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EDITORIAL
IN THIS ISSUE

HUGO™ RAS System in Robotic-Assisted Radical prostatectomy is highligheted in International Brazilian Journal of Urology

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The March-April number of *Int Braz J Urol* is the 21th under my supervision. In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Testicular cancer, SARS-CoV-19, Robotic Surgery, Prostate Cancer, Endometriosis, Infection and Profilaxy in Urology, Translational Research, Male Health and Renal stones. The papers came from many different countries such as Brazil, Panama, China and USA, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Barros and collegues from Brazil and USA, presented in page 175 (1) a nice review about the Changes in male sexuality after urologic cancer and concluded that male sexual dysfunction is very common after urologic cancer diagnosis and treatment. Changes in body image and anatomical damage can be associated with impaired masculinity and sexual function, especially after prostate, penile or testicular cancer treatment. Moreover, anxiety, depression, and fear of recurrence have an impact on quality of life and sexual function regardless of the cancer location. Therefore, patients need be counseled about the likely changes in sexual function before treatment of any urological cancer.

Dr. Danilovic and collegues from Brazil, presented in page 184 (2) an important systematic review about the topic: "the use for one week pre-operative oral antibiotics for percutaneous nephrolithotomy reduce risk of infection" and concluded that one week of prophylactic oral antibiotics based on local bacterial sensi- tivity pattern plus a dose of intravenous antibiotics at the time of surgery in patients undergoing PCNL reduces the risk of infection.

Dr. Liao and collegues from China, presented in page 194 (3) a interesting comparative study about the topic: "dusting to basketing for renal stones ≤ 2 cm during flexible ureteroscopy" and concluded that dusting has advantages in shortening the operation time and reducing the operation cost, but the lasing time was longer compared with the basketing. Although there is no difference in long-term effect, basketing is superior to dusting in terms of short-term SFR. Moreover, dusting should be avoided in some special cases and basketing a better choice. Both techniques are effective for the treatment of renal stones ≤ 2 cm and choice depends on patient demographic and stone characteristics.

Dr. Silva Filho and collegues from Brazil, presented in page 202 (4) a original study about the use of dynamic cystoscopy (DC) to optimize preoperative assessment of bladder endometriosis and concluded that dynamic cystoscopy appears to be a highly specific test with lower sensitivity. DC abnormalities are associated with a higher ratio of bladder surgery for the treatment of deep endometriosis, and bladder endometriosis type 2 seems to be associated with a greater ratio (9.72) of partial cystectomy.

Dr. Alfano and collegues from USA, presented in page 211 (5) the cover paper of this edition, a nice study about robotic surgery. The authors described the experience with the implementation of the HugoTM RAS robot and report the clinical data of patients who underwent Robotic-assisted Radical Prostatectomy and concluded that this preliminary results with safe and feasible procedures performed with HugoTM RAS System robotic platform. The surgeries were successfully executed with acceptable perioperative outcomes, without conversions or major complications. However, as this technology is very recent, further studies with a long-term follow-up are awaited to access postoperative functional and oncological outcomes.

Dr. Hong and collegues from China, presented in page 221 (6) a interesting study about a Predictive model for urosepsis in patients with Upper Urinary Tract Calculi based on ultrasonography and urinalysis using artificial intelligence learning and concluded that a preliminary screening model for urosepsis based on ultrasound and urinalysis was constructed using ANN. The model could provide risk assessments for urosepsis in patients with upper urinary tract calculi.

Dr. Viana and collegues from Brazil, presented in page 243 (7) a interesting study about sex with animals (SWA) and sexual infections (STIs) and concluded that SWA practices increase STIs vulnerability. The association between hepatitis B and SWA highlights the importance of educational campaigns and conclusive studies on the topic.

Dr. Andrade and collegues from Brazil, presented in page 233 (8) a interesting study about the Impact of COVID-19 pandemic on prostate cancer outcomes at an uro-oncology referral center and concluded that there was no delay between diagnosis and treatment at our institution during the COVID-19 pandemic period. No worsening of the prostate cancer features was observed.

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

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Changes in male sexuality after urologic cancer: a narrative review

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ABSTRACT

Objective: To describe the most common sexual problems and changes experienced by male urological cancer survivors, focusing on evidence-based practices for assessment and intervention.
Materials and Methods: We search the PubMed, Embase, and SciELO databases between 1994 and 2022, using the following key words: "urological cancer", "urological malignances", "genitourinary cancer", "male sexual health", and "male sexual dysfunction".
Results: This narrative review provides an overview of the current literature involving the impact of diagnosis and treatment of urological cancers on male sexual function. Male "genital" or "reproductive" tumors, such as prostate, penile, and testicular tumors, clearly appear to affect sexual function. However, tumors that do not involve genital parts of the body, such as the bladder and kidney, can also affect male sexual function.
Conclusion: Male sexual dysfunction is very common after urologic cancer diagnosis and treatment. Changes in body image and anatomical damage can be associated with impaired masculinity and sexual function, especially after prostate, penile or testicular cancer treatment. Moreover, anxiety, depression, and fear of recurrence have an impact on quality of life and sexual function regardless of the cancer location. Therefore, patients need be counseled about the likely changes in sexual function before treatment of any urological cancer.

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INTRODUCTION

Sexual function is an important component of quality of life and can be adversely impacted by cancer and its treatment. Moreover, the fear of death, along with psychological and social factors, often deeply affects the quality of life of cancer patients (1).

Treatment of urological cancers can have especially significant impacts on sexual function, body image, well-being, and mental health (2, 3). Most studies of male sexual dysfunction after urologic cancer focus on prostate cancer (PCa) survival after surgical and hormonal treatments (4, 5). However, cancers that do not involve parts of the

body designated as ''sexual'' or ''reproductive'', such as kidney (KC) and bladder cancer (BC), can also affect sexuality independent of the treatment, and their relation to sexual function is poorly understood (6, 7).

Sexual function is a critical quality-of-life predictor and, as such, should be addressed during the treatment of all urological malignancies (8). Professionals working in this field should be aware of the impact of cancer on male sexuality. Therefore, it is important to address these topics in the urological literature. In this review, we describe the most common sexual problems and changes experienced by male urological cancer survivors, focusing on evidence-based practices for assessment and intervention.

MATERIAL AND METHODS

We analyzed published papers contained in the PubMed, Embase, and SciELO databases between 1994 and 2022, searching by the following key expressions: "urological cancer", "urological malignances", "genitourinary cancer", "male sexual health", and "male sexual dysfunction". Special emphasis was given to relevant articles reporting the changes in sexual health of men with urological cancers, such as prostate, penis, testicular, bladder, and kidney cancers. In this search, we included only papers published in English and excluded case reports, editorials, and opinions of specialists.

RESULTS

This narrative review provides an overview of the current literature involving the impact of diagnosis and treatment of urological cancers on male sexual function. Male "genital" or "reproductive" tumors, such as prostate, penile, and testicular tumors, clearly appear to affect sexual function. However, tumors that do not involve genital parts of the body, such as the bladder and kidney, can also affect male sexual function.

Prostate cancer (PCa)

PCa is the second most often diagnosed cancer among men worldwide (9). Different treatment modalities for PCa can negatively affect sexual function. Surgery is the reference standard for treatment of localized PCa. Nerve-sparing radical retropubic prostatectomy was developed many years ago to preserve sexual potency and urinary continence. Catalona et al. (10) evaluated the results of 1,870 open retropubic prostatectomies (ORP) performed by a single surgeon and found recovery of erectile function in 68% of preoperatively potent men treated with bilateral (543 of 798) and 47% treated with unilateral (28 of 60) nerve sparing surgery. Today, minimally invasive techniques such as laparoscopic radical prostatectomy (LRP) and robotic-assisted laparoscopic radical prostatectomy (RALP) have replaced ORP to improve post-operative outcomes such as erectile function (11). Guillonneau et al. (12) evaluated their experience with 550 patients who underwent LRP and found that 66% preserved erection and could engage in spontaneous intercourse. Patel et al. (13) analyzed the initial outcomes of 500 RALPs and found that after one year, 78% of patients were potent with or without the use of oral medications. More recently, Barisi et al. (4) conducted a systematic literature review comparing ORP, LRP, and RALP, where one of the outcomes was erection dysfunction (ED). According to this study, there were no differences in post-operative rates of ED between ORP and LRP or RALP. Interestingly, LRP was associated with greater post-operative rates of ED when compared with RALP. However, this review should be interpreted with caution due to the lack of randomized clinical trials, selection bias, and heterogeneous definitions of ED. In addition to ED, sexual changes after radical prostatectomy include loss of penile length, reduced sexual desire, and orgasmic dysfunction, including painful orgasm and climacturia, or involuntary loss of urine at the time of orgasm (14-16). True rates of climacturia are unknown and probably underreported in the literature (17). Clavell-Hernandez et al. (18) conducted a review of the literature on climacturia after radical prostatectomy and found prevalence ranging from 20% to 93%.

ED after radiotherapy (RT) usually occurs due to penile neurovascular and cavernosal damage. While ED is an immediate side effect of radical prostatectomy, it usually occurs after six months

post radiation therapy. Donovan et al. (5) report that only 22% of men-maintained erections firm enough for intercourse six months after RT with neoadjuvant androgen deprivation therapy (ADT). Likewise, Kikuchi et al. (19) evaluated erectile function after RT in 55 patients with PCa and observed a decrease in the erectile function and intercourse satisfaction after RT. Another study evaluated sexual functions of 50 PCa patients receiving RT. The authors used the IIEF (International Index of Erectile Function) questionnaire before and on the last day of treatment. They found a statistically significant decline in erectile function, sexual desire, sexual satisfaction, orgasmic function, and general satisfaction after RT. Considering that ED is usually chronic side effect of RT, these findings might reflect a psychological side effect of RT (20).

While radical treatment with surgery or radiation offers excellent cancer control, it comes with significant side effects as discussed previously. Alternative treatments with less impact in quality of life and sexual function have gained popularity in recent years.

Focal therapy (FT) is an a less invasive option that treats only the cancerous area of the prostate (aka index lesions) and maintains patient's quality of life by avoiding some of the adverse effects of radical therapy, including ED. Several studies with large sample size and long follow up showed benefits of FT on functional outcomes (21-24). Nahar et al. (22) reported short--term outcomes of FT for primary treatment of localized PCa and observed that sexual function returned to baseline at within 9-12 months. Similarly, Rischmann et al. (23) evaluated 111 patients with unilateral localized PCa treated with high intensity focused ultrasound (HIFU). Erectile function was preserved in 78% of patients after 12 months of HIFU half-gland treatment. A recent study compared the impact of focal (N = 195) and whole gland (N = 105) therapy for PCa on erectile and urinary function. Twelve months after treatment, 81.3% of men who underwent FT (vs. 61.7% of whole gland patients) could achieve erection strong enough for sexual penetration (24).

Similarly, Active surveillance (AS) is one the preferred choice for patients with low-risk prostate cancer. However, even men under AS can suffer negative impacts on sexual function. Soloway et al. (25) followed men in AS for PCa and observed 49% of patients experiencing ED. Another study compared the sexual function of men with low-risk PCa monitored through AS with patients undergoing RT or radical prostatectomy and found that the AS group had less ED (26).

Patients with metastatic prostate cancer are usually treated with androgen deprivation therapy (ADT) with the goal of reducing serum testosterone levels. Therefore, castration levels of testosterone results in multiple side effects, including loss of libido and ED. It's extremely important to correctly inform patients about these well-known side effects before starting treatment (27, 28).

Penile cancer (PEC)

PEC is rare in North America and Europe; the incidence is higher in regions of Africa, Asia, and South America due to due socioeconomic factors and the high incidence of the human papilloma virus (HPV), phimosis, and smoking in these regions (29-31). The treatment modalities of PEC depend on the area involved and include some organ-sparing treatments such as topical therapy, laser therapy, RT, glansectomy, wide-local excision, and partial penectomy. Total penectomy is reserved for cases with more advanced primary disease (32).

All types of treatment for PEC can impact quality of life and sexual function. Glansectomy seems to preserve sexual function by maintaining the ability to perform vaginal penetration and leaving libido and ejaculation function intact; however, the few studies available evaluating the results of the procedure had small sample sizes and several methodological flaws (33-35). Palminteri et al. (36) described the techniques and results of surgical reconstruction of glans penis lesions (benign, premalignant, and malignant). In their series, five cases were treated with glans resurfacing, five glansectomies with neoglans reconstruction were performed, and seven patients underwent partial penectomy and reconstruction of the neoglans. All patients maintained sexual function and activity. Patients who underwent glans resurfacing reported glandular sensory restoration while sensitivity was reduced after glansectomy and partial

penectomy. Partial or total penectomy can be associated with significant psychological morbidity and sexual dysfunction. Feelings of shame due to the small penis size and the absence of the glans are some reasons for the negative impact on male sexual function. In one such study, Romero et al. (37) investigated 18 patients who underwent partial penectomy and reported a statistically significant reduction in erectile and orgasmic function after surgery. According to the authors, only 33.3% of patients maintained their preoperative sexual intercourse frequency and were satisfied with their overall sex life after the procedure. Monteiro et al. (38) evaluated the erectile function of 81 patients who underwent partial penectomy and reported that approximately 62% experienced ED after surgery. The authors found that smaller penile shaft length, clinically positive lymph node, and older age significantly increased the incidence of ED. In the study conducted by Opjordsmoen et al. (39), four of 30 men treated for PEC underwent total penectomy, and all of them reported severely reduced global sexual score. Due to the rarity of PEC, there are few studies available exploring sexual outcomes after treatment. Although most of the papers are retrospective with a small sample, it is clear that an penile malignancies and treatments negatively impact patients' sexuality. Therefore, physicians should counsel patients with this rare malignancy about the impact and changes of male sexual function that they are likely to experience after PEC treatment. Referral to psycho-oncology might be beneficial to patients.

Testicular cancer (TC)

TC accounts for about 1% of all male cancers and characteristically affects mostly young men (aged 20–40 years). TC has a good prognosis with excellent cure rates in the early stages when treated by one of the standard treatment options, including orchiectomy, RT, and cisplatin-based chemotherapy (40, 41). Treatment of TC can cause changes in body image and negatively impact sexuality, fertility, mental health, and quality of life. An Australian study found that TC survivors experienced anxiety and depression in 19% and 20% of cases respectively (42). Rincones et al. (43) conducted a systematic review of anxiety, depression, fear of cancer recurrence and distress in TC survivors. The authors concluded that greater anxiety and depression seemed to be associated with impaired masculinity, sexual function, and quality of life. Changes in body image after orchiectomy can impact self-confidence and sexuality, and it is extremely important that physicians offer a testicular prosthesis implant at the time of surgery (44). A systematic review conducted by Nazareth et al. (45) of sexual dysfunction in men treated for TC indicated significantly reduced or absent orgasm and ejaculatory dysfunction that persisted for up to two years after treatment. Not surprisingly, ejaculatory dysfunction was most frequently related to retroperitoneal lymph node dissection (RPLND) surgery (46). Palotti et al. (47) evaluated the possible effect of TC and orchiectomy on sexual function. They administered the IIEF-5 to TC patients at the post-orchiectomy baseline before chemotherapy and found that 37.7% of patients had ED. According to the authors, the sexual dysfunction in these patients might be associated with psychological burden. In fact, sexual dysfunction in TC is not clearly related to disease or treatment factors and may instead arise from psychological vulnerability (46).

Bladder cancer

Bladder cancer (BC) is the fifth most common cancer in men worldwide (48). Most patients have non-muscle-invasive bladder cancer (NMIBC), which is commonly treated with transurethral resection of bladder tumor (TURBT). There is scarce research on the effect of treatment for NMIBC on male sexual function. Existing research suggests that TURBT may adversely affect male sexuality and lead to anxiety and depression, especially in younger patients (49). Guo et al. (7) investigated the incidence of ED in patients before and after TURBT to treat NMIBC. According to the authors, the incidence of ED increased in patients under the age of 45 years after TURBT (15.8% before vs. 52.6% after), and they concluded that psychological and emotional burden are the main causes of sexual dysfunction in these cases. Yoshimura et al. (50) prospectively evaluated the impact on general health-related quality of life of patients with NMIBC who underwent TURBT. They found

physical and mental problems after the first TURBT, but these problems gradually waned as TURBT was repeated, although the patients' general quality of life remained affected. More than a half of NMIBC cases will recur and intravesical bacille Calmette–Guérin (BCG) treatment has an important role in reducing this recurrence (51). Patients who received intravesical BCG might present with pelvic pain and may experience a negative impact on sexual activity after the initial treatment. Nonetheless, patients improved their psychological distress and physical symptoms as they continued the treatment (52, 53). ED after BCG treatment is generally transient and reversible but is still another source of psychological distress (54). Radical cystectomy (RC) remains the gold standard treatment in cases of muscle invasive bladder cancer (MIBC). It consists of removal of the bladder, prostate, and seminal vesicles (55). ED after RC is a prevalent problem due to surgical trauma to the neurovascular bundle, and one study found that only 14% of sexually active men-maintained potency after surgery (56). However, nerve-sparing RC can often provide preservation or recovery of erectile function, and 36% of RC patients recovered sexual intercourse at 3 years and 57% at 5 years. This recovery depends on the preoperative erectile function and age of the patient. Function can be improved after sexual rehabilitation with intracavernous injection therapy or oral phosphodiesterase inhibitors after surgery (57, 58). The type of urinary diversion can also affect sexual activity. Patients with ileal conduit diversion may have a greater impact on sexual function compared to those who underwent orthotopic diversion likely due to depression or anxiety associated with changes in body image (59). Trimodality therapy (TMT) can be used as an alternative to immediate RC in the management of MIBC. TMT consists of maximal TURBT followed by radical RT with concurrent chemotherapy (60). Radical RT for BC can result in sexual dysfunctions such as impotence and lack of desire (61). Zietman et al. (62) performed a small retrospective study of TMT and found male sexual function to be less impaired by this modality than after RC. A total of 39% of men reported no erections in the last 4 weeks, 54% were capable of orgasm and 50% of ejaculation, while only 8% were dissatisfied with their sex lives.

Kidney cancer (KC)

KC incidence is increasing, and over 50% of KC tumors are diagnosed incidentally in asymptomatic individuals during investigation for other conditions using imaging techniques (63, 64). The literature is scarce about the impact on male sexual function after treatment for KC. Anastasiadis et al. (65) published the first study addressing sexual function in patients with KC after treatment (operation, radiation, or chemotherapy). They observed that most patients remained sexually active in non-distressed relationships, but 51% of men reported depressive symptoms, and sexual functioning may be worse than in comparable chronically ill populations. Christiansen et al. (6) evaluated patients who underwent nephrectomy or nephroureterectomy and found that 54.7% of sexually active males reported having some degree of ED after surgery. Moreover, 61% of patients reported being worried about their sex lives. Interestingly, only 5% of patients were informed about these potential negative effects prior to surgery. Few studies have investigated sexual disorders in men with advanced KC treated with molecular targeted therapy (MTT); antiangiogenic therapies (sunitinib, sorafenib, and bevacizumab) and mTOR inhibitors (temsirolimus and everolimus) caused a decline of erectile function scores and sexual activity after treatment (66, 67). These studies concluded that treatment of KC can negatively affect male sexual function. The diagnosis of cancer, life stress, and losses can explain the sexual dysfunction after treatment, which is information that should be provided to patients (1, 68). Table-1 summarizes the risk of ED after type of urologic cancer treatment.

CONCLUSIONS

Male sexual dysfunction is very common after urologic cancer diagnosis and treatment. Changes in body image and anatomical damage can be associated with impaired masculinity and sexuality, especially after PCa, PEC, or TC treat-

ment. Moreover, anxiety, depression, and fear of recurrence have an impact on quality of life and sexual function even in "nonreproductive" cancers, such as BC and KC.

Therefore, patients need be counseled about the likely changes in sexual function before treatment. Urologists and oncologists should systematically inform, educate, and comfort these patients during the treatment. Multidisciplinary medical teams, including sexual medicine physicians and psycho-oncologist, play a fundamental role in this scenario and need to be proactive by offering psychological support to mitigate the impact on male sexuality. However, more studies are needed to clarify the impact urological malignances and their treatments may have on the sexual function of men, and clinicians need better training about the best way topproach these issues.

Table 1 - Risk of ED after type of urologic cancer treatment.

Study	Year	Treatment	Risk of ED
Catalona et al. (10)	1999	ORP	32%
Guillonneau et al. (12)	2002	LRP	34%
Patel et al. (13)	2007	RALP	22%
Donovan et al. (5)	2016	RDT + NEOADJUVANT ANDROGEN THERAPY	78%
Borges et al. (24)	2021	FOCAL HIFU	18%
Soloway et al. (25)	2010	AS	49%
Monteiro et al. (38)	2021	PARTIAL PENECTOMY	62%
Guo et al. (7)	2022	TURBT	56%
Palotti et al. (47)	2019	ORCHIETOMY	37%
Zippe et al. (26)	2004	RC	86%
Miyao et al. (57)	2001	NERVE-SPARING RC	43%
Zietman et al. (62)	2003	TMT	39%
Christiansen et al. (6)	2020	NEPHRECTOMY OR NEPHRO-URETERECTOMY	54%

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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One week pre-operative oral antibiotics for percutaneous nephrolithotomy reduce risk of infection: a systematic review and meta-analysis

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ABSTRACT

Purpose: The aim of this meta-analysis is to assess the efficacy of extended dose of preoperative antibiotics to reduce infectious risk in patients undergoing percutaneous nephrolithotomy (PCNL).

Materials and Methods: A literature search for prospective case-control studies or randomized controlled trials was done. PICO framework was used. Population: adult patients that underwent to PCNL; Intervention: extended dose preoperative antibiotic prophylaxis before PCNL; Control: short dose preoperative antibiotic prophylaxis before PCNL; and Outcome: systemic inflammatory response syndrome (SIRS) or sepsis, fever after PCNL and positive intraoperative urine and stone culture. This meta-analysis was registered in PROSPERO database under the number: CRD42022359589.

Results: Three RCT and two prospective studies (475 patients) were included. SIRS/sepsis outcome was retrieved from all studies included. Seven days preoperative oral antibiotics for PCNL was a protective factor for developing SIRS/sepsis (OR 0.366, 95% CI 0.234 - 0.527, p < 0.001). There was no statistical association between seven-day use of antibiotics and fever (OR 0.592, 95% CI 0.147 – 2.388, p = 0.462). Patients who received seven days preoperative antibiotics had lower positive intraoperative urine culture (OR 0.284, 95% CI 0.120 – 0.674, p = 0.004) and stone culture (OR 0.351, 95% CI 0.185 – 0.663, p = 0.001) than the control group.

Conclusion: one week of prophylactic oral antibiotics based on local bacterial sensitivity pattern plus a dose of intravenous antibiotics at the time of surgery in patients undergoing PCNL reduces the risk of infection.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the current gold standard treatment for kidney stones > 20 mm (1). Although effective, PCNL is associated with complications such as prolonged urinary leakage in up to 10% and blood transfusion in up to 7% of the patients (2-5). Approximately 10% of the patients develop a postoperative fever after PCNL, while sepsis is reported in 0.3% to 0.5% (5, 6). Despite being rare, urosepsis is a life-threatening complication of PCNL, and every

effort should be made to prevent its occurrence.

There is no specific recommendation for a preoperative antibiotic regimen in patients undergoing PCNL due to insufficient data (1, 7). Previously published meta-analyses evidenced significant heterogeneity between included studies. Retrospective and prospective studies were analyzed together, preoperative, and postoperative antibiotic regimens were compared in the same meta-analysis, and duplicates were included making it impossible to determine the role of preoperative antibiotics(8-10). There is no consensus on the definition of high infectious risk patients. Several possible risk factors for infection were investigated. Patient positioning in PCNL, tract size, obesity and solitary kidney do not seem to impact infectious rates (11-14). Some investigators consider high risk for infection stone size ≥ 20 mm and/or dilation of the collecting system with sterile urine. However, other authors define high infectious risk for PCNL as those with a positive preoperative urine culture within three months of the planned procedure or an indwelling stent or nephrostomy tube at the time of surgery, without considering stone size or dilation of the collecting system (15-17). As the definition of high infection risk is unclear, this study aims to perform a high-quality meta-analysis using only prospective studies to define the role of preoperative antibiotics in patients undergoing PCNL.

MATERIALS AND METHODS

Identification and Eligibility of Trials

The meta-analysis protocol was registered on the PROSPERO database on September 22, 2022 (CRD42022359589). This review was conducted according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement (18). We selected prospective studies and randomized controlled trials (RCT) that compared extended to short-dose preoperative antibiotic prophylaxis in patients undergoing PCNL. On May 2022, the key words "percutaneous nephrolithotomy" and "antibiotic" were searched on EMBASE, PubMed, and Web of Science platforms. Retrospective studies, case reports, case-control studies, letters to the editor, editorials, congress abstracts, and studies in patients < 18 years old were excluded.

Development of Prospective Meta-analysis Protocol

The PICO (population, intervention, control, and outcome) framework was agreed upon before the collection of data:

- Population: adult patients that underwent PCNL;
- Intervention: extended dose preoperative antibiotic prophylaxis before PCNL;
- Control: short dose preoperative antibiotic prophylaxis before PCNL; and
- Outcome: systemic inflammatory response syndrome (SIRS) or sepsis, fever after PCNL, positive intraoperative urine culture, and stone culture.

Outcomes and Comparisons

The primary outcome measure was SIRS or sepsis after PCNL. Primary comparison investigated extended dose preoperative antibiotic prophylaxis vs. short dose preoperative antibiotic prophylaxis before PCNL. Secondary outcome measures investigated included fever after PCNL, positive intraoperative urine, and stone cultures. We considered extended dose the use of preoperative antibiotics for seven days before PCNL and short dose for ≤ 2 days. SIRS or sepsis were defined according to each study (19, 20).

Assessment of risk of bias in included studies

Risk of bias assessments were done independently by two of the investigators with agreement, without discrepancy. The risk of bias for each RCT was assessed using version 2 of the Cochrane Risk of Bias Assessment Tool (RoB 2). RoB 2 is structured into domains of bias (trial design, conduct, and reporting results) and classified as unclear, low, and high risk (21). The risk of bias for each prospective study was defined using The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I), recommended by the Cochrane Scientific Committee. ROBINS-I is structured into the selection of patients, conduct, and reporting results and is classified as low, moderate, serious, and critical risk (22).

Data Analyses

All analyses were performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). The primary outcome was extracted from all included studies. Secondary outcomes were not available in all studies. We calculated each study's odds ratio (OR) and 95% confidence interval (CI) to evaluate their differences. Chi-squared test and I2 were used to assess heterogeneity. When heterogeneity was present, the random effects model was used. The alpha risk was defined as < 0.05.

RESULTS

Search results and selection process

As shown in Figure-1, literature search identified 1362 publications. Abstracts and titles were screened, excluding all studies that were not prospective or RCT. After full-text screening, eight articles were selected, and three were excluded (another outcome evaluated, and duplicated database). The final selection included five articles (three RCT and two prospective studies) with a total of 475 patients studied.

Risk of bias

As shown in Figure-2, Bag 2011, Chew 2018, and Sur 2021 were considered to have a low risk of bias in all criteria according to RoB 2 (16, 17, 23). Mariappan 2006 and Xu 2022 were considered to have some moderate/serious risk of bias according to ROBINS-I (15, 24). Xu 2022 did not have specific criteria for antimicrobial choice – "antibiotics (type and duration) were given at the discretion of the surgeon; the urine culture took 48-72h, and some patients did not get the results before the procedure" (24).

Characteristics of included studies

Mariappan et al. 2006 were the first to demonstrate in a prospective study that one week of

Figure 1 – PRISMA flowchart.

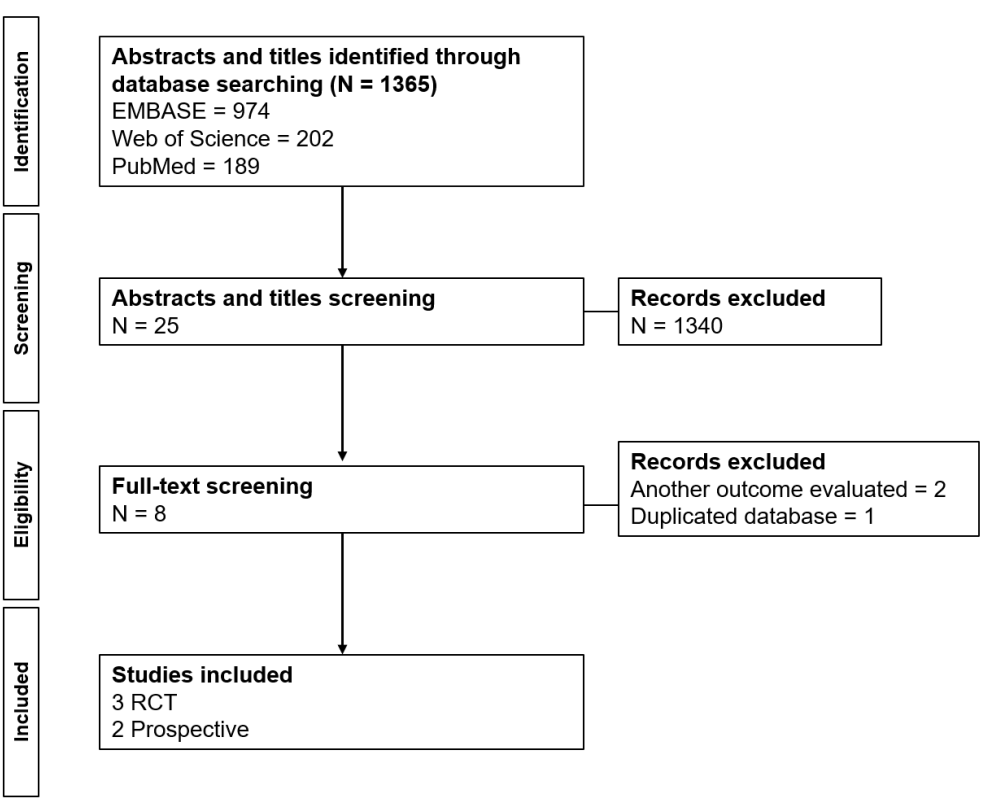
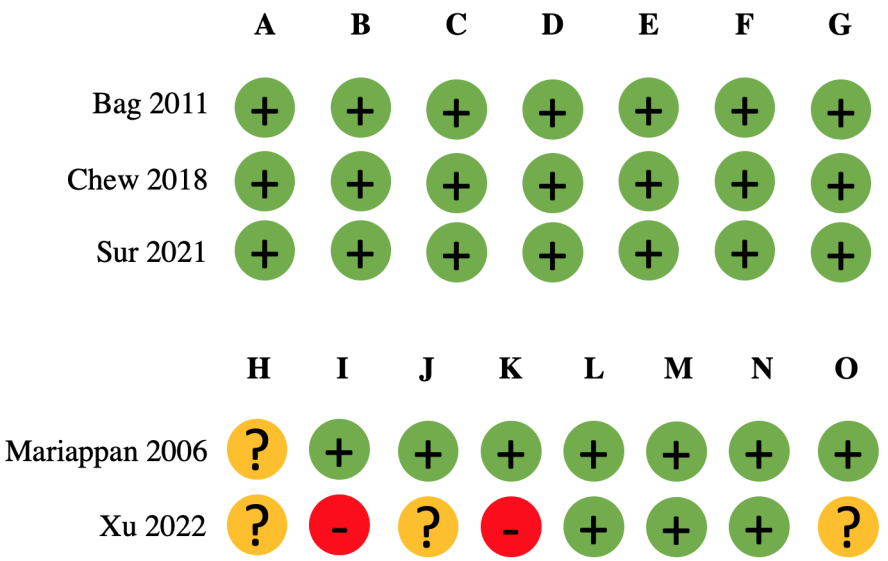


Figure 2 - Risk of bias of randomized controlled trials.



(A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias); (G) Other bias; (H) Bias due to confounding; (I) Bias in selection of participants into the study; (J) Bias in classification of interventions; (K) Bias due to deviations from intended interventions; (L) Bias due to missing data; (M) Bias in measurement of outcomes; (N) Bias in selection of the reported result; (O) Overall bias.

antibiotics in patients with high infectious risk undergoing PCNL reduces urosepsis. Results showed a three times less chance of urosepsis in patients receiving antibiotics one week before intervention (RR 2.9; 95% CI 1.3-6.3, p = 0.004)(15).

Bag et al. demonstrated in a RCT of 110 patients with stones ≥ 25 mm or hydronephrosis undergoing PCNL that prophylaxis with nitrofurantoin 100 mg twice daily for a week before PCNL prevents urosepsis and fever. Results showed that patients using nitrofurantoin had less SIRS (19% vs. 49%, OR 0.31, p = 0.01), less positive pelvic urine culture (0 vs. 9.8%, RR 4.95, p = 0.001), and less positive stone culture (8.3% vs. 30.2%, OR 0.22, p = 0.016) (16).

The EDGE Consortium reported two multicenter RCTs addressing preoperative oral antibiotics in patients undergoing PCNL. Chew et al. conducted a RCT with patients with sterile preoperative urine cultures and no urinary drains, which was deemed "low risk." There was no difference in the incidence of sepsis (12 vs. 14%, p = 1.0), fever (0 vs. 2.3%, p = 0.24), positive intraoperative renal pelvis urine culture (9.3 vs. 9.3%, p = 1.0) and positive stone culture (2.3 vs. 2.3%, p = 1.0) between antibiotic and control groups (23). In the EDGE Consortium's subsequent publication, Sur et al. demonstrated that seven days vs. two days of preoperative 100 mg nitrofurantoin twice daily decreases the risk of urosepsis in moderate to high infectious risk patients undergoing PCNL. Both groups received intravenous antibiotics at the induction of the procedure. It was observed that patients who received two days of antibiotics had a higher risk of sepsis (OR 3.1, 95% CI 1.1 - 8.9, p = 0.031) (17).

Xu et al. 2022 (24), prospectively studied the optimal duration of preoperative antibiotic therapy was prospectively studied in consecutive patients with positive urine culture submitted to PCNL. In this "real-world" study, authors concluded that ≥ 7 days of antibiotics before procedure in high infectious risk patients reduces the risk for urosepsis. A significant limitation of this study is that a wide range of antibiotics was used according to sensitivity test of positive urine culture of patients undergoing the procedure. We managed to extract data from patients that used single-dose

(28 patients) vs. seven-day (30 patients) antibiotics before PCNL to include in our meta-analysis. It was evidenced that receiving antibiotics seven or more days before the procedure was a protective factor independently associated with SIRS (24) (Table-1).

Outcomes

SIRS/sepsis outcome was retrieved from all studies included. Postoperative fever outcome was extracted from three studies. Intraoperative urine culture and stone culture outcomes were extracted from four and three studies, respectively. Funnel plots demonstrating studies' bias and heterogeneity are shown in Figure-3. Forest plots (Figure-4) evidenced that using antibiotics for seven days in the preoperative period of PCNL was a protective factor for developing SIRS/sepsis (OR 0.366, 95% CI 0.234 - 0.527, $p < 0.001$). There was no statistical association between the seven-day use of antibiotics and fever (OR 0.592, 95% CI 0.147 – 2.388, $p = 0.462$). Patients who received the intervention had lower positive intraoperative urine culture (OR 0.284, 95% CI 0.120 – 0.674, $p = 0.004$) and stone culture (OR 0.351, 95% CI 0.185 – 0.663, $p = 0.001$) than the control group.

DISCUSSION

This meta-analysis shows that seven days of oral preoperative antibiotics plus a dose of intravenous antibiotics at the time of surgery reduces the risk of infection in patients undergoing PCNL. Extended preoperative antibiotic use reduced the risk of SIRS and positive intraoperative urine culture and stone culture, regardless of the patient's risk of infection. Due to a lack of consensus in defining high infectious risk patients for PCNL, this meta-analysis included all adult patients undergoing PCNL. Our meta-analysis included only studies that investigated preoperative and not postoperative use of antibiotics to avoid confounding timing in antibiotics use in patients undergoing PCNL. The previous meta-analysis joined studies of preoperative and postoperative use of antibiotics, reducing its clinical application (8).

Nowadays, sepsis definition is as a life-threatening organ dysfunction caused by a dysregulated host response to infection (25). However, in the past, sepsis was described as a systemic inflammatory response syndrome (SIRS) to infection (19). In some studies, researchers referred to urosepsis as SIRS resulting from infection in the urinary tract in patients undergoing PCNL. Mariappan et al. and Bag et al. considered SIRS as fever > 38° C and/or leukocyte counts > 12,000 and attributed to urosepsis after excluding perinephric collection, pleural effusion, chest infection, and thrombophlebitis (15, 16). The EDGE Consortium used the more current definition of sepsis, which includes two or more of the following criteria at least 12 hours after the procedure: temperature above 38.3°C or below 36°C, heart rate above 90/minute, respiratory rate greater than 20/minute, altered mental status, systolic blood pressure less than 90 mmHg, mean arterial pressure less than 70 mmHg or systolic blood pressure decrease of more than 40 mmHg, and white blood cells greater than 12,000 or less than 4,000 (17, 23). Despite the definition used at the time of performance of the study, researchers investigated whether preoperative antibiotics could prevent infection, and the incidence of this event was similar between studies. This was the main reason we maintained the definition of sepsis in each original study.

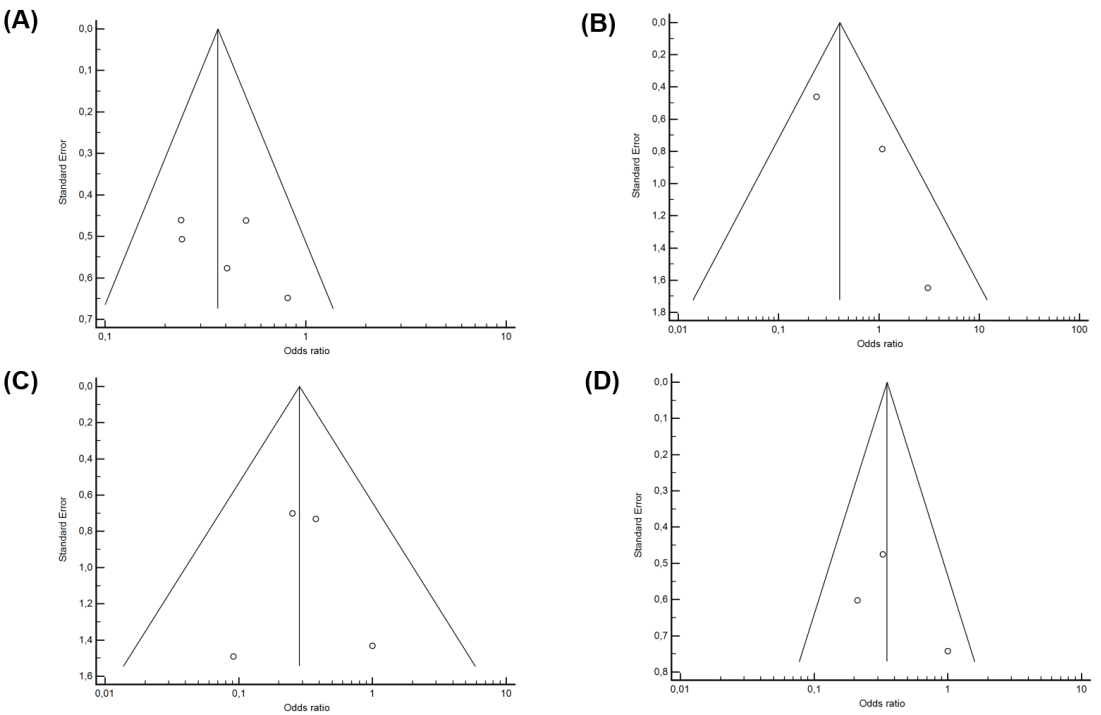
We choose to include in this meta-analysis adult patients undergoing PCNL regardless of their risk of infection. The definition of high infectious risk patients for PCNL varies among studies and is controversial. Patients with sterile urine and dilated pelvicalyceal systems and/or stones of ≥ 20 mm were considered at high infectious risk by Mariappan et al. based on a previous publication from their group (26). Other authors considered sterile urine, hydronephrosis, and/or stones ≥ 25 mm high risk (16). However, it is unclear if those patients had positive urine culture weeks before PCNL and were treated. In contrast to Mariappan et al. and Bag et al., stone size or dilated collecting system were not considered risk factors in the Sur et al. study. A previous RCT of the EDGE group did not demonstrate a benefit for the preoperative use of nitrofurantoin for seven days in patients with sterile urine and no urinary drain undergoing PCNL (23). Therefore, EDGE Consortium created a definition of moderate to high infectious risk pa-

Table 1 - Description of included studies.

Study	Country	Design	Inclusion criteria	Definition of SIRS or Sepsis	Procedure	Patients, n	Mean age, years	Stone size, mm
Mariappan, et al. 2006 (15)	UK	Prospective	Stones ≥ 20 mm and/or dilated pelvicalyceal system	SIRS was defined as the systemic response to infection, manifested by two or more of the following conditions as a result of infection: - Temperature ≥ 38º C or ≤ 36º C - Heart rate > 100 beats/min - Respiratory rate > 20/min - White blood cell count > 12,000 white blood cells/mL or < 4,000 white blood cells/mL	7 days of antibiotic (250 mg of ciprofloxacin twice daily) before PCNL vs. No antibiotic before PCNL	52 vs. 46	55.5 vs. 53.1	30.8 vs. 32.8
Bag et al. 2011 (16)	India	RCT	Patients with stones ≥ 2,5 cm and/or hydronephrosis and sterile urine	Hard criteria for SIRS were fever > 38º C and/or leukocyte counts > 12,000	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. No antibiotic before PCNL	48 vs. 53	39.2 vs. 40.4	34.1 vs. 36.7
Chew et al. 2018 (23)	USA/ Canada	RCT	Patients with sterile urine and no urinary drain	Sepsis was defined as having an infection source in addition to 2 or more of the following criteria at least 12 hours after the procedure: temperature > 38,3ºC or < 36ºC, heart rate > 90/minute, respiratory rate > 20/minute, altered mental status, systolic blood pressure < 90mmHg, mean arterial pressure decrease of more than 40 mmHg and white blood cell count > 12,000 or < 4,000.	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. No antibiotic before PCNL	43 vs. 43	56 vs. 62	19 vs. 17
Sur et al. 2021 (17)	USA/ Canada	RCT	Patients ≥ 18 years old who had stone burden of any size for which PCNL was recommended. Subjects had to have had either a positive preoperative urine culture within 3 months of the planned procedure or an internalized ureteral stent, nephrostomy tube or nephroureteral stent at time of PCNL.	Sepsis was defined as having an infection source in addition to 2 or more of the following criteria at least 12 hours after the procedure: temperature > 38,3ºC or < 36ºC, heart rate > 90/minute, respiratory rate > 20/minute, altered mental status, systolic blood pressure < 90mmHg, mean arterial pressure decrease of more than 40 mmHg and white blood cell count > 12,000 or < 4,000.	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. 2 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL	68 vs. 55	61 vs. 54	20 vs. 23
Xu et al. 2022 (24)	China	Prospective	Patients with positive urine culture undergoing primary PCNL	SIRS was defined as the co-existence of at least two of the following items during the whole hospitalization: temperature > 38ºC or < 36ºC, heart rate > 90/min, respiratory rate > 20/min or PaCO2 < 32 mmHg, and white blood cell count > 12,000 or < 4,000.	7 days of empiric antibiotic before PCNL vs. No antibiotic before PCNL	30 vs. 28	NA	NA

SIRS = systemic inflammatory response syndrome; PCNL = Percutaneous Nephrolithotomy; RCT = randomized controlled trials; NA = not available

Figure 3 – Funnel plot – (A) patients with SIRS or sepsis; (B) patients with fever; (C) positive intraoperative urine; (D) positive stone culture.



tients with a positive preoperative urine culture within three months of the planned procedure or an internalized ureteral stent, nephrostomy tube, or nephro-ureteral stent at the time of surgery (17). Xu et al. considered patients receiving antibiotic treatment for a positive urine culture, regardless of stone size, as high infectious risk patients for PCNL (24).

It was consensual amongst investigators that the choice of which antibiotic to use preoperatively in patients undergoing PCNL should be based on local bacterial sensitivity patterns (15-17, 23, 24). Mariappan et al. chose ciprofloxacin, while Bag et al., Chew B et al., and Sur et al. chose nitrofurantoin (15-17, 23). Although the level of bacterial resistance to nitrofurantoin is low, it is essential to note that nitrofurantoin has poor penetration into the tissues, and *Proteus sp*. and *Pseudomonas sp*. have inherited chromosomal resistance to it (27-29).

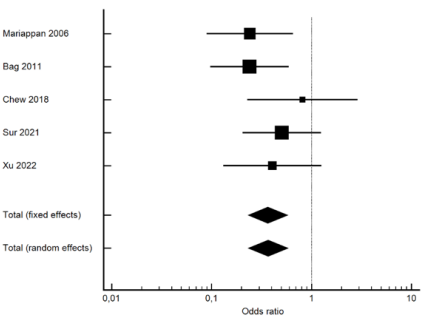
This meta-analysis demonstrated the protective role of one week of preoperative oral antibiotics for patients undergoing PCNL. Still, we recognize limitations, including a low number of subjects, heterogeneity of definitions of sepsis, and antibiotic use. The low number of participants is explained by our strict inclusion criteria of only prospective or randomized controlled trials in this meta-analysis. Nevertheless, the quality of a meta-analysis depends on the quality of the original studies included. As we aimed to investigate whether an intervention could reduce the risk of a serious complication, it was essential to have only prospective data due to its reliability and to minimize selection and report bias (30). Retrospective studies tend to underreport complications compared to their prospective counterparts. The definition of sepsis is an ongoing process, and we choose to keep the author´s definition at the time of the performance of the study. It is impossible to define the best prophylactic antibiotic based on this meta-analysis. Although the antibiotic used varied among studies, authors preferred ciprofloxacin or nitrofurantoin based on local bacterial flora.

Figure 4 – Forest plot – (A) SIRS or sepsis in control vs. intervention; (B) fever in control vs. intervention; (C) positive intraoperative urine culture in control vs. intervention; (D) positive stone culture in control vs. intervention.

(A)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	18	46	7	52	20.8%	0.242 (0.0897 – 0.653)
Bag 2011	26	53	9	48	25.2%	0.240 (0.0971 – 0.591)
Chew 2018	6	43	5	43	12.7%	0.811 (0.228 – 2.890)
Sur 2021	14	55	10	68	25.1%	0.505 (0.204 – 1.248)
Xu 2022	12	28	7	30	16.1%	0.406 (0.131 – 1.256)
Total	76	225	38	241	100%	0.368 (0.234 – 0.579)*

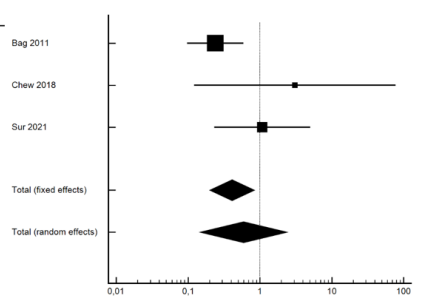
* p < 0.001; Test for heterogeneity: Chi2 = 3.5401, DF = 4, p = 0.4718, I2 = 0% (0.0 – 77.88).



(B)

	Control		Intervention		Weight (random events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Bag 2011	26	53	9	48	49.9%	0.240 (0.0971 - 0,591)
Chew 2018	0	43	1	43	14.4%	3.071 (0.122 – 77.504)
Sur 2021	3	55	4	68	35.7%	1.083 (0.232 - 5.059)
Total	29	151	14	159	100%	0.592 (0.147 – 2.388)*

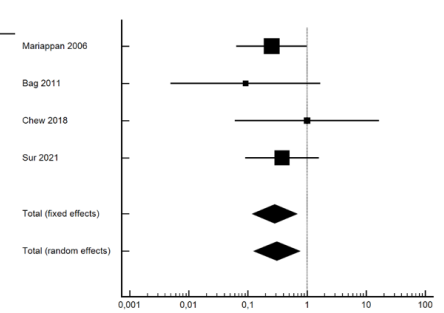
* p = 0.462; Test for heterogeneity: Chi2 = 4.3786, DF = 2, p = 0.1120, I2 = 54.32% (0.0 – 86.93)



(C)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	9	46	3	52	42.0%	0.252 (0.0637 – 0.995)
Bag 2011	5	53	0	48	9.3%	0.0909 (0.00489 – 1.690)
Chew 2018	5	53	0	48	10.1%	1.000 (0.0605 – 16.522)
Sur 2021	6	55	3	68	38.6%	0.377 (0.0898 – 1.582)
Total	21	197	7	211	100%	0.284 (0.120 – 0.647)*

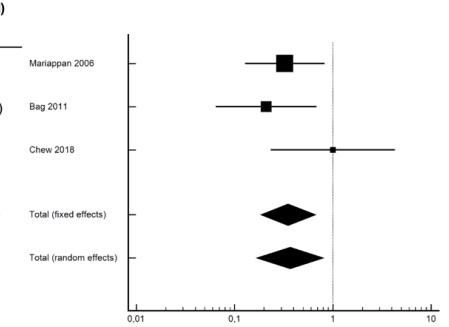
* p = 0.004; Test for heterogeneity: Chi2 = 1.5370, DF = 3, p = 0.6738, I2 = 0% (0.0 – 74.80)



(D)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	18	46	9	52	49.2%	0.326 (0.128 – 0.826)
Bag 2011	16	53	4	48	30.4%	0.210 (0.0646 – 0.684)
Chew 2018	4	43	4	43	20.1%	1.000 (0.233 – 4.286)
Total	38	142	17	143	100%	0.351 (0.185 – 0.663)*

* p = 0.001; Test for heterogeneity: Chi2 = 2.7390, DF = 2, p = 0.2541, I2 = 26.98% (0.0 – 97.55)



CONCLUSIONS

We conclude that one week of prophylactic oral antibiotics based on local bacterial sensitivity pattern plus a dose of intravenous antibiotics at the time of surgery in patients undergoing PCNL reduces the risk of infection. To optimize preoperative antibiotic use, more prospective data are needed to define better which patients are at a higher risk of infection after PCNL.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A study comparing dusting to basketing for renal stones ≤ 2 cm during flexible ureteroscopy

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ABSTRACT

Objectives: To compare the dusting efficiency and safety with basketing for treating renal stones ≤ 2 cm during flexible ureteroscopy (fURS).

Materials and methods: This study included 218 patients with renal stones ≤ 2 cm treated with fURS. Among them, 106 patients underwent dusting, and 112 patients underwent fragmentation with basket extraction. All patients were followed up for 3 months postoperatively. The operating time, lasing time, stone-free rate (SFR) and complication rate were compared.

Results: The mean stone size in the dusting group was 1.3 cm, whereas 1.4 cm in the basketing group. The mean operative time was significantly lower in the dusting group than in the basketing group (43.1±11.7 minutes VS 60.5±13.4 minutes, P <0.05), but the lasing time was significantly longer for the dusting group than for the basketing group (17.7±3.9 minutes VS 14.1±3.6 minutes, P <0.05). SFR was significantly higher in the basketing group immediately after the operation and follow-up after 1 month (76.8% vs 55.7%, P= 0.001 and 88.4% vs 78.3%, P = 0.045). However, the SFR was similar for both groups (88.8% in the dusting group vs. 90.2% in the basketing group) after 3 months postoperatively. There was no statistical difference in the complication rates between the two groups.

Conclusions: Dusting has advantages in shortening the operation time and reducing the operation cost, but the lasing time was longer compared with the basketing. Although there is no difference in long-term effect, basketing is superior to dusting in terms of short-term SFR. Moreover, dusting should be avoided in some special cases and basketing a better choice. Both techniques are effective for the treatment of renal stones ≤ 2 cm and choice depends on patient demographic and stone characteristics.

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INTRODUCTION

Many treatment options are available for patients with renal stones (1). Flexible ureteroscopy (fURS), characterized by minimally invasive and fast recovery, is more effective than SWL and safer than PCNL (2). It is currently recommended by the European Association of Urology (EAU) as one of the best choices for renal stones ≤ 2 cm (3). With the innovation of technology, fURS are now widely used in treating renal stones ≤2 cm (1, 4). It can also be considered for stones > 2 cm,

especially for patients who are poor candidates for PCNL due to anatomic challenges, medical comorbidities, and an inability to stop anticoagulation (5, 6).

The main concerns of fURS are how to achieve optimal stone clearance with a minimal rate of complications. One of the techniques which has been described as 'basketing', is using a basket for active extraction of fragments after the primary stone has been broken into 3-4 mm size (7). The other option has been described as 'dusting'. This technique uses laser to disintegrate the stone into tiny dust-like particles (mostly mentioned ≤ 2 mm), which can pass spontaneously through the ureter (8, 9). There are limited clinical trials comparing dusting and basketing published (7-9). However, studies comparing these two techniques in a large sample size have not been published yet. There is currently no evidence to prove which technique is better. What are the advantages of dusting compared with basketing and will dusting become a better choice for the treatment of renal stones? The present study was conducted to address these issues to compare the clinical results of dusting and basketing during fURS.

PATIENTS AND METHODS

Patients

Our study included 218 patients with renal stones ≤ 2 cm treated with fURS (dusting or basketing) using a 100W high-power Ho: YAG system in our department from March 2018 to January 2021. All patients were prospectively randomized into two groups and informed consent (IRB number: NO.2018-KY-E-276) prior to the procedure. Patients who could not complete the procedure due to ureteral stenosis or anesthesia problems were excluded. Abdominopelvic computed tomography (CT) was done to determine the stone size and location, with CT density value. Patient demographics, routine serum creatinine examination outcomes, urine analysis and culture were also prospectively recorded (Table-1). Patients were treated with a single dose of third-generation cephalosporin before the operation. Patients with positive urine cultures received culture-specific antibiotics until the urine culture results were negative before any intervention.

Surgical procedures

All patients received general anesthesia and were operated on by the same surgeon in the lithotomy position. We first used the standard ureteroscopy technique to insert a guide wire into the renal pelvis. Then a ureteral access sheath (UAS) (Proxis, Boston Scientific, MA, United States) was placed through the guide wire for basketing patients and optional for dusting patients (patients with tortuous ureters or to obtain a fragment for analysis). The size of the UAS was 12/14Fr. The tip of the UAS was placed in the ureteropelvic junction. Afterward, a flexible ureteroscope (Olympus, Japan) was inserted to observe the pelvicalyceal system's structure and identify the stones' location.

A 100W high-power Ho:YAG system and 200 μm reusable laser fibers were used for lithotripsy irrespective of the stone size or location (Lumenis, Inc.). We renewed the tip of laser fibers using simple sterile scissors before every operation. The pulse energy settings used were 0.2–0.4 J with a frequency of 30–60 Hz giving a total power of 6–24 W in the dusting group. We gently placed the tip of the laser fiber over the stone surface and dusted stones into tiny pieces (≤ 2 mm) which can pass spontaneously. While for the basketing group, the procedure was completed using the energy of 0.8–1.2 J and a frequency of 8–10 Hz giving a total power of 8–12W.The stones were broken into 2–4 mm fragments that can be actively extracted using a nitinol basket rather than leaving it in situ for spontaneous passage. After completing the lithotripsy, the degree of injury to the ureter caused by the UAS was evaluated during the withdrawal of the fURS. Finally, a 4.7 F ureteric stent was placed at the end of the procedure.

Follow-up

After the operation was completed, the operative time was recorded. On the first day after surgery, all patients were requested to have plain abdominal radiography (KUB) to confirm the proper placement of the double-J stents. The patients were then discharged within 24 h after surgery and received alpha-blocker therapy (tamsulosin 0.4mg daily) for 1 month. However, patients with

Table 1 - Patient baseline characteristics in the Dusting versus Basketing Cohorts.

	Dusting (N=106)	Basketing (N=112)	P
Age (years,Mean±SD)	46.6±12.7	47.2±13.2	0.748#
Gender (male, %)	67(63%)	65(58%)	0.435*
Side, n (%)			**0.301***
Right	40 (37.7)	50 (44.6)	
Left	66 (62.3)	62 (55.4)	
Stone number, n (%)			**0.593***
Single	52 (49.1)	59 (52.7)	
Multiple	54 (50.9)	53 (47.3)	
Stone location, n (%)			**0.632***
Renal pelvis	24 (22.6)	30 (26.8)	
calyx	53 (50.0)	49 (43.7)	
Multiple sites	29 (27.4)	33 (29.5)	
Stone size (mm, Mean±SD)	13.5±3.8	14.3±3.7	0.099*
UTI (positive culture)	16 (15.1)	18 (16.1)	0.842*
Creatinine (µmol/L, Mean±SD)	86.2±20.1	88.7±21.4	0.373#

*Results assessed statistically using the chi-squared test; #Results assessed statistically using the Student t test.

complications such as fever were discharged after treatment. KUB was again performed after 4th week; if the patient had no kidney stone in the report, an ultrasound was also recommended to double-check the SFR. The stents were removed for those patients without residual fragments, or the residual fragments were smaller than 4mm. If the patients had residual stones bigger than 4mm or too many stone fragments which would not pass spontaneously after 4 weeks, we removed the double J after 6 weeks postoperatively. Whilst if the patients had residual stones which required a second session of fURS, the stents would be removed in the operating theatre. KUB and renal ultrasonography were again performed to reevaluate SFR after 3 months postoperatively. SFR was defined as no residual fragments of any size on KUB and renal ultrasonography. Postoperative complications were classified using the modified Clavien classification.

Statistical analysis

The continuous variables were compared using means value (SD) with the Student t test, while the chi-squared test was used for categorical variables. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 18.0 for Windows. A $p<0.05$ was considered statistically significant for all analyses.

RESULTS

The study included a total of 218 consecutive patients. Among them, 106 patients underwent 'dusting' and 112 underwent 'basketing'. The mean stone size in the dusting group was 1.3 cm (0.5–1.9 cm) and 1.4 cm (0.7–2.0 cm) in the basketing group. There was no statistically significant difference in patients' baseline demographic characteristics between the two groups (Table-1).

The operation data and postoperative outcomes are presented in Table-2. The mean operative time was significantly lower in the dusting group than in the basketing group (43.1±11.7 minutes vs 60.5±13.4 minutes, p <0.05), but the lasing time was significantly longer for the dusting group than for the basketing group (17.7±3.9 minutes vs 14.1±3.6 seconds, p<0.05). Both the groups had similar overall complication rates and the total period of hospital stay. Ureteric perforation (Grade 3 injury) occurred in 1 patient in the basketing group, which took place during the removal of the UAS and was treated by placing ureteric stents for 4 weeks. No gross hematuria was encountered in the groups. Postoperative fever (> 38°C) was seen in 4 patients in the dusting group, whereas 3 patients in the basketing group and were successfully treated by antibiotics therapy. One patient in the dusting group was admitted to the intensive care unit (ICU) due to septic shock and was successfully treated with culture-specific antibiotics.

The immediate SFR after surgery was significantly higher in the basketing group (76.8%) compared with the dusting group (55.7%, p=0.001). The SFR was also higher in the basketing group at 88.4 % vs. 78.3% (p=0.045) than in the dusting group after 1 month postoperatively. However, the SFR was higher and similar for both groups (88.8% in the dusting group vs 90.2% in basketing group, P=0.719) during the follow-up period after 3 months postoperatively. The secondary session of fURS was required in the dusting group and basketing groups, in 9.4% and 7.1% (P=0.539) of patients, respectively. There was no statistical difference in postoperative creatinine and symptomatic residual fragments between the two groups.

DISCUSSION

In recent years, fURS have become the most common treatment for renal stones ≤ 2 cm due to its minimally invasive characteristic and short learning

Table 2 - Operative and Follow-up outcomes between the Dusting and Basketing cohorts.

	Dusting (N=106)	Basketing (N=112)	P
Postoperative creatinine (µmol/L,Mean±SD)	89.9±16.8	90.5±17.0	0.805#
Access sheath used, n (%)	23(21.7%)	112(100%)	<0.05*
Operative time(min,Mean±SD)	43.1±11.7	60.5±13.4	<0.05#
laser time(min,Mean±SD)	17.7±3.9	14.1±3.6	<0.05#
Hospitalstay (days,Mean±SD)	1.2±0.5	1.3±0.6	0.673#
Complications, n (%)			**0.563***
Intraoperative	0(0%)	1(0.9%)	
Postoperative	4(3.8%)	3(2.7%)	
Symptoms due to fragments	16(15.1%)	13(11.6%)	0.550 *
Second session of fURS	10(9.4%)	8(7.1%)	0.539 *
Stone-free rate, n (%)			
1 day PO	59 (55.7%)	86 (76.8%)	0.001 *
1 month PO	83(78.3%)	99 (88.4%)	0.045 *
3 months PO	94 (88.8%)	101 (90.2%)	0.719 *

*Results assessed statistically using the chi-squared test; #Results assessed statistically using the Student t test.

curve (10-12). There are two alternative strategies for fURS. The first is fragmenting the stone, then basketing of fragment, and the second is stone dusting followed by spontaneous passage. Basketing uses high power and low frequency to break the stones into 2 to 4 mm fragments, followed by active removal with a basket through the UAS until all visible fragments have been cleared. This technique theoretically provides for a complete stone removal rate under direct visualization. A stone sample is also available for analysis, which will help provide accurate metabolic therapeutic treatment and lifestyle modification. Many clinical studies have demonstrated its safety and efficacy for many years (7, 9, 13, 14). However, the high cost is frequently cited as the main drawback of this technique, as active extraction generally has longer operative times and requires a disposable basket and a UAS (15, 16). Unlike basketing, the presence of a dusting technique may offer an excellent solution to this problem by using low power and high frequency to fragment stones into dust-like particles for spontaneous passage rather than using the basket and possibly a UAS (8, 17). Additionally, this procedure can eliminate the need for additional staff, as the surgeon can perform the procedure without much assistance. Moreover, dusting has been associated with shorter operating times reported by some authors, which can also reduce operating costs. However, according to some of the comparative studies, SFRs were similar between these two techniques (16, 18). In our research, UAS usage rates were lower with dusting, and the immediate procedure cost was significantly reduced compared to basketing. Consistent with previous studies, the dusting group's mean operative time was significantly shorter. Meanwhile, there were no statistical differences in SFR and complication rate after 3 months postoperatively follow-up. As mentioned above, dusting appears to be the better choice for the fURS.

However, the potential risk factors, such as recurrent stone formation due to dust failing to pass, were also described in some studies, especially in patients with lower pole stones or acute infundibulo-pelvic angle (16, 19). Lower pole stone is a challenging clinical entity and account for approximately 35% of renal stones. The lower pole stone with an acute infundibulo-pelvic angle not only increases the technical difficulty which needs better surgeon skill and experience, but also relates to the fragment clearance after operation due to the anatomy (19, 20). This may be a disadvantage of the dusting technology, which needs further research in the future. In our study, we found that stones encrusted with abscess substance were also difficult to pass. The possible reason was that the small stone fragments will soon be covered by abscess substance after the stones are dusted into fragments, which will make it fail to pass. On the other hand, the dusting technique fragments stones into dust, resulting in the frequent poor vision field, especially for larger stones, and makes it difficult for surgeons to ensure that the stone is dusted small enough to pass spontaneously. In this situation, surgeons normally increase irrigation flow rates in order to get a better field view, which may increase intra-renal pressure and rise potential complications, especially sepsis risk (21). Furthermore, our results showed that basketing could not give an advantage in the complete SFR, while the immediate postoperative SFR and SFR observed 1 month postoperatively were significantly better in the basketing group. This may not increase short-term complications but influences treatment confidence and increases patient concern about the risk for long-term treatment due to repeated sessions of the same intervention, resulting in time lost for the patient. Moreover, working without active fragment retrieval and UAS can be associated with a shorter operating time in the dusting group, but this can lead to increased intraoperative pelvic pressure and the risk of postoperative infection. This was the most probable reason for the postoperative fever, which was more found in the dusting group than in the basketing group in our study. Among the total patient, only one of them developed septic shock, which was recorded in the dusting group.

When discussing the safety of both techniques, basketing theoretically increases the risk of injury because of the 100% use of UAS in these patients (22, 23). However, this was not observed in our study. We did have one ureteric perforation in the basketing group, there was no statistical difference in complication rates between the two

groups. In contrast, although the overall operative time was shorter in the dusting group, but the lasing time was significantly longer for the dusting group, especially in tackling the hard stones (CT value >800). Additionally, the power settings were also routinely higher during dusting. Studies showed laser has thermal effects on surrounding tissue and intra-renal temperature can reach 60°C after only 10 seconds with 40W laser activation. Although the changes in temperature inside the renal pelvis during the procedure could not be confirmed in our study, longer lasing time might theoretically increase the risk of thermal damage to the renal collecting system (21). Aldoukhi and his colleagues evaluated the temperature change according to the fluid irrigation rate in a in vivo study. They reported that the internal temperature could be maintained under 50°C with 40W laser activation when the irrigation flow rate was 40 mL/min. However, the temperature could be increased up to 70°C when the irrigation flow rate was 15 mL/min (24). According to literature reports, tissue damage and cellular death will occur after short exposure of temperature above 40-60°C. Temperatures above 43°C could promote the protein denaturation of urothelium and therefore should be avoided (25, 26). A longer follow-up study might be necessary to compare the ureteral stenosis between the two groups.

As previously stated, each method does have its own advantages and disadvantages. Thus, the question regarding which technique is better for treating renal stones remains controversial. An optimal approach should depend on the patient's anatomic features and numerous stone factors, such as location, size, and density, as well as the patient's economic conditions and personalized care. Therefore, it is clear that not all stones are suitable for a single approach. However, in our experience, dusting should be avoided in some patients: (1) patients having an acute infundibulo--pelvic angle with a long lower calyx or severe hydronephrosis, the stone fragments are easy to deposit in the lower calyx and are challenging to pass, resulting in residual stones. (2) the stones covered with abscess substance should be broken and retrieved by baskets as much as possible. (3) The hard stones with CT value >1000 need longer lasing time and higher power settings to slowly ablate the stone, which will increase the risk of thermal damage. Additionally, the damage to the pelvis mucosa will increase the viscosity of mucosa to stones, resulting in the stone fragments being difficult to pass spontaneously.

There are some limitations in our present study. Firstly, stone composition analysis has not been performed, which might explain its impact on lasing time. Secondly, patients used KUB and renal ultrasonography for the determination of SFR rather than CT, which may result in some detection bias in the SFR. Thirdly, our study did not present temperature changes inside the renal pelvis during surgery. Therefore, the thermal damage coming from longer lasing time or higher power settings was difficult to assess. Furthermore, the long-term differences over 6 months period results from the thermal injury were also unknown.

CONCLUSIONS

Dusting has advantages in shortening the operation time and reducing the operation costs, but the lasing time was longer compared with the basketing. Although there is no difference in long-term effect, basketing is superior to dusting in terms of short-term SFR. Moreover, dusting should be avoided in some special cases and basketing may be a better choice. Both techniques have their relative advantages and disadvantages, they are all effective to treat renal stones ≤ 2 cm. The question regarding which technique is better depends on patient demographic and stone characteristics. However, future well-designed studies with longer follow-ups may be required to compare these two techniques for better results and improved recommendations.

ETHICAL APPROVAL

The study was approved by the ethical committee of first affiliated hospital of Guangxi Medical University. All procedures performed in this study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Dynamic cystoscopy to optimize preoperative assessment of bladder endometriosis

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ABSTRACT

Purpose: Bladder endometriosis (BE) accounts for 84% of cases of urinary tract involvement. The use of cystoscopy for preoperative evaluation is limited. The aim of this study was to evaluate the accuracy of preoperative dynamic cystoscopy (DC) in patients undergoing surgery for deep endometriosis and to describe the main findings and their impact on surgical planning.

Materials and Methods: This cross-sectional observational study was conducted from January 2011 to March 2022. DC findings were divided into two groups according to the depth of involvement. To estimate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), laparoscopic findings of bladder involvement and histopathological report were used as the gold standard.

Results: We included 157 patients in this study. 41 had abnormalities in DC. Of these, 39 had abnormalities that were confirmed intraoperatively. The sensitivity and specificity of the test were 58.21% and 97.78%, respectively. PPV was 95.12%, and NPV was 75.86%. The presence of any lesions in the DC had a diagnostic odds ratio (OR) of 61.28 for BE. Patients with BE type 2 had a higher rate of partial cystectomy than those with BE type 1 lesions (OR 9.72 CI 95% 1.9-49.1)

Conclusion: DC appears to be a highly specific test with lower sensitivity. DC abnormalities are associated with a higher ratio of bladder surgery for the treatment of deep endometriosis, and BE type 2 seems to be associated with a greater ratio (9.72) of partial cystectomy.

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INTRODUCTION

Endometriosis is a chronic condition defined by the presence of endometrial tissue outside the uterus (1). Retrograde menstruation of endometrial cells is believed to promote their implantation into the peritoneum, resulting in inflammation and fibrosis (2). Endometriosis affects 6-10% of women of reproductive age (3), and lesions can be of three types: superficial lesions, ovarian endometriomas, or deep endometriosis (infiltration greater than 5 mm in depth) (1). The urinary tract is affected in 1-2% of cases, and bladder endometriosis (BE) is the most common presentation (84% of these cases), mainly in the dome and bladder base (4).

Bladder involvement can be primary when it occurs spontaneously and secondary when it results from a previous pelvic procedure, such as

hysterectomy. It is associated with injuries in other locations in 90% of the cases (4). There are two distinct pathophysiological mechanisms of BE. The dome is affected with the development of implants in the cul-de-sac. Trigonal lesions are secondary to anterior wall adenomyosis (5). Urinary symptoms may occur when deep endometriosis affects the lower urinary tract and adjacent structures. Parametrial involvement is associated with urinary voiding symptoms, whereas bladder infiltration is mainly associated with storage symptoms (6).

Transvaginal ultrasonography (TVUS) may be considered the first-line technique for the diagnosis of BE (4) and has a specificity of almost 100%; however, it is worse when the lesions are smaller than 3 cm or if the patient has already undergone surgical procedures. In these cases, the sensitivity did not exceed 50% (7).

Magnetic resonance imaging (MRI) may also be used for the evaluation of BE; however, there are no well-established protocols for its performance (7). MRI sensitivity reached 88%, and specificity was greater than 98% (8).

Cystoscopy may be particularly important in patients in whom MRI or TVUS findings suggest endometriosis in the anterior compartment and may define the exact location of the lesion, size, and distance to the ureteral ostia as well as its projection along the intramural ureter (4).

Although TVUS and MRI have a role defined in the preoperative evaluation with a good level of evidence, data on the use of cystoscopy in this scenario are scarce, with small samples and no established accuracy (4, 9). Dynamic cystoscopy (DC) differs from conventional cystoscopy in that it combines bimanual palpation.

Our hypothesis is that DC can be useful in the preoperative evaluation of deep endometriosis, and we aimed to determine the accuracy of this diagnostic method, in addition to describing the main findings in the evaluation.

MATERIAL AND METHODS

The protocol was approved by the Committee for Ethical Human Experimentation of our university and was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation (IRB number 30732420.3.0000.5259). This manuscript is based on the STARD statement (10).

This was a cross-sectional observational study, with prospective preplanned data collection to evaluate the accuracy of preoperative DC in a series of patients undergoing minimally invasive surgery for the treatment of deep endometriosis between January 2011 and March 2022. All included patients were treated at reference centers for assistance and research on patients with deep endometriosis. Therapeutic conduct followed the guidelines of the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) (11).

Inclusion criteria were women with deep endometriosis in the anterior, middle, or posterior compartment who underwent preoperative DC. It is important to highlight that the use of this method changed in this historical series. Initially, in the first years around 2011, this test was used in all patients preoperatively. After the second half of 2017, DC had a more restricted use, mainly limited to patients with suspected involvement of the anterior compartment of the pelvis. In recent years, since 2019, its use has become even more limited, being only performed in patients with suspected bladder involvement on MRI.

Exclusion criteria were patients who referred some condition that, although not associated with endometriosis or its treatment, were evidently liable to confuse the analysis, such as previous pelvic or perineal surgeries, urological or not (except for normal and uncomplicated cesarean deliveries), women who had already undergone pelvic radiation, and those with pelvic organs prolapses.

Dynamic cystoscopy (DC)

Cystoscopy under sedation was performed using a Storz® 17-French rigid cystoscope and a 30-degree objective lens. In conventional cystoscopy, the bladder is systematically evaluated under maximal irrigation with saline solution. Initially, the floor of the bladder and trigone are surveyed. The ureteral orifices are noted, and the remainder of the bladder wall are inspected (12).

We denominated DC as the evaluation performed concomitantly with a physical examination

of the pelvis. Associated vaginal and bimanual palpation allows evaluation of adhesions, retractions, and reduced bladder mobility (Figure-1A).

Concomitant palpation also allows the location of possible deep nodules in the posterior bladder wall, noticed as indurated and immobile lesions, which cannot be identified by conventional cystoscopy (Figure-1B).

Dynamic cystoscopy classification of bladder involvement

We classified the abnormal DC findings in two types: Type 1 lesions included extrinsic nodules in the bladder wall that did not extend beyond the muscular layer and were seen only as a protrusion adhered to the bladder wall. Type 2 lesions affected the mucosa and were identified as typical adenomatous red or bluish masses on the inner surface (Figure-2).

Assessing accuracy of dynamic cystoscopy (DC)

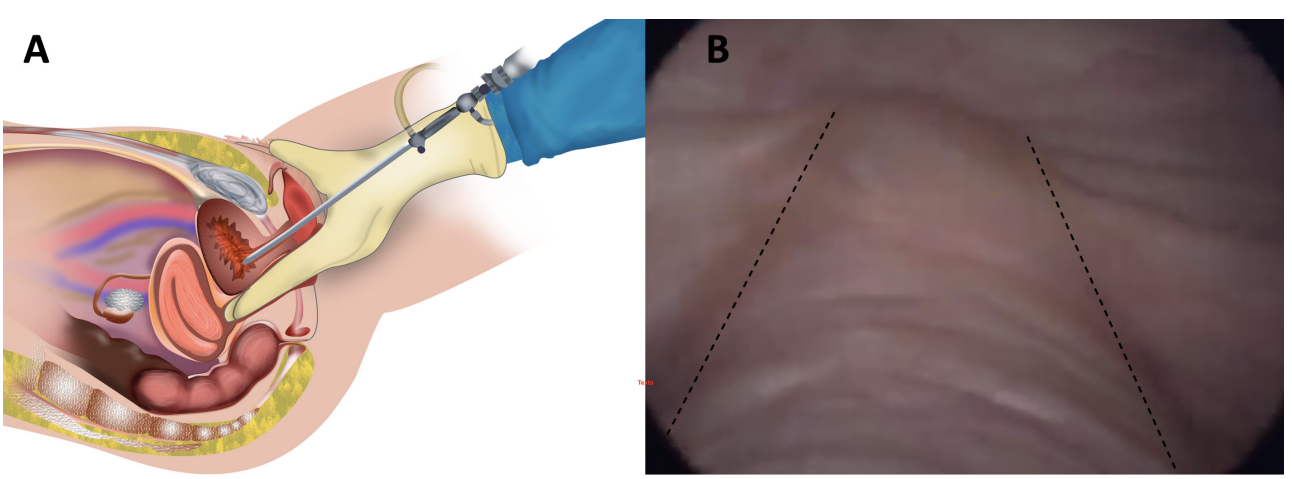
To assess the accuracy of the DC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), laparoscopic findings of bladder involvement were used as the gold standard. When endometriosis was detected through laparoscopic observation, the lesions were resected, and histopathological analysis was performed to confirm the diagnosis in all surgical specimens.

Laparoscopic findings considered abnormal included peritoneal disease on the bladder surface or infiltrative deep endometriosis that reached the muscular layer or bladder mucosa. The surgical technique for the treatment of bladder endometriosis involves partial cystectomy, defined as complete resection of the bladder wall in the affected region, or bladder shaving, an adapted technique for the treatment of intestinal endometriosis that consists of superficial resection of the organ, preservation of the mucosa, and maximum disease-free wall thickness (Figure-2) (13).

Disease confined to the vesico-uterine septum was not considered BE, and this involvement did not show an association with urinary alterations in another study (6). We also included MRI findings. The major anatomical sites were selected based on the Lasmar diagram (14).

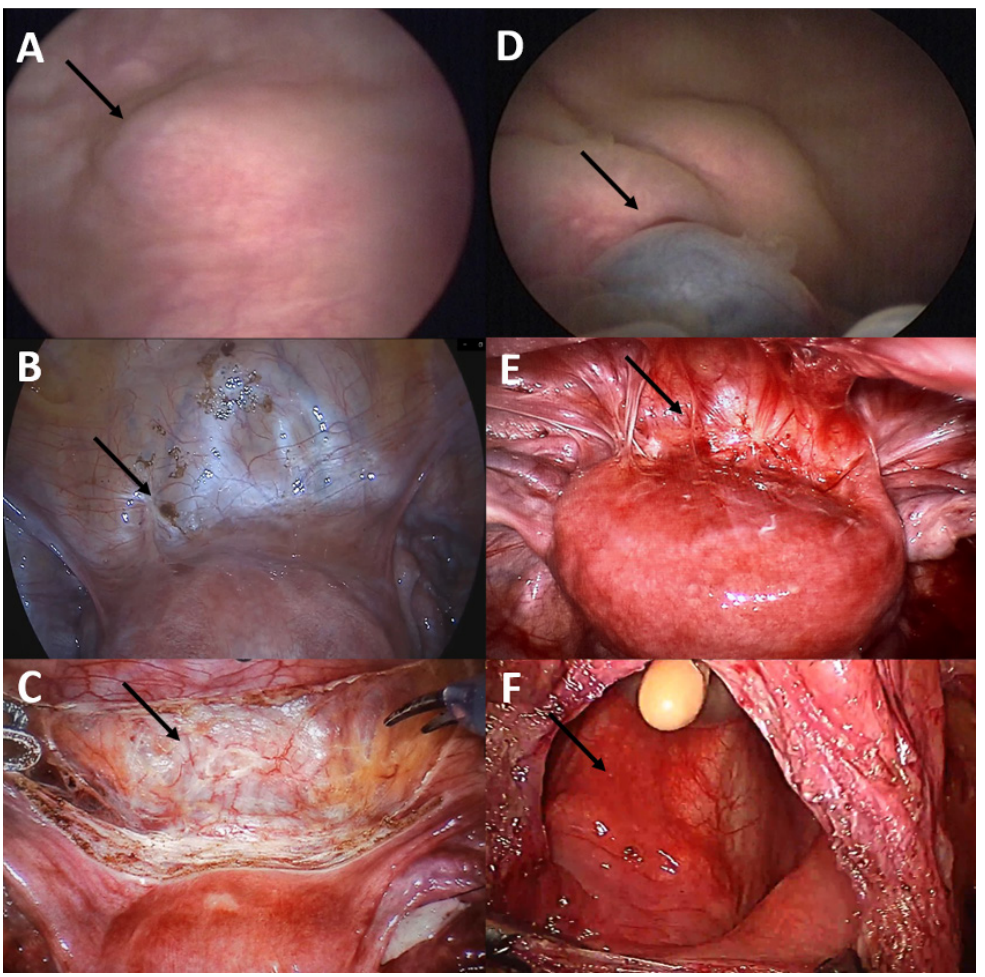
All laparoscopies and DC were performed by the same multidisciplinary team, which systematically performed the surgery. Whether identified during the preoperative evaluation or intraoperatively, all suspected lesions were carefully explored. Endometriosis was histologically confirmed when endometrial glands and stroma were present on microscopic examination. The same experienced pathologists were responsible for the histological reports.

Figure 1 - Dynamic cystoscopy (DC).



1A) Illustration demonstrating the procedure, which consists of a conventional cystoscopy associated with vaginal palpation. 1B) Vaginal palpation (dashed line) allows to identify and delimit a deep lesion in the bladder (type 1 lesion), nontender and fixed, which could go unnoticed as a roughness in its wall in a conventional cystoscopy.

Figure 2 - The figure shows 2 different cases of bladder endometriosis (BE). A, B, C) Thirty-two-year patient with BE saving the inner layer.



Dynamic cystoscopy (DC) evidencing BE type 1, a nodule adhered to the bladder wall, without mucosal involvement (arrow). B) Laparoscopic view of the anterior compartment of the female pelvis. Minor bladder involvement in the peritoneal surface of the bladder (arrow). C) Treatment of BE in a more conservative resection- bladder shaving (arrow). D, E, F) -thirty three- year patient with BE involving bladder mucosa. D) DC evidencing BE type 2, an infiltrative lesion involving bladder mucosa with a typical blush mass (arrow). E) Laparoscopic view of the anterior compartment of the female pelvis with extensive adhesions and endometriotic lesions on the surface of the bladder (arrow) F) Treatment of BE: partial cystectomy, with opening of the mucosa (arrow).

Statistical analysis

Statistical and graphical analyses were performed using the IBM® SPSS® Statistics Standard Grad Pack 20 (NY, USA). A 95% confidence interval (CI) was used.

RESULTS

During this period, 170 patients underwent preoperative DC, aged 22 to 54 years (median age of 36 years). Thirteen patients were excluded because they had pelvic prolapse or previous pelvic surgeries. The demographic data are shown in Table-1.

Among the 157 patients included, 41 (26.1% of all sample) had abnormalities in the DC. Of these, 39 (95.12%) had BE confirmed intraoperatively and 38 (92.8%) were confirmed by histopathology. Of the 41 patients with DC lesions, 31 (75.6%) underwent partial cystectomy and 8 (19.5%) underwent bladder shaving.

Table 1 - Demographic data of the patients.

					Partner				Ethnicity			Schooling			Smoking	
	Age (Years)	Height (cm)	Weight (kg)	BMI	Married	Divorced	Single	Widow	White	Mixed	Black	<12th grading	Graduated	Post graduated	Non-smoking	Smoker
Min	22	153	45	18												
P25	32	160	60	22.5												
Median	39	164	65	24.1												
P75	45	167	70	26												
Max	54	178	108	40.2												
N					109	13	34	1	78	65	14	35	97	25	156	1
Percentage (%)					69.43	8.28	21.66	0.63	49.68	41.4	8.92	22.29	61.78	15.92	99.36	0.64
CI 95%					61.83-76.10	4.9-13.65	15.93-28.73	0.64-4.11	41.96-57.42	33.99-49.22	5.39-14.41	16.49-29.42	53.99-69.02	11.02-22.45	96.48-99.89	0.11-3.52

Min: Minimum; P25: Percentile 25; P75: Percentile 75; Max: Maximum; CI: Confidence interval; BMI: Body mass index.

When the DC findings were divided, 13 (31.7%) patients had type 1 lesions. Among these patients, 6 (46.1%) underwent bladder shaving and 6 (46.1%) underwent partial cystectomy. One patient (7.69%) showed normal laparoscopic findings. In contrast, 28 (68.29%) had type 2 lesions. In this group, 25 (89.29%) underwent partial cystectomy and 2 (7.14%) underwent bladder shaving. The other 1 patient (3.57%) had normal laparoscopic findings.

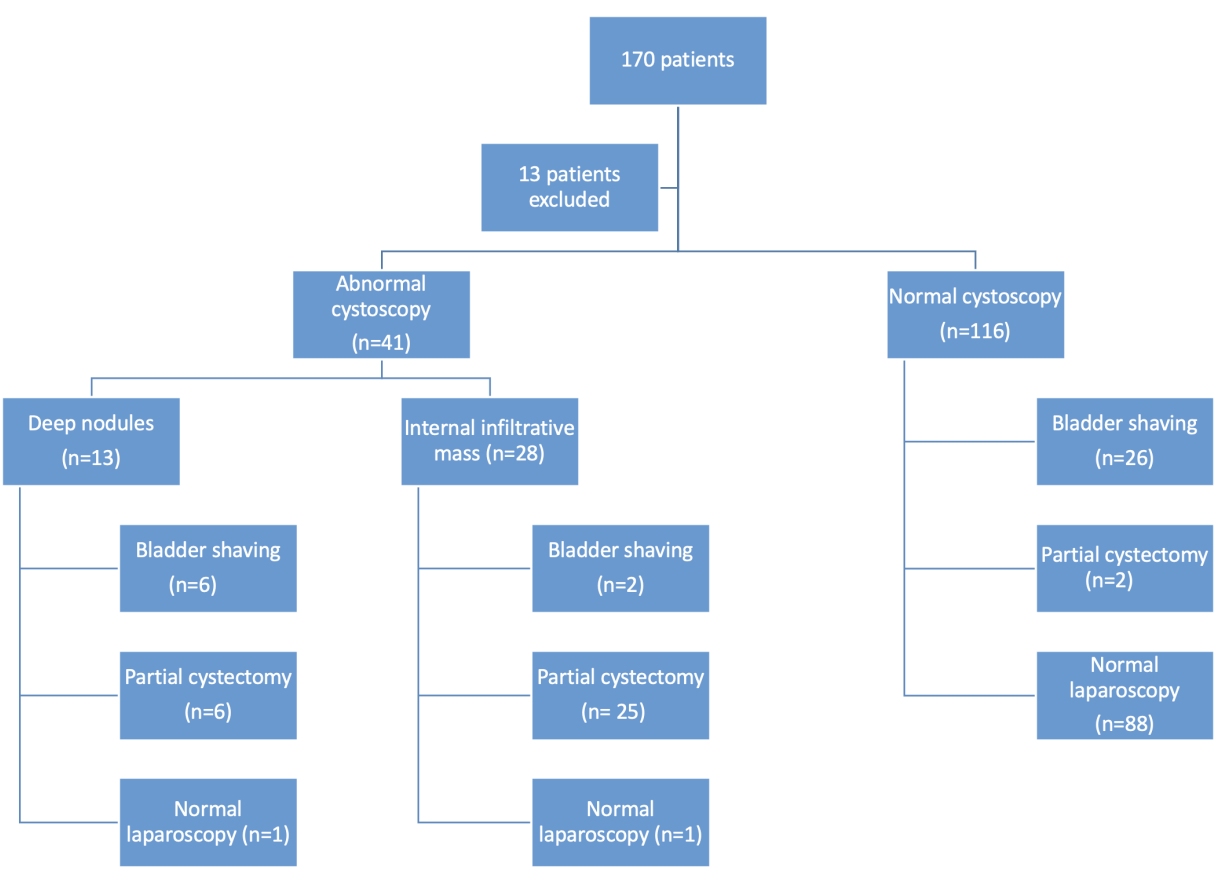
In the group with normal DC (116 patients, 73.89% of all sample), 28 (24.14%) had BE confirmed intraoperatively and 20 (17.24%) had histopathological confirmation. Of these 28 patients, 26 (92.86%) underwent bladder shaving and 2 (7.14%) underwent partial cystectomy. Figure 3 summarizes the DC findings.

In our sample, diagnostic odds ratio (OR) of DC was estimated by 61.28 (13.9-270.1 CI 95%) for bladder involvement and subsequent surgery by any technique. Patients with BE type 2 had a higher rate of partial cystectomy than those with BE type 1 lesions (OR 9.72 CI 95% 1.9-49.1). Using laparoscopic findings as the gold standard, DC had a calculated sensitivity and specificity of 58.21% (46.27 - 69.26% CI 95%) and 97.78% (92.26 - 99.39% CI 95%), respectively. Furthermore, predictive positive value (PPV) and negative predictive value (NPV) were 95.12% (90.54-97.54% CI 95%) and 75.86% (68.60-81.88% CI 95%), respectively.

Among the 41 patients with abnormalities in DC, 5 had a normal MRI evaluation. Among this subgroup, four patients underwent laparoscopic confirmation and bladder resection (partial cystectomy or shaving). Histopathological analysis was confirmed in all resected specimens.

In contrast, in the normal DC group, MRI detected 14 more patients with bladder changes,

Figure 3 - Flowchart highlighting the main findings in the sample. Thirteen patients were excluded because they had pelvic prolapses and previous pelvic surgeries. BE: Bladder endometriosis.



and 11 had laparoscopic confirmation and bladder resection. Histopathological analysis was confirmatory in 8 of the patients.

DISCUSSION

Performing a DC rather than conventional cystoscopy is intended to increase the accuracy of BE type 1 lesions. In our study, this method had lower sensitivity but higher specificity for BE. It also has a high diagnostic odds ratio (DOR). Thus, the presence of the disease is very likely in front of a positive test result. DC may still not detect BE in many females with peritoneal or muscular diseases.

During DC, the findings can be decisive in predicting the surgical approach. Vaginal palpation associated with cystoscopy is important for assessing the disease or areas of adhesions located in the vesico-uterine septum. It is also possible to identify deep nodules in the posterior bladder wall and visualize their distance from the ureteral orifices. Palpation may also reveal thickening of the round ligaments and other indirect findings of uterine/bladder retraction. Endometrial lesions far from the ureteral orifices are simpler to resect, and those closer (<2 cm) usually require an ureteroneocystostomy (15).

BE findings vary according to menstrual cycle. During the menstrual period, an elevated area can be detected with surrounding edema. Small translucent or bluish-looking cysts can be observed due to the accumulation of blood. In the intermenstrual period, the tumor regresses in size, and only a few cysts can be seen (16).

Diagnosis through deep bladder biopsy is poorly performed because of the potential risk of bleeding and perforation. Additionally, the sensitivity is approximately 26% (17) as the lesion develops from the serosa towards the mucosa (4). In our practice, we did not perform this procedure.

However, the efficacy of cystoscopy remains unclear. A recent systematic review of BE recommended the non-routine use of this method but with a level of evidence of IV (4). Tardieu et al. concluded that no study has prospectively evaluated the diagnostic performance of cystoscopy for BE (9).

Thonnon et al. compared the effectiveness of TVUS, MRI, and cystoscopy for identifying and characterizing BE. Despite the small number of patients (n = 8), TVUS and cystoscopy were able to identify all the cases. Both methods were equivalent in measuring the distance between the lesions and the ureteral orifices (18).

A more recent study argued that TVUS alone would be able to diagnose BE and calculated an accuracy of 95% for the method compared with conventional cystoscopy. Of the 22 patients studied, TVUS identified 9 patients with BE without involvement or protrusion in the mucosa, and therefore, had normal findings on cystoscopy (19).

DC abnormalities were associated with a high OR for the need for any bladder surgery, estimated to be 61.28. The extent of transmural involvement seems to be a significant predictor of the need for partial cystectomy, since almost all women (89.29%) with BE type 2 required this more aggressive approach, with an estimated OR of 9.72, compared to BE type 1.

These data may be important, as they may predict greater surgical complexity and the need for an experienced urologist to perform a partial cystectomy or even ureteral reimplantation.

Compared with MRI, this method did not detect five patients with abnormalities in DC but identified 14 patients with BE and normal DC. Considering that MRI, in addition to TVUS, seems to have greater sensitivity and is a non-invasive diagnostic method, it seems reasonable to infer that these methods should be used preferentially instead of DC in the initial preoperative evaluation. These methods have the advantage of simultaneously identifying lesions in other structures. MRI is also intended to estimate the depth of lesions in the bladder wall and, therefore, may also be a good predictor of the need for partial cystectomy. However, there is still no standardization for this type of assessment. It should be noted that the estimation of the distance to the ureteral ostia by imaging examinations can be underestimated, depending on the degree of bladder depletion. In addition, a standard urine volume at which all patients will undergo MRI has not been established (20). Performing an MRI with a completely empty

bladder allows better visualization of the vesico--uterine recess, which is one of the most affected sites (7). In contrast, MRI with a full bladder allows the assessment of bladder lesions and ureteral involvement (21).

It is important to remember that in this historical series, with a better understanding of the disease and improvement in diagnostic methods, especially the use of MRI, cystoscopy has had more restricted use over the years, as described in our methods. Thus, we may face a bias.

However, by definition, the sensitivity and specificity of a test do not vary according to pre-test probability. Thus, they can be used in different populations and to compare the diagnostic potential of different tests. On the other hand, other variables such as PPV and NPV are dependent on the prevalence of the disease; therefore, they cannot be generalized for patients with a profile different from that of the study and do not allow comparison between different diagnostic tests (22). Another limitation of our study is that it is not a prospective study. However, we used a reliable database system in which preplanned data collection was systematically performed for several years.

Therefore, in patients with lesions suspected of endometriosis on initial imaging, we recommend that DC should be performed as a preoperative strategy, considering that their findings can help the multidisciplinary team, especially the urologist, in choosing the best approach for BE.

CONCLUSIONS

Dynamic cystoscopy seems to be a highly specific test (97.78%) at the expense of lower sensitivity (58.21%). This method also had a high positive predictive value (95.12%) and a negative predictive value of 75.86%. However, cystoscopy abnormalities are associated with a higher ratio (OR 61.28) of bladder surgery for the treatment of deep endometriosis, and BE type 2 seems to be associated with a greater ratio (9.72) of partial cystectomy, and these findings may change surgical strategy.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Implementation and outcomes of Hugo™ RAS System in robotic-assisted radical prostatectomy

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ABSTRACT

Background: The results and benefits of Robotic-assisted Radical Prostatectomy (RARP) are already established in the literature. However, new robotic platforms have been released recently in the market and their outcomes are still unknown. In this scenario, our objective is to describe our experience implementing the Hugo™ RAS robot and report the clinical data of patients who underwent Robotic-assisted Radical Prostatectomy.
Material and Methods: We retrospectively analyzed fifteen consecutive patients who underwent RARP with Hugo™ RAS System (Medtronic, Minneapolis, USA) from June to October 2021. The patients underwent transperitoneal RARP on lithotomy position, using six trocars (4 robotic trocars and 2 for the assistant). We reported the clinical feasibility and safety of this platform, assessing perioperative data, including complications and early outcomes. Continuous variables were reported as median and interquartile ranges, categorical variables as frequencies and proportions.
Results and Limitations: All procedures were safe and feasible with no major complications or conversion. Median operative time was 235 minutes (213-271), and median estimated blood loss was 300ml (100-310). Positive surgical margins were reported in 5 patients (33%). The median hospitalization time was 2 days (2-2), and the median time to remove the foley was 7 days (7-7). On the first appointment four weeks after surgery, all patients had undetectable PSA values, and 61% were continent.
Conclusions: We described preliminary results with safe and feasible procedures performed with Hugo™ RAS System robotic platform. The surgeries were successfully executed with acceptable perioperative outcomes, without conversions or major complications. However, as this technology is very recent, further studies with a long-term follow-up are awaited to access postoperative functional and oncological outcomes.

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INTRODUCTION

The outcomes and benefits of Robotic-assisted Radical Prostatectomy (RARP) are already described and established in the literature. Since the first platform was approved by the Food and Drug Administration (FDA) in 2000, numerous models of da Vinci robots were produced in the market, and several groups described their experience with robotic surgery (1-5). However, only after Intuitive's (Intuitive Surgical, Sunnyvale, CA) patent ended in 2019 different brands and

models of robotic platforms were released worldwide. In this scenario, RARP with Hugo™ RAS System (Medtronic, Minneapolis, USA) was approved in 2021 by the Panama healthcare regulatory agency (Ministry of Health, Minsa) for clinical use in urologic procedures.

This multiport platform has some modifications compared to the conventional da Vinci (Intuitive Surgical, Sunnyvale, CA) consoles. The arms are placed in separate karts for independent docking, while the console provides an open design with a 3D screen visualized by the 3D glasses used by the surgeon. However, due to the recent release of Hugo™ RAS in the market, the literature still lacks studies describing the performance of this robot in clinical settings. In this scenario, our study describes our experience implementing the Hugo™ RAS robot and the clinical data of patients who underwent Robotic-assisted Radical Prostatectomy.

MATERIAL AND METHODS

The data of fifteen consecutive patients who underwent RARP with Hugo™ RAS System (Medtronic, Minneapolis, USA) from June to October 2021 were analyzed retrospectively. All surgeries were performed by two surgeons (E.B. and R.U.) and a proctor (J.P.) using the same surgical technique and OR staff in the Hospital Pacifica Salud (Punta Pacifica, Panama). All surgeries were approved by the Hospital Internal Boards. During the preoperative consultation, the patients were advised and explained about the settings and details of this new platform, as well as the use of the data collected for analysis and studies. All patients signed a consent term of knowledge and agreement before the surgical procedure.

Respecting the patient's privacy, the data of this study was collected with no personal identification by investigators from the center where the patients were operated (Hospital Pacifica Salud, Panama) and analyzed by investigators from AdventHealth Global Robotics Institute, USA.

We defined surgical conversion as a change in the surgical approach to laparoscopy, robotic (da Vinci), or open surgery. We reported complications according to the Clavien-Dindo classification (6). Major complications were considered as Clavien grade ≥ 3. Continence was defined as the capacity to hold urine without pads or patients using one security pad. PSA values ≥ 0.2 in two or more consecutive exams were defined as biochemical recurrence (BCR).

Endpoints

The primary endpoint of our study is to describe the clinical feasibility and safety of the Hugo™ RAS System (Medtronic, Minneapolis, USA) platform in patients who underwent robotic-assisted radical prostatectomy. We also provided a video compilation illustrating the key points of the surgery. Feasibility and safety were considered as procedures performed without conversions or major complications (see video).

The secondary endpoints were the intraoperative performance (assessed with operative time and blood loss), and perioperative outcomes from the first incision until the first postoperative visit after the catheter removal (four weeks after surgery). We also described early continence and PSA value reported in this first visit. Potency outcomes were not collected due to the short-term follow-up.

Hugo™ RAS training and robotic surgery experience

Before performing the first case with this new robot, our whole team underwent hours of training to approach the new settings and details of this technology. Each surgeon realized 17 exercises (3 times each) in a Dry Lab followed by 16 hours of system knowledge, docking, and troubleshooting. Then, the surgeons spent 16 to 20 hours performing renal and prostate surgery in cadavers while the staff members learned how to deal with the robotic arms and instruments during the procedure.

The day before the first surgery, we simulated a room set up by positioning the operative table, robotic components, and anesthesia equipment, which allowed us to save time during the clinical cases.

The surgeons involved in this study (E.B. and R.U.) are references in robotic surgery in Panama and had done more than one hundred robotic-assisted radical prostatectomies with the da Vinci console before starting Hugo™ RAS training.

Inclusion criteria

While establishing the clinical application of the Hugo™ RAS robot, we selected favorable cases for RARP. We included patients with low BMI (≤ 30 Kg/m2), small prostates (≤ 70gr), no previous abdominal surgeries, and no previous prostate interventions to treat BPH or cancer. We also selected confined tumors and avoided clinical stages (cTNM) T3 or T4.

Hugo Platform details

Robotic arms (individual karts)

One of the modifications of this platform regards the robotic arms. Instead of all arms attached to a central tower, as the standard multiport robots, the Hugo™ RAS robot has 4 independent arms attached to individual karts (Figure-1A and Figure-1B).

Each arm has a different docking angle (Figure-1C and Figure-1D) to achieve an optimal trocar placement and instrument movement during the surgery:

1- Scope (185-degree angle), Tilt - 45-degree angle

2- Right arm (230-degree angle), Tilt - 30-degree angle

3- Left arm (140-degree angle), Tilt - 30-degree angle

4- Fourth arm on the left side (105-degree angle), Tilt + 15-degree angle

Patient positioning and trocar placement

The patient is positioned in lithotomy to allow the placement of the scope kart between the legs. Before placing the trocars, we mark the abdomen according to Figure-2A. We initially mark 2 lines; the first is supraumbilical, 20cm from the pubis, and the second is 6 to 8 cm below the first line, on an infraumbilical position. Then, the 8mm Hugo™ RAS trocars are placed respecting the 9 to 10 cm distance between the ports. After placing the scope trocar on the supraumbilical midline position (1st line), the other trocars are positioned under direct view. Finally, a 12mm assistant trocar is placed on the right lower quadrant and a 5mm trocar between the scope and the right arm.

Docking and Instruments

The docking is performed after parking each kart on the correct position and setting the appropriate angle of each arm (Figures 2B-E). After attaching the trocars to each arm, we place the

Figure 1: A and B: HugoTM RAS System individual karts. C and D describing the lateral with of the karts with the angulation adjustment.

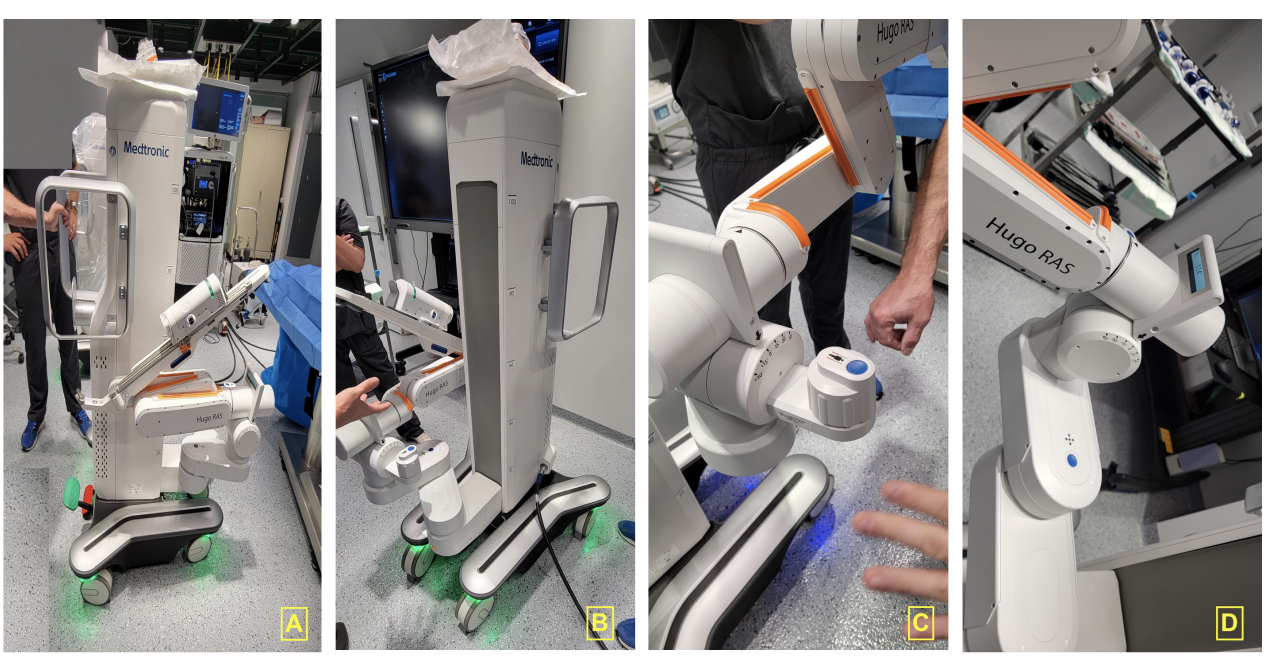
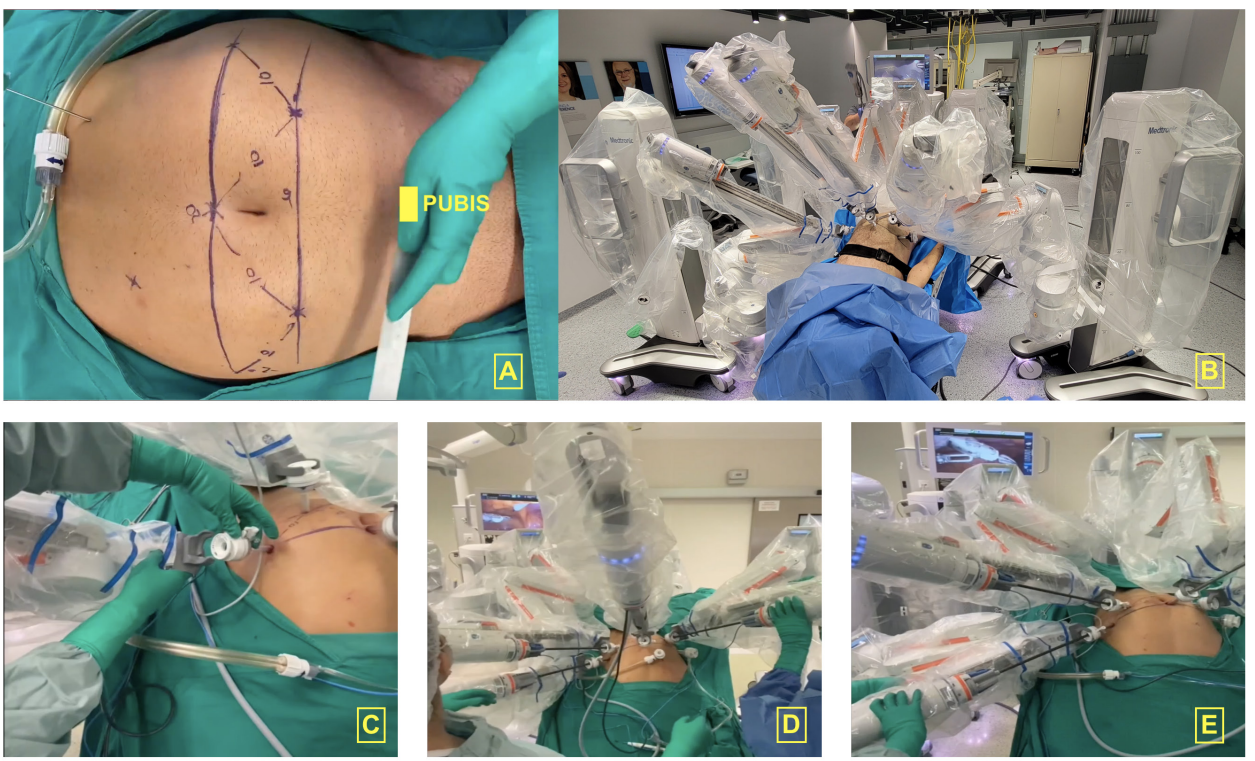


Figure 2: A: port placement configuration. B: final aspect after docking. C: docking the left arm. D, and E: final aspect after instrument placement.



scope, which is a 3D laparoscopic scope attached to a robotic adapter (Figure-3) to fit and work with the robotic command.

Console

The console is also another innovation compared to the previous robotic platforms in the market. This robot provides an open console with a 3-dimensional view glasses for the surgeon and other visitors in the room (Figure-4). The surgeon's glasses are different than the visitors due to a security device is implanted to activate or lock the robot during surgery.

Another modification is seen on the design and settings provided by the hand controllers, which consist of a pistol shape device with clutch on the second finger and unlocking command activated by the third finger (Figure-5).

SURGICAL TECHNIQUE

All patients underwent surgery in lithotomy position with all articulations and parts in contact with the table protected by pads. We performed a transperitoneal technique according to the previously described following steps: (2, 7-11).

1. Patient positioning and trocar placement
2. Bladder dropping and Retzius space access
3. DVC control and suspension stitch
4. Anterior bladder neck dissection
5. Posterior bladder neck dissection and seminal vesicles approach
6. Nerve sparing (posterior access and lateral dissection)
7. Prostatic pedicles control with Hem-o-lock clips
8. Apical dissection and urethra division
9. Lymphadenectomy
10. Posterior reconstruction and anastomosis

Postoperative care and follow-up

After surgery and anesthesia recovery, patients were stimulated to walk. Liquid diet was

Figure 3: 3D scope attached to the robotic adapter.

Figure 4: HugoTM RAS System open console.

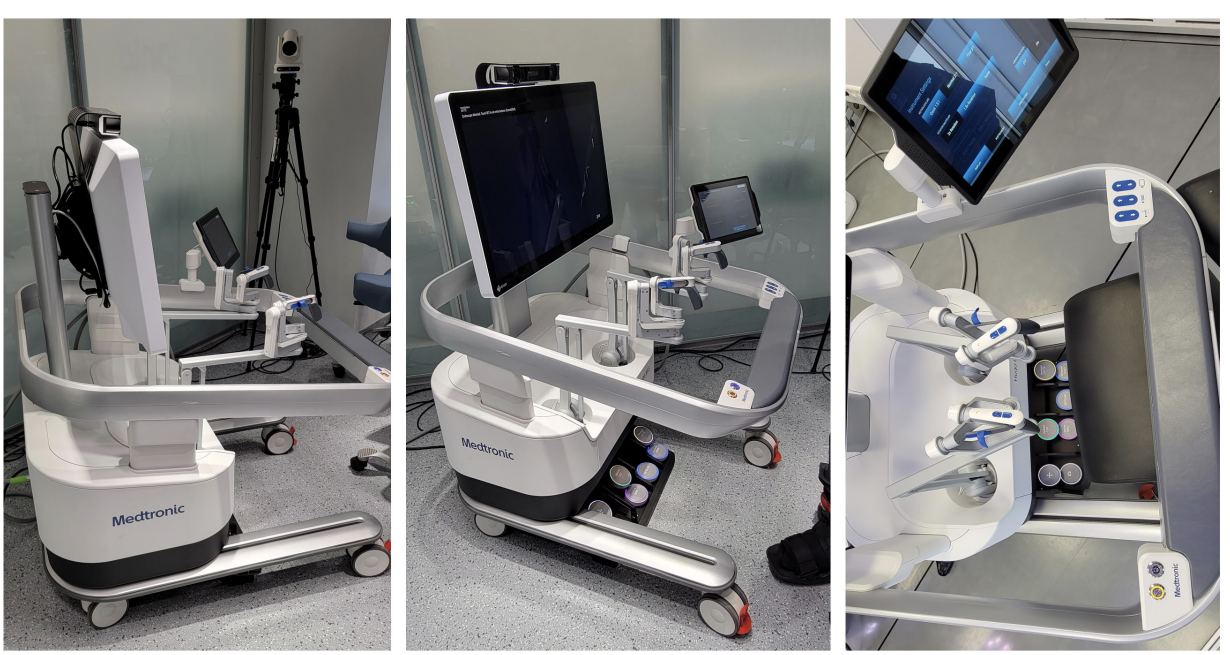
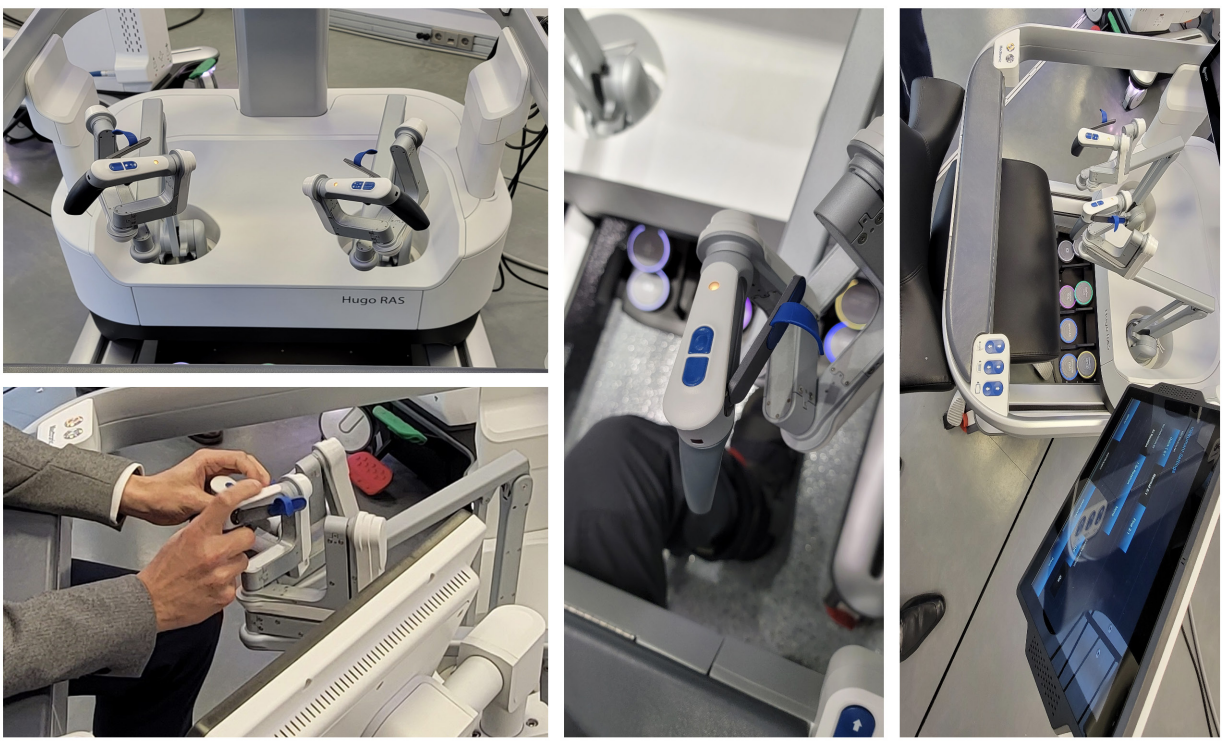


Figure 5: Hugo™ RAS System hand control (pistol-like).



given in the afternoon of the surgery for those operated on in the morning and the next morning for those operated on in the afternoon. Compressive socks were used until ambulation in the first postoperative day. Prophylactic enoxaparin was also used from the first until the fifth postoperative day. Patients were released home in the second day after surgery (morning) and returned for Foley removal on the seventh day.

Statistical analysis

The statistical analysis performed was based on established guidelines describing continuous variables as the median and interquartile range (IQR) (12, 13). Absolute and percentage relative frequencies were used for categorical variables.

RESULTS

Preoperative demography

Table-1 illustrates the preoperative demography of this cohort. We reported median values with interquartile range (IQR) and the number of patients with the percentage. We reported the biopsy according to the International Society of Urologic Pathology (ISUP) Grade Groups (GrGp) (14).

Perioperative

Table-2 describes the perioperative outcomes. All procedures were safe and feasible with no major complications or conversion. We had only one postoperative complication (gastrointestinal bleed due to gastritis). The median operative time was 235 minutes (213-271), and the median estimated blood loss was 300ml (100-310). Positive surgical margins were reported in 5 patients (33%). The median hospitalization time was 2 days (2-2) and the median time to remove the foley was 7 days (7-7). On the first appointment four weeks after surgery, all patients had indetectable PSA values and 61% were continent.

DISCUSSION

In the recent years, after the end of Intuitive's (Intuitive Surgical, Sunnyvale, CA) ex-

Table 1 - Preoperative demography of 15 patients reporting the median value with the interquartile range (IQR) and the number of patients with the percentage. PSA (Prostate Specific Antigen), BMI (Body Mass Index), ISUP (International Society of Urological Pathology).

Parameters of 15 patients	
Age (years)	62 (59 - 67)
PSA (ng/mL)	7.3 (4.8 - 8.1)
BMI (Kg/m^2)	24.9 (23 - 28)
Clinical Stage, n (%)	
cT1	8 (53)
cT2a	4 (26)
cT2b	2 (13)
cT2c	1 (7)
≥cT3	0
Biopsy ISUP grade, n (%)	
Group 1	7 (47)
Group 2	6 (40)
Group 3	0
Group 4	2 (13)
Group 5	0

clusivity in the robotic surgery field, several brands, and models of multiport and single-port robots were released in the market with promising technology (15-20). However, as most of them are still under a validation process, the literature still lacks robust data describing the performance and outcomes of these new platforms in urologic procedures. In this scenario, our study described the first clinical experience and perioperative outcomes of 15 patients who underwent robotic-assisted radical prostatectomy with Hugo™ RAS System (Medtronic, Minneapolis, USA).

Using new technologies to operate patients in clinical settings is always challenging (17, 19). However, before the implementation of this robot in our center, our team had previous expertise with robotic surgery after performing numerous cases of radical prostatectomy with the da Vinci console (Intuitive Surgical, Sunnyvale, CA). In addition, Panama was one of the first countries in the world to approve this robot for clinical use and our hospital (Hospital Pacifica Salud) was the first to acquire this technology to approach General Surgery, Gynecologic, and Urologic surgeries. In our experience, the main challenge during the implementation process was the learning curve of staff and surgical team associated with the modified docking and some console settings.

The patient positioning (lithotomy) and trocar placement are very similar to the da Vinci platform (Intuitive Surgical, Sunnyvale, CA). The appropriate distance and angles between the trocars must be respected to achieve the correct triangulation and instrument movement. However, the docking process is more challenging and demands training because all arms are attached to individual karts that must be placed in the correct position with an appropriate arm angulation. If these parameters are not respected, the optimal angles and arm movements will be compromised during the surgery. The first docking had the longest time (approximately 15 minutes) due to the setup of the karts. Then, we had a median time of 7 minutes docking per case in the following procedures.

Table 2 - Perioperative characteristics of 15 patients reporting the median with the interquartile range (IQR) for continuous variables and the number of patients with percentage for categorical variables. ISUP (International Society of Urological Pathology).

Parameters in 15 patients	
EBL (mL)	300 (100-310)
Total operative time (minutes)	235 (213 - 271)
Lymphadenectomy n, (%)	5 (33)
Intraoperative Complications n, (%)	0
Postoperative Complications n, (%) *	1(6)
Positive Surgical Margins n, (%)	5 (33)
Pathological Stage n, (%)	
pT2	11 (74)
pT3	4 (26)
Final Pathology ISUP grade, n (%)	
Group 1	2
Group 2	11
Group 3	1
Group 4	0
Group 5	1
Prostate volume (cc)	52 (41-56)
Hospital Stay (days)	2 (2-2)
Time to remove Foley (days)	7 (7-7)
Continence in 4 weeks n, (%)	
Continent	9 (61)
Stress incontinence	5 (33)
Not continent	1 (6)
Undetectable PSA in 4 weeks n, (%)	15 (100)
Follow-up (weeks)	4 (4-4)

In our first impression, the open console and new design of the hand controls could be faced as a challenge to our learning curve due to years of experience in a different platform with another operative setting. However, once the robot is docked and the instruments are placed, the high-definition 3D image provided by the 3D glasses did not change our approach to the surgery. In addition, by using extra glasses, other surgeons and visitors around the console can see the same operative 3D image as the surgeon. We also believe that the hand commands (pistol-like) and settings did not interfere in the surgical technique, but it demands an adaptive period until mastering the different buttons to lock and unlock the arms.

During consecutive steps of robotic-assisted radical prostatectomy, we believe that the instruments provided appropriate traction and dis-

section capacity without delaying or interfering on the intraoperative performance. The operative time is compatible with what we usually perform in other robotic platforms, and we did not have any operative complications related to the robotic technology. However, as this robot is still new in the market, and not available in most countries yet, we still need a longer follow-up to assess functional and oncological outcomes compared to other consoles.

Despite its strengths, our study is not devoid of limitations, especially due to its retrospective design and all its inherent risk of bias. In addition, the small number of patients and lack of a comparison group limits the analysis of outcomes compared to other platforms. Also, the short-term follow-up restricts the assessment of functional and oncological outcomes. However, to the best of our knowledge, this is one of the first clinical reports of Hugo™ RAS System application in Robotic-assisted Radical Prostatectomy. Our study provided data describing safe and feasible procedures with acceptable short--term continence recovery, which is in line with our primary endpoints. We did not assess long-term results due to the short period of this console in the market. Finally, we believe that the illustrations and data of this study are crucial for understanding the first steps of the implementation process of this new technology.

CONCLUSIONS

We reported the clinical application of Hugo™ RAS System in patients who underwent radical prostatectomy. Our data described preliminary results with safe and feasible procedures performed with this novel robotic platform. The surgeries were successfully performed with acceptable perioperative outcomes and without conversions or major complications. However, as this technology is very recent, further studies with a long--term follow-up are awaited to access postoperative functional and oncological outcomes.

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Claudia González Alfano and Marcio Covas Moschovas The authors had equal contribution on this study

DISCLOSURE

According to the International Committee of Medical Journal Editors conflict of interest (ICMJE), the authors declare that they have no conflict of interest or competing financial interests related to the manuscript. Dr. Elias Bodden and James Porter are consultants for Medtronic (Minneapolis, USA).

CONFLICT OF INTEREST

None declared.

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Predictive model for urosepsis in patients with Upper Urinary Tract Calculi based on ultrasonography and urinalysis using artificial intelligence learning

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ABSTRACT

Purpose: To construct a predicting model for urosepsis risk for patients with upper urinary tract calculi based on ultrasound and urinalysis.

Materials and Methods: A retrospective study was conducted in patients with upper urinary tract calculi admitted between January 2016 and January 2020. The patients were randomly grouped into the training and validation sets. The training set was used to identify the urosepsis risk factors and construct a risk prediction model based on ultrasound and urinalysis. The validation set was used to test the performance of the artificial neural network (ANN).

Results: Ultimately, 1716 patients (10.8% cases and 89.2% control) were included. Eight variables were selected for the model: sex, age, body temperature, diabetes history, urine leukocytes, urine nitrite, urine glucose, and degree of hydronephrosis. The area under the receiver operating curve in the validation and training sets was 0.945 (95% CI: 0.903-0.988) and 0.992 (95% CI: 0.988-0.997), respectively. Sensitivity, specificity, and Yuden index of the validation set (training set) were 80.4% (85.9%), 98.2% (99.0%), and 0.786 (0.849), respectively.

Conclusions: A preliminary screening model for urosepsis based on ultrasound and urinalysis was constructed using ANN. The model could provide risk assessments for urosepsis in patients with upper urinary tract calculi.

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INTRODUCTION

Urosepsis is a life-threatening organ dysfunction caused by the dysregulated host response to infection originating from the urinary tract and/or male genital organs (1). The latest definition states that urosepsis is more severe than an uncomplicated urinary infection, implying the need for prompt recognition and intervention (2). Urosepsis must be diagnosed early and treated promptly to prevent progression to septic shock and multiple organ dysfunction (3, 4). Upper urinary tract obstruction caused by calculi is an important cause of urosepsis (5). Currently, most of the studies focus on the risk factors of urosepsis following endoscopic lithotripsy (6-8). However, in the clinic, many patients are diagnosed with upper urinary tract calculi complicated with urosepsis before or after

admission (9). Therefore, the early identification of high-risk upper urinary tract calculi patients at risk of developing urosepsis and the implementation of effective intervention methods have become a priority recognized by the World Health Organization (2, 10).

Ultrasound is a common emergency imaging technique in patients presenting severe loin pain and fever. It can reveal the size, location, and degree of obstruction of urinary calculi and also help evaluate complications of acute pyelonephritis, such as renal abscess, emphysematous pyelonephritis, and perirenal abscess (11, 12). Urinalysis, including the assessment of white and red blood cells and nitrite, can reflect the urinary inflammatory response quickly. It is recommended as a routine detection and suggested for repetitive analysis. In addition, urine culture and antimicrobial susceptibility testing must be performed in all cases of pyelonephritis (13).

Nowadays, artificial intelligence is commonly used in disease diagnosis, treatment, and prognosis prediction (14, 15). Artificial neural network (ANN) is the most popular method for machine learning. It is a kind of non-parametric modeling technique, which is suitable for complex phenomenon that investigators do not know underlying functions. ANN is in analogue to the human brain. There are input and output signals transmitting from input to output nodes. Input signals are weighted before reaching output nodes according to their respective importance. Then the combined signal is processed by activation function. ANN has better predictive performance and can grasp the inherent data patterns more effectively than traditional statistical methods (16, 17). It has been applied widely in urological practice, including distinction between tumor grade or subtype of genitourinary malignancies, prediction of treatment response, tumor recurrence, and patient survival. The most common ANN application in urolithiasis is in the prediction of endourologic surgical outcomes and stone-free status after Extracorporeal Shock Wave Lithotripsy (18, 19). Currently, no studies using ANN data mining approach to explore the risk of upper urinary tract calculi complicated with urosepsis are available.

This study aimed to construct a urosepsis risk prediction model based on ultrasound and urinalysis for patients with upper urinary tract calculi using the ANN data mining approach. This model can be used as a preliminary screening tool to identify patients who are at high risk of urosepsis and be helpful in guiding targeted examinations or interventions.

MATERIALS AND METHODS

Study design and population

This retrospective study included patients with upper urinary tract calculi admitted to Shantou Central Hospital between January 2016 and January 2020. The inclusion criteria were 1) imaging results, including urinary system ultrasound, excretory urogram, or abdominopelvic computed tomography (CT) indicating a diagnosis of ureteral calculi, and 2) complete medical history, laboratory, and imaging data available. The exclusion criteria were 1) <14 years of age or pregnancy (women), 2) bilateral upper urinary calculi, 3) diseases of the blood or immune system, malignancy, or use of immunoregulatory therapy, or 4) other sites of primary infection, including lung or abdomen. Urosepsis was diagnosed based on the guidelines for diagnosis and treatment of urosepsis in 2018 (2).

The study followed the Declaration of Helsinki and was approved by the ethics committee for medical research at Shantou Central Hospital (IRB Number: 2019-sci-No.070). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Data collection

Data including sex, age, body temperature, abdominal pain, hematuria, urinary irritation symptoms, hypertension, diabetes, calculi surgery history, urine leukocytes (U-LEU), urine nitrite (U-NIT), urine erythrocytes (U-ERY), urine glucose (U-GLU), laterality of calculi, location of calculi, degree of hydronephrosis, and the maximal diameters of calculi were collected from medical records. Urinalysis was performed on a Mindray (UA-5800) automatic dry chemi-

cal urine analyzer and matching test strips. Ultrasound analysis was performed on a Hitachi (EUB 5500) full digital color Doppler ultrasound diagnostic system.

Sample sets for ANN development and validation

For ANN model construction and validation, the patients were randomized into the training (1214 patients; 135 cases and 1079 controls) and validation (502 patients; 51 cases and 451 controls) sets (Figure-1). Randomization was performed using SPSS 25.0 (IBM, Armonk, NY, USA).

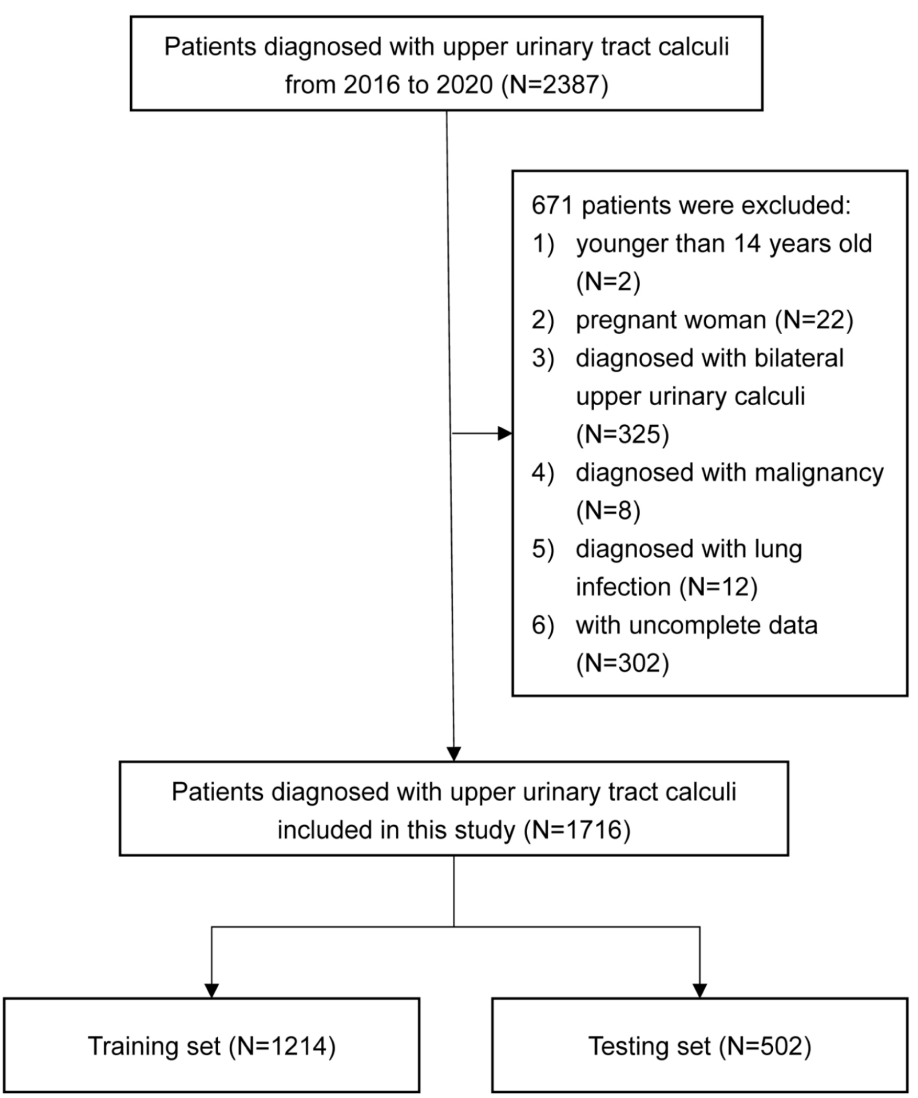
Selection of the variables for ANN model development

Univariable and multivariable logistic regression analyses were performed to evaluate variables associated with urosepsis and generate the ANN model for the training set. Variables with $p<0.05$ were selected for predictive model establishment.

Development of the ANN model

A standard feed-forward backpropagation neural network (BPNN) was applied, consisting of three layers: an input layer that receives informa-

Figure 1 - Flow diagram of the selection of eligible A



tion, a hidden layer that processes information, and an output layer that calculates results. BPNN was run with significant predictors as input variables and urosepsis risk as the output variable. The number of neurons in the input layer was the total number of covariables. The output variable was dichotomous (two neurons in the output layer). The number of neurons in the hidden layer was not an actual variable. The optimal H was determined by trial and error since no authoritative theory is available. The optimal hidden layer was determined from the predictive model with the highest sensitivity and specificity. In BPNN, the variables of the upper layer were weighted and related to the next layer by transfer functions. In the constructed BPNN, hyperbolic tangent functions were used as the transfer functions of the hidden layers, and SoftMax functions were used as transfer functions for the output layers. Training parameters, including learning rate and momentum, were set at the default values. The networks were trained at a maximum of 100 epochs or until the minimum average square error was <0.001.

Validation of the ANN model

The accuracy, positive (PPR) and negative (NPR) predictive rates, sensitivity, specificity, Youden Index, and area under the receiver operating characteristics (ROC) curve (AUC) were determined in both sets. The Hosmer-Lemeshow goodness-of-fit test was performed for ANN model calibration ($p>0.05$).

Statistical analysis

Normally distributed continuous variables were presented as means ± standard deviation (SD). Categorical were presented as numbers and proportions. Student's t-test and Pearson chi-square test were used to analyze continuous and categorical variables, respectively. SPSS 25.0 (IBM, USA) was used for data analysis. Two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Initially, 2387 patients were screened, and 1716 were included. There were 186 (10.8%) patients with urosepsis (cases) and 1530 (89.2%) without (controls). In both sets, the proportion of males was 56.8%. In the training set, 186 (15.3%) patients had diabetes, 302 (24.9%) had hypertension, and 165 (13.6%) underwent calculi surgery, while in the validation set, there were 62 (12.4%), 127 (25.3%), and 66 (13.1%) patients, respectively (Table-1).

The input variables in the predictive model included sex, age, body temperature, diabetes history, U-LEU, U-NIT, U-GLU, and degree of hydronephrosis. The multivariable analysis showed that old age (OR=1.055, 95%CI: 1.030-1.08), abnormal body temperature (high vs. normal, OR=7.636, 95%CI: 4.102-14.216; low vs. normal, OR=85.545, 95%CI: 3.316-2206.854), positive U-LEU (1+ vs. negative, OR=4.250, 95%CI: 1.336-13.518; 2+ vs. negative, OR=6.452, 95%CI: 2.050-20.308; 3+ vs. negative, OR=10.092, 95%CI: 3.416-29.818), positive U-NIT (positive vs. negative, OR=6.173, 95%CI: 3.409-11.178), positive U-GLU (2+ vs. negative, OR=5.639, 95%CI: 1.609-19.771; 3+ vs. negative, OR=14.255, 95%CI: 2.652-76.630), and mild and moderate degree of hydronephrosis (mild vs. no, OR=3.793, 95%CI: 1.577-9.124; moderate vs. no, OR=2.488, 95%CI: 1.018-6.081) were independent risk factors of urosepsis for upper urinary calculi patients (Table-2).

An ANN model was built based on the significantly associated variables. The input variables were the eight significant variables mentioned above, and the output variable was dichotomous (urosepsis or not). The ANN model consisted of an input layer, a hidden layer, and an output layer. The input and output layers contained 22 and two neurons, depending on the number of input and output variables, respectively. The number of neurons in the hidden layer was calculated automatically according to the model's architecture, including the number of hidden layers and the activation function of the hidden layer and output layer. Each neuron in the different layers was connected by a mathematical function that simulates synapses. Finally, a 3-layer BPNN model with 22, nine, and two neurons in the input, hidden, and output layers, respectively, was constructed as the best predictive model (Figure-2).

The ROC AUC was used to validate the ANN model. The AUCs of the training (Figure-3a)

Table 1 - Baseline characteristics of the patients with upper urinary tract calculi in the training and validation sets.

Characteristics	Training set (n=1214)	Validation set (n=502)	χ^2/t	p
Urosepsis (n, %)			0.339	0.560
Yes	135 (11.1%)	51 (10.2%)		
No	1079 (88.9%)	451 (89.8%)		
Sex (n, %)			0	0.994
Male	689 (56.8%)	285 (56.8%)		
Female	525 (43.2%)	217 (43.2%)		
Age (yeas old, std)	52.7(12.3)	52.3(12.4)	0.620	0.535
Body temperature (n, %)			0.441	0.802
Normal	1055 (86.9%)	442 (88.0%)		
High	153 (12.6%)	58 (11.6%)		
Low	6 (0.5%)	2(0.4%)		
Abdominal pain (n, %)			0.666	0.414
Yes	559 (46.0%)	242 (48.2%)		
No	655 (54.0%)	260 (51.8%)		
Hematuria (n, %)			2.651	0.103
Yes	221 (18.2%)	75 (14.9%)		
No	993 (81.8%)	427 (85.1%)		
Urinary irritation symptoms (n, %)			2.073	0.150
Yes	571 (47.0%)	217 (43.2%)		
No	643 (53.0%)	285 (56.8%)		
Diabetes (n, %)			2.535	0.111
Yes	186 (15.3%)	62 (12.4%)		
No	1028 (84.7%)	440 (87.6%)		
Hypertension (n, %)			0.034	0.854
Yes	302 (24.9%)	127 (25.3%)		
No	912 (75.1%)	375 (74.7%)		
Treatment history (n, %)			0.060	0.806
Yes	165 (13.6%)	66 (13.1%)		
No	1049 (86.4%)	436 (86.9%)		
U-LEU (n, %)			5.620	0.132
(-)	364 (30.0%)	155 (30.9%)		
(1+)	338 (27.8%)	113 (22.5%)		
(2+)	220 (18.1%)	103 (20.5%)		
(3+)	292 (24.1%)	131 (26.1%)		
U-NIT (n, %)			0.060	0.806
(+)	165 (13.6%)	66 (13.1%)		
(-)	1049 (86.4%)	436 (86.9%)		
U-ERY (n, %)			3.492	0.322
(-)	341 (28.1%)	135 (26.9%)		
(1+)	304 (25.0%)	127 (25.3%)		
(2+)	269 (22.2%)	130 (25.9%)		

(3+)	300 (24.7%)	110 (21.9%)		
U-GLU (n, %)			4.797	0.187
(-)	1044 (86.0%)	448 (89.2%)		
(1+)	49 (4.0%)	15 (3.0%)		
(2+)	94 (7.7%)	34 (6.8%)		
(3+)	27 (2.2%)	5 (1.0%)		
Laterality of calculi (n, %)			0.928	0.335
Right	609 (50.2%)	239 (47.6%)		
Left	605 (49.8%)	263 (52.4%)		
Location of calculi (n, %)			0.529	0.467
Ureter	968 (79.7%)	408 (81.3%)		
Kidney	246 (20.3%)	94 (18.7%)		
Max-diameter of calculi (mm, std)	18.9 (9.2)	18.2 (8.5)	1.575	0.116
Degree of hydronephrosis (n, %)			3.061	0.382
No	199 (16.4%)	71 (14.1%)		
Mild	364 (30.0%)	152 (30.3%)		
Moderate	346 (28.5%)	161 (32.1%)		
Severe	305 (25.1%)	118 (23.5%)		

U-LEU = urine leukocytes; U-NIT = urine nitrite; U-ERY = urine erythrocytes; U-GLU = urine glucose.

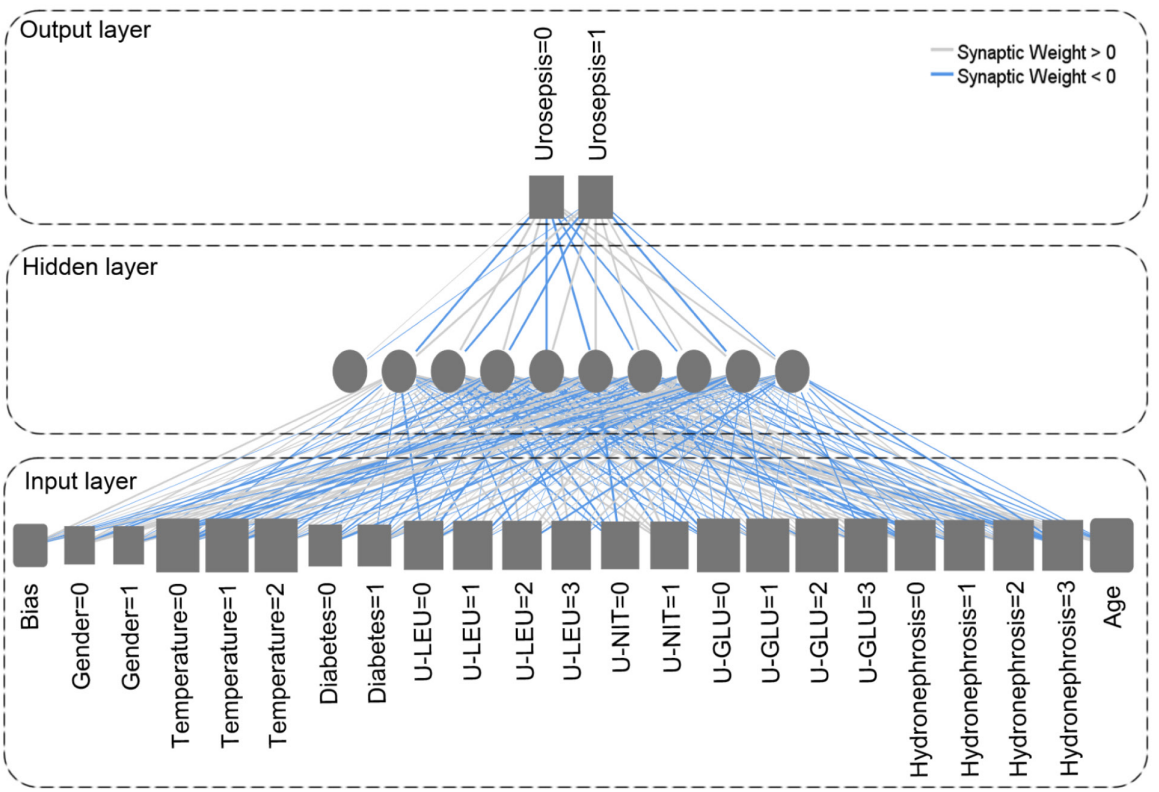
Table 2 - Univariable and multivariable logistic regression analyses for the development of urosepsis in the training set of patients with upper urinary tract calculi.

	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P	OR (95%CI)	P
Sex				
Male vs. female	0.592 (0.413-0.848)	0.004	1.004 (0.594-1.698)	0.987
Age				
Continuous	1.055 (1.038-1.073)	<0.001	1.055 (1.030-1.080)	<0.001
Body temperature				
High vs. normal	33.830 (21.637-52.893)	<0.001	7.636 (4.102-14.216)	<0.001
Low vs. normal	123.537 (14.111-1081.554)	<0.001	85.545 (3.316-2206.854)	0.007
Abdominal pain				
Yes vs. no	1.096 (0.764-1.572)	0.619		
Hematuria				
Yes vs. no	1.395 (0.907-2.145)	0.13		
Urinary irritation symptoms				
Yes vs. no	1.374 (0.959-1.967)	0.083		

Diabetes				
Yes vs. no	9.299 (6.301-13.725)	<0.001	0.452 (0.135-1.514)	0.198
Hypertension				
Yes vs. no	1.367 (0.923-2.024)	0.118		
Treatment history				
Yes vs. no	1.524 (0.954-2.437)	0.078		
U-LEU				
(1+) vs. (-)	4.999 (1.871-13.355)	0.001	4.250 (1.336-13.518)	0.014
(2+) vs. (-)	11.777 (4.505-30.783)	<0.001	6.452 (2.050-20.308)	0.001
(3+) vs. (-)	25.714 (10.246-64.537)	<0.001	10.092 (3.416-29.818)	<0.001
U-NIT				
(+) vs. (-)	22.216 (14.612-33.778)	<0.001	6.173 (3.409-11.178)	<0.001
U-ERY				
(1+) vs. (-)	0.933 (0.563-1.545)	0.788		
(2+) vs. (-)	1.352 (0.833-2.193)	0.222		
(3+) vs. (-)	0.879 (0.526-1.468)	0.623		
U-GLU				
(1+) vs. (-)	2.845 (1.282-6.313)	0.01	1.154 (0.302-4.410)	0.834
(2+) vs. (-)	15.216 (9.471-24.447)	<0.001	5.639 (1.609-19.771)	0.007
(3+) vs. (-)	11.666 (5.250-25.922)	<0.001	14.255 (2.652-76.630)	0.002
Laterality of calculi				
Left vs. right	1.059 (0.740-1.515)	0.753		
Location of calculi				
Ureter vs. kidney	0.796 (0.521-1.217)	0.292		
Max-diameter of calculi				
Continuous	1.011 (0.993-1.030)	0.239		
Degree of hydronephrosis				
Mild vs. no	3.710 (1.958-7.031)	<0.001	3.793 (1.577-9.124)	0.003
Moderate vs. no	2.450 (1.266-4.738)	0.008	2.488 (1.018-6.081)	0.046
Severe vs. no	0.313 (0.115-0.847)	0.022	0.201 (0.055-0.728)	0.015

U-LEU = urine leukocytes; U-NIT = urine nitrite; U-ERY = urine erythrocytes; U-GLU = urine glucose.

Figure 2 - Artificial neural network for predicting urosepsis in patients with upper urinary tract calculi. The gray boxes and circles represent neurons, and the lines between boxes and circles represent modifiable connections. For urosepsis, 0 and 1 present no and yes, respectively; for gender, 0 and 1 present female and male, respectively; for temperature, 0, 1 and 2 present normal, and high and low, respectively; for diabetes, 0 and 1 present no and yes, respectively; for U-LEU, U-NIT, and U-GLU, 0, 1, 2 and 3 present(-), (+), (2+) and (3+), respectively; for hydronephrosis, 0, 1, 2 and 3 present no, mild, moderate and severe, respectively.



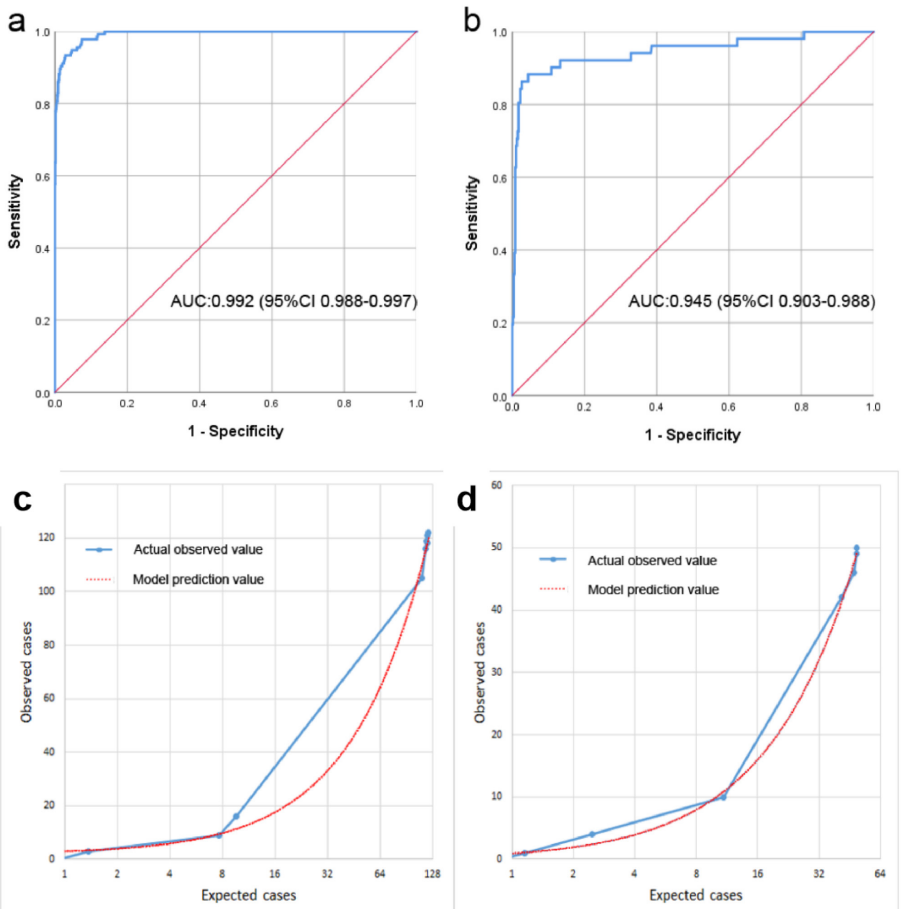
and validation (Figure-3b) sets were 0.992 (95% CI: 0.988-0.997) and 0.945 (95% CI: 0.903-0.988), respectively. The accuracies of the training and validation sets were 97.5% and 96.4%, respectively. The PPR and NPR of the validation set (training set) were 83.7% (91.3%) and 97.8% (98.3%), respectively. The sensitivity, specificity, and Youden Index of the validation set (training set) were 80.4% (85.9%), 98.2% (99.0%), and 0.786 (0.849), respectively.

The ANN model was calibrated using the Hosmer-Lemeshow goodness-of-fit test and calibration plot. The Hosmer-Lemeshow test revealed high concordance between the predicted and observed probabilities for the training (p=0.093) and validation (p=0.868) sets. The calibration plot also showed good agreement between the predicted and observed outcomes for the training (Figure--3c) and validation (Figure-3d) sets.

DISCUSSION

The present study developed a prediction model for urosepsis using ANN, involving eight significant predictors, including sex, age, diabetes history, body temperature, U-LEU, U-NIT, U-GLU, and degree of hydronephrosis. The ANN model showed encouraging outcomes regarding its ability in the early identification of urosepsis in patients with upper urinary tract calculi urosepsis based on ultrasound and urinalysis. The prediction model could be a rapid, clinically applicable risk assessment method to predict urosepsis in patients with upper urinary tract calculi.

Figure 3 - ROC curve and calibration of the nomogram for predicting urosepsis for upper urinary tract calculi patients. (a) ROC curve in the training set; (b) ROC curve in the validation set. Calibration curve of the ANN model for the training set (c) and the validation set (d).



Recent studies consistently found the superiority of the ANN analysis over traditional statistical methods (18). In this study, the ANN model was proved to have a better performance compared to the Nomogram model, which was used to predict probability of patients with ureteral calculi developing into urosepsis in a previous study (9). The AUC values of the ANN model and Nomogram model in the training (validation) groups were 0.992 (0.945) and 0.914 (0.874) respectively. Compared to conventional regression methods, ANN did not require a predefined mathematical relationship between the dependent and independent variables, and could model any arbitrarily complicated nonlinear relationship (20). Theoretically, the ANN model could be built more accurately and perfectly by increasing the sample size and repeated training. These advantages enable ANN to be a useful tool in solving the complex challenge of prediction.

Few clinical studies assessed the probability of patients with upper urinary calculi developing urosepsis (9, 21). The risk factors for upper urinary tract calculi complicated by urosepsis remain unclear. In this study, we revealed age, fever, urinary white blood cells, urinary nitrite, urinary glucose, and hydronephrosis were independent risk factors for urosepsis in upper urinary calculi patients. Aging is often accompanied by liver, kidney, cardiovascular, and immune system dysfunctions. Older patients often have comorbidities, including hypertension and diabetes. Once ureteral obstruction occurs, they are prone to secondary infections and progress to systemic in-

flammatory response syndrome and even sepsis (22, 23). This study suggested that body temperature alterations in patients with upper urinary tract calculi could also independently predict urosepsis. Fever occurs in response to endogenous and/or exogenous pyrogenic substances, including lipopolysaccharide (LPS) produced by Gram-negative bacteria (24). Most patients with sepsis have a fever, while only 10%-29% of the patients are hypothermic, showing even higher disease severity and mortality rate (25).

Consistent with previous studies (9, 26), two infection-related indicators in urinalysis, U--LEU and U-NIT, were confirmed as independent risk factors for urosepsis in patients with upper urinary tract calculi. Positive urine culture is also associated with urosepsis (7, 8). However, in this study, urine culture was not selected as a candidate risk factor due to its hysteresis characteristic. In the clinic, urine culture often takes 2-3 days or more to produce results, which is inconsistent with the purpose of this study to identify high-risk patients with urosepsis as soon as possible. Positive U-LEU often indicates purulent inflammation of the urinary tract, whose commonest cause is bacterial infections. In addition, Gram-negative bacilli in the urinary tract reduce nitrate, a protein metabolite in urine, to nitrite. Therefore, U-LEU and U-NIT detection can quickly and indirectly determine the possibility of bacterial infection in the urinary system (27, 28).

The common causes of U-GLU positivity include elevated blood glucose and decreased renal glucose threshold. When blood glucose rises and exceeds the upper limit of renal tubular reabsorption, glucose is excreted in the urine, resulting in positive U-GLU. In addition, some kidney diseases also decrease the ability of renal tubules to reabsorb glucose. In this case, even if the blood glucose is normal, U--GLU positivity occurs (29). This study found that U-GLU 2+ and 3+ were risk factors for urosepsis. Positive U-GLU of 2+ or 3+ indicates poor control of diabetes or the possibility of chronic kidney disease. Once a patient suffers from urinary tract infection, the risk of developing into urosepsis is higher.

Among ultrasound-related indicators, only the degree of hydronephrosis independently predicted urosepsis. Hydronephrosis mainly indicates urinary tract obstruction. Once the patients have urinary tract infections, bacteria in the urine retrograde into the blood after reaching a certain pressure, resulting in urosepsis (30). Interestingly, this study showed that severe hydronephrosis was negatively correlated with urosepsis risk. Urosepsis commonly appears as an acute course. Severe hydronephrosis indicates a tight and prolonged obstruction, which makes it difficult for bacteria to cause retrograde infection.

This study had limitations. Firstly, it was a retrospective observational study with unavoidable selection bias. However, strict eligibility criteria were adopted. In addition, we randomly composed the training and validation sets to minimize selection bias. Secondly, the training and validation sets were from the same population, so the model might not be generalizable. Therefore, large multicenter studies are needed. Thirdly, the ANN model was based on general information, symptoms, ultrasound, and urinalysis. Data collection, especially for symptoms, was based on self-reports, with inevitable recall bias. Lastly, certain populations were excluded, e.g., patients with bilateral upper urinary calculi. In this study, the inclusion of patients with bilateral upper urinary calculi would lead to difficult grouping, and some indicators could not be well grouped. In addition, the study also excluded people with malignant tumors or immune system diseases because these patients have more interference factors. Although these populations were unsuitable for this study model, they were also those we need to focus on clinically.

CONCLUSIONS

Despite the limitations, this is the first study using ANN to estimate the urosepsis risk for upper urinary tract calculi base on ultrasound and urinalysis. This model could help determine the probability of urosepsis and then perform targeted examinations or interventions, which would be more efficient to improve the efficiency of diagnosis and treatment.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

The study was conducted following the Declaration of Helsinki and was approved by the ethics committee for medical research at Shantou Central Hospital (IRB Number: 2019-sci-No.070). Due to the retrospective nature of the study, the informed consent was waived by the review board.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Impact of COVID-19 pandemic on prostate cancer outcomes at an uro-oncology referral center

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ABSTRACT

Introduction: To evaluate the possible effects of the coronavirus disease 2019 (COVID-19) pandemic on the oncologic results of patients with prostate cancer regarding clinical staging, presence of adverse pathological outcomes, and perioperative complications.

Materials and methods: This retrospective study included patients who underwent radical prostatectomy. The time between biopsy and surgery, staging tests, final histopathological evaluation after surgery, lymphadenectomy rate, postoperative complications, and prostatic specific antigen (PSA) levels (initial and 30 days after surgery) were analyzed and compared in a group of patients before and during the pandemic period.

Results: We included 226 patients: 88 in the pre-pandemic period and 138 during the pandemic period. There was no statistically significant difference in mean age, body mass index, ASA, pathological locally advanced disease, the proportion of patients who underwent lymphadenectomy, and ISUP grade in the biopsy between the groups. Positive surgical margins, prostatic extracapsular extension, and PSA levels at 30 days were also similar between the groups. The mean time between medical consultation and surgery was longer in the pandemic period than in the pre-pandemic (124 vs. 107 days, p<0.001), and the mean time between biopsy and medical consultation (69.5 days vs. 114 days, p<0.001) and between biopsy and surgery (198.5 days vs. 228 days, p=0.013) was shorter during the pandemic. The incidence of severe early and late perioperative complications was similar between the periods.

Conclusions: There was no delay between diagnosis and treatment at our institution during the COVID-19 pandemic period. No worsening of the prostate cancer features was observed.

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INTRODUCTION

The first patient with coronavirus disease 2019 (COVID-19) in São Paulo, Brazil was confirmed on February 26, 2020. The number of confirmed cases grew in a classical exponential curve, with a rapid rate per day (~25%) comparable to that observed in other countries (1). Within 23 days of the first case, emergency public health decisions were taken to protect the vulnerable, minimize its impact on healthcare, and reduce community transmission (2, 3). On March 11, 2020, the

World Health Organization declared COVID-19 a pandemic (1). The COVID-19 pandemic is the most recent and largest pandemic we have experienced in recent decades. Thus, the health system is undergoing profound changes related to the use of resources and distribution of health inputs (4-6).

Electing a patient for a urological surgical procedure within the context of the pandemic involves great responsibility because it increases the risk of contagion for the patient, healthcare professionals, and other patients (7, 8). In view of the high demand for hospital beds and the relocation of health professionals to face the disease worldwide, elective surgeries have been postponed or canceled in favor of the operation of high-risk patients, urgencies, or emergencies (9-13). From a urological surgery perspective, many questions have arisen regarding the immediate and long--term care of patients.

There is some evidence in the literature that suggests that delays in the treatment of patients with prostate cancer (PCa) lead to higher rates of adverse factors in the final pathology (Gleason score, surgical margin, and extracapsular prostate extension) (14). Thus, identifying the impact of delayed diagnosis of PCa during the COVID-19 pandemic is essential for the organization of uro-oncology services and for dealing with future pandemics (15).

Based on these findings, we aimed to evaluate the possible detrimental effects of the COVID-19 pandemic on the oncologic outcomes of patients with PCa regarding clinical staging, presence of adverse pathologic outcomes, and perioperative complications compared with the pre--pandemic period.

MATERIAL AND METHODS

The design, analysis, interpretation of data, drafting, and revisions followed the Helsinki Declaration and the strengthening of the reporting of observational studies in epidemiology (STROBE) statement, which is available through the enhancement of the quality and transparency of health research (EQUATOR) network (www.equator--network.org). The study design was approved by the local independent Research Ethics Committee (approval code: CAAE 54077521.4.0000.0071). The requirement for informed consent was waived by the research ethics committee.

This retrospective, observational study included patients who underwent treatment for non-metastatic PCa with curative intent from June 2019 to June 2021.The study was conducted in a public hospital in Sao Paulo that is managed by the *Hospital Israelita Albert Einstein* as a result of a public-private partnership with the City Hall of São Paulo. This hospital is associated with the Medical Residency Program in Urology of the *Faculdade Israelita de Ciências da Saúde Albert Einstein* (Medical School). Patients were divided into two groups: pre-pandemic (November, 2018 to February, 2020) and pandemic (from March, 2020 to June, 2021).

Patients

The inclusion criterion was patients who underwent treatment for non-metastatic PCa with curative intent through radical prostatectomy with or without lymphadenectomy. All patients were diagnosed with PCa after a change in screening, and subsequent biopsies were performed at a primary health service. After diagnosis, patients were referred to our specialized center for treatment. Patients with PCa undergoing treatment without a curative proposal or treatment other than radical prostatectomy, and patients with synchronous or metachronous neoplasms were excluded from the study.

Data Collection

Data were collected from the electronic medical records of each patient, including age, initial prostatic specific antigen (PSA) levels, lymphadenectomy, International Society of Urological Pathology (ISUP) grade, surgical margin, prostatic extracapsular extension found in the surgical specimen obtained after radical prostatectomy, PSA level at 30 days, time between biopsy and first medical consultation (medical appointment in our tertiary center when the patient had already undergone biopsy and the diagnosis of PCa was established by the primary healthcare center), interval between first medical consultation and surgery, total time between biopsy and surgery, and severe complica-

tions in the early and late perioperative period of radical prostatectomy (Clavien Dindo III or IV).

Statistical Analysis

Data analysis was used to determine differences between the groups of patients who attended before and during the COVID-19 pandemic. Categorical data were analyzed using absolute and relative frequencies. Numerical data were tested for normal distribution using Shapiro–Wilk test, and none of the variables presented a normal distribution. All data were presented as median and interquartile range (IQR). Missing numerical data were treated with median imputation if the missing values did not exceed 10% of the total observations. No policy was implemented for missing categorical data. Mann–Whitney U test was used for bivariate comparisons between numerical variables, and the Chi-squared test was used for categorical data and comparisons between numerical and categorical data. Bonferroni correction was used for groups with more than two categories when differences were observed. The significance level was set at $P<0.05$. The analyses were performed using Python™, version 3.8 on the Jupyter Notebook, version 6.4.8.

RESULTS

A total of 226 patients were included in this study: 88 in the pre-pandemic period and 138 in the pandemic period. The general characteristics of the patients and comparisons between the groups are shown in Table-1 and Figure-1.

There were no differences in age, body mass index (BMI), American Society of Anesthesiologists Classification score (ASA), pathological locally advanced disease, proportion of patients who underwent lymphadenectomy, and ISUP grade found in the transrectal biopsy between the groups. The initial PSA levels were significantly higher in the pre-pandemic group (10.1 ng/dL vs. 7.7 ng/dL, p=0.007). Most patients in both groups presented intermediate D'amico risk, and the proportion of the high-risk group was similar pre- and during the pandemic (40.9% vs. 34%, p=0.564). The number of patients who underwent neoadjuvant androgen deprivation was higher in the pandemic group (10.9% vs. 1.1%, p=0.011), whereas the number of patients who underwent adjuvant radiotherapy was significantly higher in the pre-pandemic group (37.5% vs. 15.2%, p≤0.001).

The type of prostatectomy differed between the pre- and pandemic groups (open, 63.6% vs. 77.5%; and video laparoscopic, 36.4% vs. 22.5%; p=0.023). During the pre-pandemic period, major complications (Clavien Dindo 3 and 4) occurred in five patients (5.7%): compartment syndrome requiring fasciotomy, two urinary leaks (one with a cystoscopy procedure for diagnostic confirmation), one patient was referred to the intensive care unit because of altered mental status and confusion after surgery, and a ureteral lesion during lymphadenectomy was visualized and sutured during the surgery. During the pandemic period, major complications were present in eight patients (5.8%): two rectal lesions, five patients with bleeding referred to the intensive care unit to control blood pressure, and one patient lost the bladder catheter and needed a new catheterization.

The histological characteristics according to the final pathology showed differences in the ISUP grade between the groups. Although there was no difference in ISUP >3, post hoc analysis showed a statistically significant difference in the proportion of ISUP grade 2 (42.1% vs. 63.1%, p<0.001) between the pre- and pandemic groups. Positive surgical margins, prostatic extracapsular extension, and positive PSA levels at 30 days were similar between the groups. Although the mean time between medical consultation and surgery was longer during the pandemic period than during the pre-pandemic period (124 days vs. 107 days, p<0.001), the mean time between biopsy and medical consultation (69.5 days vs. 114 days, p<0.001) and biopsy and surgery (198.5 days vs. 228 days, p=0.013) was significantly shorter during the pandemic period. Albeit the mean time of anesthesia was significantly higher in the pandemic group (250.0 min vs. 255.0 min, p=0.043), the mean time of surgery, and severe early and late perioperative complications were similar during the pre- and pandemic periods.

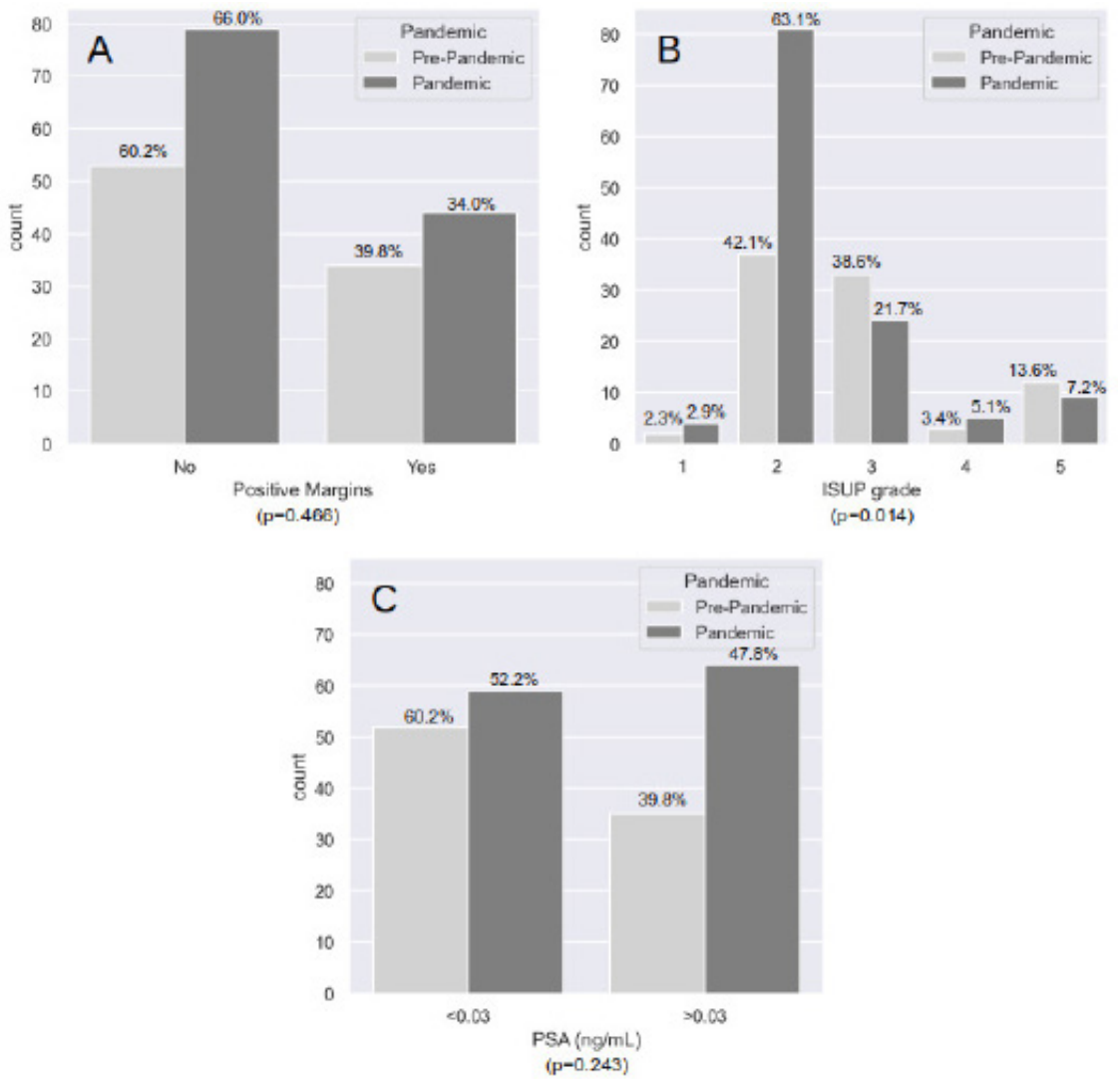
Table 1 - Baseline demographic and pathological characteristics of patients studied.

Variables	Pre-Pandemic	Pandemic	p-value
Patients (n, %)	88 (38.9%)	138 (61.1%)	---
Age (years)	64.0 [58.0-69.0]	63.0 [59.0-67.0]	0.373 [a]
BMI (Kg/m^2)	27.3 [24.5-28.9]	27.3 [25.3-29.9]	0.249 [a]
ASA (n, %)			
1	10 (11.4%)	10 (7.3%)	
2	64 (72.7%)	114 (82.6%)	0.208 [b]
3	14 (15.9%)	14 (10.1%)	
Initial PSA (ng/dL)	10.1 [6.0-17.2]	7.7 [5.4-11.3]	0.007 [a]
Neoadjuvant androgen deprivation (n, %)	1 (1.1%)	15 (10.9%)	0.011 [b]
Adjuvant Radiotherapy (n, %)	33 (37.5%)	21 (15.2%)	<0.001 [b]
Prostatectomy (n, %)			
Open	56 (63.6%)	107 (77.5%)	0.023 [b]
Videolaparoscopic	32 (36.4%)	31 (22.5%)	
Lymphadenectomy (n, %)	40 (45.5%)	76 (55.1%)	0.203 [b]
Pathological locally advanced disease (pT3–4) (n, %)	33 (37.5%)	34 (24.6%)	0.081 [b]
D'amico Risk Group			
Low Risk	10 (11.4%)	16 (11.6%)	
Intermediate Risk	42 (47.7%)	75 (54.4%)	0.564 [b]
High Risk	36 (40.9%)	47 (34.0%)	
ISUP_Biopsy (n, %)			
1	21 (23.8%)	26 (18.9%)	
2	40 (45.5%)	71 (51.4%)	

3	20 (22.7%)	27 (19.6%)	0.739 [b]
4	4 (4.5%)	10 (7.2%)	
5	3 (3.5%)	4 (2.9%)	
ISUP Surgery (n, %)			
1	2 (2.3%)	4 (2.9%)	
2	37 (42.1%)	87 (63.1%)	
3	34 (38.6%)	30 (21.7%)	0.014 [b, c]
4	3 (3.4%)	7 (5.1%)	
5	12 (13.6%)	10 (7.2%)	
ISUP >3 Surgery (n, %)	15 (17.0%)	17 (12.3%)	0.425 [b]
Positive surgical margin (n, %)	35 (39.8%)	47 (34.0%)	0.466 [b]
Prostatic extracapsular extension (n, %)	38 (43.2%)	43 (31.1%)	0.089 [b]
Positive PSA level in 30 days	35 (39.8%)	66 (47.8%)	0.293 [b]
Time between biopsy and medical consultation (days)	114.0 [90.0-176.3]	69.5 [42.5-118.5]	<0.001 a
Time between medical consultation and surgery (days)	107.0 [64.0-114.3]	124.0 [76.0-213.0]	<0.001 [a]
Time between biopsy and surgery (days)	228.0 [185.5-323.75]	198.5 [132.5-291.0]	0.013 [a]
Time of anesthesia (minutes)	250.0 [241.5-250.0]	255.0 [210.0-300.0]	0.043 [a]
Time of surgery (minutes)	200.0 [199.0-200.0]	202.5 [165.0-240.0]	0.084 [a]
Severe early perioperative complications (n, %)	5 (5.7%)	8 (5.8%)	0.797 [b]
Severe late perioperative complications (n, %)	2 (2.3%)	5 (3.6%)	0.858 [b]

* Qualitative variables were presented by absolute and relative frequency, and quantitative variables by median and interquartile range.
ASA = American Society of Anesthesiology score; BMI = Body mass index; ISUP = International Society of Urological Pathology; PSA = Prostate Specific Antigen.
a = Mann-Whittney U test; b = Chi-Square test; c =Post hoc analysis showed statistical significant difference regarding the proportion of ISUP grade 2 (p<0.001) between pre and pandemic groups.

Figure 1 - Pathological characteristics of patients studied. (A) Positive Margin, (B) ISUP grade according to final pathology, and (C) Positive PSA level in 30 days after surgery.



The variables were compared using the chi-square test.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the possible detrimental effects of the COVID-19 pandemic on oncological treatment outcomes in patients with PCa in South America.

According to the Brazilian Society of Urology, the number of prostate biopsies performed in Brazil decreased from 2019 to 2020, and there was a delay in performing biopsies and diagnosing prostatic diseases. In the state of São Paulo, this decrease was 6%, but in other states, it reached 90% (16). These numbers are probably due to better screening and treatment of patients with PCa in São Paulo than in other regions of Brazil. In the present study, we observed lower initial PSA levels during the pandemic period (7.7 ng/dL vs. 10.1 ng/dL) and also a shorter time between the biopsy (diagnosis) and first consultation (114 days vs. 69.5 days), possibly as a reflection of PCa screening that has been improving over the years, in spite of the COVID-19 outbreak.

The teaching hospital of Albert Einstein Medical School, associated with the medical residence in Urology, underwent restructuring due to the overoccupancy of hospital vacancies during the pandemic. There was a reduction and some suspension of elective procedures, such as prostatectomies and biopsies, which caused delays in the treatment of patients with cancer. Thus, there was a change in the treatment strategy (patients who would undergo surgery were referred for radiotherapy), and some patients underwent initial hormone block therapy to receive definitive treatment (surgery or radiotherapy). The same redistribution of patients was described by Korkes et al. (17), who observed that an increase in adjunctive advanced disease occurred during the years of COVID-19. This might indicate that patients were preferably sent for neoadjuvant advanced disease following the recommendations of the guidelines during the COVID-19 pandemic.

During the pandemic, there was an increase in the referral of patients with PCa to our institution. Consequently, the number of patients undergoing radical prostatectomy was 56% higher during this period (88 during the pre-pandemic period and 138 during the pandemic period). This movement of greater referral of patients with cancer to our center is the result of a complex infrastructure and specialized multidisciplinary staff, which involves oncologists, urologists, radiologists, radiotherapists, and advanced technology to treat these patients. Despite this absolute increase in the number of patients, the surgeons who performed the surgery, the surgical technique used, the material used in the surgeries, and the postoperative care were identical in both groups, which would not justify the difference in the results between them.

In the present study, the number of patients who underwent neoadjuvant androgen deprivation was higher in the pandemic group (10.9% vs. 1.1%), whereas the number of patients who underwent adjuvant radiotherapy was significantly higher in the pre-pandemic group (37.5% vs. 15.2%). The higher rate of salvage radiotherapy in the pre-pandemic period can be explained by the longer time that these groups experienced between surgery and follow-up in comparison with the shorter time in the pandemic group to relapse of prostate cancer. Therefore, the patients operated during the pandemic may still be under the risk of presenting biochemical recurrence during the following years. In turn, the difference in the proportion of neoadjuvant androgen deprivation after and during the pandemic can also be explained by the strategy of forwarding patients to this treatment to postpone definitive treatment during the period when elective surgeries were canceled, and the radiotherapy service was already overcrowded. This highlights the importance of the organization of health services in the management of pandemics.

Despite the pandemic, we observed that the time between biopsy and surgery was significantly shorter during the pandemic period (198.5 days vs. 228 days). The time between biopsy and surgery has been extensively discussed in the literature to better understand if and how the delay could affect the oncological results. Berger et al. (14) reported that delays of 150 days in the low-risk group and 30 days in the high-risk group lead to worse pathological outcomes. Similarly, Auffenberg et al. (4) observed in a prospective cohort study that patients who underwent delayed prostatectomy were more likely to have a Gleason score of 7 or greater than those who underwent immediate surgery (69.2% vs. 48.8%).

On the other hand, the impact of delayed prostatectomy on pathological outcomes is questionable by some studies, even in high-risk patients (18-23). A large cohort study found that among 32,184 patients, delay up to 6 months performing radical prostatectomy did not lead to an increase in the incidence of positive surgical margins, positive lymph nodes, or increases in T3 and T4 cases (24). Likewise, a retrospective study of 128,062 men with intermediate- and high-risk PCa treated with radical prostatectomy in the American National Database did not show a significant difference in the odds of adverse pathology, upgrading, node-positive disease, or post-radical prostatectomy secondary treatments between men treated with immediate radical prostatectomy and any level of delay up to 12 months (25).

Several recommendations have recently been published to guide the management of uro-

logical conditions during these troubled times (26, 27). Based on the findings of the aforementioned studies, accumulating evidence supports the idea that radical prostatectomy can be safely postponed when the availability of healthcare resources is limited (20, 28, 29).

The proportion of video-laparoscopic prostatectomies performed during the COVID-19 period was lower than that during the pre-pandemic period (36.4% vs. 22.5%). The operating room environment has historically been prepared to prevent infection by agents transmitted mainly through contact with blood and body fluids. However, aerosol protection was not part of this routine. Surgical centers are structured in a closed area with little air exchange and generally no negative pressure. These conditions favor the transmission of SARS-CoV-2 among patients, members of the surgery team, and employees of the sector. Video-laparoscopic surgery is based on the creation of an intracavitary, peritoneal, or extraperitoneal space with carbon dioxide insufflation, which raises concerns about the possibility of SARS-CoV-2 transmission via this route (30). Thus, especially in the first months of the pandemic, the concern of contamination during laparoscopic surgeries may have impacted the increase in open prostatectomy. Nevertheless, the incidence of major complications in the pre- and pandemic periods was similar (5.7% vs. 5.8%) and unrelated to the COVID-19 pandemic.

The rate of positive PSA results (greater than 0.03 ng/dL) before and during the COVID-19 pandemic was not statistically different (39.8% vs. 47.8%). In the present study, the first PSA level was often assessed in a period of less than 30 days, so the positive value in many patients is in fact a PSA level in the decline of the half-life curve.

In agreement with Oderda et al. (29), we also believe that the centralization of uro-oncological activity in referral centers is essential to guarantee safe and high-quality treatments, and even more so in times of crisis, such as the COVID-19 pandemic. No delay between diagnosis and surgery was observed in our study compared to the procedures of the pre-pandemic period; no significant difference in terms of main pathologic features was observed, likely as a consequence of our role as a referral center.

Concerning study limitations, our study was performed at a single center, and the short time span of the study might have hampered the evaluation of the effects of delayed screening due to COVID-19. In addition, the physical structure and clinical staff of our hospital have grown gradually over the last three years, so that even during the pandemic, there was a greater number of patients in our clinics and, consequently, resulted in an increase in prostatectomies performed during the pandemic. All patients were screened for SARS-CoV-2 using rapid antigen tests 48 h prior to surgery during the COVID-19 pandemic. Surgery was postponed for at least six weeks for those who tested positive. No modification was required for the anesthesia protocol that remained a general anesthesia with endotracheal intubation and spinal block. Even though the number of rooms available decreased by 25-70% between 2020 and 2021, surgeries were still performed in the same operating room usually designated to the team. Nonetheless, oncological surgeries were prioritized compared to other cases. Due to the drastic shortage of SARS-CoV-2 rapid antigen tests, asymptomatic patients were not retested after surgery. Therefore, it was not possible to obtain data regarding post-treatment COVID-19 infection rates in this sample. Finally, protective procedures were adopted by all professionals according to the current protocols.

CONCLUSIONS

It is noteworthy that there was an absence of delay in the treatment of PCa at our institution during the COVID-19 pandemic, as well as no worsening of pathological features. This study reinforces that even with the challenges and limitations imposed by the pandemic outbreak, well-structured facilities allied to an agile management are of paramount importance for a healthcare center to provide in-time treatment for prostate cancer preserving adequate clinical and perioperative outcomes.

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CONFLICT OF INTEREST

None declared.

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Sex with animals among men attended in referral centers for sexually transmitted infections in northeast Brazil: prevalence, associated factors and behavioral aspects

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ABSTRACT

Purpose: Our objective was to investigate the prevalence of SWA, associated factors, relationship with STIs, and behavioral aspects in men attended at Referral Centers for STIs and acquired immunodeficiency syndrome (AIDS)/CR-STI/AIDS in northeast Brazil.
Materials and Methods: In this cross-sectional study, a questionnaire with sociodemographic, clinical, sexual and SWA practices information was applied to 400 men attended at two CR-STI/AIDS in Northeast Brazil on the years of 2018 and 2019. Clinical and laboratory diagnoses of STIs were confirmed in medical records. Logistic regression models were performed to identify the independent predictors for SWA.
Results: The prevalence of SWA over total samples was 15.00%. Of the participants, 239 (59.75%) of the participants were diagnosed with STIs, and of these 37 (15.48%) reported SWA. Most men practiced SWA in adolescence, being the last episode more than 20 years ago, usually with asinine and mules, in vaginal route and without a condom. SWA practitioners have higher percentages of occurrence of some viral STIs. SWA was associated with increasing age, history of residence in a rural area with remained over 12 years, married or widowed/separated, heterosexuals, with less than 7 years of study, Catholics, with hepatitis B, former user of alcoholic beverages and smokers, with a history of STI and intercourse with sex workers.
Conclusion: SWA practices increase STIs vulnerability. The association between hepatitis B and SWA highlights the importance of educational campaigns and conclusive studies on the topic.

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INTRODUCTION

The term "Sex With Animals" (SWA) has been used to portray human sexual behavior, without reinforcing the moral stereotypes that permeate the term bestiality or associating it with a medical diagnosis, such as zoophilia or zoophilic disorder (1). In these situations, the paraphilic di-

sorder causes suffering or harm to the individual, in addition to the possibility of harming himself or others for his satisfaction (2).

Researchers suggest that this sexual interest may be triggered by hypersexuality associated with dementia (3) or secondary to drugs used to treat Parkinson's Disease (4). Behavioral factors such as autism spectrum disorder are also mentioned (5) and some psychiatric disorders (6, 7), and identify characteristics associated with possible sexual orientation (8). Although the SWA practice can result in health damage such as arthritis (9), herpes B (10), anogenital traumas (11), and penile cancer (1), few studies relate this behavior to Sexually Transmitted Infections (STIs).

In sexual relations between humans and animals, injuries resulting from the disproportionate size of the external genital organs (11), damage genital tissues caused by bites and scratches, and secondary traumas while attempting to disengage from the animal with penile dilation on penetration (12) can increase vulnerability to infections. The risk is even more remarkable when humans assume the receptive position in anal sex because of the fragility of the human rectal mucosa and the absence of a protective immune barrier such as the cervicovaginal secretions (13). STI of an animal pathogen for people was proven in Budapest, with *Kurthia gibsonii* as an etiologic agent, a bacterium present in swine feces, isolated in the urethra and glans of an adult individual (14).

Since the Kinsey studies (15) when an 8% prevalence of zoophilia was established among American men (usually from rural areas), there has been an attempt to estimate the occurrence of this sexual practice in other population groups. In Brazil, SWA was reported by 3.2% of the adult population (16). The Northeast region has one of the highest rates, 4.5%, which may be related to the more significant extension of rural areas. Research that included Northeastern men with SWA practice identified a history of STI, without clinical or laboratory proof, greater than 50% of the sample (1, 17). We hypothesize that men with a history or practice of SWA have more records of STI occurrences than those without SWA. Given this scenario, the present study analyzed the prevalence of SWA, its associated factors, its relationship with STIs, and behavioral aspects in men attended at Refer Centers for STIs and acquired immunodeficiency syndrome (AIDS) / CR-STI/AIDS in northeastern Brazil.

In Brazil, there is no specific legislation that prohibits sexual acts between humans and animals. However, abusive situations that promote mistreatment, injuries or mutilations are considered environmental crimes and can be penalized with a minimum detention of 3 months which can reach 5 years - in the case of dogs and cats. In these cases, the death of the animal can increase the penalty by up to 1 third (18). Legislators analyze the approval of a bill that typifies and criminalizes zoophilia, regardless of physical injuries. In this case, erotic and/or sexual acts can be penalized with imprisonment of up to five years (19). Those who mediate or publicly expose sexual acts between humans and animals can also be penalized (20). In most American states, several countries in Europe, Iran and other Islamic countries SWA are considered a crime (12).

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of Federal University of Vale do São Francisco (UNIVASF), number 2.133.407. We conducted a cross-sectional study with men treated at two Referral Centers for Sexually Transmitted Infections and AIDS (CR-STI/AIDS) located in Juazeiro (Bahia) and Petrolina (Pernambuco), both in Northeast Brazil. The service offers STI prevention actions, diagnosis, treatment, and monitoring of these conditions, with rapid testing for HIV, syphilis, Hepatitis B, and C performed on all new entrants. Data collection took place over 24 months (2018 and 2019) and included men over 18 years of age, regardless of serological or syndromic conditions for HIV or other STIs. The study excluded people with mental or intellectual disabilities because they pose risks to the veracity of the information or difficulties in expressing themselves.

Considering the scarcity of previous studies to estimate the population of men with SWA practice attended in CR-STI/AIDS, one researcher collected data with as many participants as possible in the pre-established two-year period. We

approached 542 men in waiting rooms recruited at random and taken to a restricted location. The non-probabilistic sample comprised 400 individuals who accepted the invitation and answered a structured questionnaire built by the researchers with questions about sociodemographic data, alcoholism, and smoking, sexuality, STI/AIDS, sex with animals, the current condition of the anogenital region, and results of rapid tests for HIV, syphilis, and hepatitis B and C. All subjects provided written informed consent.

Variables

The sociodemographic variables selected were age, residence history in rural areas, time lived in rural areas, race, marital status, schooling, and religion. We also analyzed smoking, use of alcoholic beverages, duration of alcohol consumption/year, use of illicit drugs in the last year, age of first sexual intercourse, sexual orientation, sexual relations with sex workers, and occurrence of current anogenital complaints according to a medical record.

We investigated the time that the individual "has been living with HIV" (less than 1 year, from 1 to 3 years, from 4 to 6 years, from 7 to 9 years, from 10 to 19 years, and ≥ 20 years) and the occurrence of "hepatitis B + HIV + hepatitis C" coinfection.

In "STI patients," the following cases were validated as sexually transmitted infections with clinical or laboratory diagnostic evidence registered in the medical record: genital herpes, chancroid, anogenital warts (caused by the human papilloma virus-HPV), and other STIs. In this last category, only candidiasis was included when the possibility of an endogenous condition was ruled out. Urethral Discharge Syndrome (UDS) was inserted to cover urethritis, since in CR-STI/AIDS these cases are diagnosed, treated, registered in medical records, and notified as UDS. We considered syphilis situations that followed the criteria established by the Brazilian Ministry of Health (MH) for asymptomatic and symptomatic individuals (21). HIV infection cases (22), Human T-lymphotropic virus- HTLV, Hepatitis B and C (21) followed only laboratory diagnosis recommended by the MH.

SWA issues involved the date of the last episode; the age of onset and termination of these sexual practices; species and sex of the animal used; frequency of SWA relationships (weekly, monthly, yearly, and only once in a lifetime intervals); possibility of variation of the animals at each sexual intercourse; presence or absence of human companions during SWA; a sexual position assumed by the individual (insertive, receptive or both); type of sexual practice performed (vaginal, anal, oral, masturbation, others); condom use (not always, more than half the time, less than half the time); internet access to search for SWA content (yes, no); type of virtual content accessed (pornographic films, images, social networks) and SWA versus HIV infection (SWA only before HIV diagnosis, SWA only after HIV diagnosis, SWA before and after HIV diagnosis).

Statistical Analysis

The patients' characteristics were expressed as absolute and relative frequencies for qualitative and mean, median, range, and standard deviation for quantitative variables. The chi-squared test or Fisher's exact test were applied to evaluate a possible association between the independent factors with the dependent (SWA) variable. The student's t-test or Mann-Whitney U test was applied to compare the data of the quantitative variable in relation to the SWA group. Shapiro-Wilk test was applied to test the data normality.

In addition, we fitted the univariable and multivariable logistic regression models to evaluate the associations between exposure and outcome (SWA). The assumption of linearity was assessed for all continuous variables. No imputation method was used for missing data. The assessment of model significance and performance was performed through the Hosmer-Lemeshow goodness-of--fit test, receiver operating characteristics (ROC) curve, and c-statistic, representing the area under the ROC curve (AUC). The significance level of the tests was fixed at 0.05 (two-sided). All analyses were performed using the R software 4.0 version (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The prevalence of SWA practice among the participants was 15% (n = 60), 95%CI= [11.65% - 18.88%]. These men were older (50.07, standard deviation-SD: 13.65) than those who denied SWA (35.41, SD: 13.92, $p < 0.0001$), usually married or living in a stable union (58.33%, $p = 0.012$), catholic (63.33%, $p = 0.031$), self-defined blacks (black or brown, 85.00%, $p = 0.564$), heterosexual (91.67%, $p = 0.023$), less schooling (70% with 0 to 7 years of study, $p < 0.0001$) with 10 (16.7%) illiterate SWA men (versus 15, 4.4% among non-SWA men). They lived in a rural area during childhood or adolescence (86.67%, $p < 0.0001$), where they generally stayed for more than 12 years (78.85%, $p = 0.002$). They also sought more sex with sex workers (43.33%) than non-SWA men (14.71%, $p < 0.0001$) Table-1.

Participants with SWA reports had higher percentages for "ex drinker" (36.67%), while the majority without a history of SWA identified themselves as "social drinkers" (46.76%, $p = 0.012$). The average length of consumption (in years) was also longer among the group with SWA practice (22.82 years - SD: 13.8, versus 13.01 years - SD: 10.8, $p < 0.0001$). Most respondents denied using nicotine cigarettes (66.75%, $p < 0.0001$). We did not identify any statistically significant differences between men with and without a SWA report for the categories related to the use of illicit drugs. At the time of the interview, only 33.75% of the interviewees reported anogenital complaints ($p = 0.415$), usually urethral discharge, warts, and vesicles Table-1.

For most respondents, the first sexual intercourse with humans occurred on average at 15.10 years of age (SD: 2.76, $p = 0.795$), while SWA practices started at around 12.37 (SD: 3.78) years and ended at 16.43 (SD: 7.86) years (Table-1), having had the last SWA intercourse more than 20 years ago (n = 47, 78.33%). There were no records for the last SWA in the year leading up to the survey. Participants mentioned multiple responses for the animals most used during SWA. There was a predominance of females (n = 56, 93.33%), asinine and mule species (n = 46, 76.66%), goats (n = 27, 45,00%) and chickens (n = 20, 33.33%) Table-2.

The SWA frequency was generally 1 to 3 times a week (n = 19, 31.67%). Most sexual intercourse occurred with different animals at each episode (n = 32, 53.33%), usually the men were alone with the animal (n = 35, 58.33%), in an insertive position (n = 59, 98.33%). Among the mentioned mammals, the main sexual intercourse was vaginal (n = 58, 96.67%), without using condoms (n = 57, 94.99%). The minority of participants used internet to access content about SWA (n = 17, 28.33%) such as pornographic films (n = 16, 94.12%) and images (n: 9, 52.94%). Everyone denied access to social networks on SWA. Among the 15 HIV-infected SWA men, 14 of them stated that sex with animals occurred only before diagnosis and only 1 declared SWA before and after.

We identified 179 (46.49%, $p = 1.000$) men in the sample with one or more STIs, with clinical or laboratory evidence, in the 12 months preceding the research. This variable totaled a sample of 385 participants because 15 of them had no documentary evidence of STI and were excluded. Among the participants, 239 (59.75%, $p = 0.853$) had STIs, and of these, 37 (61.67%) reported a history of SWA. Only the hepatitis B category had a statistically significant difference between the groups of SWA and non-SWA men (p: 0.048) Table-3.

Among individuals living with HIV (n = 89, 22.25 %%), we observed a trend that those with a history of SWA accumulated higher percentages in periods of seropositivity greater than ten years (11.67%) while in the others diagnoses prevailed in the last six years (13.33%, $p = 0.247$). HIV + HBV (hepatitis B virus) + HCV (hepatitis C virus) coinfection cases were not significantly higher among SWA men (3.33% versus 0.29%, $p = 0.060$) than among those who denied such behavior.

The univariate analysis revealed that the greater probability of developing SWA practices is associated with increasing age; rural area residence history, mainly with an over-12 years permanence; being married or widowed/separated; heterosexual; with less than seven years of study; catholic; ex-alcoholic drinker and cigarette; having a history of sexual relations with sex workers and STIs throughout life and having hepatitis B.

Table 1 - Sociodemographic, clinical, and sexual characteristics of men with SWA practice and without SWA practice attended at the CR-IST/AIDS of Juazeiro-BA and Petrolina-PE in the years 2018 and 2019, Brazil.

Variable	Category	Total sample n=400		Men with SWA practice n=60		Men without SWA practice n=340		*p*
Age (years)	Mean (SD)	37.61	(14.8)	50.07	(13.65)	35.41	(13.92)	< 0.0001
	Median (Range)	34	(18-83)	51.50	(21-78)	32.00	(18-83)	
Marital status	Not married	196	(49.00%)	19	(31.67%)	177	(52.06%)	0.012
	Married/stable relationship	179	(44.75%)	35	(58.33%)	144	(42.35%)	
	Widowed/ Separated/ Divorced	25	(6.25%)	6	(10.00%)	19	(5.59%)	
Religion	Without religion	114	(28.50%)	10	(16.67%)	104	(30.59%)	0.031
	Catholic	194	(48.50%)	38	(63.33%)	156	(45.88%)	
	Others[a]	92	(23.00%)	12	(20.00%)	80	(23.53%)	
Race	Blacks[b]	326	(81.50%)	51	(85.00%)	275	(80.88%)	0.564
	Others[c]	74	(18.50%)	9	(15.00%)	65	(19.12%)	
Schooling	From 0 to 7 years of study	153	(38.25%)	42	(70.00%)	111	(32.65%)	< 0.0001
	Over 8 years of study	247	(61.75%)	18	(30.00%)	229	(67.35%)	
Living in a rural area	No	201	(50.25%)	8	(13.33%)	193	(56.76%)	< 0.0001
	Yes	199	(49.75%)	52	(86.67%)	147	(43.24%)	
Time lived in rural area	Less than 3 years	36	(18.09%)	4	(7.69%)	32	(21.77%)	0.002
	From 4 to 11 years	48	(24.12%)	7	(13.46%)	41	(27.89%)	
	More than 12 years	115	(57.79%)	41	(78.85%)	74	(50.34%)	

Use of alcoholic beverages	No	54	(13.50%)	5	(8.33%)	49	(14.41%)	0.012
	Social drinker	180	(45.00%)	21	(35.00%)	159	(46.76%)	
	Ex drinker	85	(21.25%)	22	(36.67%)	63	(18.53%)	
	Current drinker	81	(20.25%)	12	(20.00%)	69	(20.30%)	
Duration of alcohol consumption/ years	Mean (SD)	15.02	(12.14)	22.82	(13.80)	13.01	(10.85)	< 0.0001
	Median (Min-Max)	10	(1-55)	22.50	(1-55)	10	(1-50)	
Smoking	No smokers	267	(66.75%)	29	(48.33%)	238	(70.00%)	< 0.0001
	Smokers	76	(19.00%)	13	(21.67%)	63	(18.53%)	
	Ex smokers	57	(14.25%)	18	(30.00%)	39	(11.47%)	
Use of illicit drugs in the last year	No	314	(78.50%)	49	(81.67%)	265	(77.94%)	0.633
	Yes	86	(21.50%)	11	(18.33%)	75	(22.06%)	
	Cannabis	65	(16.25%)	6	(10.00%)	59	(17.35%)	0.217
	Cocaine	43	(10.75%)	8	(13.33%)	35	(10.29%)	0.635
	Crack	9	(2.25%)	3	(5.00%)	6	(1.76%)	0.139
	Volatile solventes (shoe glue)	1	(0.25%)	0	(0.00%)	1	(0.29%)	0.999
	Injecting drugs	5	(1.25%)	0	(0.00%)	5	(1.47%)	0.999
Current anogenital condition	No changes or complaints	265	(66.25%)	43	(71.67%)	222	(65.29%)	0.415
	Yes	135	(33.75%)	17	(28.33%)	118	(34.71%)	
Sexual orientation	Heterosexual	320	(80.00%)	55	(91.67%)	265	(77.94%)	0.023
	No heterosexual	80	(20.00%)	5	(8.33%)	75	(22.06%)	
Sex with sex workers	No	324	(81.00%)	34	(56.67%)	290	(85.29%)	< 0.0001
	Yes	76	(19.00%)	26	(43.33%)	50	(14.71%)	
Age of 1st sexual intercourse	Mean (SD)	15.10	(2.76)	15.18	(3.06)	15.08	(2.71)	0.795
	Median (Min-Max)	15	(5-23)	16	(8-22)	15	(5-23)	

[a] includes blacks and browns
[b] includes white, yellow and indigenous
[C] includes Evangelical, Protestant, Spiritist, Candomblé and Umbanda

Table 2 - Characterization of SWA practice among men treated at CR-IST/AIDS in Juazeiro-BA and Petrolina-PE (Northeastern Brazil) in 2018 and 2019.

Variable	Category	n	%
SWA	Yes	60	15.00
Last SWA	1 to 4 years ago	3	5.00
	5 to 9 years ago	0	0.0
	10 to 19 years ago	10	16.67
	More than 20 years	47	78.33
Animal	Asinines and mules	46	76.66
	Goats	27	45.00
	Gallinaceous	20	33.33
	Calf	15	25.00
	Horses (Horse / mare)	13	21.66
	Sheep	11	18.33
	Adult Cattle	7	11.66
	Swine	4	6.66
	Canine	1	1.66
	Feline	1	1.66
	Duck / mallard / goose	1	1.66
Animal sex	Only Females	56	93.33
	Only males	1	1.67
	Females and males	3	5.00
Exposure time (years)	Mean initial age (DP)	12.37 (3.78)	
	Median (Min-Max)	12 (7-31)	
	Mean final age (DP)	16.43 (7.86)	
	Median (Min-Max)	15 (7-60)	

Frequency	Once to 3 times a week	19	31.67
	Once to twice times a month	11	18.33
	Once every 2 months	6	10.00
	2 to 4 times a year	7	11.67
	Anual	6	10.00
	Once in a lifetime	11	18.33
Variation of animals with each coitus	Always with the same animal	28	46.67
	Different animals in coitus	32	53.33
Presence of human companionship during SWA	Generally individual	35	58.33
	Generally, in a group	22	36.67
	Both	3	5.00
Position during SWA	Insertive	59	98.33
	Receptive	0	0
	Both	1	1.67
Type of relationship with the animal	Vaginal	58	96.67
	Oral	0	0.0
	Anal	5	8.33
	Masturbation	3	5.00
Condom use during SWA	No	57	94.99
	Always	1	1.67
	More than half the time	1	1.67
	Less than half the time	1	1.67
Uses internet to search for SWA content	No	43	71.67
	Yes	17	28.33
Type of content searched for on the internet related to SWA	Porn movies	16	94.12
	Imagens	9	52.94
	Social networks	0	0.0
SWA X HIV infection	Not applicable	45	75.00
	SWA only prior to HIV diagnosis	14	23.33
	SWA only after HIV diagnosis	0	0.0
	SWA before and after HIV diagnosis	1	1.67

Table 3 - Characteristics related to STIs among the groups of men who stated and denied SWA practice attended at the CRIST/AIDS in Juazeiro-BA and Petrolina-PE (Northeastern Brazil) in 2018 and 2019.

Variable	Category	n	(%)	Men with SWA practice	(%)	Men without SWA practice	(%)	P
STI in the last year	No	206	(53.51)	31	(53.45)	175	(53.52)	0.999
	Yes	179	(46.49)	27	(46.55)	152	(46.48)	
STI older than 12 months	No	206	(52.42)	19	(31.67)	187	(56.16)	0.001
	Yes	187	(47.58)	41	(68.33)	146	(43.84)	
STI carriers	Yes	239	(59.75)	37	(61.67)	202	(59.41)	0.853
	No	161	(40.25)	23	(38.33)	138	(40.59)	
	UDS	47	(11.75)	4	(6.67)	43	(12.65)	0.267
	Syphilis	53	(13.25)	5	(8.33)	48	(14.12)	0.312
	Warts /HPV	18	(4.50)	2	(3.33)	16	(4.71)	0.999
	HIV	89	(22.25)	15	(25.00)	74	(21.76)	0.699
	Hepatitis B	10	(2.50)	4	(6.67)	6	(1.76)	0.048
	Chancroid	2	(0.50)	0	(0.00)	2	(0.59)	0.999
	Genital herpes	14	(3.50)	4	(6.67)	10	(2.94)	0.242
	Hepatitis C	36	(9.00)	9	(15.00)	27	(7.94)	0.129
	HTLV	1	(0.25)	0	(0.00)	1	(0.29)	0.999
	Others (candidiasis)	5	(1.25)	1	(1.67)	4	(1.18)	0.558
Living with HIV	No	311	(77.75)	45	(75.00)	266	(78.24)	
	Less than 1 year ago	24	(6.00)	3	(5.00)	21	(6.18)	
	1 to 3 years	26	(6.50)	2	(3.33)	24	(7.05)	
	4 to 6 years	10	(2.50)	3	(5.00)	7	(2.06)	0.247
	7 to 9 years	4	(1.00)	0	(0.00)	4	(1.18)	
	10 to 19 years	19	(4.75)	6	(10.00)	13	(3.82)	
	over 20 years	6	(1.50)	1	(1.67)	5	(1.47)	
HIV+HBV+HCV Co-infection	No	397	(99.25)	58	(96.67)	339	(99.71)	
HIV+HBV+HCV Co-infection	Yes	3	(0.75)	2	(3.33)	1	(0.29)	0.060

The study excluded from this simple logistic regression model the variable "duration of alcohol consumption" because it considered another one related to the theme of alcoholism (Table-4).

The multivariable logistic regression model indicated that men who were more likely to have sex with animals were older (OR = 1.061, 95% CI = 1.039 - 1.084; p < 0.0001), resided in a rural area (OR = 7.163, 95% CI = 3.174 - 16.164; p < 0.0001) and had sex with sex workers in the last year (OR = 2.861, 95% CI = 1.463 - 5.594; p = 0.002). Discrimination analysis of the model showed a c-statistic of 85.4 (95% CI = 81-90) and the calibration showed a very good matching (Hosmer-Lemeshow test: χ^2 = 7,493; df=8; p value = 0.485).

DISCUSSION

The SWA prevalence in the surveyed men (15%) exceeds the percentage found among Americans (8%) of the Kinsey sample (15), however, it was lower than the Brazilian series (1, 17). We also obtained a higher prevalence percentage in men with STIs with a history of SWA (15.48%) than a survey in Pakistan that identified this sexual behavior

Table 4 - Univariable logistic regression model for the primary outcome (SWA practices).

Variable	Category	OR	95% CI		p value
			Lower	Upper	
Age (years)	unit increment	1.066	1.046	1.088	< 0.0001
Rural area inhabitant	Yes	8.534	3.933	18.518	< 0.0001
Time lived in a rural area	≤3 years	Ref			
	4 to 11 years	1.366	0.368	5.075	0.642
	≥12 years	4.432	1.465	13.413	0.008
Marital status	Single	Ref			
	Married/stable relationship	2.264	1.242	4.127	0.008
	Widower/separated	2.942	1.048	8.262	0.041
Schooling	Over 8 years	Ref			
	From 0 to 7 years of study	4.814	2.65	8.744	< 0.0001
Religion	Non-religious	Ref			
	Catholic	2.533	1.209	5.307	0.014
Consumption of alcoholic beverages	No use	Ref			
	Ex drinkers	3.422	1.209	9.685	0.020
Smoking	Non-smokers	Ref			
	Ex-smokers	3.788	1.922	7.466	< 0.0001
Sexual orientation	Heterosexual	3.113	1.203	8.056	0.019
Sex with sex workers	Yes	4.435	2.453	8.02	< 0.0001
STI older than 12 months	Yes	2.637	1.47	4.731	0.001
Having hepatitis B	Yes	3.976	1.088	14.538	0.037

in 0.5% of a sample of 465 men with sexually transmitted infections (23).

The sociodemographic variables associated with SWA are similar to literature or to medical evidence reported (1, 17): men with low schooling, married, and who lived in rural areas, especially in childhood. These characteristics differ from those observed in individuals with SWA practice through studies that used virtual methodologies (24): adults, singles, with more than eight years of study, living in urban centers. We do not know, however, whether there is a transition in this profile due to the rural exodus and sexual freedom seen in large cities, or whether this is the reflection of digital approaches, easing access to these populations and, at the same time, hampering the less educated, of rural origins and who do not access virtual digital groups, as verified in our investigation.

The behavioral aspects of the SWA practice demonstrated similarities with findings from other studies, such as limited exposure to adolescence (1, 15, 25), a predilection for farm animals (1, 25), and weekly frequency (1). However, the interest in diversifying the animals at each intercourse and prioritizing performing them at the individual level differed from the previous findings (1). Considering that the region we investigated has numerous herds of goats and sheep, the variation of animals at each coitus may reflect the supply of available specimens. The interest in practicing SWA in a restricted way does not exempt the possibility of later socializing it in a group or being a choice influenced by the fear of condemnation by peers, especially after marriage (25).

Although the results related SWA to alcohol consumption in the past, we did not discover whether, during sexual intercourse with animals, they were under the influence of alcohol. In this case, alcohol could be used intentionally to encourage sexual intercourse, or SWA could be a consequence of chronic alcoholism. In India, researchers believe that alcohol abuse by a teenager may have caused the death of a calf penetrated during SWA (26).

The lack of statistical significance between SWA men and non-SWA men for variables that assessed the occurrence of STIs "in the last 12 months" and "STI patients" may influence the time between the last SWA and data collection. Considering that 78.3% of those who reported SWA had their last sexual intercourse with animals more than 20 years ago, it is presumed that acute bacterial STIs conditions directly related to this sexual practice have already been cured. The present research did not investigate whether the participants remembered any anogenital discomfort after practicing SWA and how they led with possible complaints.

The statistical association between SWA and carriers of HBV adds elements to discussing the possibility of transmitting this virus between humans and animals. HBV belongs to the *Hepadnaviridae* family and includes several genera among animal species, including the *Orthohepadnavirus* genus commonly found in mammals such as non-human primates (27). There are indications of a possible variant of endemic *Hepadnavirus* in swine (28) and in chickens (29), where molecular analyzes revealed 92.2% to 97.9% similarity with human HBV. Despite this, there is no overwhelming evidence that HBV transmission can occur between human and animal species, as it is a host--specific virus (27).

Given the lack of genetic and viral findings that justify the transmission of hepatitis B between humans and animals, these results may be supported in sociodemographic, biological, and behavioral aspects. National data (30) indicates that individuals diagnosed with hepatitis B have the same predominant sex, race/color and schooling level identified in SWA men.

Exposure to genital trauma and abrasions common during SWA (11), and the consequent ease of penetration by infectious viral agents in sexual relations with humans, including HIV, may increase vulnerability to HBV and other STIs. Our prevalence of SWA men infected with HVB + HCV + HIV (3.3%,) exceeds the percentages of Africans (0.15%) (31) and injecting drug users from Iran (1.25%) (32).

In our study, behavioral aspects associated with SWA such as long-lasting consumption of alcoholic beverages, history of STI infection, sexual involvement with sex workers, and low schooling

may also represent an increased risk context for STIs. In addition, most of these men have a history of residing in rural areas, where access and health care are deficient in much of the country, including low vaccination coverage for hepatitis B among adults (33).

The use of condoms during sexual activities with animals was denied by most participants who reported their last SWA during adolescence, which seems to be compatible with the age of these participants (around 50 years) and their history of living in rural areas. Many lived adolescence between the 80s and 90s when the HIV epidemic was still restricted to large urban centers and the call for condom use limited. We are pioneers in presenting data on condom use in SWA intercourse.

The men who reported regular or occasional use of condoms during sex with animals (n=3) were the only ones who reported the most recent SWA (1 to 4 years before the survey), which is consistent with the increasing stimulus to the use of condoms, for the prevention and control of HIV and other STIs. We did not investigate whether these participants used condoms frequently in sexual intercourse with humans and the reasons for using condoms in SWA acts, whether they would be to make coitus more comfortable or safer from the point of view of the transmission of human-animal diseases or animal-human.

Most HIV-seropositive men with a history of SWA reported sex with animals just before diagnosis. This decision did not privilege aspects of animal self-care or well-being because, upon receiving the diagnosis, they had ended their experiences with animals since adolescence. Their average age was 54.2 years, the last SWA occurred between 13 and 19 years of age, and most were diagnosed with HIV in the last two decades.

Our research stands out for being the first cross-sectional study on SWA and STI realized in the world, in addition to identifying a statistical association between men with SWA and hepatitis B practice. Although our sample of hepatitis B patients was small, this result can add knowledge to support conclusive studies on HBV transmission between human and animal species.

This investigation adds to the small number of studies on SWA performed through face-to-face interviews published in the last decade. We verify a growing trend of recruitment via the internet, which is vulnerable to different biases even though it is an accessible and promising strategy. We also included participants from different age groups, regardless of health status and serological status for STIs, which brings the results closer to the profile of the general population. Most of the recent research conducted in health services conducted face-to-face interviews with SWA individuals were linked to penile cancer (1, 17).

One of the limitations of this study concerns the last SWA occurrence reporting more than 20 years ago for most participants, which may have hidden complaints associated with this sexual practice. Although this is an important topic, the cross-sectional nature of the study with behaviors that were essentially long ago limits the value of the examined and identified associations. We did not investigate the time between SWA and STI diagnosis, which could be relevant since part of these men had, on average, three years of coitus exclusively with animals before starting sex with humans. We have not investigated the use of illicit drugs throughout life, especially injectable drugs and the possible sharing of syringes and needles. We recognize the limitation of cross-sectional studies to analyze the history of STIs in this population and suggest that prospective studies be conducted for this purpose.

It is necessary to consider the inclusion of new population groups in studies that articulate SWA and STI as women, given the existence of SWA practices in large urban centers (24); indigenous, forestry, and aborigines, who traditionally live in harmony with animals and who have registered high percentages of STIs in several countries (34). Research involving young adults living in rural areas can provide important information about the current context of SWA practices in this population group and allow comparisons with studies that included young populations from well-developed urban spaces (24).

CONCLUSIONS

Our study showed that SWA is part of the sexual repertoires of adult men treated at the investigated Reference Centers for Sexually Transmitted Infections, with a prevalence of 15.00% in the investigated sample. Among men with a clinical or laboratory diagnosis of STI, we identified the highest prevalence ever recorded in the world literature, 15.48%.

SWA is associated with some sociodemographic and behavioral aspects capable of increasing vulnerability to STIs, such as: increasing age, history of residence in rural areas and sexual involvement with sex workers. The relationship between SWA and hepatitis B may provide important support for future studies that investigate the possibility of human-animal transmission. Intersectoral actions and harm reduction strategies should be considered to ensure/promote the sexual health of those involved.

Articulated actions among professionals who assist individuals with STIs, dealing with sexual health, human sexuality, animal health, and well-being should be discussed to produce scientific knowledge on the subject, approach strategies, and assist SWA supporters. It is worth considering the ethical limits that permeate actions for harm reduction, such as condoms and intimate lubricants, the impact on animal health, and the emergence of new strains of sexually transmitted pathogens.

ABBREVIATIONS

AIDS = Acquired Immunodeficiency Syndrome
CR-IST/AIDS = Refer Center for STI/AIDS
HBV = Hepatitis B Virus
HCV = Hepatitis C Virus
HIV = Human Immunodeficiency Virus
HTLV = Human T-lymphotropic Virus
MH = Ministry of Health
STI = Sexually Transmitted Infections
SWA = Sex With Animals
UDS = Urethral Discharge Syndrome

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Federal University of Vale do São Francisco (June 22, 2017 / nº 2.133.407).

CONSENT

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

CONFLICT OF INTEREST

None declared.

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Translational research in pediatric urology: methods of investigation of urogenital system in human fetuses

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COMMENT

Knowledge of the structure of the urogenital organs in human fetuses is of great importance for understanding the main congenital anomalies. In this editorial, we will comment on the main study methods carried out in basic research on human fetuses in our unit, with the aim of bringing information that will help in the diagnosis and treatment of anomalies of the kidney, ureter, bladder, urethra, penis and testicle.

The first step of fetal investigation applied to translational research in pediatric urology is the determination of fetal age. After determination of death, the fetuses are kept in refrigeration (temperature lower than 4 centigrade grades) for 24 to 72 hours. After reaching the laboratory, the fetuses are defrosted, cleaned, identified and analyzed morphologically. Fetuses with malformations or not well preserved are excluded for analysis. After cataloguing, the first step is to weight, using a precision scale of 1 gram. The fetuses are also evaluated regarding crown-rump length (CRL), total length (TL) and foot-length immediately before dissection (Figure-1). The same observer analyses all measurements. For the evaluation of the CRL and TL it is used a metric tape, and to check the length of the bigger foot (more posterior region from the heel to the tip of the most prominent toe, first or second) it is used a Starrett® digital pachymeter 0.01 cm precision (Figure-2). The measures of the right and left feet are repeated three times each, using the millimeter precision pachymeter (mm) (1, 2).

The foot with the higher median is used to determine the gestational age, lowering the risk of error. That measure is analyzed in a graphic (3) that relates the length of the bigger foot with gestational age, according to weeks after conception (WPC). The gestational age of the fetuses is determined in WPC, according to the foot-length criterion, which is currently considered the most acceptable parameter to calculate gestational age (3-7).

After the fetal measurements, the fetuses are carefully dissected with the aid of a stereoscopic lens with 16/25X magnification. The abdomen and pelvis are opened to identify and expose the urogenital organs (Figure-3) and take the organs to histologic analysis. The samples are separated from the other structures and fixed in 10% buffered formalin, and routinely processed for paraffin embedding, after which 5-µm thick sections are obtained at 200-µm intervals. Smooth muscle and connective tissue, elastic system fibers and collagen are studied by histochemical and immunohistochemical methods. Sections are stained with hematoxylin-eosin to assess the integrity of the tissue. The following staining methods are used: Masson's trichrome, to quantify connective and smooth muscle tissue; Weigert resorcin fucsin with previous oxidation, to observe elastic system

fibers; and picrosirius red with polarization for observation of different collagen types. The main used immuno-histochemistry technique is avidin-biotin to identify collagenous proteins, elastin, and glycoproteins (8) and tubulin (Tubulin, beta III, Mouse Monoclonal Antibody) for nerves analysis.

Connective tissue, smooth muscle tissue, nerves and elastic system fibers are quantified by a stereological method (9). We study 5 microscopic fields chosen at random, totaling 25 test areas studied for each gubernaculum for the quantitative analysis. We use the Image J software, version

Figure 1 - Fetal morphometric measures of the total length of a 22 weeks post conception fetus using a metric tape.

Figure 2 - Precision pachymeter to check the measure of the bigger foot from the most prominent toe to heel. This measure is the most important for the determination of the gestational age.

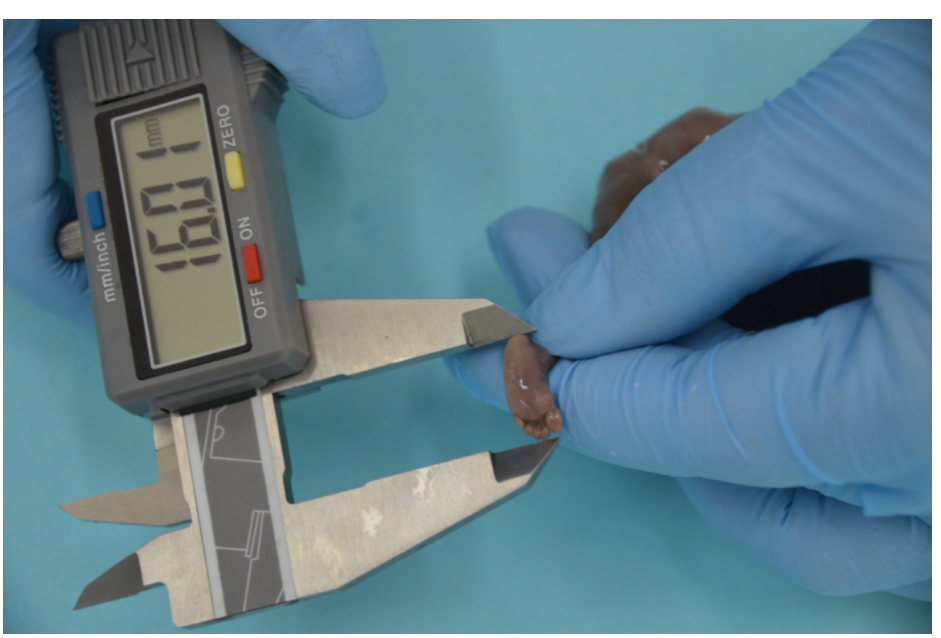
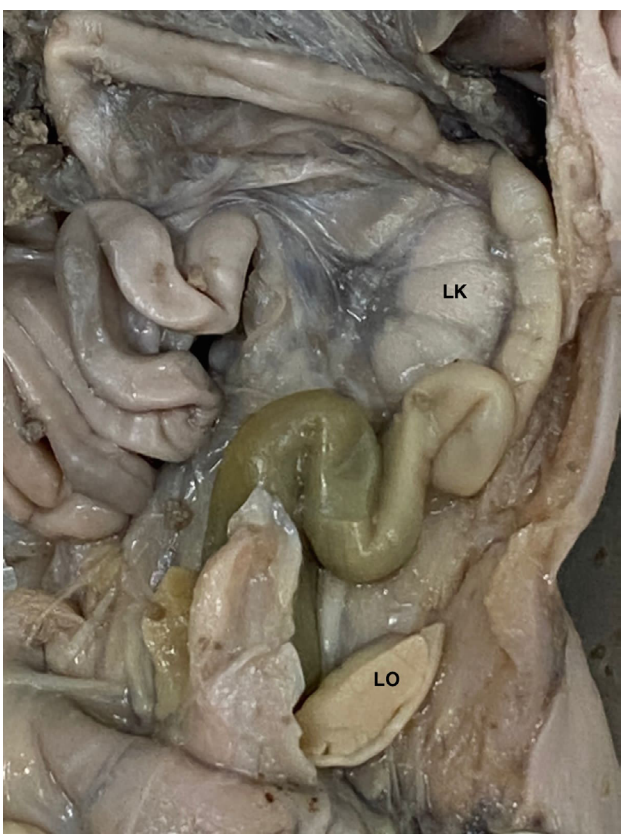


Figure 3 - The figure shows the steps of fetal dissection of urogenital organs. The abdominal wall of a female fetus with 23 weeks post conception is opened and the urogenital organs (Left kidney –LT and Left ovaries –LT) are dissected for posterior histological analysis.



1.46r, loaded with its own plug-in (http://rsb.info.nih.gov/ij/). All sections are photographed with a digital camera (DP70, Olympus America, Inc., Melville, New York) under the same conditions at a resolution of 2,040 1,536 pixels, directly coupled to the microscope (BX51, Olympus America, Inc.) and stored in a TIFF file. To quantify the smooth muscle tissue, we use the Color Segmentation of Image J software, where the program selects structures of different colors and calculates the amount of each component (Figures-4).

For quantification of elastic fibers and nerves we use the Image J software to determine the volumetric density (Vv) of each component. Results for each field are obtained through the quantification assessment method, by superposing 100 points test grid (multipurpose test system) on the video monitor screen. The arithmetic mean of the quantification in 5 fields of each section is determined. Afterwards, we obtain the mean quantification value for the 5 sections studied from each sample (total of 25 test areas) (Figure-5).

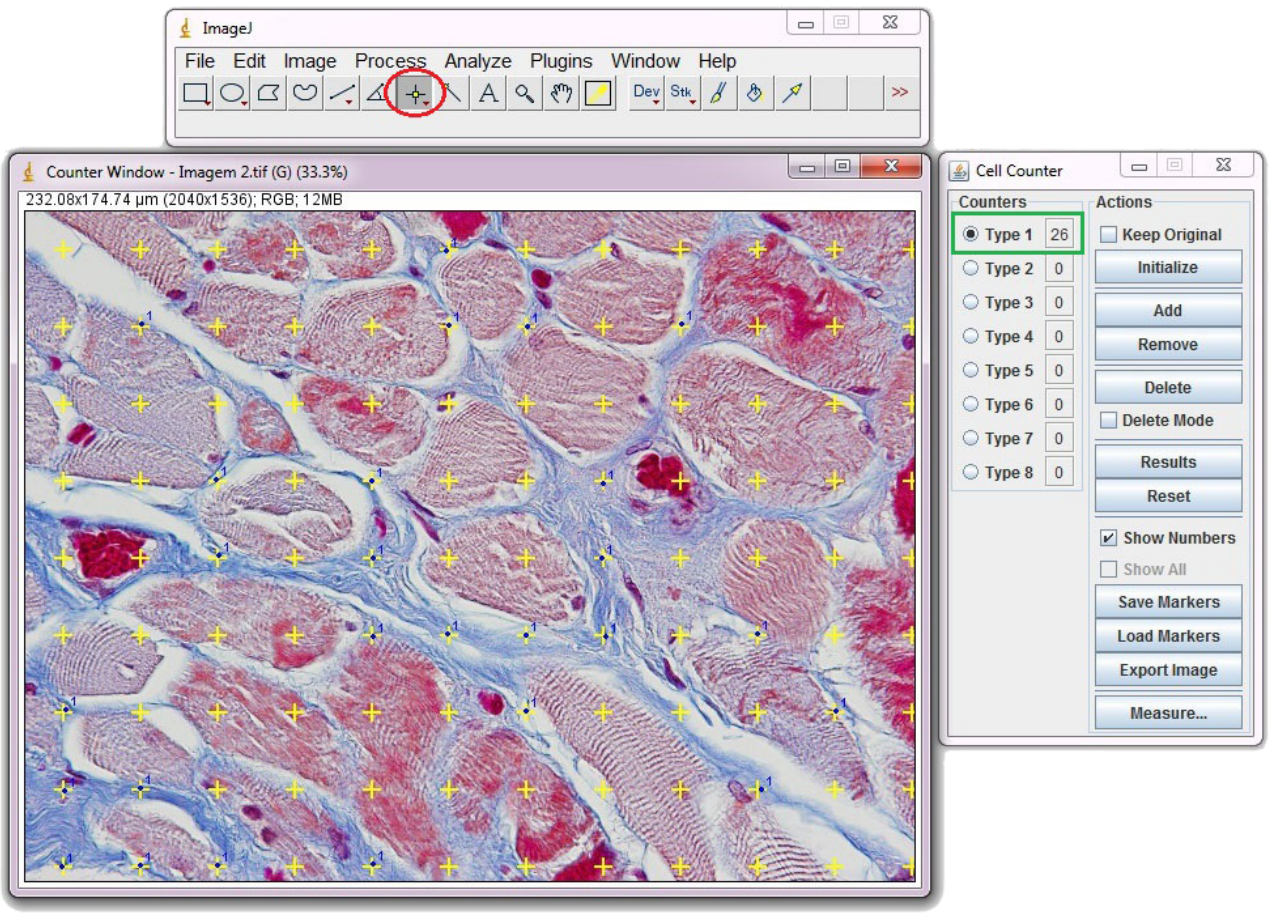
In order to quantify the area of collagen fibers, elastic fibers, blood vessels and nerves, it is used a plug-in cell counter and a point tool, that allows for the quantification of more than one structure in the same photography. The quantity of each analyzed structure is presented in the cell counter window, where the values are tabled, and the media obtained for each patient for statistical analysis.

For the analysis of the connective tissue and elastic system fibers it is used photography of the slices stained by the histochemistry techniques: Masson trichrome and Weigert resorcin--fucsin with previous oxidation, respectively. In both analyses, the microphotographs are obtained under 600X, and five random fields are analyzed by section. For the analysis of blood vessels and nerves it is used microphotographs of slices stained by the immune-histochemistry method: immune-labeling with anti-CD31 and anti-tubulin βIII, respectively. In both analyses, the microphotographs are obtained under 400X, and five random fields are analyzed by section, totalizing 35 fields in control group and 70 fields in the stained group.

For qualitative analysis of connective tissue, we studied 5 samples from each foreskin, with 2mm length. The samples are submitted to fixation for scanning electron microscopy (SEM) by immersing tissue fragments in a modified Karnovsky solution for 48 hours at 4ºC. This fixative consists of 2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M sodium phosphate buffer, pH 7.4. To better visualize the 3-dimensional organization of the vesicle stroma under SEM, tissue samples are submitted to an alkali treatment to solubilize and remove cells. The obtained acellular preparations are then processed for high-vacuum SEM, and observations are performed on a LEO 435 (Zeiss, Oberkochen, Germany) scanning electron microscope with an acceleration voltage of 15 to 20 kV (Figure-6).

The injection corrosion techniques using resins and anatomic models are very important for

Figure 4 - Quantification methods: To quantify the smooth muscle tissue we use the Color Segmentation of Image J software, where the program selects structures of different colors and calculates the amount of each component. After calibration and measure of the image area (red circle 39737.034), select the options plugins, analyze, and grid.



translational research. These techniques allows for the tridimensional study of several organs, the study of micro-vascularization, analysis of anatomic relations in humans, and experiment and animal models (10). Resins are polymers capable of produce solid and saturated compounds (anatomic models). The ideal resin should be cheap, with minimal retraction, producing a strong and consistent mold with unchanged color and easy to manipulate. There are several kinds of resins: plastic material, synthetic resins and silicon resins. The plastic include nylon, vinilyte and Justi h. This kind of resin shows too much retraction (distortion), is fragile, changes its color and needs a high pressure for injection, complicating its routine use.

The synthetic resins include Resapol T208 and Perpex tensol, routinely used in our laboratory with great experience. This class of resin is very resistant to caustic agents. We obtained an easy viscosity regulation with minimal retraction, and they have a low cost. We routinely use Resapol. It is composed by resin, a styrene monomere, a catalyzing agent and a dye (pigment paste).

The styrene monometer allows for the co-polymerization and produces a mixture with good viscosity. The catalyzing agent (Ethyl-methyl-ketone peroxide) stiffens the resin, a fundamental step for the confection of molds. The catalyzing agent is liquid, easy to mixture, unstable, with a short limit time for use, and bubbles indicate deterioration.

In order to perform the injection, we use the following method: for each 100 ml of resin, we add 10 ml of styrene monomer and 2 to 5 ml of catalyzing agent, and the dye (we standardized the

Figure 5 - Quantification of muscle tissue with color segmentation of Image J software - grid window configuration overlapping the microphotograph.

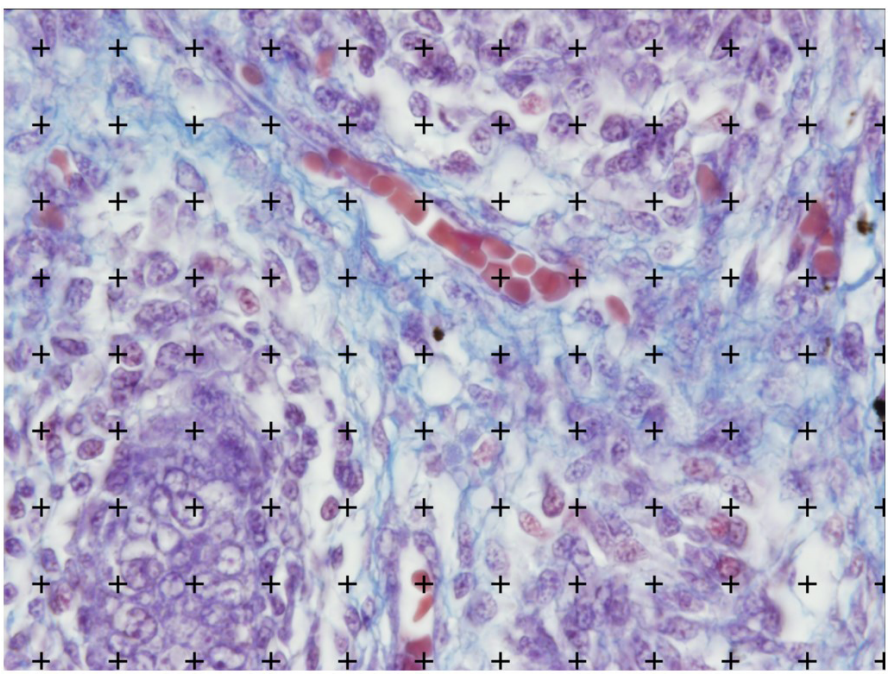
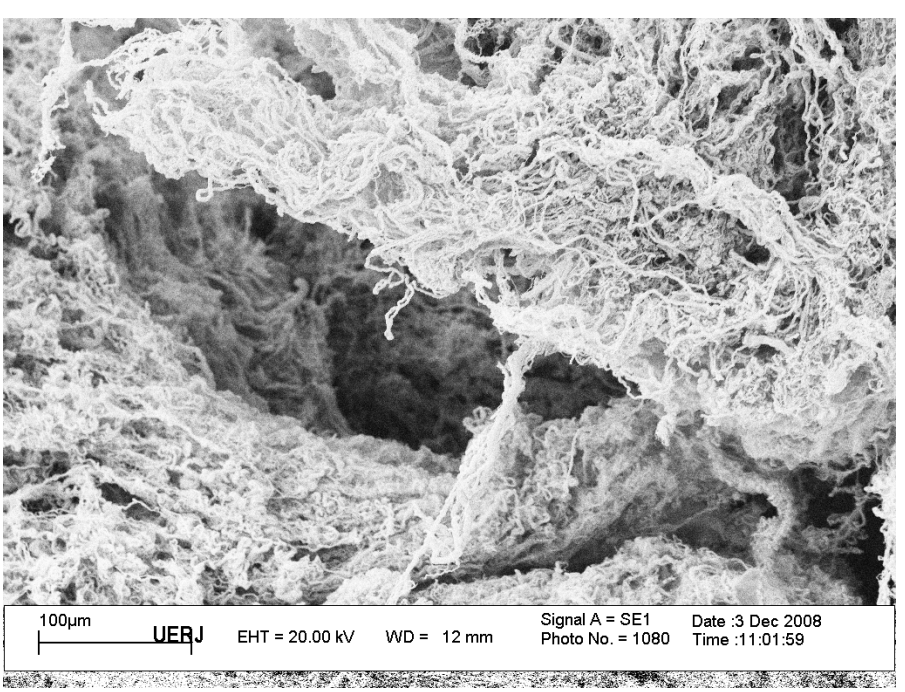


Figure 6 - Scan electronic microscopy of fetal renal pelvis. Fetal renal pelvis of a male fetus with 18 weeks post conception.



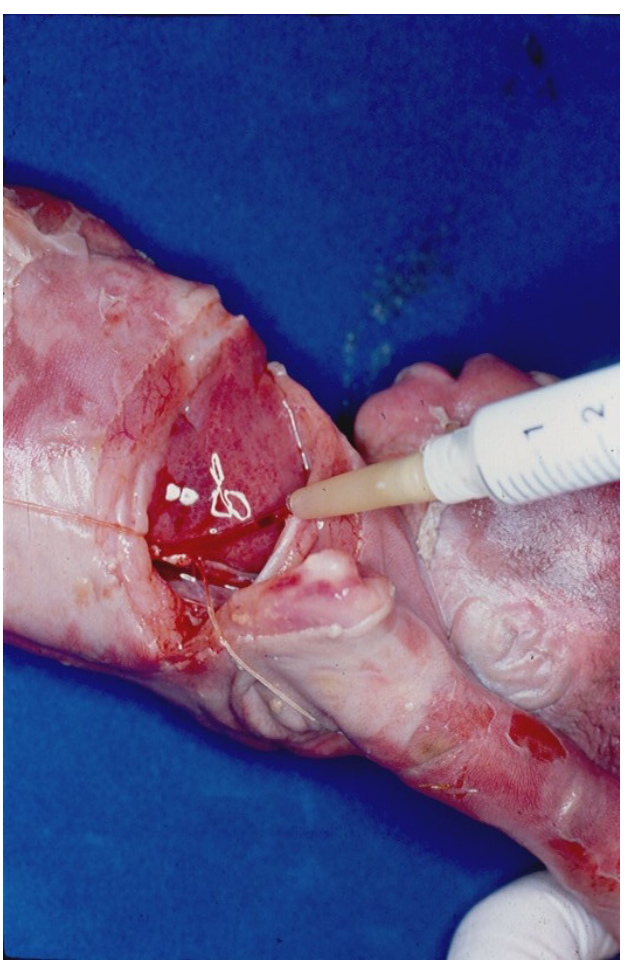
following colors: yellow for the collecting system, red for arteries and blue for veins). Following the resin hardening, we initiate the process of corrosion in order to remove all organic material and confection of the mold (Figure-7). After injection, the material must be dipped in hydrochloric, sulfuric, or muriatic acids for 24 hours. After this time, the mold must be removed from the recipient, cleaned, and dried for analysis (10).

Silicon resin Microfil can also be used, particularly when the purpose is to highlight the organ vasculature. This kind of resin has high cost and is difficult to obtain. We use it in special to study the renal and testicular vasculatures. By thoracostomy, we identify the thoracic aorta and inject the resin inside the vessel (Figures 8). After injection, the abdominal cavity is open and with the aid of a stereoscopic magnifying glass we carefully dissect the organ vessels.

The use of these techniques allows the development of several lines of research on the urogenital system during the human fetal period, which is of fundamental importance for translational medicine.

Figure 7 - The figure shows the final aspect of a kidney endocast in a fetus with 25 weeks post conception.

Figure 8 - Silicone (Microfil) Resin injection Technique: The fetal thoracic cavity is open and the descendent aorta is catheterized and injected.



CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

NEURO-UROLOGY

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Editorial Comment: Sacral neuromodulation for neurogenic Lower Urinary Tract Dysfunction

Liechti MD [1], van der Lely S [1], Knüpfer SC [1, 2], Abt D [3, 4], Kiss B [5], Leitner L, [1], et al.

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NEJM Evid 2022; 1 (11). Online ahead of print

DOI: 10.1056/EVIDoa2200071 | ACCESS: 35731251

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COMMENT

This is a sham-controlled, double-blind, multicenter trial, which included patients with refractory neurogenic lower urinary tract dysfunction (NLUTD) at four Swiss referral centers. Patients underwent sacral neuromodulation (SNM) test phase with lead placement into the sacral foramina S3 (rarely, S4). Neurostimulator was implanted for permanent stimulation only in patients presenting ≥50% improvement in key bladder diary variables (successful test phase). For 2 months, neuromodulation was optimized using subsensory stimulation with individually adjusted parameters. Thereafter, the neurostimulator remained on or was switched off (1:1 random allocation to group SNM ON or SNM OFF, respectively) for 2 months, followed by a neurourologic reevaluation. The primary outcome was success, as defined above, of SNM compared with baseline.

Of 124 patients undergoing SNM test phase, 65 (52%) were classified as therapy responders. Of these, 60 patients were randomly assigned to the intervention. After 2 months of intervention, the SNM ON group demonstrated a success rate of 76%. In the SNM OFF group, 42% of patients showed sustained SNM effects despite their neurostimulator being switched off during the last 2 months (odds ratio, 4.35; 95% confidence interval, 1.43 to 13.21; P=0.009).

This the first well-designed RCT demonstrating that SNM effectively corrected refractory NLUTD in the short term in well-selected neuro-urological patients. The use of subsensory stimulation allowed

switching off the implantable neurostimulator in the control group without jeopardizing blinding. Additionally, this study did not detect notable carryover effects (>2months), therefore supporting a need for continuous stimulation in neuro-urological patients. The heterogeneity of neurologic patient population, which precluded a disease-specific analysis, may be seen as the main limitation of this trial.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Thulium fibre laser versus Holmium:YAG for ureteroscopic lithotripsy: outcomes from a prospective randomised clinical trial

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Eur Urol . 2022 Jul;82(1):73-79.

DOI: 10.1016/j.eururo.2022.02.027 | ACCESS: 35300888

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COMMENT

This randomized controlled trial is the first to compare the outcomes after ureterorenoscopic lithotripsy (URS) with low power Holmium:YAG (Ho:YAG) and Thulium Fibre Laser (TFL). Primary endpoint was the stone-free rate (SFR) by computed tomography (CT) at 3 months after URS. Secondary endpoints were the operative time and complications (1).

This is a very important paper since the authors demonstrated for the first time a superiority of TFL over Ho:YAG for the treatment of renal stones. Overall higher SFR was achieved with TFL (57% vs. 80%, p=0.006). Ureteral stones SFR was 100% in both groups but renal stones SFR was 33% for Ho:YAG vs. 66% for TFL (p=0.005). Operative time was shorter with TFL (49 min) than with Ho:YAG (57 min). There was no difference in readmissions between groups (12% TFL vs. 13% Ho:YAG, p=1) and no ureteral strictures or hydronephrosis were observed on 3-month CT (1).

The reported 33% SFR for renal stones of Ho:YAG arm and 66% for TFL are very disappointing. The SFR reported by Ulvik et al. is comparable to the SFR of shockwave lithotripsy (SWL) reported by Bosio et al. in their randomized controlled trial of URS vs. SWL and to the 34.1% SFR of SWL evaluated by CT of the prospective study by Torricelli et al. (2, 3). Also, Ulvik et al. results are inferior to many previously reported studies using low power Ho:YAG as the 74.8% SFR evaluated by 3-months CT using basketing strategy and ureteral access sheath (UAS) in every case (4). The facts that UAS was not used in any case and that nine

different (three faculty and six residents) surgeons performed 120 URS (mean of 13.3 procedures/surgeon) could help to explain low SFR. Of note, the authors decided to start laser settings in 0.4J/6Hz and limit laser settings to 0.8J/20Hz in renal pelvis. These settings are more consistent with basketing strategy. Despite there is no definitive evidence for superiority of dusting versus basketing, the later requires more operative time to achieve better SFT (5). Since the authors recommend low laser settings, it would be interesting to use basketing more efficiently to increase their SFR for both Ho:YAG and TFL.

Other groups should report their experience with TFL in randomized controlled trial to confirm TFL superiority over Ho:YAG in different scenarios.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Primary laparoscopic RPLND for pure seminona metastasis: feasibility of supine and lateral approaches

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ABSTRACT

Introduction: Retroperitoneal lymphadenectomy (RPLND) is well established as a primary treatment, especially for high--risk stage I and stage IIA/B nonseminomatous tumors, but its value in seminomatous tumors is underreported (1).
Classically, seminomas with isolated retroperitoneal lymphadenopathy are treated with external beam radiation therapy or systemic chemotherapy. Although these modalities are effective, they are associated with significant long-term morbidity (2, 3). Some retrospective studies have demonstrated the potential of RPLND as a first-line treatment for stage IIa seminoma, and two very recent prospective trials, still with interim results: SEMS TRIAL and PRIMETEST(3-7).
The RPLND robotic technique has been previously described in the post-chemotherapy scenario, however, surgical videos of primary laparoscopic approach are lacking, especially in seminomatous disease (8).
Materials and Methods: We present two cases of primary videolaparoscopic RPLND, using different approaches.
Case 1: Thirty four years-old, with prior right orchiectomy for mixed tumor. After 8 months he presented an two cm enlarged interaortocaval lymph node. Percutaneous biopsy showed pure seminoma metastasis.
Case 2: Thirty three years-old, with previous left orchiectomy for stage I pure seminoma, without risk factors. After nine months, the patient had a three cm enlarged para-aortic lymph node.
Results: The surgical time ranged from 150 to 210 minutes, with a maximum bleeding of 300 mL and hospital discharge in 48 hours. In one of the cases, we identified a significant desmoplastic reaction, with firm adhesions to the great vessels, requiring vascular sutures, however, no major complication occurred. Pathological anatomy confirmed pure seminoma lymph node metastases in both cases.
Conclusion: Laparoscopic primary RPLND proved to be technically feasible, with less postoperative pain and early hospital discharge. We understand that more studies should be performed to confirm our oncological results.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic-assisted repair of colovesical anastomosis after Hartmann's reversal procedure

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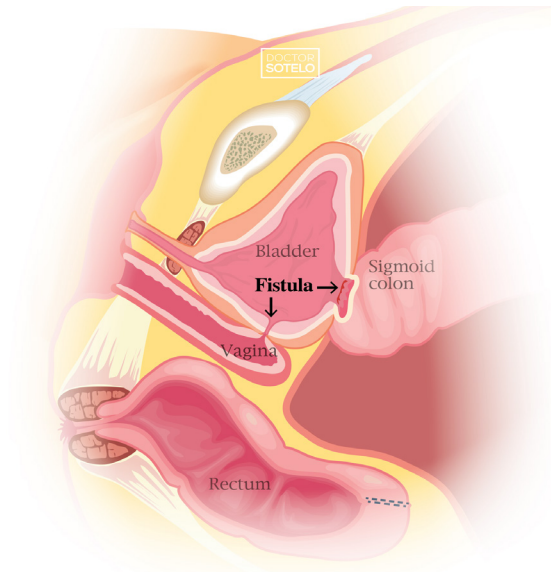
ABSTRACT

Purpose: Hartmann's procedure is the resection of the rectosigmoid colon with an end colostomy formation and closure of the anorectal stump (1). Its reversal has a morbidity rate up to 58% (2, 3) with an incidence of fistulae formation of 4.08% (1). Herein, we present a robotic-assisted repair of a complex fistula that occurred as complication of Hartmann's reversal when the stapler was introduced inadvertently through the vaginal canal.
Patient and methods: Eighty-three-year-old female with past medical history of hysterectomy and ischemic colitis that required colectomy and colostomy placement in December 2020. In March 2022, the patient underwent a colostomy takedown, after which she reported fecaluria, urine leakage per vagina, and recurrent urinary tract infections. Cystoscopy and vaginoscopy revealed a large colovesical fistula, a staple in the bladder trigone, and several staples in the anterior vaginal wall. Robotically, extensive adhesiolysis was performed, the sigmoid was separated from the bladder, and the intact rectal stump was dissected free. The staple from the bladder trigone was removed. Bladder was closed in two layers with 3-0 V-Loc. Colorectal anastomosis was not feasible due to the short length of both ends. Therefore, a permanent colostomy was placed.
Results: Operative time was 454min., and estimated blood loss was 100cc. Discharged on postoperative day 4 with a JP drain and a 20Fr Foley catheter. Drain, and Foley were removed on postoperative days 9 and 23, respectively. No postoperative complications were reported.
Conclusion: Robotic-assisted repair represents an effective approach for the management of colovesical fistulae after Hartmann's reversal.

CONFLICT OF INTEREST

None declared.

Figure 1 - Colovesical and Vesicovaginal fistulae.



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