuals under 18 years old, those that were not considered Latin Americans, as well as those who did not consent to the use of their data.

The research followed the Good Clinical Practice Guidelines, adopting the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Measurement and quantitative variables

PTSD triggered by the COVID-19 pandemic: The isolation/social distancing measures during the COVID-19 pandemic were considered as triggering events to PTSD, which was investigated by the validated IES-R, asking the participants to consider the memories triggered by COVID-19 in the past seven days to answer the questionnaire. The IES-R is a self-applicable questionnaire originally developed in English language (5), translated and validated to Portuguese language by Santesso et al., (2012) (9) and to Spanish by Caamaño et al., (2011) (10). The scale is composed of 22 items distributed in three subscales (avoidance, intrusion

and hyperarousal domains), each question varies from zero to four (0-4) points, total score ranging from 0 to 88, meaning that a higher score implies greater impairment. Cut-off point: 24 points, classified in: ≥ 24: PTSD is a clinical concern - higher score means a higher degree of PTSD; ≥ 33: best cut-off point for a likely PTSD diagnosis; ≥ 37: extreme PTSD, with enough consequences to cause immune system suppression, even 10 years after the triggering event.

Sexological outcomes: The sexual/erectile function was investigated considering the past four weeks, compared with before the COVID-19 pandemic, using the following variables:

Female sexual function: Clinical condition associated with the sexual act, it was investigated by the validated Female Sexual Function Index (FSFI) (11), self-applicable translated questionnaires for both Portuguese (12) and Spanish (13) languages. The FSFI questionnaire analyzes sexual response, considering desire, arousal, lubrication, orgasm, satisfaction and pain. Total score is calculated by adding the six scores weighted by the respective factor of each domain, varying from two (worst sexual function) to 36 (best sexual function); Cut-off point: 26.55, classified as: without sexual dysfunction: ≥ 26.55; with sexual dysfunction: <26.55 (11, 14).

Male erectile function: Male sexual function, a man's clinical condition linked to the sexual act, was investigated by the Erectile Function domain (IIEF-5) (15) from the International Index of Erectile Function (IIEF) (16), with the purpose of measuring erectile function in a simple and direct way. IIEF was translated and validated in Portuguese language by Gonzales et al. 2013 (17) and Spanish by Zegarra et al. 2011 (18). IIEF-5 consists of five questions and the total score can vary from 5 to 25 points. A score lower than 22 is indicative of erectile dysfunction (15). Therefore, the following variables were considered: IIEF-5 total score: from five (05) (worst erectile function) to 25 (best erectile function); Cut-off point: 22, classified as: Without Erectile Dysfunction: ≥ 22; With Erectile Dysfunction: <22.

Sex life aspects

Presence and frequency of sexual activity were investigated and classified as: present (increased frequency; no change in frequency; decreased frequency); suspended or no sexual activity; as well as sexual complaint (never displayed; previously presented; currently without complaint; currently present); partner at home during breakout of COVID-19 pandemic (lives with or without partner) and personal impression of the pandemic impact over sex life (numerical analog scale from 0 to 5).

Demographic data: Gender (male, female); age (18-33 years; 34-77 years, based on sample median); partner cohabitation status (living with or without partner); educational level (less than 10 years of education; 10 or more years of education) and family income (up to 2 minimum wages, 3 or more minimum wages).

Bias

The study was performed anonymously, thus avoiding participants to be afraid or ashamed to answer questions of sexual nature. The researchers strived in divulgating the study within the Latin American population, encompassing most of Latin America countries and providing the questionnaire in Portuguese and Spanish.

Statistical Analysis

The binary categorical variables (demographic and sexual dysfunction) were presented in absolute and relative frequencies, while the continuous variables (IES-R scores) were presented in central tendency values (average) and dispersion (standard deviation).

The cut-off point of 33 years old was the median of the sample, in order to create equivalent groups. The comparison for the total score average, pandemic impact and the three domains, between males and females, with and without indicative report for sexual dysfunction was performed by Student's T test.

Bivariate logistic regression followed by a multivariate adjusted model (also adjusted for multicollinearity) were used. In all models, significance was analyzed by Wald test, considering $p<0.05$. All associations were evaluated by odds ratio (OR) values (confidence interval of 95%). The analysis were performed in the 4.0.0 version of the statistical software R (https://www.r-project.org/)

RESULTS

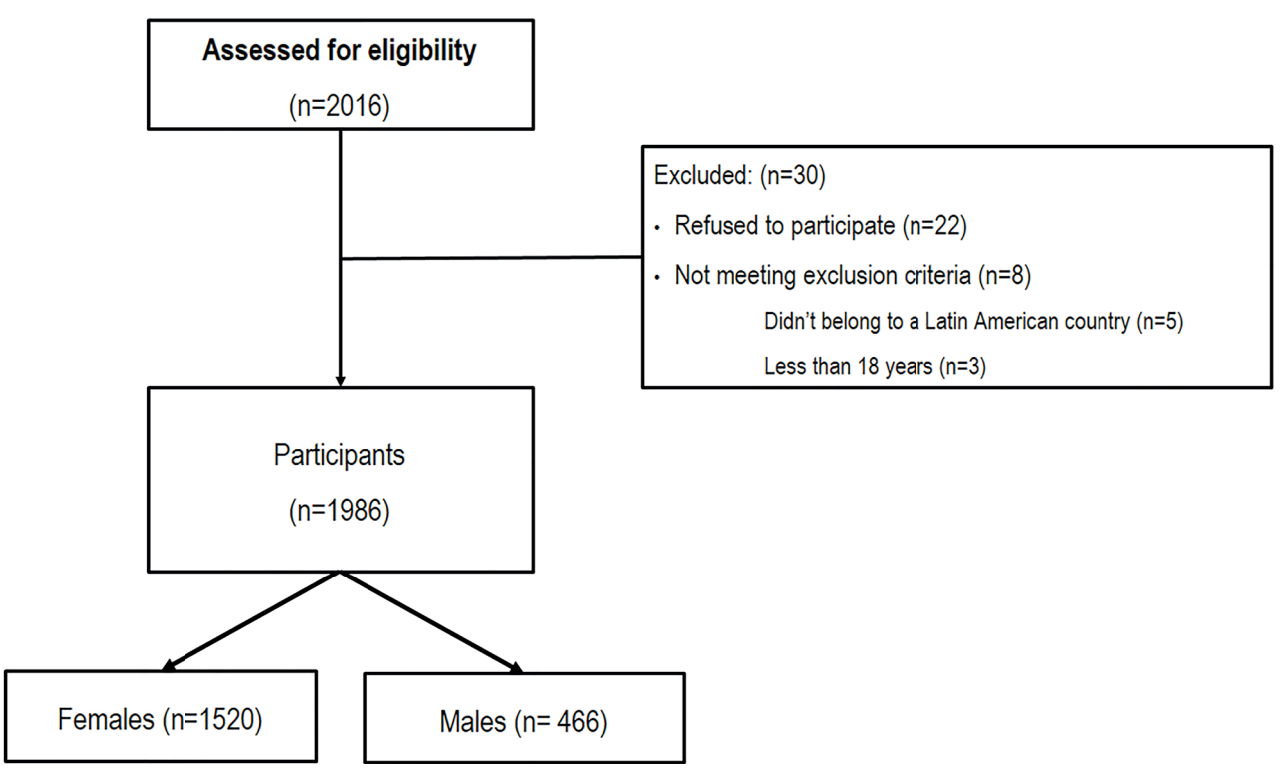
As shown in Figure-1, this study's questionnaires were answered by 2016 individuals, of whom 30 were excluded (22 refused to participate, five didn't belong to a Latin American country and three had less than 18 years), remaining 1986 participants (466 males, 1520 females) from 17 Latin American countries (Brazil, Chile, Colombia, Argentina, México, Costa Rica, El Salvador, Bolivia, Ecuador, Perú, Venezuela, Nicaragua, Panamá, Guatemala, Paraguay, Puerto Rico, Uruguay).

The impact of the COVID-19 pandemic measured with IES-R was 36.7(±19.66), considering 33 the best cut-off point for PTSD diagnosis. It was found in the FSFI and IIEF-5 questionnaires that 37.5% of the participants had sexual disfunction. Also, the participants classified their impression of the pandemic impact on sex life, in a numeric scale from 0 to 5, which resulted in 2.45 (±1.78) (Table-1).

Comparing individuals with and without E/S dysfunction we found that individuals with E/S dysfunction had a higher IES-R score: total score (male [p<0.001]: without erectile dysfunction (ED): 26.01 [±19.25], with ED: 36.5 [±19.10]; female [p 0.001]: without sexual dysfunction (SD): 36.55 [±19.10], with SD: 41.28 [±18.99]); intrusion domain (male: p<0.001; female: p=0.011); avoidance domain (male: p<0.001; female: p=0.003) and hyperarousal domains (male: p<0.001; female: p<0.001) in both genders (Table-2).

In the association between demographic characteristics and E/S dysfunction evaluated by an unadjusted model we didn't observe an association between gender (p<0.000 [CI 0.79-1.22]), however we did observe between the age group of 18-33 years old (p<0.000 [CI 0.69-1.00], OR 0.83), marital status of living without a partner (p<0.000 [CI 1.45-2.09], OR 1.74), family income of up to 2

Figure 1 - Flow diagram of the study.



This diagram reports the numbers of participants of the study, including potentially eligible, examined for eligibility, confirmed eligible, included in the study.

Table 1 - Demographic characteristics, impact of event (IIES-R) and sexological outcomes during COVID-19 pandemic.

Variables	Participants
Gender f(%)	
Male	466 (23.4)
Female	1520 (76.6)
Age range* f(%)	
18 - 33 years old	1050 (52.9)
34 - 77 years old	933 (47.1)
Partner cohabitation status f(%)	
Living with partner	1002 (50.4)
Living without partner	984 (49.6)
Educational level f(%)	
10 or more years of study	1636 (82.3)
Less than 10 years of study	350 (17.7)
Family income f(%)	
Three or more minimum wages	1475 (74.2)
Until 2 minimum wages	511 (25.8)
Pandemic Impact** M(±SD)	
Total score	36.37 (±19.66)
Intrusion	12.61 (±7.86)
Avoidance	13.48 (±7.53)
Hyperarousal	10.27 (±6.25)
Sexual Function*** f(%)	
Without sexual dysfunction	1242 (62.5)
With sexual dysfunction	743 (37.5)

Impression of the pandemic impact on sexual life M(±SD)	2.45 (± 1.78)
Sexual Activity f(%)	
Had not sexual activity and continued not to	124 (10.7)
Decreased in frequency	426 (36.8)
Suspended	142 (12.2)
Without change	341 (29.2)
Increased	122 (11.1)
Sexual Complaint f(%)	
Never presented	533 (47.8)
I had earlier, but currently I have no complaints	322 (27)
I currently have a sexual complaint	280 (24.4)

The data are presented in absolute (f) and percent (%) frequencies as well as mean (M), standard deviation (SD).
*The cut-off point of 33 years old (median of the sample, in order to create equivalent groups.
**The Event Impact Scale - Revised (IES-R) questionnaire was used to investigate the COVID-19 pandemic impact, using the total score and the Intrusion, Avoidance, and Hyperarousal domains(9,10)
*** Sexual function was investigated using the Female Sexual Function Index (FSFI: ≤ 26.55) (14) and International Simplified Erectile Function Index (IIEF-5: ≤ 22) (15)

Table 2 - Relationship between the IES-R comparing individuals with and without erectile/sexual dysfunction. Analysis stratified by gender.

IES-R	Male (n=466)			Female (n=1520)		
	Without ED* (n=291)	With ED* (n=175)	p-value	Without SD* (n=952)	With SD* (n=568)	p-value
Total Score	26.01 (±19.25)	36.50 (±19.10)	<0.001	36.55 (±19.10)	41.28 (±18.99)	0.001
Intrusion	9.94 (±7.54)	13.88 (±7.13)	<0.001	13.74 (±7.53)	14.71 (±7.10)	0.011
Avoidance	8.88 (±7.46)	12.82 (±7.71)	<0.001	12.58 (±7.65)	14.50 (±7.80)	0.003
Hyperarousal	7.17 (±6.04)	9.80 (±5.98)	<0.001	10.23 (±6.03)	12.06 (±6.15)	<0.001

The Table shows the Impact of Event Scale Revised (IES-R) total score and the Intrusion, Avoidance and Hyperarousal domains (9, 10)
*** Sexual function was investigated using the Female Sexual Function Index (FSFI: ≤ 26.55) (14) and International Simplified Erectile Function Index (IIEF-5: ≤22) (15)
Test T Student (p=0.05)
ED = Erectile dysfunction; SD = Sexual dysfunction

minimum wages (p<0.011 [CI 1.05-1.59], OR 1.30) and the E/S function. On the other hand in the adjusted model, only marital status maintained the association (p<0.000 [CI 1.42-2.13]), as those who do not live with their partner are 74% more likely to have E/S dysfunction (OR 1.74).

In the association between the IES-R and IIEF-5 or FSFI, we found a positive association in the IES-R total score (p<0.00 [CI 1.01-1.02], OR 1.02), intrusion domain (p<0.00 [CI 1.01-

1.04], OR 1.02), avoidance domain (p<0.00 [CI 1.02-1.05], OR 1.03) and hyperarousal domain (p<0.00 [CI 1.03-1.06], OR=1.05). It is observed that with each score taken from the IES-R questionnaire, the chance of sexual dysfunction increases (OR>1) or decreases (OR<1).

In the interaction model between IES-R and the significant demographic variable (marital status) for the E/S function, we found that those who live with a partner had greater impact of the pandemic on E/S function in the total score and the avoidance and hyperstimulation domains, but not in the intrusion domain (Table-3).

DISCUSSION

This study demonstrated the relation between the COVID-19 pandemic and PTSD, with a negative interaction between IES-R and erectile/sexual function on the Latin American population. PTSD was a predictor of sexual dysfunction like in the Letica-Crepulja 2019 study (7). During the COVID-19 pandemic, Fang et al. (2020) also used the IES-R and IIEF-5 questionnaires to evaluate male healthcare professionals. Their findings corroborate with our study by the negative interaction found between them (6).

In addition, among the demographic factors, the participants marital status stood out, demonstrating that individuals who live without partner presented higher prevalence of erectile/sexual dysfunction; while individuals who are living with partner presented higher pandemic impact over erectile/sexual function. We hypothesize that during the COVID-19 pandemic people who live without a partner have greater difficulties in engaging in sexual intercourse, but those who live with their partners may have more impact because they have to stay together at all times, affecting their relationship and, consequently, their sexual lives.

Table 3 - Interaction between the Impact of Event Scale Revised (IES-R) and the significant demographic characteristics for the erectile/sexual function.

Variables	No interaction OR (CI 95%)	Principal effects OR (CI 95%)	Interaction term OR (CI 95%)
IES-R total score			
Marital status	1.62	2.70	0.98
Without partner	(1.34 – 1.95)	(1.80 – 4.07)	(0.97 – 0.99)
IES-R total score	1.02 (1.01 – 1.02)	1.02 (1.01 – 1.03)	---
Intrusion domain			
Marital status	1.68 (1.39 – 2.02)	2.30 (1.56 – 3.41)	0.97 (0.95 – 1.01)
Without partner			
Intrusion domain	1.02 (1.01 – 1.03)	1.03 (1.02 – 1.05)	---
Avoiding domain			
Marital status	1.63	2.43	0.97
Without partner	(1.35 – 1.97)	(1.69 –3.50)	(0.94 – 0.99)
Avoiding domain	1.03 (1.02 – 1.04)	1.05 (1.03 – 1.07)	---
Hyperarousal domain			
Marital status	1.59 (1.32 – 1.92)	2.79 (1.92 – 4.07)	0.94 (0.92 –0.97)
Without partner			
Hyperarousal domain	1.04 (1.03 – 1.06)	1.07 (1.05 – 1.10)	---

Verified by a Multivariate Logistic Regression model

IES-R = Impact of Event Scale – Revised; **OD** = odds ratio; **CI** = Confidence Interval

Additionally, it can be harder to engage in moments of sexual activity with their families staying at home all day long.

Schiavi et al. (2020) in their study with females during the COVID-19 pandemic found a lower total FSFI score among women with higher level of education, but in this study no relation with educational level was identified (2).

During the pandemic, Mollaioli et al. interviewed 2,608 sexually active individuals, and they found a prevalence of 18.5% for erectile dysfunction in males and 28.8% for sexual dysfunction in females (19). In our study, it was found in 37.55% of males and 37.37% of females. There was a bigger participation of females, but no differences were found in the E/S function ($p<0.000$ [CI 0.79-1.22]).

This study did not find any relation between age and the presence of sexual dysfunction, which differs from the studies carried out before the COVID-19 pandemic, which found a strong influence of age over erectile dysfunction (20).

FSFI was also used in Schiavi et al. and Yuksel. et al. studies in the COVID-19 pandemic in females. Both observed worse scores compared to data prior to the COVID-19 pandemic (2, 21).

Pennanen-Iire et al. (2020) reported that the stress triggered by the COVID-19 pandemic for long cohabiting times could compromise the couple's sex life, including an increase in anxiety and fear of failing in sexual performance (22). Associated with this, we must consider the limitation of individual space and the difficulty to find moments of intimacy while the family stays at home during the whole time (23).

To our knowledge, this is the first study about sexual function during the COVID-19 pandemic in Latin America. The study was performed online, which facilitated the access to individuals from 17 out of the 20 Latin American countries, allowing for reflection about the reality experienced by the population during the COVID-19 pandemic.

This study compared the male and female population using specific instruments to each population and considering aspects related to the male and female sexual function, such as penetrative vaginal sex and erection, respectively; which the researchers considered a limitation of the used instruments.

Therefore, we emphasize the importance of developing, in future studies, questionnaires that are more inclusive in relation to non-penetrative sex, masturbation and non-heterosexual orientations. In the same way, to date there are no validated questionnaires for the evaluation of general sexual function in males.

Clinical guidelines during the COVID-19 pandemic are being consolidated for Latin America professionals (24) and we believe that this study can have clinical implications that contribute to the knowledge about the COVID-19 pandemic impact over erectile/sexual function of Latin Americans, allowing for future intervention proposals that consider sexual health care in post-pandemic times. A study by Gomes et al. 2021 shows that more quality research and apps are necessary before the widespread use of mobile health technologies (25).

The COVID-19 pandemic and its implications, such as quarantine, labor or wage losses, close familiar interaction with all inhabitants on the domestic ambient, privation of liberties both at home and on the outside, privation of routine activities, fear of the unknown and the repercussions of the disease, limitation of the routine consultations for physicians and other health professionals, double workday for some and idleness for others, among many other aspects may have contributed to the impact on sexual function, drawing a necessary and special attention for the years to come.

More attention is needed for the Latin American population, especially non-heterosexual individuals. Future studies should seek for alternatives in remote solutions and treatments for people whose sexual function was affected by the COVID-19 pandemic and apply it in these times, and after the pandemic ends.

Our study presents limitations that are inherent to online surveys, such as containing information that is not completely understood by the respondents, demanding for internet access and also proficiency in technological resources. Moreover, the propagation of the survey by the researchers' and collaborators' social media may have been biased, since members of other social media may have not been reached. Similarly, since the invitations are open to contact networks, normally those who are more interested and participative tend to answer readily. On the other side, the access through social media can favor larger sample size for online surveys.

It is important to consider that the individual's state prior to the pandemic was not consulted. Furthermore, quarantine conditions may have differed among countries, which can influence the interpretation of results.

CONCLUSIONS

An interaction between the COVID-19 pandemic impact and erectile/sexual function was found. Individuals that do not live with their partners presented higher prevalence of sexual dysfunction. However, the pandemic triggered greater impact over the erectile/sexual function of people who live with a partner.

ABBREVIATIONS

COVID-19 = Coronavirus disease 2019
E/S = Erectile/sexual
IIEF-5 = Simplified International Index of Erectile Function
FSFI = Female Sexual Function Index
PTSD = Post-traumatic stress disorder
IES-R = Impact of Event Scale Revised

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CONFLICT OF INTEREST

None declared.

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APPENDIX – 1

Impact of the Covid-19 pandemic on people's sexual function

Impact of the Covid-19 pandemic on people's sexual function

Hello! Welcome!

We are researchers of the Post Graduate Program in Rehabilitation Sciences at the Federal University of Alfenas (PPGCR/UNIFAL-MG) and we would like to invite you to participate in a survey with the aim of assessing the impact of the pandemic by covid -19 about your sexual function. Your participation is free and voluntary and YOUR INFORMATION WILL BE KEPT IN COMPLETE PRIVACY. Please note that you do not need to identify yourself, however, if you want to receive more information on the subject you can leave a contact email.

Questions can be sent to the e-mail: luciana.michelutti@unifal-mg.edu.br (gynecologist - group researcher).
Thank you for your contribution!

* Required

Informed Consent

Informed Consent Form

FEDERAL UNIVERSITY OF ALFENAS - UNIFAL / MG

MOTRICITY SCIENCES INSTITUTE

GRADUATE PROGRAM IN REHABILITATION SCIENCES

Introduction and objectives: You are being invited to participate in a survey that aims to assess the impact of the covid-19 pandemic on your sexual function. Your participation is voluntary and free, that is, at any time you can withdraw from participation or withdraw your consent, without any penalty. Your data will be kept completely confidential and your answers will be used only for research through reports, bibliographic materials, articles and scientific events.

Study Procedure: During this survey you will answer some questions about your personal data, your health and sexual function through simple questions and standardized questionnaires, using approximately 15 minutes to answer.

Benefits: Your participation is voluntary and free. As a direct benefit you will receive general guidance on sexual function. In addition, you will be able to receive the answer to your questionnaire upon completion. If you want, check the option "Send me a copy of my answers". This work will help the scientific community to better understand if the pandemic could influence the sexual function of individuals and then contribute to future studies and strategies for its promotion and recovery.

Risks and discomforts: There are no direct risks, however, when answering the questionnaire, you may have memories that are not necessarily pleasant related to your sex life, which could bring some embarrassment. To minimize this effect, if it occurs, you will be able to communicate with the researchers responsible for receiving guidance through the email: luciana.michelutti@unifal-mg.edu.br

Privacy and security: Your privacy will be guaranteed by the researchers, that is, your data will be kept confidential and your personal information is not requested. Please note that in order to safeguard your privacy as much as possible, we do not ask for a name or other information that identifies you, with the exception of your email and year of birth. All data will be used anonymously when the results are released. You should also provide greater privacy by answering this questionnaire in a place and situation where you feel comfortable and safe.

We thank you in advance for your contribution and participation! You can request your copy at the end of the questionnaires.

1. Do you declare to have read and agreed to the above consent, agreeing to voluntarily participate in this research? *

Mark only one oval.

- ◯ Yes, I agree.
- ◯ No, thank you.

To start we need some data and information

2. Date of birth *

3. City/Country *

_____

4. Marital status *

Mark only one oval.

- ◯ Single
- ◯ Married
- ◯ Divorced
- ◯ Widower

5. Study time (years of study) *

Mark only one oval.

- ◯ Study or studied up to 5 years
- ◯ Study or studied up to 9 years
- ◯ Study or studied up to 13 years
- ◯ Study or studied more than 14 years

6. Family income? *

Mark only one oval.

- ◯ 1 to 2 minimum wages
- ◯ 3 to 4 minimum wages
- ◯ + 4 minimum wages

7. Associated diseases *

Check all that apply.

- [ ] Chronic obstructive disease (COPD)
- [ ] Diabetes
- [ ] Hypertension
- [ ] Cancer
- [ ] Chronic cough
- [ ] Autoimmune disease
- [ ] I don't have comorbidities

Other: [ ] _____

8. Medicines in use

Please skip this question if you do not use medications

_____

_____

_____

_____

_____

9. Do you practice physical activity? *

Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ Suspended due to quarantine

Skip to question 10

Pandemic Impact Scale by COVID-19

We list below the difficulties that people sometimes have after going through stressful situations. This questionnaire was adapted from the Event Impact Scale - Revised (IES-R).

Regarding the memories of COVID-19, please read each item below and then check the option that best corresponds to your stress level, in the last SEVEN DAYS, considering:

0 - Not at all
1 - A little
2 - Moderately
3 - Very
4 - Extremely

YOUR INFORMATION WILL BE KEPT SECRETLY.

10. 1. Any reminder brought back feelings about it *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

11. 2. I had trouble staying asleep *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

12. 3. Other things kept making me think about it. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

13. 4. I felt irritable and angry *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

14. 5. I avoided letting myself get upset when I thought about it or was reminded of it. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

15. 6. I thought about it when I didn't mean to. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

16. 7. I felt as if it hadn't happened or wasn't real. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

17. 8. I stayed away from reminders of it *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

18. 9. Pictures about it popped into my mind. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

19. 10. I was jumpy and easily startled. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

20. 11. Think about COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

21. 12. Tell me that I have a lot of feelings without resolving related to COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

22. 13. My feelings about COVID-19 were asleep *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

23. 14. Find me as if you were feeling the pandemic function by COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

24. 15. I had trouble falling asleep *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

25. 16. I was invaded by waves of strong feelings related to what happened by COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

26. 17. I tried to get everything of the COVID-19 out of my head *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

27. 18. I had concentration problems *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

28. 19. Things that reminded me of COVID-19 caused physiological reactions such as perspiration, difficulty breathing, nausea or tachycardia. *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

29. 20. I dreamed of things related to COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

30. 21. I felt vigilant and on guard *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

31. 22. I tried not to talk about COVID-19 *

Mark only one oval.

	0	1	2	3	4	
Not at all	◯	◯	◯	◯	◯	Extremely

Skip to question 32

Professional performance

32. Currently, what is your professional area? *

Mark only one oval.

◯ I work as a health professional *Skip to question 33*

◯ I work in other areas *Skip to question 40*

To health professionals

33. What is your profession? *

_____

34. What is your situation at the moment? *

Mark only one oval.

- ◯ Working
- ◯ Unemployed
- ◯ Working at home
- ◯ Maintaining activities in call centers
- ◯ Serving only urgent cases
- ◯ Other: _____

35. I'm working on the front line of Covid-19? *

Mark only one oval.

- ◯ Yes
- ◯ No

36. If so, and you were currently removed, why?

Only for those who answered "yes" in the previous question

_____

37. Are you currently with a partner? *

Mark only one oval.

- ◯ Yes
- ◯ No

38. Regarding sexual activity during the pandemic period. *

Mark only one oval.

- ◯ I maintain my sexual activity normally
- ◯ Decreases sexual frequency
- ◯ Increased sexual frequency
- ◯ I suspended my sexual activity
- ◯ I did not and still do not have sexual activity

39. Do you have any sexual complains? *

Mark only one oval.

- ◯ Never presented
- ◯ I have already presented at some point in my life and I have no more
- ◯ I currently present

Skip to question 53

Evaluation sheet

40. Profession

_____

41. What is your situation right now? *

Mark only one oval.

- ◯ unemployed
- ◯ Employed
- ◯ Other: _____

42. How is your work situation currently? *

Mark only one oval.

- ◯ Working from home
- ◯ Working normally
- ◯ Away
- ◯ Other: _____

43. If you were away, why?

Only for those who answered "away" in the previous question

_____

44. Are you currently with a partner? *

Mark only one oval.

- ◯ Yes
- ◯ No

45. Regarding sexual activity during the pandemic period. *

Mark only one oval.

- ◯ I maintain my sexual activity normally
- ◯ Decreased sexual frequency
- ◯ Increased sexual frequency
- ◯ I suspended my sexual activity
- ◯ I did not and still do not have sexual activity

46. Do you smoke? *

Mark only one oval.

- Yes
- No

47. What is your weight? (approximately) *

_____

48. What's your height? (approximately) *

_____

49. How much time in total do you spend exercising for a week (7 days). (Respond approximately in hours).

_____

50. How long do you stay seated during a normal day of the week? (Respond approximately in hours)

_____

51. Sexual activity in the last 4 months? *

Mark only one oval.

- Present
- Absent

52. Do you have any sexual complaints? *

Mark only one oval.

- ◯ Never presented
- ◯ I have already presented at some point in my life and I have no more
- ◯ I currently present

Skip to question 53

Sexual health assessment

We need to know what gender is stated on your birth certificate to direct you to the questionnaire

53. Sex declared on your birth certificate *

Mark only one oval.

- ◯ Feminine *Skip to question 54*
- ◯ Male *Skip to question 73*

Female Sexual Function Index (FSFI)

These questions are about your sexual feelings and responses over the past FOUR WEEKS. Please answer honestly. Your answers will be kept completely confidential.

The following explanations are applied to answer the questionnaire:
Sexual activity: may include caresses, preliminary sexual stimulation, masturbation and vaginal intercourse.
Sexual intercourse is defined as the penetration (entry) of the penis into the vagina.
Sexual stimulation: includes preliminary sexual stimulation with the partner, auto eroticism (masturbation) or sexual fantasy.

FOR EACH ITEM, SCORE ONLY AN ANSWER Sexual desire or interest is a feeling that encompasses the desire to have a sexual experience, the receptivity to the partner's sexual initiatives, and thoughts or fantasies about the sexual act.

54. 1. How often did you feel sexual desire or interest? *

Mark only one oval.

- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

55. 2. How would you rate your level (degree) of sexual desire or interest? *

Mark only one oval.

- ◯ Very high
- ◯ High
- ◯ Moderate
- ◯ Low
- ◯ Very low or none at all

Sexual arousal is a sensation with physical and mental aspects. A sensation of heat or vibration may appear in the genitals, lubrication (moisture), or muscle contractions.

56. 3. How often did you feel sexually aroused ("turned on") during sexual activity or intercourse? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

57. 4. How would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse? *

Mark only one oval.

- No sexual activity 5 = Very high
- Very high
- High
- Moderate
- Low
- Very low or none at all

58. 5. How confident were you about becoming sexually aroused during sexual activity or intercourse? *

Mark only one oval.

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence

59. 6. How often have you been satisfied with your arousal (excitement) during sexual activity or intercourse? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

60. 7. How often did you become lubricated ("wet") during sexual activity or intercourse? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

61. 8. How difficult was it to become lubricated ("wet") during sexual activity or intercourse? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Extremely difficult or impossible
- ◯ Very difficult
- ◯ Difficult
- ◯ Slightly difficult
- ◯ Not difficult

62. 9. How often did you m ain tain your lubrication ("wetness") until completion of sexual activity or intercourse? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

63. 10. How difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or inter- course? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Extremely difficult or impossible
- ◯ Very difficult
- ◯ Difficult
- ◯ Slightly difficult
- ◯ Not difficult

64. 11. When you had sexual stimulation or intercourse, how ofte n did you reach orgasm (climax)? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Almost always or always
- ◯ Most times (more than half the time)
- ◯ Sometimes (about half the time)
- ◯ A few times (less than half the time)
- ◯ Almost never or never

65. 12. When you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)? *

Mark only one oval.

- ◯ No sexual activity
- ◯ Extremely difficult or impossible
- ◯ Very difficult
- ◯ Difficult
- ◯ Slightly difficult
- ◯ Not difficult

66. 13. How satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse? *

Mark only one oval.

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

67. 14. How satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner? *

Mark only one oval.

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

68. 15. How satisfied have you been with your sexual relationship with your partner? *

Mark only one oval.

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

69. 16. How satisfied have you been with your overall sexual life? *

Mark only one oval.

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied

70. 17. How ofte n did you experience discomfort or pain during vaginal penetration? *

Mark only one oval.

- Did not attempt intercourse I
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

71. 18. How ofte n did you experience discomfort or pain follow- ing vaginal penetration? *

Mark only one oval.

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

72. 19. How would you rate your level (degree) of discomfort or pain during or following vaginal penetration? *

Mark only one oval.

- ◯ Did not attempt intercourse
- ◯ Very high
- ◯ High
- ◯ Moderate
- ◯ Low
- ◯ Very low or none at all

Skip to question 78

Internations index of Erectile Function (IIEF)

These questions are about your feelings and sexual responses. Please answer honestly. Your answers will be kept in COMPLETE CONFIDENTIALITY. At the past seven days:

FOR EACH ITEM, JUST ONE RESPONSE

73. 1. How do you consider your confidence in being able to have and maintain an erection? *

Mark only one oval.

- ◯ Very low
- ◯ Low
- ◯ Moderate
- ◯ High
- ◯ Very high

74. 2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? *

Mark only one oval.

- ◯ Almost never or never
- ◯ A few times (less than half the time)
- ◯ Sometimes (about half the time)
- ◯ Most times (more than half the time)
- ◯ Almost always or always

75. 3. During sexual intercourse, how often were you able to maintain your erection after penetrating / entering your partner? *

Mark only one oval.

- ◯ Almost never or never
- ◯ A few times (less than half the time)
- ◯ Sometimes (about half the time)
- ◯ Most times (more than half the time)
- ◯ Almost always or always

76. 4. During sexual intercourse, how difficult was it for you to maintain your erection until the end of the relationship? *

Mark only one oval.

- ◯ Extremely difficult
- ◯ Very difficult
- ◯ Difficult
- ◯ Slightly difficult
- ◯ Not difficult

77. 5. When did you try to have sex how often was it satisfactory to you? *

Mark only one oval.

- ◯ Almost never or never
- ◯ A few times (less than half the time)
- ◯ Sometimes (about half the time)
- ◯ Most times (more than half the time)
- ◯ Almost always or always

Skip to question 78

Finally, we'd like to know if you think Covid-19 Pandemic has impacted your sexual function

Consider:
0 - Not at all
1 - A little
2 - Little
3 - Moderately
4 - Very
5 - Extremely

78. From zero (not at all) to five (extremely), how would you rate Covid-19's impact of Pandemic on your sexual function?

Mark only one oval.

	0	1	2	3	4	5	
Not at all	◯	◯	◯	◯	◯	◯	Extremely

79. Would you like to receive more information on the subject? If so, leave a contact e-mail here.

Thank you for participating!

EDITORIAL COMMENT

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Editorial Comment: Interaction between the impact of the Coronavirus disease 2019 pandemic and demographic characteristics on sexual/erectile dysfunction in Latin America: crosssectional study

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COMMENT

The global outbreak of coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the consequent lockdown had dramatic repercussions at both macrosocial, such as the economy and policy, and microsocial level, such as on the psychological and relational well-being of persons represents an unprecedented challenge for healthcare (1).

In June 2020, more than 7.5 million COVID-19 cases have been confirmed worldwide, with more than 420,000 lives lost due to the disease (2), and increased rates of post-traumatic stress disorder (PTSD), depression and anxiety were already expected in the general population, and even more in COVID-19 survivors, following the pandemic (3-6).

It has already been shown that sexual dysfunction may be observed in PTSD patients (7), and that emotional numbness can prevent emotional intimacy and connectedness with a partner. So, PTSD symptoms can cause problems in sexual functions, and PTSD can be used as a predictive parameter for sexual dysfunction in these patients (8). The high level of anxiety, anger and irritability observed in PTSD patients not only creates sexual dysfunction independently but also affects sexual dysfunction indirectly due to negative effects on social or romantic relationships and intimacy with the opposite sex (9). It can worse preexisting dysfunctions. Moreover, anger and anxiety might have a bidirectional relationship with erectile function. That is, anger and anxiety can create erectile dysfunction, and sexual dysfunction can induce or increase these symptoms (10).

The relationship between erection dysfunction and psychological state has also been examined in large-scale studies. In the National Health and Social Life Survey (NHSLS) study, data show that emotional problems and stress-related problems pose a risk of difficulty being experienced at all stages of sexuality. The researchers concluded that psychological state was an independent factor affecting sexual function (11).

In 'The multinational men's attitudes to life events and sexuality' (MALES) study conducted in Europe and North and South America, which included 2,912 men, depression or anxiety was found in 25% of the patients who reported to have ED, while was found in 26% of the patients who reported to have depression or anxiety (12).

So, as sexual activity is closely associated with mental and psychological health, it is unsurprising that sexual desire and frequency have declined in both genders during this pandemic (13, 14).

An interesting paper from Spain suggested that the social impact of the lockdown is related to gender, age and socioeconomic conditions. Authors found that women and young people had worse mental

health outcomes during lockdown (15).

Another Italian paper confirmed that COVID-19 lockdown dramatically impacted on psychological, relational, and sexual health of the population and found that sexual activity played a protective effect, in both genders (16).

Chinese authors conducted a cross-sectional survey using an online questionnaire applied in young individuals (15-35 years old) and found that many young people had decreased sexual desire and frequency of sexual intercourse due to COVID-19. In addition, a relatively large number of participants reported a significant reduction in alcohol-related sexual consequences and risky sexual behavior, an increase in masturbation and in the use of pornography. They speculate that increased family supervision or interference, less personal freedom overall, and poor mental health and partner relationships are likely contributors to these changes in sexual behavior (17).

Evaluating healthcare professionals, Bulut, et al. found that during the COVID-19 outbreak, healthcare professionals are exposed to psychological trauma and their sexual function was negatively affected (18).

Focusing on the interaction between the impact of the Coronavirus disease 2019 pandemic and demographic characteristics on sexual/erectile dysfunction in Latin America, we could make some considerations.

First is essential to recognize the importance, during a pandemic, to obtain customized data that point out the peculiarities of each affected region, allowing more effective preventive actions. But it's also known that management of sexual difficulties often requires addressing complex causes rooted in psychological, relational, and sociocultural spheres (19)

Available pre-pandemic data suggest a wide range for the prevalence of sexual dysfunction, which is influenced by ascertainment methods, age of the participants, presence or absence of various physical and psychiatric comorbidities (20). In general, it is suggested that about 43% of women and 31% of men have one or other kinds of sexual dysfunction, with premature ejaculation being the most common sexual dysfunction occurring in males and hypoactive sexual desire disorder in females (21).

Since we do not have a pre-pandemic photography of prevalence among the sample analyzed in this study nor a control group, it is hard to see the real magnitude of this interaction proposed by authors (22).

In terms of Latin America specific population characteristics, the educational level and family income of the analyzed group seems quite higher than the media of the habitants of those low and middle income countries.

As authors recognized, widely used "gold standard" instruments such as the International Index of Erectile Function (23) and the Female Sexual Function Index (24-25), are too narrowly focused. For instance, both assume vaginal penetration and have limited questions on the relationship or on patient assessment of "bother."

On the other hand, as occurs when using epidemiological tools, the main difficult is to deal with the challenge of distinguishing mild difficulties found in questionaries scores from clinical sexual dysfunction (26). Mild and transient sexual function problems are sufficiently common (27) to be considered "normal".

In the fifth edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), two new conditions for morbidity were added to the existing distress criterion stipulated in DSM-IVtr. There is now a requirement, across all diagnoses, that symptoms have persisted for a minimum duration of approximately six months; have been experienced in almost all or all (approximately 75%-100%) sexual encounters or have been persistent/recurrent; and have caused the individual clinically significant distress. The changes were specifically designed to improve precision, "reduce likelihood of overdiagnosis" and "distinguish transient sexual difficulties from more persistent sexual dysfunction" (28).

Similar to the findings of the authors who identified a greater pandemic "impact over the erectile/sexual function of people who lived with a partner" a chinese study during SARS epidemic in 2009, erectile dysfunction rates were also higher in married men but with a different explanation: they believe this was related to the mean age of the married patient group being high and the anxiety

they experienced in relation to their families being greater. It was stated that married men were more concerned about their own health and that of their families, especially their children, in some studies conducted after the SARS epidemic, and it was therefore concluded that married people showed more PTSD symptoms (29).

Finally, it is not feasible (and certainly not the aim of the manuscript) for cross-sectional surveys to provide sufficient clinical information for a definite diagnosis. For instance, the already mentioned DSM-5 stipulates that if the sexual problem is attributable to a medical condition (in this case PSTD), then a diagnosis of sexual dysfunction is not given; and off course it is even not possible to ascertain such causality in a cross-sectional survey (26).

Adding this evidence to the existing ones alerting to the negative interference of the pandemic on the mental and sexual health of the population, it is urgent to disseminate qualified information and invest in the adequate preparation of health professionals to address issues that may not be actively presented during anamnesis.

Faced with the congestion of health services generated by the pandemic and the necessary prioritization of critical care, doors were closed even for those who were trying to provide care to deal with dysfunctions. In countries where the needy population was already facing difficulties, the impact of the pandemic certainly cannot yet be full scaled (30).

Several recommendations were made on policies. For instance: the use of telemedicine and community-based programs as a way to deliver sexual services during and after a pandemic (31). The determination of the groups most vulnerable is important for the planning of training and action of psychological support teams. The fight against pandemics should include health teams with strong psychological grounding, to offer qualified medical care for patients (32). And successful use of quarantine as a public health measure requires to reduce, as far as possible, the negative effects associated with it. Officials should take every measure to ensure that this experience is as tolerable as possible for people. This can be achieved as suggested by Brooks et al. by: telling people what is happening and why, explaining how long it will continue, providing meaningful activities for them to do while in quarantine, providing clear communication, ensuring basic supplies (such as food, water, and medical supplies) are available, and reinforcing the sense of altruism that people should, rightly, be feeling (1).

CONFLICT OF INTEREST

None declared.

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Could urinary nerve growth factor and bladder wall thickness predict the treatment outcome of children with overactive bladder?

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ABSTRACT

Objective: Bladder wall thickness (BWTh) measurements and Nerve Growth Factor (NGF) /creatinine (Cr) values, as noninvasive tools, were found to predict daytime voiding problems in children with overactive bladder (OAB). The goal of this research was to examine if bladder wall thickness together with urine NGF/Cr could be a clinical utility in treatment outcome of OAB in children.

Patients and Methods: A total of 60 children with OAB, (Group 1; n=40) and healthy normal controls (Group 2; n=20), aged 6-14 years old were involved in this prospective study. Children were evaluated with detailed history and physical examination, including neurologic examination, and were asked to complete a self-reported questionnaire and a 3-day bladder diary with the aid of their parents. Uroflowmetry was performed in all cases. Urinary nerve growth factor levels were measured by the ELISA and BWTh was measured trans-abdominally by one uro-radiologist specialized in pediatric ultrasonography. Urinary NGF levels were normalized by urinary creatinine levels and compared among all subgroups. Children with OAB received urotherapy as first line treatment at least for three months. 18 children refractory to urotherapy received anticholinergic therapy defined as group 3.

Results: The median age of the study group was 10 (range 6 to 16). After urotherapy, 22 children had similar BWTh and NGF/Cr values compared to controls. (2.75 ± 1.15; 2.40 ± 1.00 mm; p=0.86 and 1.02 ± 0.10; 0.78 ± 0.15; p=0.12, respectively). After anticholinergic treatment, BWTh levels (2.25 ± 0.90; 2.40 ± 1.00 mm; p=0.94) and NGF/Cr values (0.95 ± 0.10; 0.78 ± 0.15; p=0.42, respectively) had no significantly difference compared to controls (Group 2).

In receiver operating characteristic analysis, bladder wall thickness was found to have sensitivity of 85% and specificity of 84.2% (3,20 AUC ,913; 95 %) and NGF/Cr had sensitivity of 90% and specificity of 92.1% (1,595; AUC ,947; 95 %) in predicting treatment outcome in children with OAB.

Conclusions: Bladder wall thickness measurements and NGF/Cr values, as noninvasive tools, could guide outcomes in the treatment of children with overactive bladder.

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INTRODUCTION

Daytime lower urinary tract condition (dLUTC) is a complex term that consists of heterogeneity of symptoms of LUT dysfunction (1). In the absence of other (e.g. neurological) diseases, overactive bladder is a symptom complex comprising of uncomfortable stored urine symptoms such as urinary frequency, urgency, and nocturia (2). The main diagnostic tools for overactive bladder (OAB) are a detailed history, physical exam, urinalysis (to rule out infection and microscopic hematuria), a post-void residual measured by ultrasound, and a frequency-volume chart (which can highlight fluid intake, average and maximum bladder volumes, and timing of voids). When the diagnosis is unknown or there is a high suspicion for another ailment, more advanced diagnostic modalities such as urodynamics, cystoscopy, or upper tract imaging are required (1, 2). However, daytime symptoms may overlap between conditions such as an OAB or non-monosymptomatic nocturnal enuresis accompanied by urinary frequency and nocturia with or without urinary incontinence (3). Since border cases are common, clinical examination of dLUTC including fluid intake, frequency volume chart and uroflowmetry could be inaccurate in children. In addition, urodynamic studies (UD) are not routinely used to measure volumes, pressures and flows due to the disadvantage of patient discomfort unless a suspected neuropathic bladder (4). Thus, instead of UD, simple and less invasive tests that should play a crucial role in diagnosis and treatment outcome of dLUTC are needed. Recent studies considered urinary nerve growth factor (NGF) as a biomarker for sensory urgency, detrusor overactivity and OAB by the activation of sensory receptors of urothelium and smooth muscle resulting in an increase in urinary NGF (5-7). Moreover, bladder wall thickness (BWTh) has been reported to be preferable to the UD study and could be replaced as a diagnostic parameter in children with OAB (8-10). In our previous report, we found that, BWTh and NGF /creatinine (Cr) values, as noninvasive tools, were found to predict daytime voiding problems in children (11). We hypothesized that, increased levels of BWTh and NGF /creatinine (Cr) values might decrease as a result of treatment. In this study, we aimed to evaluate the value of BWTh together with urine NGF/Cr in treatment outcome of OAB.

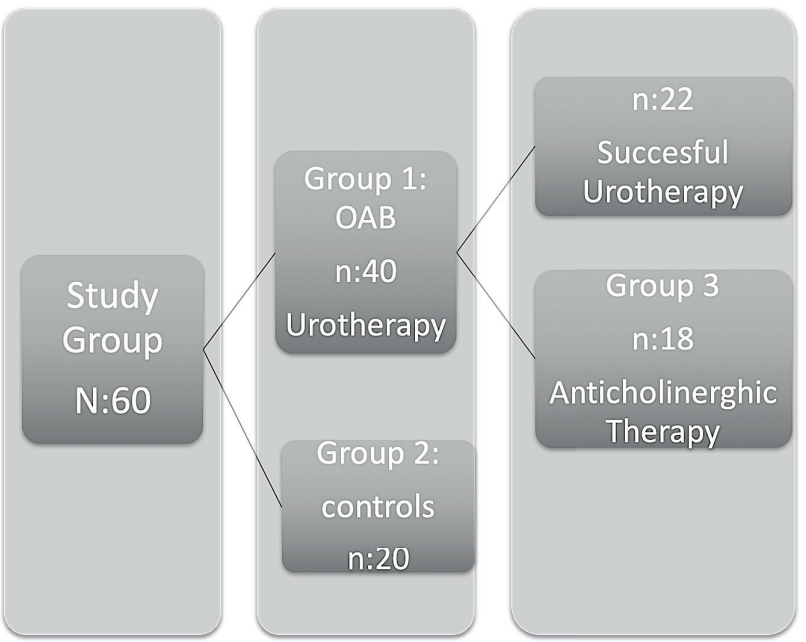
MATERIAL AND METHODS

Patients and Study Design

Between April 2015 and January 2017, 60 children aged 6 to 16 years old referred to the department of pediatric urology were prospectively recruited in the study with the agreement of the institutional review board (IRB 2015/650/15). Informed consent was obtained from all of the parents. There were three groups in the study. Group 1 included children with dLUTC (n = 40) and group 2 from pediatric urology clinic without OAB or any other urinary symptoms as controls. (n=20). Children with OAB in group 1 received urotherapy as first line treatment at least 3 months. 18 children refractory to urotherapy received anticholinergic therapy at least 3 months defined as group 3 (Figure-1).

At initial presentation, past history was taken and neurologic examination was performed. With the aid of parents, 3-day bladder and diary dysfunctional voiding symptom score were asked to be completed. It was reported that a score of 8.5 may be an optimum threshold score to determine whether the subject has clinically significant wetting and functional voiding symptoms, with a sensitivity of 90% and a specificity of 90% (12). The presence of daytime voiding symptoms as urgency, urge-incontinence, incontinence, holding maneuvers, frequency and fluid intake were recorded. Uroflowmetry was also performed in all children. Abnormal uroflowmetry patterns (plateau, staccato-shaped or interrupted pattern), children with lower urinary tract obstruction, renal dysfunction, developmental disorder, urinary tract infection documented in previous three months, congenital urothelial malformation were excluded. Urotherapy was recognized as a behavioral intervention to reduce symptoms by establishing a functional voiding

Figure 1 - Flow chart of the study.



behavior. In any case, timed voiding every three to four hours during daytime, was instituted early on with a sufficient period of time to achieve complete bladder emptying. In terms of voiding technique, children were asked to void with their legs spread apart and a footstool was advised to be used for the child's heals to touch the ground if the toilet does not have a proper height. Fluid intake was advised regularly during the day however towards bedtime suggested to be minimalized. Beverages that can trigger urgency and frequency symptoms, such as those containing caffeine, chocolate or citrus, and carbonated beverages were advised to be avoided. Bowel management staying well hydrated and having a high-fiber diet was planned as a part of urotherapy after obtaining Bristol stool scale (13). A 50% improvement rate of frequency and urgency symptoms was accepted as success as reported previously after simple behavioral therapy (14). Although the patients received at least three months urotherapy, less than 50% improvement in OAB symptoms was accepted as refractory to therapy. Patients received oxybutynin suspension with a recommended daily dose of 0.3 0.6 mg/kg to the maximum dose of 15 mg/kg/day. International Children's Continence Society was followed for the definitions of dLUTC (1).

Bladder Wall Thickness Measurement

Ultrasonography (US) with a high frequency (7.5 MHz) linear probe was performed by one pediatric radiologist in supine position from suprapubic region. Children notice to void was (first urge) accepted as the time of BWTh measurement in each patient. The technique describes the distance between two hyperechogenic lines, which represent the adventitia and mucosa and/or submucosal tissue as BWTh (10). The average of three layers as anterior, posterior and lateral, divided by three was accepted as the mean BWTh.

Urinary Marker Analysis

Urine samples were collected in a culture sterile period. The samples were put on ice immediately and centrifuged at 3000 rpm for 10min at 4°C. The supernatant was separated into aliquots in 1.5 mL tubes and stored at -80°C freezer. The total urinary NGF level was further normalized by the concentration of urinary creatinine (Cr) level (NGF/Cr level). Urinary Cr levels were measured

after 3 mL urine was taken to normalize NGF levels. Emax® ImmunoAssay System (Promega, Madison, WI, USA) was used to determine Urinary NGF concentration. Assays were validated for urine measurements according to the manufacturer's instructions. The detailed procedure was described in our previous report (11).

Statistical Analysis

Statistical analyses were performed with SPSS 25.0, and the statistical significance was set as P <0.05. Statistical analysis was performed using the nonparametric Mann-Whitney U test. Kruskal-Wallis and Wilcoxon signed-rank tests were used to analyze the groups. A receiver operating characteristic (ROC) curve was used to determine a cut-off value of BWTh and NGF/Cr rate in the treatment outcome of OAB.

RESULTS

A total of 60 children consisting of 44 girls and 16 boys with a median age of 10 (6-16) years were enrolled to the study. There were no significant differences between groups according to gender, age and functional voided volumes between groups (p > 0.05). Table-1 lists the demographic and micturition data of each group. The voiding symptom score before the treatment, was 14.6 ± 2.4 in the group 1 and this value was 4.5 ± 2.5 in controls (Group 2).

The mean bladder wall thickness was significantly higher in group 1 compared to group 2 (5.10 ± 0.70 mm, 2.40 ± 1.00 mm; p<0.001). Urinary levels of nerve growth factor corrected to urine creatine were significantly higher in group 1 compared to group 2 (2.75 ± 1.15 vs.0.78 ± 0.15; p<0.001). After urotherapy, 22 children had similar BWTh and NGF/Cr values compared to controls (2.75 ± 1.15; 2.40 ± 1.00 mm; p=0.86 and 1.02 ± 0.10; 0.78 ± 0.15; p=0.12, respectively). The voiding symptom score, which was 14.6 ± 2.4 before treatment in group 1, decreased to 6.2±1.6 after the treatment in 22 children. Before anticholinergic therapy, group 3 (refractor to urotherapy, n=18) had significantly higher BWTh (4.90 ± 0.70 mm, 2.40 ± 1.00 mm; p<0.001) and NGF/Cr values (2.55 ± 1.05 vs.0.78 ± 0.15; p<0.001) compared to controls (group 2). After anticholinergic treatment, BWTh levels (2.25 ± 0.90; 2.40 ± 1.00 mm; p=0.94) and NGF/Cr values (0.95 ± 0.10; 0.78 ± 0.15; p=0.42, respectively) had no significantly difference compared to controls (Table-2). The voiding symptom score, which was 18.4 ± 2 before anticholinergic treatment in group 3, decreased to 6.8±1.4 after the treatment.

In receiver operating characteristic analysis, bladder wall thickness was found to have sensitivity of 85% and specificity of 84.2% (3.20 AUC 0.913; 95 %, p<0.001) and NGF/Cr had sensitivity of 90.5% and specificity of 92.1% (1,595; AUC, 947; 95 %, p<0.001) in predicting treatment outcome of OAB in children refractory to urotherapy (Figure-2).

Figure 2 - Sensitivity and specificity of BWTh and NGF/Cr in predicting treatment outcome of dLUTC (BWTh sensitivity 85%, specificity 84.2%, cutoff 3.20, AUC 913; 95%, p<0.001; NGF/Cr sensitivity 90.5%, specificity 92.1%, cut-off 1.595, AUC 947; 95%, p<0.001).

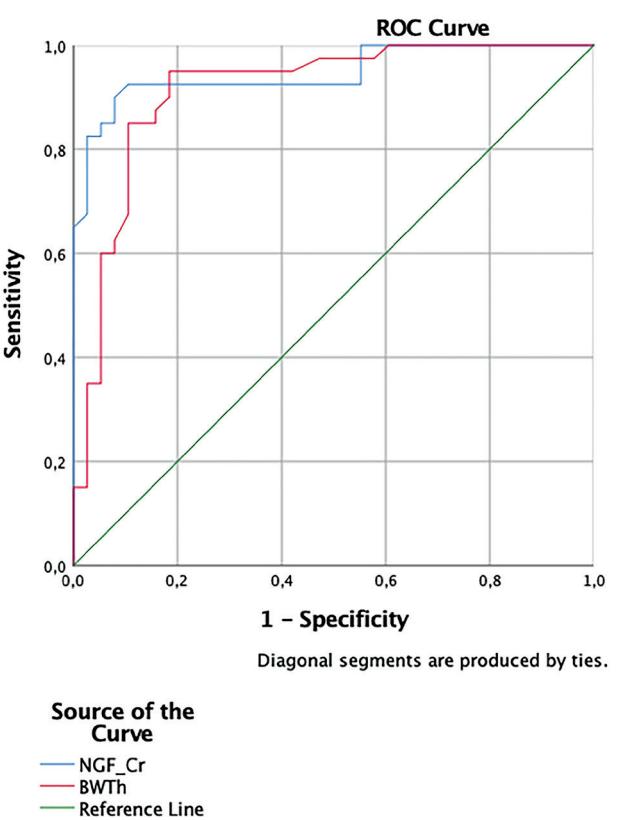


Table 1 - Patient's characteristics of treatment groups (Group 1 and Group 3) and controls (Group 2).

	Group 1 (n=40)	Group 2 (n=20)	Group 3 (n=18)	P
Median age (min-max, years)	9 (6-16)	10 (7-15)	10 (6-15)	0.523
Sex (M: F)	14/26	8/12	9/9	0.326
Mean ± SD daytime voiding				
Voids/day	7.2 ± 1.0	4.8 ± 1.2	8.0 ± 0.8	0.038
MVVw (mL)	311 ± 112	344 ± 98	291 ± 134	0.188
Daytime symptoms				
Frequency (%)	30 (60.0)	-	13(72.2)	
Urgency (%)	22 (55.0)		16 (88.8)	
Daytime incontinence (%)	18 (45.0)		7 (38.8)	
Constipation/encopresis (%)	10 (25.0)		8 (44.4)	
Symptom Score (Pre-Treatment)	14.6±2.4	4.5±2.5	18.4±2	

Table 2 - Comparison of bladder wall thickness (BWTh) and NGF/Cr levels between groups.

	Groups	BWTh (mm, mean ± SD)	P value	NGF/Cr (mean ± SD)	P value
Before Urotherapy	Group 1 vs. Group 2	5.10 ± 0.70 vs. 2.40 ± 1.00	p<0.001	2.75 ± 1.15 vs. 0.78 ± 0.15	p<0.001
After Urotherapy-Before anticholinergic therapy	Group 3 vs. Group 2	4.90 ± 0.70 vs. 2.40 ± 1.00	p<0.001	2.55 ± 1.05 vs. 0.78 ± 0.15	p<0.001
After anticholinergic therapy	Group 3 vs. Group 2	2.25 ± 0.90 vs. 2.40 ± 1.00	p=0.94	0.95 ± 0.10 vs. 0.78 ± 0.15	p=0.42

p<0.001 between patients and controls for all values compared (Mann-Whitney U or Wilcoxon test, 95% CI).
Group 1 - Children with overactive bladder; **Group 2** - Healthy normal controls**; Group 3** - Children with overactive bladder refractory to urotherapy

DISCUSSION

Urinary NGF secreted by urothelium and smooth muscles was considered as a new biomarker of lower urinary tract disorders such as interstitial cystitis, OAB, bladder outlet obstructions and chronic prostatitis (15, 16). NGF may play a role in urinary bladder dysfunction through promoting inflammation, as well as morphological and functional alterations in the sensory and sympathetic neurons that innervate the bladder. There is a disruption in the autonomic balance between the sympathetic and parasympathetic neural systems in patients with OAB, as well as less sympathetic activity at the post-voiding instant (17). Several studies have advocated the association between increased levels of NGF in urine and OAB in adult population (6, 11, 16). However, few studies focused on the link between OAB and NGF in children (7, 18). US has been reported as a non-invasive

and useful tool in lower urinary tract dysfunctions by measurement of detrusor wall thickness. Frequent detrusor contractions cause hypertrophy of detrusor muscles and therefore thickened detrusor wall in overactivity of bladder in OAB produces more NGF and measurement of BWTH.

Following our first report that clarifies a clinically useful tool with urinary NGF and BWTH in diagnosis of daytime voiding problems in children, the present study was designed to investigate the therapeutic efficacy of BWTh and urinary NGF in children with OAB which is one of the possible condition of dLUTC (11).

dLUTC has a wide range in diagnosis since criteria are mostly variable. Cases can be presented as OAB, non-monosymptomatic nocturnal enuresis or signs of detrusor overactivity. In our study, urinary NGF/Cr levels and BWTh measurements were significantly higher in patients with OAB (group 1) compared to the control (group 2). Children with OAB received urotherapy and after therapy 22 of 40 children had similar BWTh and NGF/Cr results with controls. Standard urotherapy is accepted as the first line treatment for treating OAB in children and adolescents (1). A recent meta-analysis reported standard urotherapy is an effective treatment of daytime urinary incontinence compared to a spontaneous remission rate of 15.40% per year. About 56 of 100 patients was found to be recovered after being treated with SU, whereas only 15 out of 100 remit spontaneously (19).

Eighteen children (Group 3) had significantly higher BWTh and NGF/Cr although they received urotherapy. Daytime symptoms suggestive of an overactive bladder may increase bladder wall thickness, and thus NGF levels may increase in the lower urinary system after denervation, inflammation and mechanical tension. NGF and bladder wall thickness have a similar pattern. When the BWTh increases, there is a tendency that the urine NGF increases (11). After anticholinergic treatment, the thickened bladder wall and therefore NGF/Cr decreased (similar with controls) in response to the anticholinergic treatment. As put forward by Fukui et al., OAB symptoms improved after urotherapy and anticholinergic therapy in 26 (74%) of 35 children, whereas urinary NGF/Cr levels remains significantly higher in refractory group than in improved group (7). Otherwise, Liu and coworkers found that adult patients with overactive bladder who refract to anticholinergic therapy, present with high serum NGF and urinary NGF/Cr levels, and they remain high after subsequent other anticholinergic therapies (20). Surprisingly, the current findings could aid in the treatment of a carefully selected patient population suffering from severe refractory OAB symptoms due to high urine NGF, who could be administered sacral neuromodulation as a third-line treatment (21, 22). According to video-urodynamic studies, Fukui et al. reported three cases of bladder outlet obstruction in children with OAB who were refractory to urotherapy and anticholinergic medication (two urethral stenosis and one detrusor sphincter dyssynergia). Although this is likely in only a small number of cases, it is crucial to remember that children with high urine NGF/Cr levels before treatment, as well as those who don't respond to treatment, may have bladder outlet obstruction. More research is needed to determine whether video-urodynamic tests should be used to detect urethral stenosis or bladder outlet obstruction in children with OAB who are resistant to treatment and have elevated urine NGF/Cr levels prior to treatment (7).

Our work clearly has some limitations. First one is given the small number of patients and controls with only one urinary NGF and BWTH measurement could affect the results. Secondly, serum NGF levels was not carried out in this study and could have important implications. Inconsistent fluid intake in children before US or differences in resolution of the ultrasound probe may affect the BWTh measurements. The BWTh clearly depends on degree of distension. It will be maximal when the bladder is empty and at its minimum when the bladder is at maximum actual bladder capacity. Moreover, these parameters are only meaningful when referenced to age-specific normal (since a normal bladder is thinner in a younger patient than an older patient). Measuring BWTh at intermediate volumes (between empty and full) might be useful if the same relative volume was used in all cases, for example 50% or 70% of maximal capacity Multiple measurements should be conside-

red to minimalize these effects. Lastly, BWTH and therefore NGF could be affected in bladder outlet obstructions that most of avaible data on detrusor wall thickness are from those pathologies. Thus, exclusion criteria's in diagnosis of dLUTC have a crucial point. Despite this, we believe our work could be a framework for diagnosis and treatment outcome of daytime lower urinary tract conditions by urinary NGF and BWTH.

CONCLUSION

Bladder wall thickness and urinary levels of NGF are increased in children with OAB. To our knowledge, the present study is the first to evaluate the combination of urinary NGF and bladder wall thickness in children with OAB, which may serve as a noninvasive tool for outcome of treatment in OAB. Further studies including larger number of patients would be of great interest.

CONFLICT OF INTEREST

None declared.

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Lower pole anatomy of horseshoe kidney and complete ureteral duplication: Anatomic and radiologic study applied to endourology

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ABSTRACT

Purpose: To analyze the 3-dimensional intrarenal anatomy of horseshoe kidneys (HK) and kidney with complete ureteral duplication (CUD), in polyester resin endocasts of the collecting system and in patients submitted to 3D computerized tomography scan (CT-scan).
Materials and Methods: We analyzed seven 3-dimensional polyester resin endocasts of the kidney collecting system obtained from 6 fresh adult cadavers (4 with unilateral CUD and 2 with horseshoe kidney) and CT-scan reconstruction images of kidneys from 24 patients: 6 patients with HK, 8 with CUD and 10 patients without renal anomalies that were used as controls. We analyzed the spatial distribution of the calices, the infundibula diameters, the angle between the lower infundibulum and the renal pelvis (LIP) and the angle between the lower infundibulum and the inferior minor calyces (LIICA). Measurements of the width and length of the inferior infundibulum and the infundibula of the minor calyces, as well as the angles (LIP and LIICA) were made with the aid of the LibreOffice 6.3 software. The data were analyzed with the IBM® SPSS® Statistics.
Results: There was no statistical difference in the inferior pole measurements between the groups with anomalies and the control group, both in polyester resin endocasts and CT-scan reconstruction images for LIP. When we compared the LIP in the CT-scan between HK versus CUD (p= 0.003), and HK versus the control group (p= 0.035), we observed statistical difference.
Conclusions: The knowledge of spatial anatomy of lower pole is of utmost importance during endourologic procedures in patients with kidney anomalies. In the present study we observed that horseshoe kidneys had more restrictive anatomic factors in lower pole than the complete ureteral duplication.

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INTRODUCTION

The success rate of the treatment of calculi located in the kidney lower pole, regardless of the method used, is directly related to the anatomical parameters of this region (1, 2). Knowledge of the renal collecting system anatomy and radiological analysis of urinary system is necessary for safe and successful performance of endourological procedures (2, 3).

Calculi in the lower pole of the kidney can be treated with extracorporeal shock wave lithotripsy (SWL); retrograde flexible ureteroscopy (URS) and percutaneous nephrolithotripsy (PNL) (1). Sampaio (4) showed restrictive factors for the elimination of fragments after performing

SWL (multiple calyces in the lower pole; diameter of the inferior infundibulum smaller than 04 mm and presence of angle between the lower infundibulum and renal pelvis (LIP) of less than 90°).

Horseshoe kidney is the most common of all renal fusion anomalies with a prevalence of 0.25% in the population (5, 6), and the incidence is about 1/666 births (7, 8). Ureteral anomalies of number are also frequent, with emphasis on ureteral duplications that have an incidence around 1/150 births (9). The incidence of nephrolithiasis in patients with horseshoe kidney is approximately 20% (8).

Endourologic procedures in patients with urogenital anomalies are more difficult, especially regarding the position of the renal calyces (5, 6). The knowledge of the intrarenal anatomy in these patients is important for the indication, programming and adequate performing of procedures (5-7).

There are several studies in the literature about endourologic procedures in patients with urinary system anomalies (10-12). However, studies of the intrarenal anatomy with endocasts, in cases of urinary anomalies, are rare or non-existent. The hypothesis stated in our study is that the anomalous kidneys had more restrictive anatomic factors to elimination of fragments and accessibility of URS than the normal ones.

The objective of the present study is to analyze the three-dimensional intrarenal anatomy of kidneys with congenital anomalies (horseshoe kidney and complete ureteral duplication), including: spatial anatomy of the lower pole calyces, angle between the renal pelvis and the inferior infundibulum, angle between the inferior infundibulum and the minor calyces, and width and length of inferior infundibulum, in human kidneys polyester resin endocasts and in patients submitted to abdominal 3D computerized tomography scan.

MATERIAL AND METHODS

The present work received institutional review committee approval. This study was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation. IRB= 4.492.916.

We analyzed 20 three-dimensional (3D) polyester resin endocasts of the kidney collecting system from our research unit. Among then, three were horseshoe kidneys (HK), seven had complete ureteral duplication (CUD) and ten 3D endocasts of kidneys without macroscopic anomalies (Control group - CG). We also analyzed 24 patients with 3D computerized tomography scan (CT-scan) reconstruction images of kidneys; among then, six were patients with HK, and eight had complete CUD kidneys; also, CT scans of 10 patients without kidney anomalies were used as CG.

The endocasts were obtained according to the technique previously described (2, 3, 13). The ureters were dissected and a yellow polyester resin was injected into the ureter to fill the kidney collecting system. Added to the resin was a styrene monomer as a diluent and a methyl ethyl ketone peroxide as a catalyst. For each 100mL of resin 10mL of styrene monomer were added, and also 3mL of catalyst and 2mL of the yellow pigment. After the injected resin had set, the kidneys were immersed in hydrochloric acid until total corrosion of the organic matter was achieved and the endocast was obtained.

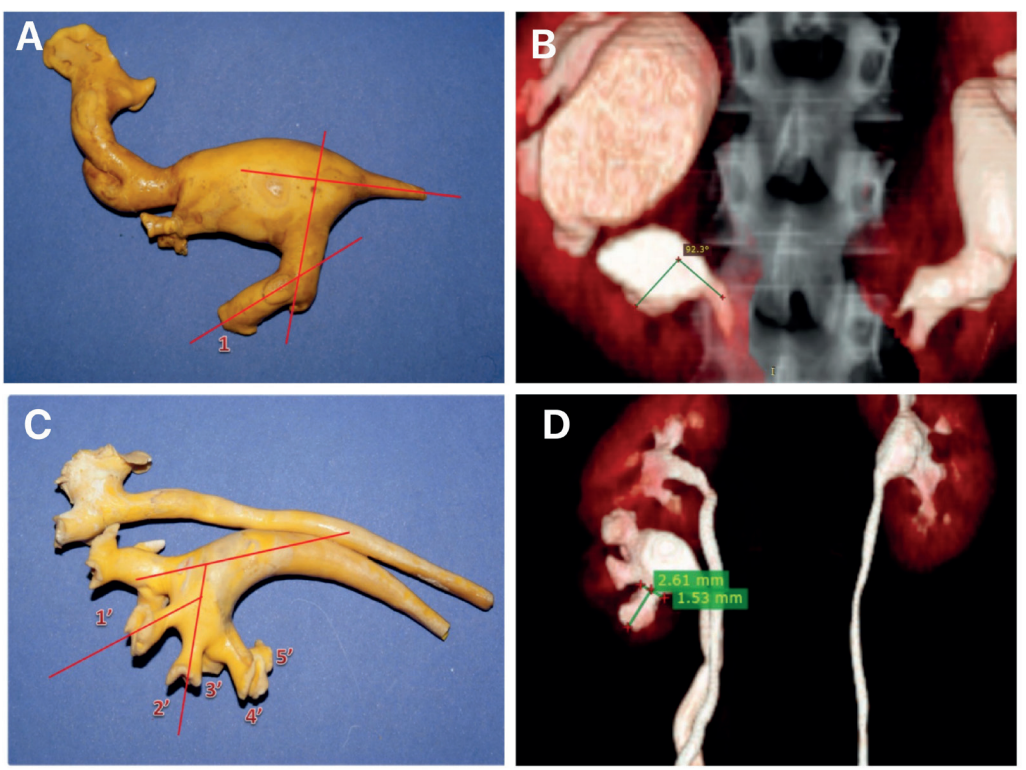
Thus, the endocasts were analyzed considering the calyceal spatial distribution and the infundibulum diameters. In the cases of duplicated pelvicalyceal collecting system we analyzed separately the superior and the inferior units. Measurements of width and length of the inferior infundibulum and infundibulum of the minor calyces and the angles were made with the aid of the LibreOffice 6.3 software (15-17), as shown in Figure-1.

The measurements on the 3D CT-scan reconstructed images were made with the Horos Project® program. In the inferior pole we studied the following parameters: (a) number of major and minor calyces; (b) width and length of the infundibulum and the minor calyces; (c) angle between the lower infundibulum and renal pelvis (LIP), measured by Sampaio's (4) and Elbahnasy's methods (14); and (d) angle between the lower infundibulum and the inferior minor calyces (LIICA) (Figure-1).

Statistical Analysis

Mean averages were statistically compared using the ANOVA with the Kruskal-Wallis test, Tukey-Krammer test and Unpaired t test (p-value < 0.05 was considered statistically significant). The data were analyzed with the IBM® SPSS® Statistics.

Figure 1 - Example of the measurements performed in this study with a computer program (15). A) The figure shows an endocast of a horseshoe kidney. The angles between the lower infundibulum and renal pelvis (LIP) are measured; B) The figure shows the computed tomography (CT) scan image of one of the horseshoe kidneys analyzed showing the measurement of the LIP; C) The figure shows an endocast of a Complete Ureteral Duplication (CUD) showing the angles measurements and D) The figure shows the CT scan image of one of the CUD analyzed showing the measurement of the length and width of the infundibulum of the lower unit.



RESULTS

The anatomical characteristics of the inferior pole analyzed in horseshoe kidneys, CUD kidneys and in the control groups, including measurements of angles, number of calyces and infundibulum measurements of the endocasts are shown in Table-1. The anatomical characteristics and measurements of the three groups studied with the 3D CT-scan are shown in Table-2. In all the 10 cases of anomalous kidneys studied we observed that the calyces are disposed in varied positions (superimposed or alternately distributed) in relation to the lateral margin of the kidney.

Horseshoe Kidney

The three horseshoe kidneys had the renal pelvis elongated and in a more anterior position. We observed 1 major calyx in the superior pole in the 3 cases; in the mid-kidney we observed 0 to 1 major calyx, and in the inferior pole only 1 major calyx in the 3 cases (Length: 6.8 - 13.66mm, mean=10.41mm, SD=3.44 and width=5.78 to 11.39mm, mean=9.34mm, SD=3.09). The number of minor calyces in the superior pole was 2 to 4, in the mid- kidney was 2 to 3 and in the inferior pole was 2 to 4 minor calyces (Length: 1.95 to 21.25mm, mean=9.16mm, SD=4.83 and width: 3.24 to 10.25mm, mean=6.54mm, SD=2.16). The LIP was between 16° and 106° (mean=71.67°, SD=48.64). The LIICA was between 13° and 87° (mean=42.67, SD=11.68).

In the sample of 3D CT-scan horseshoe kidneys, we analyzed 6 units. They followed the pattern of the endocasts, with elongated and more anterior position of renal pelvis. We observed 1 major calyx in the superior pole in all 6 cases; in the mid-kidney we observed 2 to 4 major calyx and in the inferior pole 1

Table 1 - The table shows the number of major calyces (MC) and minor calyces (mc), the mean of measurements of angles, and infundibulum of lower pole (major and minor calyces) in the sample of polyester resin endocasts of the kidney collecting system: 3 horseshoe kidneys, 7 kidneys with complete ureteral duplication (CUD) and 10 kidneys without congenital anomalies. The measurements of calyces are in millimeters (mm).

	Major Calyces (MC)	Mean Length MC ± SD	Mean Width MC ± SD	LIP ± sd	Minor Calyces (MC) ± SD	LIICA ± SD	Mean Length MC ± SD	Mean Width MC ± SD
Horseshoe Kidney	1 (1-1) ± 0	10.41 (6.80-13.66) ± 3.44	9.34 (5.78-11.39) ± 3.09	71.67° (16-106°) ± 48.64	3.33 (2-4) ± 1.15	42.67° (13-87°) ± 11.68	9.16 (1.95-21.25) ± 4.83	6.54 (3.24-10.25) ± 2.16
CUD	1 (1-1) ± 0	9.53 (5.99-12.37) ± 2.59	8.02 (4.25-13.19) ± 2.7	104.93° (70-115°) ± 9.33	2.43 (2-5) ± 1.13	36.36° (5-85°) ± 17.5	7.49 (1.95-21.25) ± 4.01	4.87 (3.24-10.25) ± 1.8
Control Group	1 (1-1) ± 0	12.86 (9.70-18.40) ± 3.12	6.37 (3.59-9.08) ± 1.82	92.8° (54-159°) ± 25.71	3.3 (2-5) ± 0.95	41.38° (2-139°) ± 10.71	8.95 (4.50-20.17) ± 2.1	4.96 (2.31-9.61) ± 0.98
p value	-	0.094	0.134	0.3003	0.227	0.0149	0.624	0.245

LIP = Angle between the lower infundibulum and renal pelvis; **LIICA** = angle between the lower infundibulum and the inferior minor calices. **SD** = standard deviation.

Table 2 - The table shows the number of major calyces (MC) and minor calyces (mc), the mean of measurements of angles, and infundibulum of lower pole (major and minor calyces) in the sample of Tridimensional Computerized Tomography scan (3D CT-scan) reconstruction images of kidneys: 6 horseshoe kidneys, 8 kidneys with Complete Ureteral Duplication (CUD) and 10 kidneys without congenital anomalies. The measurements of calyces are in millimeters (mm).

	Major Calyces (MC)	Mean Length MC ± SD	Mean Width MC ± SD	LIP ± SD	Minor Calyces (MC) ± SD	LIICA ± SD	Mean Length MC ± SD	Mean Width MC ± SD
Horseshoe Kidney	1.33 (1-2) ± 0.52	10.17 (6.28-16.8) ± 3.64	10.51 (4.99-15.28) ± 3.88	44.97° (23.57-85.16°) ± 21.91	1 (0-2) ± 1.09	132.99° (104.82-154.67°) ± 20.7	11.69 (5.43-16.3) ± 4.2	6.86 (2.55-9.2) ± 1.86
CUD	1 (1-1) ± 0	15.71 (7.3-25.03) ± 6.45	9.68 (5.37-15.7) ± 3.22	86.92° (44.38-103.57°) ± 12.65	1.37 (0-3) ± 1.19	110.24° (12-170.12°) ± 53.68	7.62 (3.5-10.52) ± 2.32	8.04 (5.37-15.7) ± 3.53
Control Group	1.1 (1-2) ± 0.32	14.54 (1.98-22.52) ± 7.39	8.31 (3.43-15.74) ± 3.85	73.95° (47.4-114.27°) ± 24.99	1.8 (0-3) ± 1.13	136.01° (106.88-171.61°) ± 12.76	9.5 (4.14-18.89) ± 1.87	5.29 (1.65-8.54) ± 2.06
p value	0.180	0.267	0.491	0.004	0.403	0.382	0.119	0.205

LIP = Angle between the lower infundibulum and renal pelvis; **LIICA** = angle between the lower infundibulum and the inferior minor calices; **SD** = standard deviation.

to 2 (Length: 6.28 to 16.8mm, mean = 10.17, SD= 3.64 and width: 4.99 to 15.28mm, mean=10.51, SD=3.88). The number of minor calyces in the superior pole was 0 to 5; in the mid-kidney we also observed 0 to 5, and in the inferior pole we observed 0 to 2 (length: 5.43 to 16.3mm, mean=11.69, SD=4.2 and width: 2.55 to 9.2mm, mean=6.86, SD=1.86). The LIP was between 23.57° to 85.16° (mean=44.97, SD=21.91) and LIICA was 104.82° to 154.67° (mean=132.99, SD=20.7).

Complete Ureteral Duplication Kidneys

In the 7 endocasts with CUD, in the superior pole we observed 1 to 2 major calyces; the number of minor calyces varied from 3 to 5. In the mid-kidney, the number of major calyces was 1 to 3. In the inferior pole we observed only 1 major calyx in all cases (Length: 5.99 to 12.37mm, mean=9.53mm, SD=2.59 and width: 4.25 to 13.19mm, mean=8.02, SD=2.7). The number of minor calyces in the inferior pole was 2 to 5 (length: 1.95 to 21.25mm, mean=7.49, SD=4.01 and width: 3.24 to 10.25mm, mean= 4.87, SD= 1.8). The LIP was between 70° and 115° (mean=104.93°, SD=9.33). The LIICA was between 5° and 85° (mean=36.36°, SD=17.5).

In the group of 8 patients with CUD analyzed with 3D CT-scan we observed in the superior pole 1 to 2 major calyces; the number of minor calyces varied from 0 to 5. In the mid-kidney, the number of major calyces was 1 to 6. In the inferior pole, we observed 1 major calyx in all cases (length: 7.3 to 25.03mm, mean=15.71, SD=6.45 and width: 5.37 to 15.7mm, mean=9.68, SD=3.22). The number of minor calyces in the inferior pole was 0 to 3 (length: 3.5 to 10.52mm, mean=7.62, SD=2.32 and width: 3.9 to 14.27mm, mean= 8.04, SD=3.53). The LIP was between 44.38° to 103.57° (mean= 86.92°, SD= 12.65) and LIICA was between 12° to 170.12° (mean=110.24°, SD= 53.68).

Control Group

In 10 endocasts of control group we observed in the superior pole, 1 major calyx in all 10 kidneys. The mid-kidney, had 0 to 3. In the inferior pole we observed 1 major calyx in all 10 kidneys (Length: 9.7 to 18.4mm, mean=12.86mm, SD=3.12 and width= 3.59 to 9.08mm, mean=6.37mm, SD=1.82). The number of minor calyces in the inferior pole was 2 to 5 (Length: 4.5 to 20.17mm, mean=8.95mm, SD=2.1 and width: 2.31 to 9.61mm, mean=4.96mm, SD=0.98). The LIP was between 54 and 159° (mean=92.8°, SD=25.71). The LIICA was between 2° and 139° (mean=41.38°, SD=10.71).

In the 10 patients of control group studied with 3D CT-scan we observed in the superior pole 1 to 3 major calyces. The mid-kidney had 1 to 4 major calyces. In the inferior pole we observed 1 to 2 major calyces (length: 1.98 to 22.52mm, mean= 14.54, SD=7.39 and width: 3.43 to 15.74mm, mean=8.31, SD=3.85). The number of minor calyces in the inferior pole was 0 to 3 (length: 4.14 to 18.89mm, mean=9.5, SD=1.87 and width: 1.65 to 8.54mm, mean=5.29, SD=2.06). The LIP was 47.4° to 114.27° (mean= 73.95, SD=24.99) and LIICA was 106.88° to 171.61° (mean=136.01, SD=12.76).

There was no statistical difference in the measurements of the inferior pole (length and width of major and minor calyces, and LIICA) between the groups with anomalies and the control group, both in polyester resin endocasts and in 3D CT-scan reconstruction images, as well for the LIP in the resin endocasts. We observed statistical difference when we compared the LIP in the 3D CT-scan between HK versus CUD (p= 0.003) and HK versus CG (p= 0.035). When we compared polyester resin endocasts versus 3D CT-scan reconstruction images, analyzing only the lower pole, we observed statistical difference: in LIP (p= 0.006), LIICA (p= < 0.001) and length of major calyces between CUD groups (0.034).

DISCUSSION

The anomalies of the urinary system are frequent and correspond to one third of all congenital malformations (1, 6). Congenital anomalies of the upper urinary tract comprise a diversity of abnormalities, including aberrant location, orientation and shape of the kidney, as well as variation of the collecting system and blood supply (6). The anatomic properties of anomalous kidneys present substantial obstacles to endourological procedures as consequence of the anatomical alterations, in special the position of the renal calices (18-20).

During embryogenesis, the normal ascent of the kidneys is stopped by the fusion of the lower po-

les, resulting in incomplete rotation, determining an anterior position of the collecting system. The horseshoe kidney has the insertion of ureter into the renal pelvis, superiorly and laterally displaced, leading to an impaired drainage of the collecting system, which predispose the patient to urinary tract infection (UTI) and urolithiasis, with an incidence of 21% to 60% (7). The anterior position of the horseshoe kidney pelvis, the varied positions of the calyx in relation to the kidney lateral margin, and the infundibula diameters (specially, in the inferior pole) are important anatomical features to be considered in patients with upper tract anomalies before endourologic procedures (6, 7).

Ureteral duplication may be incomplete or complete. If there are two separate pelvicaliceal systems joining at the ureteropelvic junction (UPJ), it is considered a bifid pelvis. On the other hand, if there are two separate ureters at the proximal aspect and they join at any point below the UPJ, before entering the bladder, the patient is considered to have bifid ureters (21).

A recent paper shows that due to the position and structure of the horseshoe kidney, the flexible ureteroscope needs to stay in large deflective status for relatively long time during the operation but remains effective in the resolution of moderate stone size in patients with horseshoe kidneys (22). LIP is one of the most important factors for successful results, although there is controversy about the limit considered unfavorable, varying from <30° to <90°, depending on the study (14, 23-25). According to Elbahnasy (14) the LIP>70° are considered a favorable factor to eliminate calculi from the lower pole.

In our sample, we observed that in the 3 endocasts of horseshoes kidneys studied, there were no differences in LIP when compared to controls. In HK endocasts the LIP has a mean of 71.67°, nevertheless, in one case (33.33%), the LIP was 16°, a very restrictive condition to ureteroscope access. In reconstructed 3D CT-scan images of horseshoe kidneys, we observed a mean of 44° in LIP with significant difference when compared to control group, nevertheless, in 5 CT-scan HK (83.3%) the LIP was lower than 70° and in one case (16.6%) the LIP was 23°, an unfavorable factor to ureteroscope access, as well as to eliminate calculi fragments.

In endocasts of kidney with CUD the LIP mean was 98.50° without differences when compared to controls, also, we did not observe cases of restrictive factors to ureteroscopic access. In 3D CT-scan of CUD the LIP mean was 88º, without differences when compared to controls, nevertheless, in 5 CUD studied (50%) the LIP was lower than 70°, and in 1 case the angle was 44°, unfavorable to uereteroscopic access.

Size and volume of calices are also limiting factors for URS success, regardless of location (26). Long infundibular length (> 3cm) and narrow width (< 5mm) lead to lower URS success rates (14). In our sample we did not observe differences in the measurements of length and width of major and minor calyces, and LIICA of inferior pole between the groups of anomalies and control group in polyester resin endocasts and 3D CT-scan reconstruction images. In CUD and horseshoe kidneys analyzed we did not observe limiting factor in lower pole regarding the size of calices, which could lead to additional difficulties during endourologic procedures (4).

When we compared polyester resin endocasts versus 3D CT-scan reconstruction images, we observed some statistical differences in measurement of lower pole highlighting the LIP (p= 0.006), the LIICA (p= < 0.001) and the length of major calyces between CUD groups (0.034). This find is very interesting and important and raises an important question: which of the measures taken is more reliable? Endocasts or 3D? The study with 3D CT-scan is more feasible but new studies with bigger samples will be necessary to answer this question.

For our surprise, we observed significant differences only in LIP of horsehoe kidney in comparation to the control group; we did not find differences in other anatomic factors. In CUD we did not observe significant differences in lower pole anatomy compared with control group, and this is a very interesting point. Some recent papers show good results with URS in horseshoe kidneys (22) and some papers showed that the PNL presented more difficulties to treat the stones in HK anomaly (less stone free, more transfusion) (7). The anatomic findings of the present paper shows that the horseshoe kidneys had more restrictive factors than the CUD in lower pole. Ectopic kidneys show great variation in origin, number, and size of renal arteries and veins (5). The complica-

tions after PNL in patients with horseshoes kidney could be more consistently explained by vascular anomalies instead of collecting system restrictive factors, nevertheless, in general, the presence of a horseshoe kidney does not affect the outcome of PNL and URS (27).

We have to mention some limitations of this study: a) the small sample size. It is important to note that the access to human kidneys to endocast obtainment is very limited; horseshoe kidney and complete ureteral duplication are very rare, so observations on a small sample may be important, although the small number is a weakness; b) it would be interesting to see if there is a correlation between our postmortem measurements and measurements taken by MRI, CT or US (either 2-D or 3-D), but due to technical difficulties this evaluation was not possible in our sample. The major limitation of the study was the impossibility of having previously performed URS and SWL in endocasts and in 3D-CT scan patients in order to confirm the caliceal accessibility with a flexible ureteroscope.

CONCLUSIONS

The spatial anatomy of lower pole is of utmost importance during endourologic procedures in patients with kidney anomalies. In the present paper we observed that horseshoe kidneys had more restrictive anatomic factors in lower pole than the complete ureteral duplication.

ABBREVIATIONS

3D = three-dimensional
CG = Control group - CG
CUD = complete ureteral duplication
HK = horseshoe kidneys
LIICA = angle between the lower infundibulum and the inferior minor calyces
LIP = angle between the lower infundibulum and renal pelvis
PNL = Percutaneous Nephrolithotripsy
SWL = Extracorporeal Shock Wave Lithotripsy
URS = Retrograde Flexible Ureteroscopy

CONFLICT OF INTEREST

None declared.

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Microdissection TESE versus conventional TESE for men with nonobstructive azoospermia undergoing sperm retrieval

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INTRODUCTION

Sperm retrieval techniques are classically used to harvest sperm from the epididymis and testis of men with azoospermia seeking fertility (1). After a successful sperm retrieval, intracytoplasmic sperm injection (ICSI) is mandatory because epididymal and testicular sperm cannot fertilize oocytes by conventional in vitro fertilization (IVF) (2).

For men with nonobstructive azoospermia (NOA) undergoing sperm retrieval (SR), the testis is the target organ because sperm production, if present, is generally minimal and restricted to the seminiferous tubules (1, 3). Both percutaneous and open methods can be used to harvest sperm from the testis of these patients. These methods are widely known by their acronyms TESA (testicular sperm aspiration), TESE (testicular sperm extraction), and microdissection TESE (microdissection testicular sperm extraction), based on the use of percutaneous or open approaches and whether or not microsurgery is utilized (1).

TESA relies on percutaneous needle aspiration, usually using a large needle connected to a syringe. The needle is inserted into the testis, negative pressure is created, and the tip of the needle is moved within the testis to disrupt the seminiferous tubules and sample different areas (1, 4). Conventional TESE (cTESE) relies on single or multiple open testicular biopsies carried out without magnification. By contrast, microdissection TESE (mTESE) relies on an operating microscope and microsurgical technique to identify and extract seminiferous tubules more likely to contain sperm (1, 4).

Despite being a relatively simple procedure, needle aspiration should be the last option for men with NOA. The reasons relate to the twice lower sperm retrieval rates (SRR) reported for TESA (~10-23%) compared with cTESE and mTESE (~40-50%) (4-7). Moreover, complications are more frequent with TESA, and according to some studies, it may affect up to 24% of patients (5).

Even if TESA is successful, the number of harvested sperm is typically lower than cTESE and mTESE, limiting the availability of sperm for cryopreservation (8). For these reasons, we do not support the routine use of TESA for NOA males. However, TESA is still carried out, for example, in low resource centers, particularly in patients with a history of previous positive retrieval by TESA or a biopsy report showing hypospermatogenesis (7, 9).

WHAT GUIDELINES RECOMMEND

According to the 2021 American Urological Association (AUA)/American Society of Reproductive Medicine (ASRM) Guidelines on 'Diagnosis and Treatment of Infertility in Men', mTESE should be performed in men with NOA undergoing sperm retrieval (10). By contrast, cTESE or mTESE is the technique of choice according to the 2021 European Association of Urology (EAU) Guidelines on 'Male

Sexual and Reproductive Health' (11).

The evidence supporting the AUA/ASRM guideline relates to the findings of two systematic reviews directly comparing cTESE and mTESE (6, 12). Based on data compilation of seven studies providing a direct comparison between both techniques, including 1254 patients, the pooled SRR was 52% for mTESE and 35% for cTESE, meaning that mTESE was 1.5 times more likely to result in successful SR than cTESE (6). The SRR ranged from 42.9% to 63% in mTESE versus 16.7% to 45% in cTESE (12). The differences were statistically significant in five of seven studies. Interestingly, in a subanalysis by histopathology of specimens taken during the operations, mTESE performed better in all categories but more remarkably among men with Sertoli cell-only (SCO) (6, 12).

By contrast, the evidence supporting the EAU guideline relates to the results of a large meta-analysis by Corona and co-workers published in 2019 (13). In this study, the authors included over 100 studies using either mTESE alone, cTESE alone, or both procedures, accounting for over twenty thousand patients with presumed NOA. Corona et al. reported an overall SRR of 47%, with no differences between cTESE and mTESE techniques.

A CRITICAL APPRAISAL OF EXISTING EVIDENCE

Although we should commend Corona and co-workers for their efforts in undertaking such an exhaustive review of the available data, their results indicating similar effectiveness using either method was based, overwhelmingly, on trials that did not directly compare both techniques. These trials, in most cases, reported SRRs one way or the other, using different patient populations (13). Therefore, their study's design was entirely different from meta-analyses compiling data of studies directly comparing cTESE and mTESE.

The methodological issue mentioned above was raised in a letter to the editor of Human Reproduction Update, which pointed out several other concerns in the study by Corona et al. (14). First, traditional meta-analytic techniques assume that effect sizes are independent. However, the reported effect sizes (i.e., SRR) are likely to be different for non-comparative trials because the studied populations vary and likely be heterogeneous. Since SRRs relate to the specific population from the primary studies, this structure creates dependence, and the pooled results based on conventional meta-analytic methods might be misleading. Indeed, we noticed substantial evidence of bias in the reporting of Corona et al., as up to 38% of mTESE trials involved selected patient populations with an unfavorable prognosis, such as patients with previous failed SR or men postchemotherapy (14). By contrast, only ~6% of the cTESE trials included the so-called unfavorable patients, thus possibly overestimating the SRR for cTESE.

Second, although it is well-known that SRR depends on histopathology results, with poorer outcomes for SCO patients than maturation arrest and hypospermatogenesis (15, 16), the study of Corona et al. was not controlled for this critical confounding factor. We carefully analyzed the studies included in the above meta-analysis and found that the proportion of patients with SCO or tubular atrophy was significantly higher in mTESE trials than cTESE trials (57.3 vs. 46.8%) (14). We, therefore, reassessed the SR estimates, pooling the data of only non-comparative studies that provided diagnostic histopathology details. On this basis, we found that, overall, mTESE resulted in significantly higher SRR than cTESE (50.3 vs. 47.4%, p=0.002) (14). Additionally, when the analysis was limited only to patients with SCO, mTESE resulted in a significantly higher SRR than cTESE (34.7% vs. 31.2%, p=0.019) (14).

We also compiled the data of controlled studies directly comparing mTESE versus cTESE. In this analysis, the differences were even higher in favor of mTESE. Overall, the relative risk (RR) of finding sperm was 1.35 times higher using mTESE (95% confidence interval [CI]: 1.14 to 1.61; p=0.0003) (14). Our analysis of controlled studies indicated that the number of patients needed to be treated (NNT) by mTESE (vs. cTESE) to obtain one additional positive SR was 7.6 (95% CI: 5.0-16.6) (14). Moreover, mTESE was even more advantageous in patients with the worst histopathology phenotype, i.e., SCO (SRR: mTESE 36.1% vs. cTESE 13.3%; RR: 2.70, 95% CI: 1.72 to 4.24; p<0.0001). In SCO patients, the NNT by mTESE (vs. cTESE) to obtain one additional successful SR was only 4.4 (95% CI: 3.2 to 7.1) (14).

Collectively, our reanalysis of Corona et al. data (13) showed that the SRR is indeed affected by

the surgical technique, provided strict diagnostic criteria are applied to identify the NOA patient. Notably, the higher the study's quality (i.e., controlled trials), the higher the magnitude of the effect size, as fewer patients need to be treated by mTESE vs. cTESE to achieve one additional positive SR when data of controlled studies (vs. non-controlled studies) are compared (14). Since SR success depends on many different factors, including patient selection criteria, surgeon's experience, embryologist's expertise, and laboratory technique to process retrieved specimens, only studies directly comparing cTESE versus mTESE can be considered in a meta-analysis assessing the effectiveness of these techniques.

Although further studies would be certainly welcomed in this area, mainly randomized controlled trials, there exists level 1 evidence from well-performed meta-analyses that compiled data of studies directly comparing mTESE vs. cTESE (6, 12). Based on these studies, there seems to be little question that mTESE provides optimized SR results in expert hands. Therefore, urologists should be judicious in interpreting the existing data as our ultimate goal is to deliver the best care to infertile men with NOA seeking biological parenthood.

BEYOND SPERM RETRIEVAL RATES

Besides SRRs, other endpoints to consider in studies comparing mTESE vs. cTESE include complication rates, quantity and quality of sperm collected, and ICSI outcomes. In a 2021 study, we summarized the published evidence on the most relevant endpoints using nearly 120 articles (17). We found that in the general population of NOA patients who have not undergone previous SR (naïve population), the pooled SRR by mTESE was 46.8%. Additionally, in studies reporting SR by mTESE for men with a history of failed TESA or cTESE, the SRR was 39.1%.

We also showed that mTESE was associated with an overall 2.6% complication rate (17). The reported complications were mainly minor and included persistent pain, infection, and hematoma. But a few cases of testicular fibrosis and atrophy were reported following mTESE. Importantly, in controlled studies directly comparing the techniques, the complication rate was lower using mTESE than cTESE (1.3% vs. 3.0%, respectively), attributed to less testicular tissue extraction and preservation of intra-testicular blood supply (17).

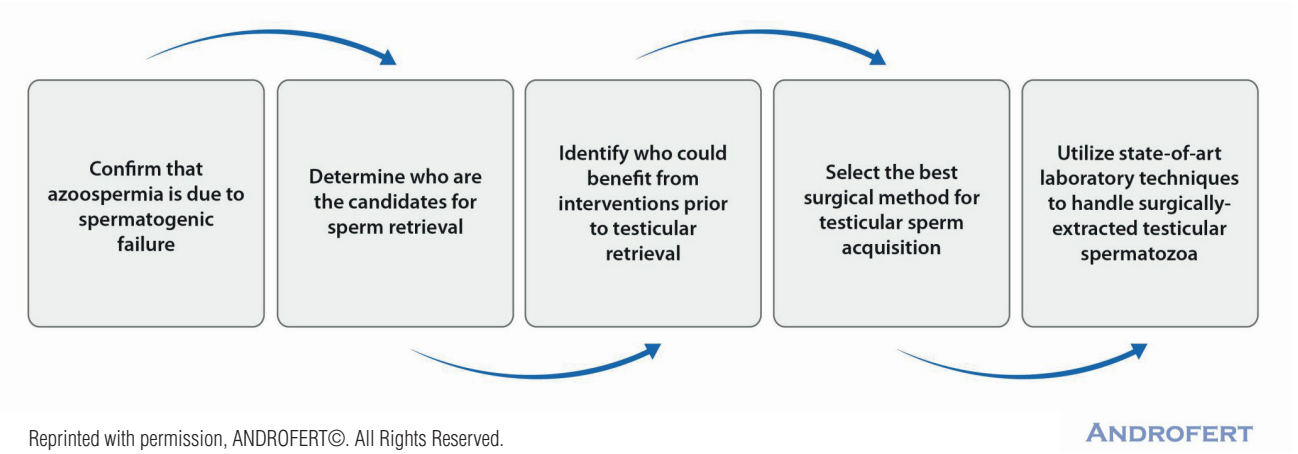
Consistent with the above findings, fewer complications have been reported on ultrasound examination after mTESE than cTESE (12). Also, the amount of tissue extracted has been reported to be lower in mTESE vs. cTESE (12, 18). But notably, in the cases where mTESE is aimed for sperm cryopreservation or when sperm-producing seminiferous tubules are minimal, it may be necessary to remove larger quantities of testicular parenchyma that may equal or even exceed that of cTESE. In these cases, the advantages of mTESE relate to a richer harvest or a poor but positive sperm recovery.

Concerning ICSI outcomes, our review mentioned above indicated that fertilization rates and pregnancy outcomes with testicular sperm retrieved by either mTESE or cTESE were inconsistently reported. Of note, no published data exist on these endpoints from studies directly comparing the techniques. Nevertheless, polled data of studies using mTESE alone indicate that the fertilization rate of testicular sperm by ICSI was about 57% (17). Along these lines, the pooled clinical pregnancy rate per embryo transfer cycle was 39%. Miscarriage, defined as the spontaneous loss of a clinical pregnancy before 22 completed weeks of gestational age, was seldom reported in the literature. Finally, live birth, defined as the delivery of at least one liveborn infant per transfer, was reported to be about 24%, but only a few articles provided data on live birth (17). These figures indicate that approximately one in four couples whose male partners had a successful sperm retrieval by mTESE take a baby home using ICSI with the patients' sperm.

OUR CLINICAL APPROACH

The clinical management of men with NOA seeking fertility has been a tremendous challenge for andrologists, urologists, and reproductive medicine specialists. We developed a five-step algorithm to most optimally manage these patients at our Clinic (Figure-1), detailed elsewhere (3). Briefly, it includes:

Figure 1 - Step-by-step approach for the clinical management of men with nonobstructive azoospermia seeking fertility.



ANDROFERT

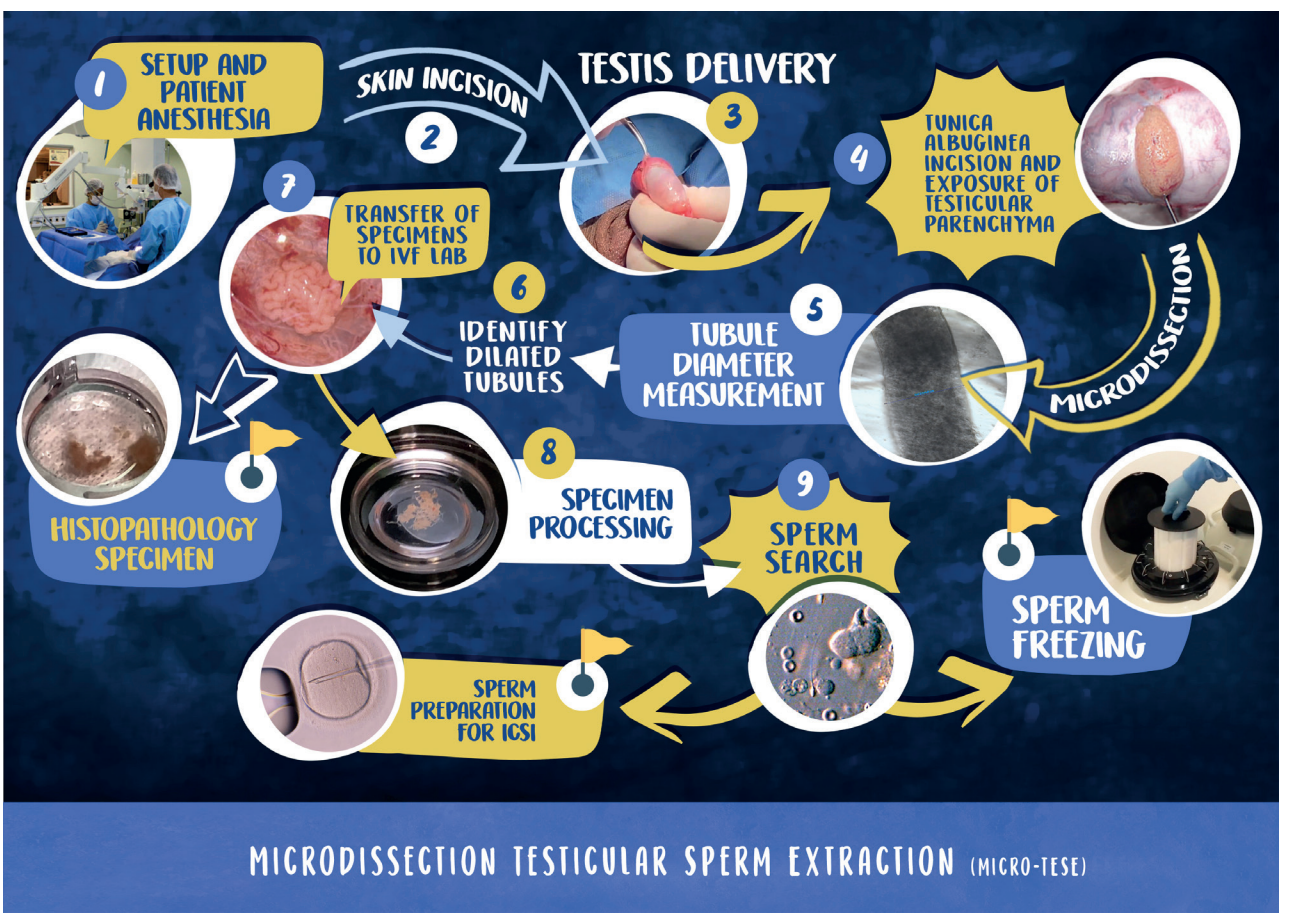
i. Differential diagnosis with other types of azoospermia (19);
ii. Patient counseling about the chances of successful sperm retrieval and biological parenthood, which includes the use of genetic testing for diagnostic purposes and treatment guidance (20);
iii. Consideration for hormonal modulation or microsurgical varicocelectomy to increase sperm retrieval success in selected cases (9, 19, 21);
iv. Application of the most effective and efficient sperm retrieval technique (6, 12, 14, 22-24);
v. Use state-of-art laboratory techniques for handling and freezing testicular sperm and cultivating the embryos resulting from testicular sperm injections (25, 26).

In our hands, mTESE is the method of choice to harvest sperm from the seminiferous tubules of NOA males. A visual map of mTESE the way we do it at our Clinic is provided in Figure-2. A short movie illustrating the key operative and laboratory aspects of the procedure is available at <www.brazjurol.com.br/videos/may_june_2013/Esteves_440_441video.htm> (23).

Our facility includes two independent cleanroom IVF laboratories side-by-side, located next door to the operating theater (25). This setup allows embryologists to dedicate enough time for the NOA cases while the routine IVF/ICSI workload is taken care of in the other lab. We feel these details can make a difference. Indeed, our results with mTESE in a population of over one thousand men with NOA have been reassuring, with an overall SRR of 56%, varying according to the predominant testicular histopathology pattern (Hypospermatogenesis: 98%; Maturation arrest: 59%; SCO: 31%; Tubular sclerosis: 25%) (unpublished data). We believe that a state-of-art IVF lab, well-trained embryologists, good laboratory practices, and quality management are critical to optimizing embryonic and pregnancy outcomes. Overall, in a cohort of 912 ICSI cycles performed from 2007 to 2020 using testicular sperm retrieved from NOA males (average male age: 34.9 years; range: 23-64; average female age: 34.6 years; range: 21-44), two-pronuclei fertilization rates, blastulation rates, live birth rates, and cumulative delivery rates per aspirated cycle were 69.2%, 45.6%, 33.6%, and 44.2%, respectively (unpublished data).

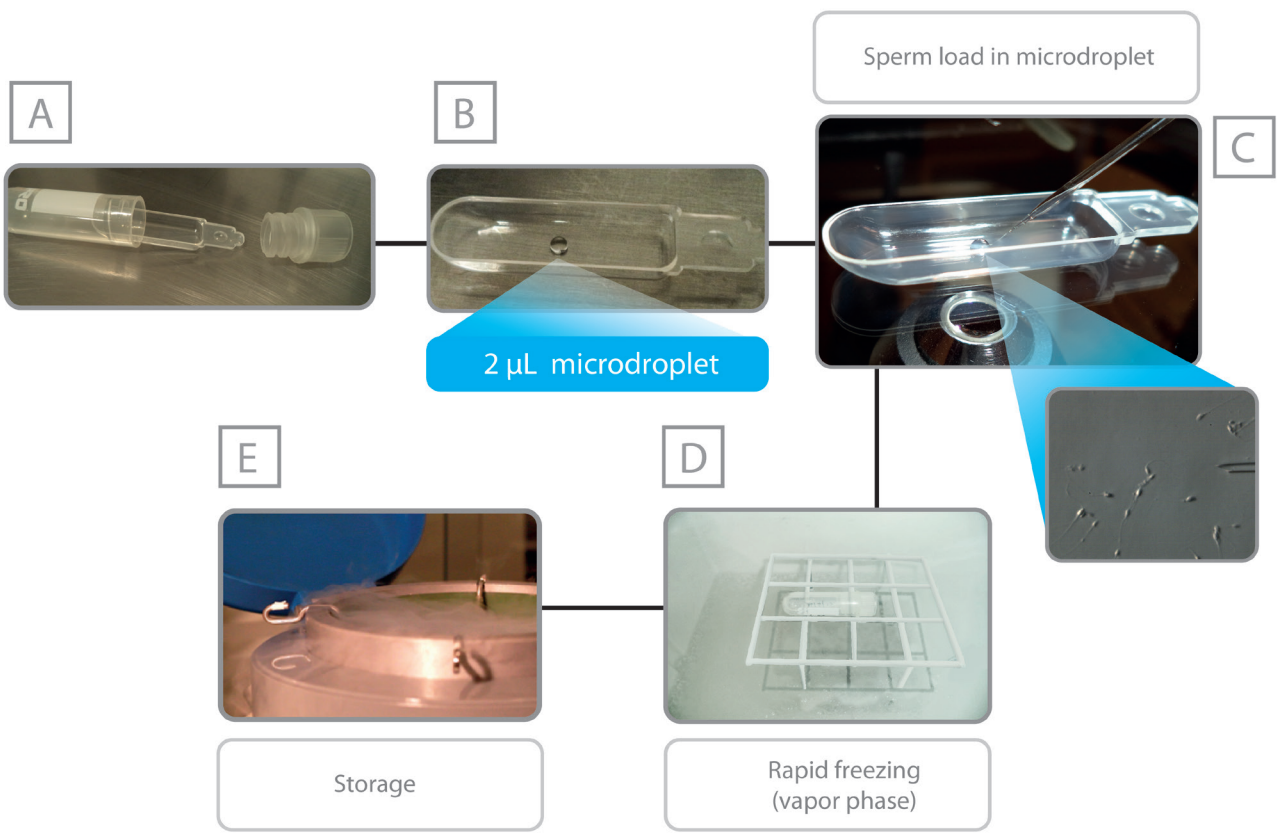
Currently, our preference is to perform mTESE as a separate procedure, before ovarian stimulation and oocyte pick-up. Sperm harvested from the seminiferous tubules are cryopreserved for future use. Our preferred method for freezing testicular sperm is vitrification using 'The Cell Sleeper method' (9, 27, 28). Briefly,

Figure 2 - Microdissection Testicular Sperm Extraction Visual Map. The patient is brought shaved to the operating room, placed supine, prepped, and draped accordingly. Microdissection TESE is usually performed outpatient, under intravenously combined with local anesthesia (1). A transversal scrotal incision is fashioned (2), and the hemiscrotum is entered. The tunica vaginalis is opened, and the testis is delivered (3). An equatorial non-linear incision is fashioned in the tunica albuginea using a knife under operating microscopy at 6 to 8 times magnification (4). Microdissection is carried out through all areas of the superior and inferior poles of the testis. Magnification of 16 to 25-times is used when searching for the largest seminiferous tubules (5). Enlarged seminiferous tubules are identified (6 and 7), removed with micro-forceps, placed in a petri dish containing sperm culture medium (8), and sent to the IVF laboratory for examination (8). One or more specimens are taken for a histopathology examination. In general, the largest the tubule diameter, the greater the chance of finding active spermatogenesis (5). The extracted tubules are squeezed mechanically, and the cell suspension is examined under the inverted microscope in search of sperm (9). The surgeon is informed promptly if any sperm are found. Additional specimens can be taken to secure enough sperm for ICSI and freezing. The albuginea and vaginalis are closed, and the testicle is placed back to the hemiscrotum. Lastly, the dartos and skin layers are closed with absorbable sutures. The patient is discharged a few hours later.



Cell Sleepers consist of an outer vial, an inner tray, and a screw cap. Sperm are picked up with the microinjection pipette and ejected into the droplet on the tray. The tray is placed into the vial, and the vial is firstly frozen on liquid nitrogen vapor, then submerged in liquid nitrogen for storage (Figure-3). This procedure is advantageous from a quality management perspective. It allows ICSI to be carried out using frozen-thawed testicular sperm without programming mTESE concomitantly to the oocyte

Figure 3 - Testicular sperm cryopreservation using Cell-sleepers. The Cell Sleeper (Nipro, Japan) consists of an outer vial, an inner tray, and a screw cap (A). The inner tray is placed onto the lid of a large culture dish, and a 2-µ L droplet of cryopreservation solution is pipetted into the tray, in a central position (B). Spermatozoa are aspirated and ejected into the droplet with the aid of a microinjection pipette (C). Immediately after that, the tray is returned to the vial, and the vial is closed with the screw cap. The vial is placed in a horizontal position 4-5 cm above the surface of liquid nitrogen (D). After 2 min, the vial is submerged in liquid nitrogen and secured into a cryopreservation cane for long-term storage (E).



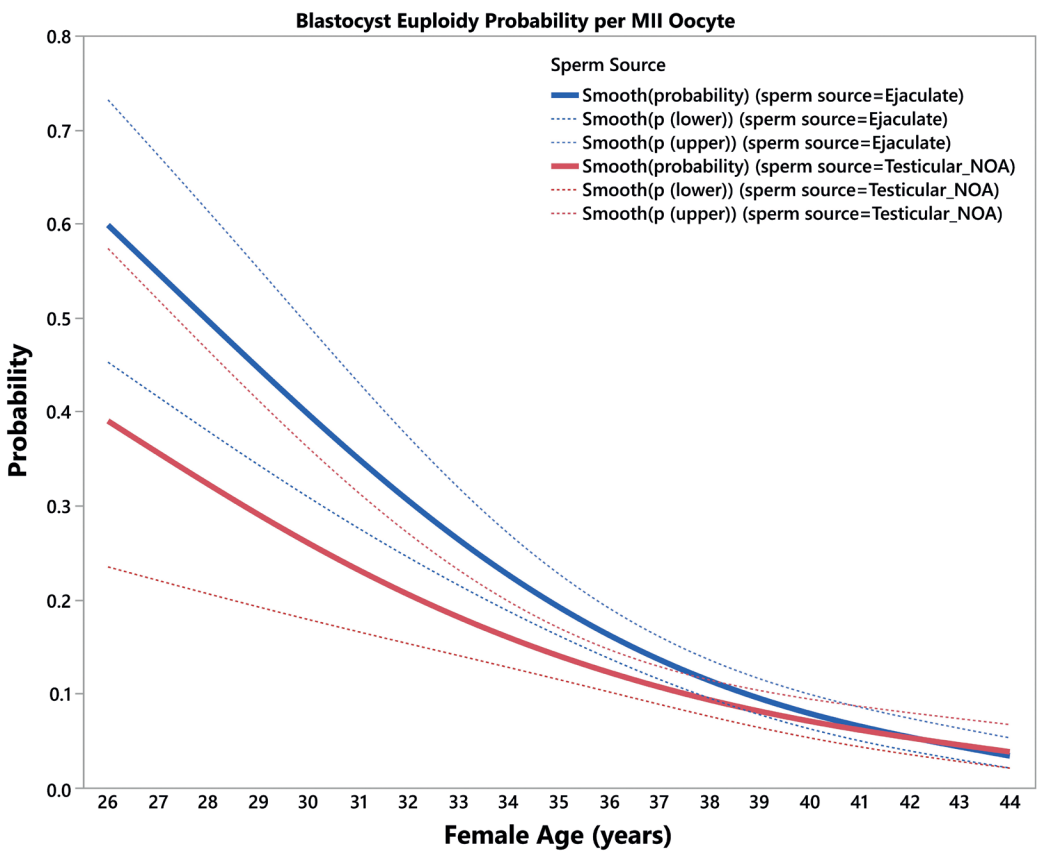
pick-up. Our experience using fresh and frozen-thawed testicular sperm for injections indicates no significant difference in outcomes, therefore consistent with what has been reported in the literature (29).

Our research has show that the probability of having genetically normal blastocysts after ICSI is adversely affected by using testicular sperm taken from men with NOA (Figure-4) (30, 31). It means more oocytes are needed to obtain at least one euploid blastocyst for transfer in each couple undergoing ICSI with testicular sperm. Therefore, planning the ovarian stimulation regimen to increase oocyte yield is critical to improving the chances of biological parenthood for these couples. In our settings, we use a predictive model to estimate the number of metaphase II oocytes needed to obtain at least one euploid blastocyst for transfer in couples undergoing IVF-ICSI (Figure-5), which is particularly helpful for couples of NOA males (30).

GAPS IN KNOWLEDGE

Although significant advances have been achieved in this area, there are still several knowledge gaps to be filled to improve our decision-making. We need more data from high--quality studies comparing cTESE and mTESE, controlling for relevant confounders, investigating SRRs and complications, quantity and quality of sperm collected, and ICSI outcomes, including the health of resulting offspring. We also need to know if there is a role for hor-

Figure 4 - Blastocyst euploidy probability per metaphase II oocyte. The plots show the probability of a metaphase II (MII) oocyte turning into a euploid blastocyst as a function of female age. The estimated probabilities (solid curves) and their 95% confidence interval (dotted curves) are presented according to sperm source to be used for IVF/ICSI, namely, ejaculated sperm (blue) and testicular sperm extracted from patients with non-obstructive azoospermia (NOA) (red). The relations are non-linear and characterized by a differential modulatory effect of sperm source across age. The effect size of female age on blastocyst euploidy probability per MII oocyte from the year (t) to year (t+1) was defined as the ratio p(t+1)/p(t) × 100. There was a significant decrease (p<0.001) in the probability of an MII oocyte becoming a euploid blastocyst with aging.

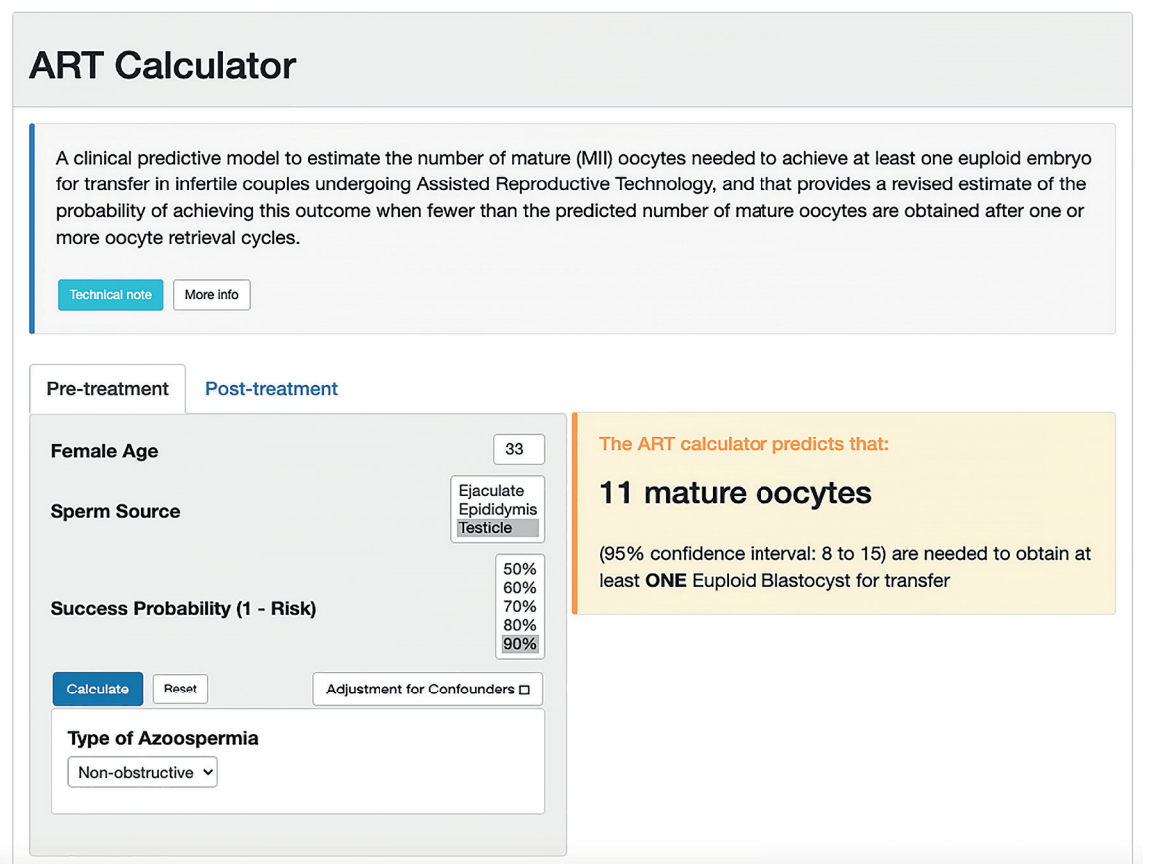


monal stimulation before SR and what type of patient might benefit from it. Further research is also warranted on predictors of SR success as it would be ideal for identifying who is eligible for SR, thus avoiding unnecessary operations. Lastly, we need to invest in better laboratory techniques to process and freeze testicular sperm and select the best sperm for injection. While we should certainly consider these limitations, they should not refrain us from using the best available evidence to guide our decisions in the best possible interest of our patients.

CONCLUSIONS

Nonobstructive azoospermia represents the most challenging male infertility condition to manage. Despite that, it is not synonymous with sterility, as ~50% of the affected men have residual intratesticular sperm production. Sperm retrieved from the seminiferous tubules can be used for ICSI and result in viable offspring. An effective and safe SR technique is critical to offer these patients the highest chance of biological

Figure 5 - ART Calculator. Online calculator to estimate the minimum number of metaphase II oocytes required to obtain at least one euploid blastocyst for transfer in infertile patients undergoing IVF/ICSI cycles. The figure shows how the calculator is used in an office-based setting. (A) Pretreatment, clinicians input the patient's age and the sperm source for IVF/ICSI. If the option "Testicle" is marked, then the type of azoospermia (obstructive or nonobstructive) should also be defined. The user sets the probability of success for the estimation, which indicates the chance of having ≥1 euploid blastocyst when the predicted number of mature oocytes is achieved. Once the button "calculate" is pressed, a text box will pop up on the right side of the screen, indicating the predicted minimum number of metaphase II oocytes needed for obtaining at least one euploid blastocyst, with its 95% confidence interval. (B) Posttreatment, i.e., when fewer than the predicted number of metaphase II oocytes are obtained after one or more oocyte retrieval cycles. Clinicians input the pretreatment information and the actual number of metaphase II oocytes collected or accumulated. The user sets the probability of success; it reflects the chance of correct estimation according to the exact number of oocytes obtained. Once the button "calculate" is pressed, a text box will pop up on the right side of the screen, indicating the predicted probability of achieving ≥1 euploid blastocyst with the number of mature oocytes available. The ART calculator can be found online at http://www.members.groupposeidon.com/Calculator/.



parenthood while preserving testicular function as much as possible. Microdissection TESE has been shown to fulfill these goals better than conventional TESE. Although SR is a critical element in the management of NOA males seeking fertility, the optimal management for the couple requires a coordinated multidisciplinary effort involving reproductive urologists, andrologists, reproductive endocrinologists, embryologists, and quality managers.

CONFLICT OF INTEREST

None declared.

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Organic or psychological? It does matter!

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COMMENT

Sexology formally began as a science in 1907 when Iwan Bloch proposed the creation of a scientific area for understanding sex and named it Sexualwissenschaft (sexual science or sexology), in German. In 1908 Magnus Hirschfeld published the first magazine dedicated to sexual science; (Zeitschrift Fur Sexualwissenschaft); in 1913 the first sexology society was founded - (the Medical Society for Sexology and Eugenics) by Magnus Hirschfeld, Iwan Bloch, Albert Eulenburg and in 1921 the first sexology congress was held (1).

Until the 20th century, it was believed that the basis of sexual dysfunctions was almost entirely psychological, mainly due to little knowledge of the human sexual response physiology. According to Masters and Johnson, in 1970, 90% of sexual impotence cases were psychogenic (2).

Human sexuality is based on perfect psyche-body functioning and dysfunctions usually result from an imbalance in this binomial. The evolution of knowledge on male and female physiology sexual responses made it possible to understand that various organic processes could also lead to erectile disorders (3). Many authors currently consider that most erectile dysfunction (ED) causes are organic (4).

This new knowledge quickly led to the medicalization of the treatment of sexual dysfunctions, reinforced by the launch of phosphodiesterase type 5 inhibitors (PDE5 i). They provide a safe and effective way to improve erectile response and also give the patient and physician the feeling that sexual dysfunctions can be solved with medications.

Although these drugs can be of great help to patients with psychogenic ED, the fact of using a drug to treat a sexual dysfunction has, in turn, led to an "organicization" of sexual dysfunctions. Everything started to have an "organic" cause.

However, on what is this "medical reductionism" as defined by Janinni et al. (4) based? Risk factors started to be confused with etiology. Diabetic men are at higher risk of developing ED, however, diabetes is not the cause, but diabetic neuropathy, which affects some diabetic men. The same occurs with other risk factors such as obesity, smoking, metabolic syndrome, etc. When a diabetic or hypertensive patient complains of ED, the doctor immediately thinks of organic ED, without being interested in an emotional cause that may be over-combined or prevalent. And immediately prescribes a pill of a PDE-5i. Sometimes, when patient does not get a good response for any reason or is not interested on use the medication, he can receive an indication of penile implant.

On the other hand, the workup for diagnosing the organic causes of ED is very imprecise. The diagnosis usually needs to be made through anamnesis and from the perspective of the investigator. Most of the complementary exams used

are inaccurate and very prone to errors, which facilitates the lack of interest in the search for the etiology of ED.

The best propaedeutic tool to differentiate between psychogenic and organic ED is nocturnal penile tumescence tests. Although some question it (5), the presence of a rigid erection during sleep proves that the nerve pathways, penile arterial irrigation, and the veno-occlusive system function properly (6). However, tests in sleep laboratories are very expensive, inaccessible and many laboratories are not equipped to measure nocturnal penile tumescence. Devices that assess nocturnal tumescence at home (eg Rigiscan™) have practically disappeared from the market due to lack of demand.

Another widely used test is the penile artery Doppler ultrasound for diagnosing penile vascular dysfunctions. This test depends on the relaxation of cavernous sinusoidal smooth muscle by vasoactive drugs injected into the penis. However, this test is influenced by the patient's state of anxiety, which negatively impacts smooth muscle relaxation (7). Additionally, frequently more than one injection is needed (8), the action of drugs can be impacted by smoking (9) and this test is very prone to false-positive results (10). The same considerations apply to the different types of cavernosometry that have been described over the years; all depend on the action of vasoactive drugs on the smooth muscles of the corpora cavernosa and are greatly influenced by the individual's adrenergic state (11).

When thinking about possible neurological etiologies such as diabetic or alcoholic neuropathies, or even damage to neurovascular bundles during radical prostatectomy, we must remember that there is no electroneuromyographic method that assesses penile autonomic innervation. According to Giuliano and Rowland, no neurophysiological exam is capable of evaluating the integrity of the pro-erectile penile innervation and should not be recommended for the evaluation of patients with ED (12). In the past, electromyography of the corpora cavernosa has been tried, but unfortunately, the results have not advanced and this method is still considered experimental (12).

The development and subsequent release of PDE-5i reinforced the "ED organicity". They have been widely studied in multicenter, randomized, placebo-controlled investigations in thousands of patients. Hatzimouratidis (13) wrote a review of sildenafil studies and reported high effectiveness in different groups of patients with ED. Except for patients with ED after radical prostatectomy, which can be considered a cause of ED, the other groups were composed of patients with risk factors: hypertensive, coronary artery disease, diabetics, etc. Every investigator who took part in these studies (14) remember that the cause of ED, whether organic or psychological, was at the investigator's discretion in most of the studies and no exam was performed to determine it.

On the other hand, the proper response of PDE-5i depends on an integral organic substrate. These drugs promote an active inhibition of the PDE-5 enzyme increasing cyclic guanosine monophosphate (cGMP), which facilitates smooth muscle relaxation (15). However, to occur an erection there must be the arrival of pro-erectile stimulation to the penis, production of neuronal nitric oxide, production of cyclic GMP, relaxation of the smooth muscles of the corpus cavernosum, increase in penile arterial flow and occlusion of the venous system. Men with substantial alteration in this system, whether due to neuropathy, occlusion of the arteries, or fibrosis that prevents veno-occlusion, do not get an adequate erectile response with these medications. It can be at least suggested that most patients who respond well to PDE-5 inhibitors have a conserved erection mechanism and may not have an organic cause for their ED.

But what does all this matter? We have adequate treatments, many of them minimally invasive, safe, and affordable. Why is it important to know whether ED is psychogenic or organic?

The use of PDE-5i in patients with psychogenic ED can take away the opportunity of treating the dysfunction with psychological therapy. Additionally, many individuals do not use the medication as they should after some time. An example is hypertensive or diabetic patients who end up abandoning treatment or not using the appropriate doses.

Non-definition of the cause of ED and its adequate treatment may be the reason for the high discontinuation rate and patient dissatisfaction that the use of PDE-5i presents. Corona et al. (16) showed that, despite being highly effective, almost 50% of patients give up on its use during the first year of treatment. They identified that problems related to partnership and lack of effectiveness are mainly responsible for these rates. At the very least, problems with the partnership could be identified and addressed by psychological intervention. Atallah et al., in a recent published systematic review, reported that the combination of psychological interventions and the treatment with PDE-5 inhibitors are more effective on restoring erectile function and sexual satisfaction in patients with erectile dysfunction when compared with any of the treatments alone (17).

Failure to identify symptoms such as anxiety and depression, which are recognized causes of ED (4), can make the patient's treatment more difficult and lead to inappropriate conduct, as well as ineffective results.

Dos Reis et al. showed that 27.6% of patients who would undergo penile prosthesis implantation for the treatment of ED and who were evaluated by a psychologist in the preoperative period presented symptoms of anxiety and depression that led to the suspension of the surgery (18). Along the same lines, Trost et al. (19) identified what they called CURSED (compulsive/obsessive, unrealistic, revision, surgeon shopping, entitled, denial, and psychiatric patients) who are patients at a high risk of dissatisfaction after penile prosthesis implantation. On many occasions, these are not easily identifiable patients, and the risks of poor selection range from postoperative complications and patient dissatisfaction to legal proceedings, loss of credibility, and harm to the patient (20).

In our practice, we seek to assess the possible causes of ED and in the same way that we make sure to check testosterone levels to assess hormonal homeostasis, or a Doppler ultrasound to assess penile circulation, we also ask for an assessment with a psychologist/sexologist to evaluate the emotional status of the patient. Recently, the European Society of Sexual Medicine (ESSM) stated that a proper assessment of ED requires a medical and psychosocial evaluation and a multidisciplinary treatment has proven to be more effective in treating ED (21). While medications are focused on treating the symptoms, psychological treatment might help by promoting treatment adherence, as well as addressing psychological correlates and it can help on preventing a recurrence of the sexual dysfunction since patients learn to manage their dysfunctional response patterns (22).

It is important to remember that ED is multifactorial and the patient needs to be fully evaluated before starting any treatment. More and more, we see patients who use PDE-5i medications successfully but also have a desire for a more definitive solution, which usually can involve the resolution of emotional conditions.

CONFLICT OF INTEREST

None declared.

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Prostate cancer mortality and costs of prostate surgical procedures in the Brazilian public health system

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INTRODUCTION

Prostate cancer (PCa) is the most frequent type of cancer in the male population in 112 countries. PCa represents 14.1% of the incidence and 6.8% of the mortality by cancer worldwide, which represents 1.4 million new cases and 375.000 deaths in 2020 (1). In the same year, the age-standardized incidence rate of PCa was 65.5, whereas the mortality was 13.6 per 100.000 individuals in South America (1). According to the Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), one of the main Brazilian cancer institutes, PCa accounts for 29.2% of all cancers in males in Brazil (2). This represents 65.840 new cases of PCa in each year in the period 2020-2022 (2).

The etiology of PCa is still poorly understood and the most well-known risk factors are older age, genetic mutations, and a family history of this type of cancer (3). Smoking, excessive body weight and diet are some environmental factors that may be related to this cancer, but further studies are still necessary to confirm this (1, 3).

The guidelines for managing localized PCa depend on the severity of the tumor and on the risk group to which the patient belongs, according to the American Society of Clinical Oncology (4). The main approaches are surgical procedures (prostatectomies), radiotherapy, and androgen deprivation therapies. They can be applied alone or in combination. For low and very low risk localized prostate tumors in patients who have a high probability of progression, physicians may offer surgical procedures as a definitive treatment. In cases of intermediate and high risk localized PCa, prostatectomy or radiotherapy with androgen deprivation therapy should be recommended (4).

In Brazil, citizens have access to the Sistema Único de Saúde (SUS, the Brazilian Unified National Health System) which is responsible for undertaking preventive exams and treating numerous disorders and diseases, including cancer. Information regarding the number of hospitalizations, procedures, costs, number of deaths, mortality rates and other factors related to the treatment of PCa by SUS are available in the public database DATASUS. Furthermore, INCA is responsible for the Atlas On-line da Mortalidade (here referred to as the Online Atlas of Cancer Mortality), a database presenting information specifically on deaths and mortality rates related to cancer in Brazil (5). The main focus of this study is to present a description of data concerning PCa mortality, diagnosed cases, and the costs of prostate surgical procedures in the SUS based on these two public databases.

MATERIAL AND METHODS

Databases search

Two publicly available databases which contain data on the Brazilian public health system were used as the primary sources for this study: the Online Atlas of Cancer Mortality of INCA and the DATASUS. The search collected information regarding

mortality due to malignant neoplasm of the prostate (ICD-10-CM C61) between 1994 and 2019 from the Online Atlas of Cancer Mortality. The following data were gathered for each year: the number of deaths, the crude mortality rate of PCa, age-specific mortality rates of PCa, the age-standardized mortality rate for the world population mortality rate of PCa (considering the standard world population described by Doll et al. (6)), and the age-standardized mortality rate for the Brazilian population (considering Brazil's standard population of 2010 (6, 7)). Age standardization was applied in order to obtain results that are independent of the effects of age. The age-standardized mortality rate for the world population mortality rate of PCa will be referred to here only as "age-standardized mortality rate" and will be used to estimate the mortality trends of this type of cancer in the country. Brazil comprises five geographic regions -the North, Northeast, Central-West, Southeast, and South. The number of deaths according to regions and age were also included.

The search of the DATASUS database collected data regarding the number of PCa diagnoses, as well as the number and costs of hospitalizations for prostate surgical procedures between 2008 and 2020. More specifically, these procedures encompassed suprapubic prostatectomy, and radical prostate-vesiculectomy, which are referred to as prostatectomy in oncology, and radical prostate-vesiculectomy in oncology in the databases when used to treat PCa.

Searches in both databases were performed in April 2021. Submission of this work to the institutions Research Ethics Committee was not necessary, as data from public domain databases were used.

Trends of mortality rates in cancer epidemiology can be estimated by the annual percent change (APC) within a certain period. A positive value represents a rise in the mortality rate, whereas a negative one indicates a decline. The joinpoint regression method (8) was used to analyze age-standardized mortality rate PCa trends in the period 1994-2019 (95% confidence interval-CI). The value of the average annual percent change (AAPC) is a summary of APCs over a period of several years. The Joinpoint Regression Program (Version 4.8. 0.1; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) was used for this analysis (9). The standard controls of the software were used, and constant variance/homoscedasticity was assumed in respect of errors.

COMMENTS

The number of deaths due to PCa increased in the Brazilian male population during the period 1994-2019, going from 5.256 in 1994 to 15.576 in 2019. Consequently, crude mortality rate and age-standardized mortality rates showed a gradual rise over the years (Table-1).

In order to evaluate trends in PCa mortality over the years in Brazil, the joinpoint regression method was used with the age-standardized mortality rates of PCa between 1994 and 2019. The algorithm identified two joinpoints in which the trends of PCa mortality of the Brazilian male population have changed significantly, located in the years 2007 and 2015 (Figure-1). For the first period (1994-2007), the APC was 2.14% (95% CI, 1.6-2.7), indicating increasing mortality. For the second period (2007-2015), the APC was -0.76% (95% CI, -2.1-0.6). The last APC calculated was 2.42% (95% CI, -0.8-5.7) and refers to the period 2015-2019. Considering the CI of the 2nd and 3rd APCs, it is not possible to affirm whether the trends of age-standardized mortality rate of PCa were increasing or decreasing during the respective periods. The AAPC for the whole period (1994-2019) was 1.3% (95% CI, 0.6-1.9; $p < 0.05$), which shows an increasing trend in the age-standardized PCa mortality rate during this period.

Data from the DATASUS database showed that the number of PCa diagnoses in SUS remained relatively constant between 2013 and 2017: the lowest number was 22.396 in 2017, and the highest was 23.942 in 2014. In 2018 and 2019, the number of PCa diagnoses increased from 32.930 to 39.953, but fell to 27.358 in 2020 (Figure-2A).

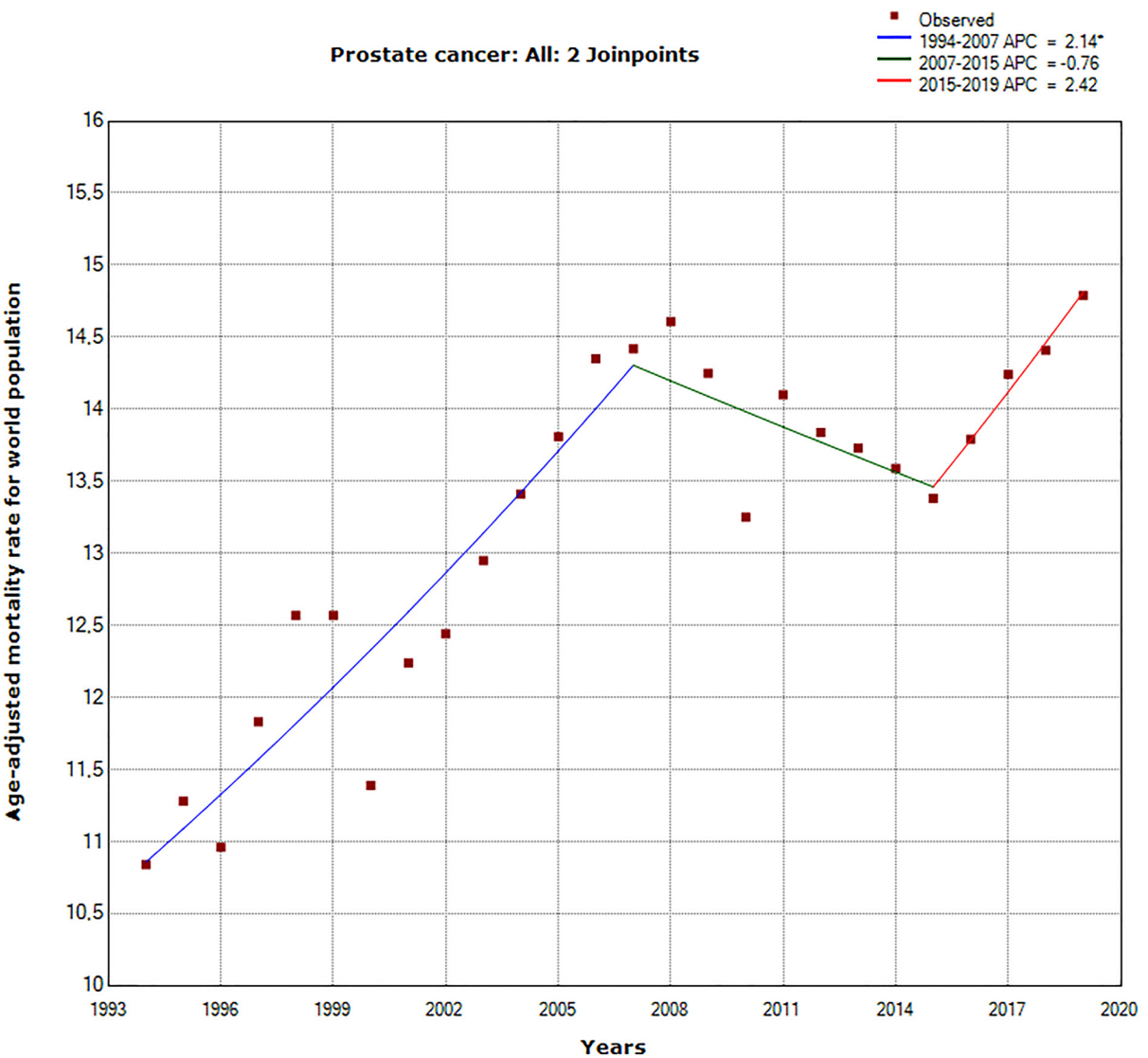
In the period 2013-2020, the number of PCa cases in SUS varied according to the age-range (Figure-2B). The yearly total of diagnoses was progressively higher in the 55-69 age group. A slightly gradual decrease was observed in the 70-74, 75-79, and ≥80 age-groups. Despite the growth in the total amount of diagnoses between 2017 and 2019 within the age-groups over 50 years old, a decrease occurred immediately after in 2020.

Table 1 - Deaths and mortality rates of PCa per 100.000 individuals 1994-2019 in Brazil.

Year	Deaths	Crude mortality rate (%)	Age-standardized mortality rate for world population (%)	Age-standardized mortality rate for Brazilian population (%)
1994	5.256	6.93	10.84	12.76
1995	5.542	7.20	11.28	13.22
1996	6.067	7.83	10.96	12.74
1997	6.652	8.45	11.83	13.88
1998	7.144	8.95	12.57	14.79
1999	7.223	8.93	12.57	14.83
2000	7.490	8.96	11.39	13.35
2001	8.033	9.20	12.24	14.48
2002	8.389	9.48	12.44	14.75
2003	8.977	10.02	12.95	15.37
2004	9.590	10.57	13.41	15.98
2005	10.214	11.13	13.81	16.55
2006	11.007	11.86	14.35	17.27
2007	11.478	12.23	14.42	17.34
2008	12.121	12.78	14.61	17.67
2009	12.274	12.82	14.25	17.24
2010	12.778	13.68	13.25	15.98
2011	13.129	13.45	14.10	17.14
2012	13.354	13.56	13.84	16.78
2013	13.772	13.86	13.73	16.70
2014	14.161	14.14	13.59	16.53
2015	14.484	14.35	13.38	16.25
2016	14.926	14.78	13.79	16.74
2017	15.391	15.25	14.24	17.25
2018	15.576	15.43	14.41	17.47
2019	15.983	15.83	14.79	17.92

*Adjusted by age according to world standard population per 100.000 individuals as described by Doll et al. (6).
#Adjusted by age according to Brazilian population of 2010 per 100.000 individuals.
Data from Online Atlas of Cancer Mortality from INCA (available at. https://mortalidade.inca.gov.br/MortalidadeWeb.

Figure 1 - Age-standardized PCa mortality rates in Brazil 1994-2019. The joinpoint regression conducted resulted in a positive AAPC of 1.3% (95% CI, 0.6-1.9; p <0.05) considering the age-standardized mortality rate of PCa in Brazil between 1994 and 2019.

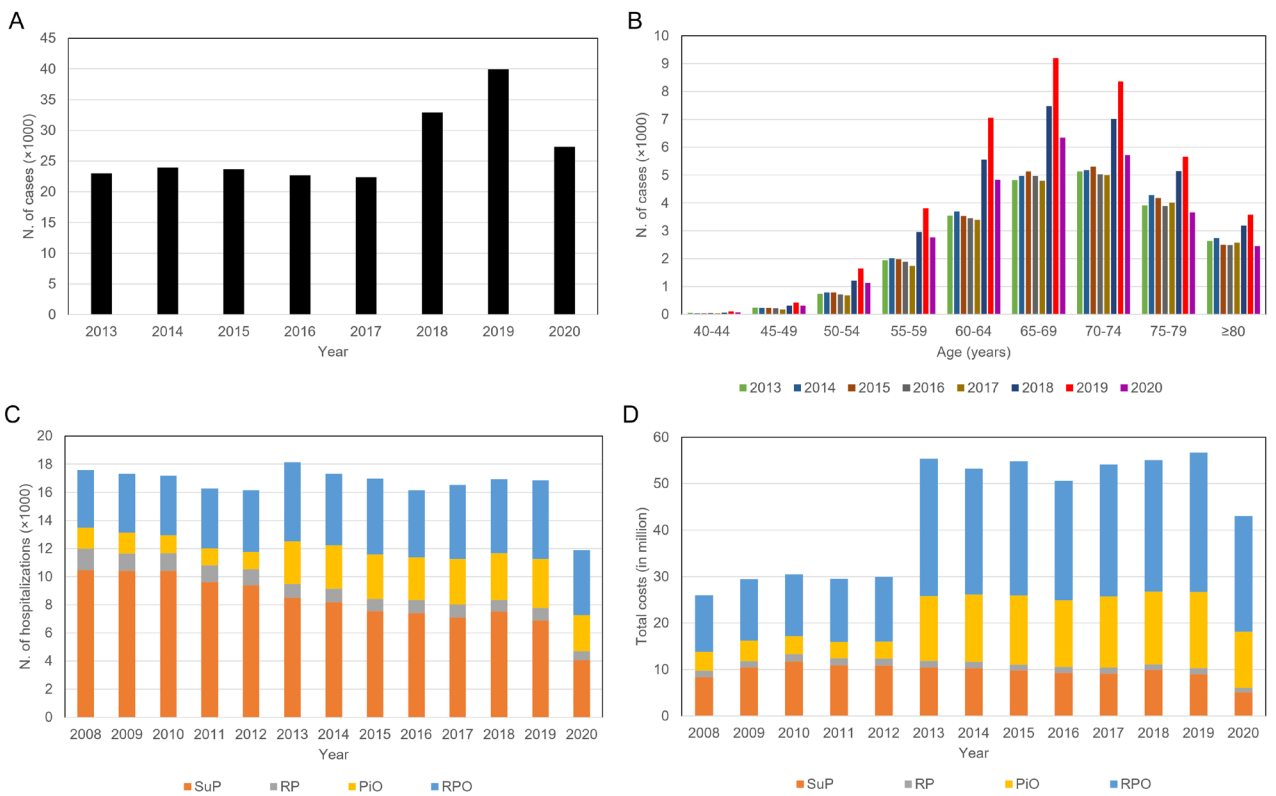


* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

An analysis of the number of hospitalizations for prostate surgical procedures reveals that it remained relatively similar between 2008 and 2019 (mean±standard deviation; 16.944±582.6 per year) (Figure-2C). In 2020, this number decreased to 11.875, which is 5.609 less than the mean of the previous years.

Between 2008 and 2012, the total costs of hospitalizations for prostate surgical procedures in SUS remained below 31 million BRL per year, and then increased to more than 50 million BRL in subsequent years, except for 2020. Radical prostate-vesiculectomy in oncology was responsible for the greatest costs in respect of prostate surgical procedures in each year in the whole period (Figure-2D). Although radical prostate-vesiculectomy in oncology represented the highest cost in all years of the period, since 2013 the total cost of this procedure per year has

Figure 2 - A) Number of PCa cases diagnosed in SUS in Brazil 2013-2020. B) Number of PCa cases diagnosed in SUS in Brazil by age 2013-2020. C) Number of hospitalizations in SUS Brazil for prostate surgical procedures 2008-2020. D) Total costs (in BRL) of hospitalizations for prostate surgical procedures in SUS Brazil 2008-2020. Procedures - SuP: suprapubic prostatectomy; RP: radical prostate-vesiculectomy; PiO: prostatectomy in oncology; RPO: radical prostate-vesiculectomy in oncology. Data from the database DATASUS (http://www2.datasus.gov.br/DATASUS/index.php).



practically doubled (27.8 million±1.7 million BRL; 2013-2020 period) compared to the period 2008-2012 (13.2 million±0.59 million BRL).

As in most countries, PCa is the most incident type of cancer in the male population of Brazil, excluding non-melanoma skin cancer (1, 2). In the period 1994-2019, the age-standardized PCa mortality rate increased in Brazil, with an AAPC value of 1.3% for the period. When considering the increase in the age-standardized PCa mortality rate in Brazil, a factor that should be considered is the aging of the population. Older adults are not homogeneously distributed throughout Brazil. The number of inhabitants over 60 years old is greater in the Southeast and Northeast regions, representing 46.4% and 25.5% of the total number of over 60s in Brazil, respectively, while the population of these two areas combined represents 70% of the total population (10). Both regions also show the highest number of deaths due to PCa. Although 70% of the Brazilian male population resides in the Southeast and Northeast regions (10) and these present the highest concentration of people over 60 years of age, the southern region of Brazil has the highest number of deaths from PCa per 100.000 individuals. This scenario suggests that male inhabitants of the South region may be under the influence of some risk factor (environmental or genetic variant) related to PCa and/or that these individuals have greater access to health services, which enables the correct notification of deaths due PCa.

The incidence and mortality rates of PCa vary widely across the regions of a country, and between different countries (11). In addition to aging, exposure to risk factors, and lack of access to preventive medicine, clinical exams, or treatments are the key components that contribute to the higher incidence and

mortality rates (1, 11). In many developing countries, there is still an increase in the incidence and mortality rates of PCa, and these may be related to more aggressive tumor types or inadequate access to health care systems (12). This last factor may not be the case of Brazil, as the growth in PCa incidence took place at the same time as access to PCa screening/diagnosis and medical care were increasing (13). Between 1999 and 2007, the number of prostatic specific antigen (PSA) tests - the main biomarker of PCa - performed in SUS increased by 573.3%, even though the Ministry of Health and INCA did not recommend PSA screening (14). The Sociedade Brasileira de Urologia (SBU, the Brazilian Urology Society) did support screening for men aged over 50 or over 45 with high risk (13). A limitation of the present study is that we can only speculate in relation to the potential factors involved in the growth trend in mortality and incidence rates of PCa. Further studies are required to evaluate this in more detail, including the evaluation of population genetic variance of target genes as a risk factor.

Although there was an increase in the number of PCa diagnoses in SUS between 2017 and 2019, this decreased in 2020. This apparent decrease observed in all ages over 50 may not be an actual decrease but may be due to the fact that COVID-19 caused a significant drop in face-to-face consultations and, therefore, diagnoses. There was also a drop in the number of hospitalizations for surgical prostate procedures in SUS in 2020 (15). However, it is important to remember that these measures of physical distancing were essential to prevent deaths and conserve the limited supplies for professionals working in the frontline of the pandemic (16). There may also have been a possible delay in notifications in respect of these data due to the disruption caused by COVID-19, although this cannot yet be confirmed.

The search for procedures related to the prostate on the DATASUS database resulted only in data in respect of hospitalizations and costs regarding the surgical approaches: suprapubic prostatectomy, radical prostate-vesiculectomy, prostatectomy in oncology, and radical prostate-vesiculectomy in oncology. The data regarding the DATASUS database refer only to information and records in the public health system in Brazil, the SUS. There is no centralized data regarding the number of PCa diagnoses in the private sector and the related surgical costs. Future studies comparing the public and private sectors should be considered.

The costs of the prostate surgical procedures presented here are a part of the total costs related to the disease (diagnosis, treatments, palliative care, follow-up, potential side effects, and human resources of health professionals), and indirect costs, relating to factors, such as the time and productivity of the patients (17). The early detection of tumors is essential for a good prognosis following treatment and to avoid the costs of more complex approaches (17). In this respect, the use of the PSA test for screening and detection of PCa has been widely discussed, and recommendations in relation to its use vary among different countries, scientific societies, and surveillance institutes (13, 18, 19). However, the positive impact of the PSA test in respect of the early diagnosis and treatment of PCa over the last four decades (19) must be considered in further discussions regarding this issue.

CONCLUSIONS

PCa, similar to several other types of cancer, is an age-related disease. Given the rapid aging trend of the Brazilian population, the number of PCa cases may increase, as other types of cancer and conditions associated with age. SUS and private health systems must be aware of this scenario. Investments need to be made in order to improve epidemiologic cancer surveillance programs, and increase clinical and hospital resources to provide the most effective and modern treatments for the population. The impact of the COVID-19 pandemic should be considered in data regarding PCa from 2020 forward, and in future epidemiological studies of this disease.

AVAILABLE DATA STATEMENT

Data presented in this study are available from the DATASUS database site Available at. <http://www2.datasus.gov.br/DATASUS/index.php?area=02> in the TABNET section, and in the Atlas On-line de Mortalidade, which is managed by the Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Both are public domain databases related to the Sistema Único de Saúde and to the Ministry of Health of Brazil.

DISCLOSURE STATEMENT

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CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis

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COMMENT

Percutaneous nephrolithotomy (PCNL) is the treatment modality for renal stones > 20 mm recommended by the European Association of Urology and by the American Urological Association (1, 2). Sepsis and bleeding are among the most feared complications of PCNL and perhaps one of the causes for this surgery represents less than 5% of all kidney stone treatment modalities in Brazil and in the World (3, 4). Also, standard 30 Fr PCNL may cause infundibular strictures in the entry calyx (5). Attempts to minimize bleeding during PCNL led to technique modifications including reducing the percutaneous tract size to decrease the area of parenchymal and infundibular injury (6, 7).

Percutaneous tract miniaturization evolved to several different techniques according to tract size. Indications for each technique vary according to stone size. Micro-PCNL (4.8-10 Fr) is more appropriate for kidney stones up to 15 mm, ultramini-PCNL (11-13 Fr) suits best for kidney stones up to 20 mm. However, there is no clear consensus about which tract size is best for kidney stones > 20 mm (8).

The systematic review and meta-analysis conducted by Qin et al compared the efficacy and safety of mini (16-20 Fr) versus standard (24-30 Fr) percutaneous nephrolithotomy for renal stones more than 2 cm (9). Authors included seven randomized controlled trials in their meta-analysis, involving 1407 mini-

-PCNL cases and 1436 standard-PCNL cases. Main finding was that mini-PCNL has a similar stone free rate than standard-PCNL. A subgroup analysis showed no difference in stone free rates between 30 Fr and 24 Fr and mini-PCNL groups. Operation time was shorter in standard-PCNL (both 30 Fr and 24 Fr) than mini-PCNL. Standard-PCNL was associated with more hemoglobin drop and blood transfusion rate than mini-PCNL. However, no significant differences were noted between 24 Fr and mini-PCNL regarding hemoglobin drop and blood transfusion rate. Shorter length of hospitalization was associated with mini-PCNL. No significant difference was noted in fever between groups.

The strength of this study is the inclusion of randomized controlled trials and exclusion of retrospective or case-control studies, whereas limitation is that the role of mini-PCNL in the treatment of staghorn stones or in infected stones was not addressed by the studies included in the meta-analysis. Infected stones are a risk factor for postoperative sepsis. Miniaturization of the percutaneous tract may increase the renal pelvic pressure and absorption of irrigation fluid due to limited outflow (10). Althought this meta-analysis showed no significant difference in postoperative fever between groups, more studies are needed to establish the best percutaneous tract size for staghorn and infectious stones. The meta-analysis presented by Qin et al. supports that standard 24 Fr PCNL is the best option for kidney stones > 20 mm combining same stone free rates than 30 Fr with similar blood loss of mini-PCNL but with shorter operation time (9).

Falahatkar et al. studied the effects of pregabalin, solifenacin and their combination therapy on urinary stent-related symptoms in a randomized controlled clinical trial (17). Patients were randomly allocated into four groups: pregabalin 75 mg BID (N=64), solifenacin 5 mg once a day (N=64), pregabalin 75 mg BID and solifenacin 5 mg once a day (N=64), and no medication (N=64). Ureteral Symptom Score Questionnaire (USSQ) was used to compare groups at 2 and 4 weeks after discharge from hospital (18). Authors reported significant beneficial effects in all indexes of USSQ only for combined pregabalin and solifenacin therapy over control group. Reported side effects were mild for all studied groups. Lack of a placebo arm and application of USSQ only at 2 and 4 weeks after discharge from hospital are some of the limitations of this study.

Urinary stent-related symptoms should not be overlooked and could be relieved by an adequate stent selection and a combination of postoperative medical therapy.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

UROANATOMY

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Editorial Comment: Anatomy of testicular artery: A proposal for a classification with MDCT angiography

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COMMENT

The knowledge of testicular arteries anatomy is important in pediatric urology and infertility surgeries. Previous studies about the testicular arteries in human fetuses shows a interesting pattern of anatomical variations (1, 2). During the Fowler-Stephens procedure in patients with high abdominal undescended testis is vey important this information is very important for the progress of the surgery (3). In the present paper the authors studied 400 patients during CT angiographies and (TAs) evaluated the number, origin, course, and caliber Testicular arteries showing some interesting anatomical variations. In more than 70% of the cases studied the testicular artery originates from the abdominal aorta, inferior to the level of renal artery. The authors shows a incidence of more than 25% of anatomical variations in anatomical pattern of testicular arteries. The figures in this paper are amazing and the authors concluded that normal anatomy and variations of testicular arteries may be effectively evaluated by CT angiography in a non-invasive manner.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

UROANATOMY

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Editorial Comment: Embryological Development and Topographic Anatomy of Pelvic Compartments-Surgical Relevance for Pelvic Lymphonodectomy

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COMMENT

The removal of pelvic lymph nodes is a important point during the radical prostatectomy and radical cystectomy. The extension of lymph node dissection is controversial and associated with more complications in post-operative period (1). In this interesting paper the topographic anatomy of pelvic compartments in relation to pelvic lymphonodectomy for rectal, uterine, and prostate cancer are reviewed. The paper has amazing figures showing the anatomy of the pelvic lymph nodes including a interesting description of the lymph nodes of Marcille fossa. The authors concluded that the comprehensive knowledge of pelvic anatomy, the exchange of surgical concepts between specialties, and minimally invasive techniques will optimize pelvic lymphonodectomy and reduce complications.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Percutaneous and endoscopic combined treatment of bladder and renal lithiasis in mitrofanoff conduit

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ABSTRACT

Introduction and Objectives: Treatment of bulky lithiasis in continent and non-continent urine storage reservoirs has been widely described and debated (1). Less is known about the optimal treatment in patients with a Mitrofanoff conduit. If voiding in these patients is incomplete, leading to recurrent symptomatic bacteriuria, formation of large lithiasis can be a common long-term complication (2, 3).
Materials and Methods: This video describes a 19-year-old woman who underwent major open surgery at the age of six, with the configuration of a continent intestinal reservoir with a Mitrofanoff conduit. In 2020, she was referred to our center with a large stone in the reservoir and a minor stone in the inferior left renal calyx.
We decided to proceed using a percutaneous approach with an "endovision technique" puncture for the bladder stone, combined with a retrograde intrarenal surgery for the renal stone. The MIP System "M size" was used to perform the percutaneous procedure, thus allowing a single-step dilation. The puncture and the dilation were followed endoscopically with a flexible ureterorenoscope avoiding the use of x-rays.
The procedure was carried out as follows. The first step consisted in the insertion of a hydrophilic guidewire through the Mitrofanoff conduit. A flexible ureterorenoscope was then inserted coaxial to the guidewire. The percutaneous puncture, using an 80G needle, was followed endoscopically. Two guidewires were inserted, the first as a safety guidewire and the second for the tract dilation. The "single-step" dilation technique using the MIP system was performed and followed endoscopically. For the bladder lithotripsy, a dual-action lithotripter that combines ultrasonic and mechanical energy was used. Finally, a flexible ureterorenoscope and a basket for the retrieval of a single inferior caliceal stone were used. The procedure ended after positioning a single J stent in the left kidney and a nephrostomy tube in the reservoir.
Results: The operative time was 80 minutes and the fluoroscopy time was 6 seconds. Hemoglobin and creatinine serum levels remained stable after the procedure and the patient was discharged on the third post-operative day, after removing both the single J and the nephrostomy tube. Follow-up lasted 12 months, with no bladder or renal stone recurrence, maintaining good continence of the Mitrofanoff conduit.
Conclusion: In patients who have undergone several major surgeries a mini-invasive approach is advisable, not only for the morbidity of an open approach, but also for the increased risk of complications while handling an intestinal reservoir. Regarding a pure endoscopic approach, the passage of a nephroscope or a cystoscope through the Mitrofanoff conduit, combined with the continuous traction during the lithotripsy, could damage and compromise its continence. For this reason, the percutaneous approach is the most suitable method in these specific and rare cases.

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CONFLICT OF INTEREST

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VIDEO SECTION

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Step-by-step optimisation of robotic-assisted radical prostatectomy using augmented reality

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ABSTRACT

Introduction: Surgical training will be complemented by digitalisation, as the COVID 19 pandemic continues (1). Proximie is an augmented reality (AR) platform that can display up to 4 native camera views, with live or semi live telementoring. It can optimise ergonomics of the surgeon at the console (2), and robotic instrument orientation. We describe the utilisation of Proximie as a step-by-step guide in a robotic assisted radical prostatectomy (RARP).
Surgical Technique: Author V. P. performed a transperitoneal multiport da Vinci Xi RARP with the Proximie platform: a laptop computer, multiple HD webcams, microphones and speakers. Using an HDMI cable to the Intuitive Surgical tower, output display from the console and an additional laparoscopic tower is shown. Each webcam was mounted to the side armrests of the console, directed at the surgeon's hands. An independent 'drop in' laparoscope via an additional 5mm left upper quadrant port was utilised. Observers can visualise the AR platform's recordings on a laptop and/or smartphone. A PTZ (pan-tilt-zoom) camera can capture the operating room, bedside assistant, ports and patient position. Our video demonstrates three of four camera views for posture, forearm, wrist, hand, and finger orientation, relative to the translated robotic steps. A pincer grasp of the endowrist manipulator during anastomosis allows optimal robotic wrist rotation. The second laparoscopic camera view demonstrated intracorporeal angles of robotic arm and bedside assistant's instrument position for critical steps such as nerve sparing and anastomosis (3). The console time was 100 minutes, no intraoperative complications, or delay in image transmission occurred with utilising the platform.
Considerations: An AR platform can create deeper learning for RARP in real time or recorded sessions. Two-way verbal and visual communication with ability to annotate on screen, allows long distance mentoring. The platform's utility can be accessed in anywhere, to project surgeons beyond their immediate environment. This allows for democratisation of access to high volume institutions and their evolution of techniques (4), to assist patients globally. Potential developments are artificial intelligence (AI) networks analysing repository of such recorded data, to identify intraoperative hand motion and robotic instrument tracking. AR is a pertinent building block to enhance robotic training, skill dissemination, precision medicine (5) and surgery overall.

CONFLICT OF INTEREST

None declared.

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In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

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and **Video Section**. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine **(http://www.nlm.nih.gov/mesh/meshhome.html)**. One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

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Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
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▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

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The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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- The Article is restricted to about 2,500 words and 6 authors.
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- Generic names are used for all drugs. Trade names are avoided.
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- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
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- A submission letter and a disclosure form, signed by all authors, are included.
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