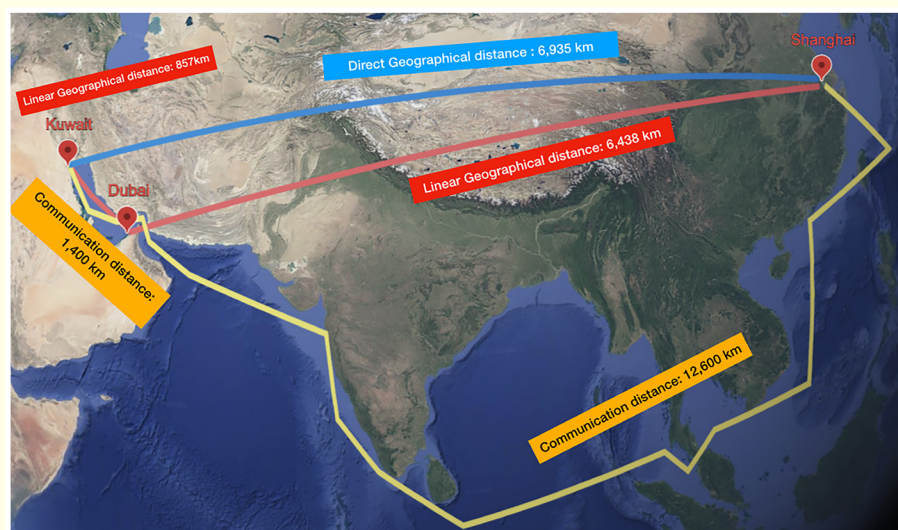


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Telesurgery and the Future of Urologic Surgery

Luciano A. Favorito ^{1, 2}

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The November–December 2025 issue of the International Brazilian Journal of Urology presents original contributions with numerous engaging papers across various fields, including urinary incontinence, bladder cancer, prostate cancer, robotic surgery, telesurgery in urology, infection, penile cancer, infertility, transitional urology, epispadias, and basic research. The papers come from several countries such as Brazil, Kuwait, Serbia, Italy, and China. As usual, the Editor's Comment highlights selected articles, and in this issue, the Editor-in-Chief wishes to particularly emphasize the paper on telesurgery.

Dr. Aldousari and colleagues from Kuwait present, on page e20250331 (1), an interesting study on telesurgery, which is featured on the cover of this edition. The objective of their work was to demonstrate the feasibility and reproducibility of ultra-long-distance, Asia-to-Middle East human telesurgery using low-latency connectivity, performed on multiple patients and across different procedures. Over a six-month period, the authors performed five human telesurgeries using a multiport robotic platform connected via fiber-optic and 5G networks. The remote surgeon (SA) was located in Shanghai, China, while the patients were in Kuwait City, Kuwait—approximately 7,000 kilometers apart. They concluded that multiple human telesurgical procedures can be feasibly and reproducibly performed through successful collaboration between two countries using a robotic system with telecommunication capabilities, achieving favorable outcomes without complications. However, they also emphasize the need to establish robust international guidelines to facilitate the global implementation of telesurgery.

In recent years, we have witnessed remarkable advancements in robotic surgery and other emerging technologies in urology (2–6). Among them, telesurgery stands out as the most striking innovation. This technology has enabled a previously unimaginable achievement in surgery: the ability for a surgeon to perform a procedure from a completely different location—another city, country, or even continent. This pioneering progress is largely due to the dedicated work of Dr. Patel, Dr. Moschovas, and their team (7). The demonstrated feasibility of long-distance telesurgery not only marks a milestone in urologic surgery but also underscores its potential to improve surgical outcomes, facilitate advanced training, and provide remote assistance for complex cases. Telesurgery could play a pivotal role in expanding access to specialized care and enhancing robotic surgical training worldwide.

The Editor-in-chief expects everyone to enjoy reading the original contributions with a lot of interesting papers in this number.

CONFLICT OF INTEREST

None declared.

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New Evidence on an old Question: a Meta-Analysis of Wallace versus Bricker Anastomoses

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ABSTRACT

Purpose: This meta-analysis compares the efficacy and safety of the Bricker and Wallace techniques, focusing on updating previously unassessed clinical outcomes to inform surgical decision-making.

Material and Methods: A systematic review and meta-analysis followed PRISMA and Cochrane guidelines, with the protocol in PROSPERO (CRD42024621076). Searches in MEDLINE/PubMed, EMBASE, and Cochrane Library included Randomized Clinical Trials and cohort studies comparing both anastomosis techniques. Analyses used Odds Ratio (OR) and mean differences with a random-effects model.

Results: Fourteen studies with 1,903 patients (980 Bricker; 923 Wallace) were included. No significant difference was found in overall stricture rates. However, the Bricker technique had more unilateral strictures (OR 0.47; 95% CI 0.30-0.75; $p < 0.01$), while the Wallace technique had lower stricture rates in patients who underwent ileal-conduit urinary diversion (OR 0.35; 95% CI 0.19-0.64; $p < 0.001$), and patients without prior radiotherapy (OR 0.29; 95% CI 0.14-0.61; $p < 0.001$). Wallace also presented reduced hydronephrosis (OR 0.37; 95% CI 0.17-0.79; $p < 0.05$). No significant differences were observed in patients undergoing neobladder diversion or those with bladder cancer.

Conclusion: No difference in main analyses of stricture rates was found, supporting that technique choice should rely on surgeon preference and expertise. Therefore, beyond surgeon preference, the choice of technique should consider the patient's history of radiotherapy, and the type of urinary diversion planned, aiming to optimize postoperative outcomes and minimize the risk of specific complications.

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INTRODUCTION

Radical cystectomy (RC) is commonly performed on patients with muscle-invasive bladder cancer, non-urothelial malignancies, dysfunctional bladder, and chronic pelvic pain syndrome (1). Besides the emergence of innovative techniques and platforms in the management of these patients (2, 3), the type of surgical approach chosen, whether open, laparoscopic, or robot-assisted, may influence key operative outcomes (4). The life expectancy and subsequent morbidity and mortality rates of these patients depend, to a large extent, on the urinary diversion performed following the procedure (1). Over the years, several techniques for urinary diversion using intestinal segments (5) have been described in literature, each with its own advantages and disadvantages. (6) The most widely used approaches are the Bricker and Wallace methods (6).

The Bricker technique, described in the early 1950s, was one of the first methods for ureteroenteric anastomosis (UEA). In this approach, each ureter is individually connected to the intestinal segment in an end-to-side configuration using absorbable sutures (7). By contrast, the Wallace approach, which was delineated later, around the 1960s, involves an end-to-end anastomosis, where the two ureters are spatulated, joined side by side, and connected as a single unit to the end of the intestinal segment (8).

At the time, prominent surgeons who popularized the Wallace technique in the United Kingdom believed that this method offered several advantages over Bricker's approach. Specifically, the Wallace technique involves creating a single, large anastomosis, which was thought to reduce the risk of strictures and eliminate the need for separately closing the proximal end of the conduit (9). However, over time, no robust scientific evidence has demonstrated a clear superiority of one technique over the other. As a result, the choice of approach generally depends on the surgeon's preference and experience rather than on definitive differences in clinical outcomes (10).

A previously published meta-analysis (10) found no significant differences in the risk of stric-

ture when comparing the two techniques; however, other potential outcomes were not evaluated. Since then, new studies have emerged, allowing for a re-evaluation of the previous findings and the inclusion of additional outcomes in the analysis. Therefore, this meta-analysis aims to explore the main differences in the impact of outcomes between the two approaches, providing a more comprehensive understanding of their clinical implications.

MATERIAL AND METHODS

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook of Systematic Review of Interventions and the Preferred Reporting Items for the Systematic Reviews and Meta-analysis (PRISMA) statement guidelines (11, 12). The protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024621076).

Search Strategy

We systematically searched PubMed (MEDLINE), Embase, and Cochrane Central Register of Controlled Trials from inception to August 2024. The search strategy included the terms "Wallace", "Bricker", and "Urinary Diversion" in both "AND" and "OR" combinations to maximize the results obtained. The complete search strategy is detailed in Supplementary Methods 1. Two authors (F.R.C.S. and F.J.A-N.) independently screened titles and abstracts and fully evaluated the studies for eligibility. Duplicates identified through title, author, and journal comparison were removed prior to eligibility assessment. To identify additional literature, we conducted reference mining in the included studies. Discrepancies were settled in a discussion panel with a third author (C.R.A.).

Eligibility Criteria

We restricted the inclusion in this study to articles that met all the following eligibility criteria: (I) randomized clinical trials (RCTs) or cohort studies (prospective or retrospective); (II) studies that enrolled participants who underwent either the Bricker

or Wallace anastomosis techniques; (III) studies reported any outcomes of interest. Our exclusion criteria were studies published solely as conference abstracts; reviews; studies that were not written in English; studies with mixed populations where the data for Bricker and Wallace techniques could not be clearly separated.

Data extraction

Two authors (F.R.C.S and F.J.A-N.) conducted data extraction independently, following predefined search criteria and quality assessment. The data extracted included article characteristics (publication year, surgical indication, authors, country, follow-up), population characteristics (age, sex, BMI, intervention used, radiotherapy pelvic history), intervention characteristics (type of urinary diversion technique), and outcomes.

Outcomes and definitions

The efficacy prespecified outcomes were ureteroenteric stricture rates; unilateral ureteroenteric stricture rates, considering strictures affecting only the left or right ureteral unit; and bilateral ureteroenteric stricture rates, considering strictures occurring simultaneously on both the left and right ureteral units; time to stricture (in months); length of stay (LOS); urinary leakage rates; mean operative time (in minutes). The safety outcomes analyzed included electrolyte disturbance rates; blood transfusion rates; ileus rates; hydronephrosis rates. The analyses were stratified by comparison between Bricker technique group and Wallace technique group.

Statistical Analysis

All statistical analyses were performed using Review Manager 5.4.1. We employed Odds Ratio (OR) with 95% confidence interval (CI) as the measure of effect size to report binary outcomes. Mean Differences (MD) with 95% CI were used for continuous outcomes. Heterogeneity was assessed with the Cochran Q test and I^2 statistics. $I^2 \geq 50\%$ were considered significant for heterogeneity. We used

the Restricted Maximum Likelihood random-effects model (13). Sensitivity analyses, employing the leave-one-out approach, were conducted when significant heterogeneity was observed. We also performed a subgroup analysis based on patients without previous radiotherapy, patients undergoing ileal conduit urinary diversion, patients without previous radiotherapy who underwent ileal conduit urinary diversion, patients undergoing neobladder urinary diversion, and patients with bladder cancer.

Quality Assessment

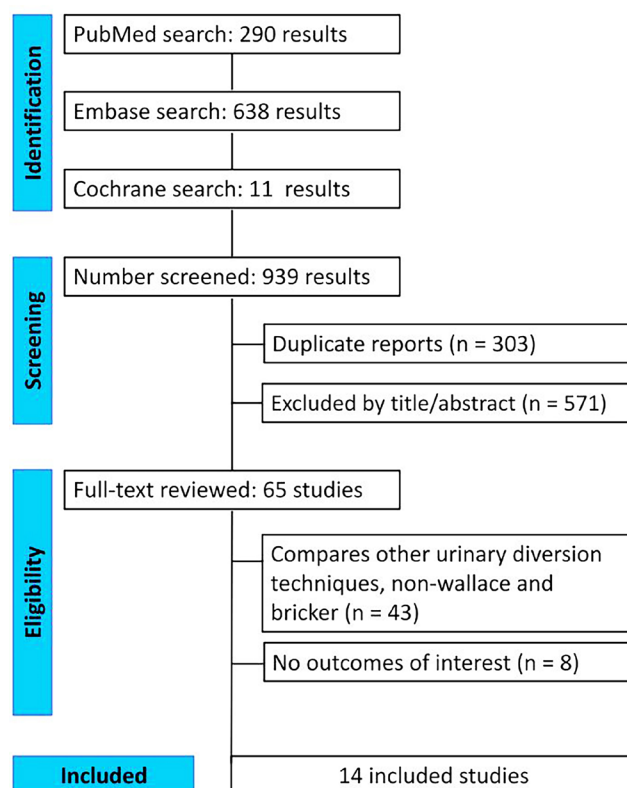
The risk of bias and quality assessment in non-randomized studies were evaluated with the Newcastle Ottawa Scale (NOS), which includes the following domains: selection, comparability, and exposure (14). Two independent authors (G.B.J.M and C.R.A) completed the risk of bias assessment. Disagreements were resolved through a consensus with a third author (F.J.A-N.). Studies scoring from 0 to 3, 4 to 6, and 7 to 9 were considered as low, moderate, and high quality, respectively.

RESULTS

Study Selection and Characteristics

After a search of the literature, 939 studies were found. From these, 636 studies were eligible for title and abstract screening after duplicate removal. Out of these, 65 studies were eligible for full-text screening. Finally, 14 studies were included in this meta-analysis (Figure-1) (15-28).

A total of 1,903 patients underwent urinary diversion, with 980 (51.5%) in the Bricker technique group and 923 (48.5%) in the Wallace technique group. The mean age in the Bricker group was 66.13 years, compared to 61.89 years in the Wallace group. The most common surgical procedure preceding these anastomoses was RC performed for bladder cancer, with the ileal conduit being the predominant type of urinary diversion. Detailed baseline characteristics of the included studies are summarized in Table-1. More information is provided in Supplementary Methods 2.

Figure 1 - Diagram showing the study selection process according to PRISMA guidelines.

The diagram illustrates the identification, screening, eligibility and inclusion of studies for the meta-analysis, resulting in 14 included studies.

Stricture analyses

The main analysis of stricture rates (patients with stricture relative total patients) was not significantly different between Bricker and Wallace techniques (OR 0.76; 95% CI 0.50 to 1.15; $p = 0.19$; $I^2 = 33\%$; Figure-2a). The analysis also indicated no statistical difference between groups when compared the occurrence of ureteral strictures relative to the total number of ureteral units (OR 0.53; 95% CI 0.08 to 3.38; $p = 0.50$; $I^2 = 74\%$; Figure-2b) and the occurrence of ureteral strictures relative to the total patient count (OR 0.73; 95% CI 0.30 to 1.80; $p = 0.50$; $I^2 = 79\%$; Figure-2c).

The analysis indicated no significant difference on bilateral stricture between Wallace group and Bricker group (OR 2.29; 95% CI 0.43 to 12.15; $p = 0.33$; $I^2 = 67\%$; Figure-3a), while in the Bricker technique there was a significant increase of unilat-

eral stricture (OR 0.47; 95% CI 0.30 to 0.75; $p < 0.01$; $I^2 = 0\%$; Figure-3b). The analysis of the median time to stricture revealed no significant difference across these groups (MD -0.57; 95% CI -1.85 to 0.71; $p = 0.39$; $I^2 = 0\%$; Figure-3c).

Other Efficacy Outcomes

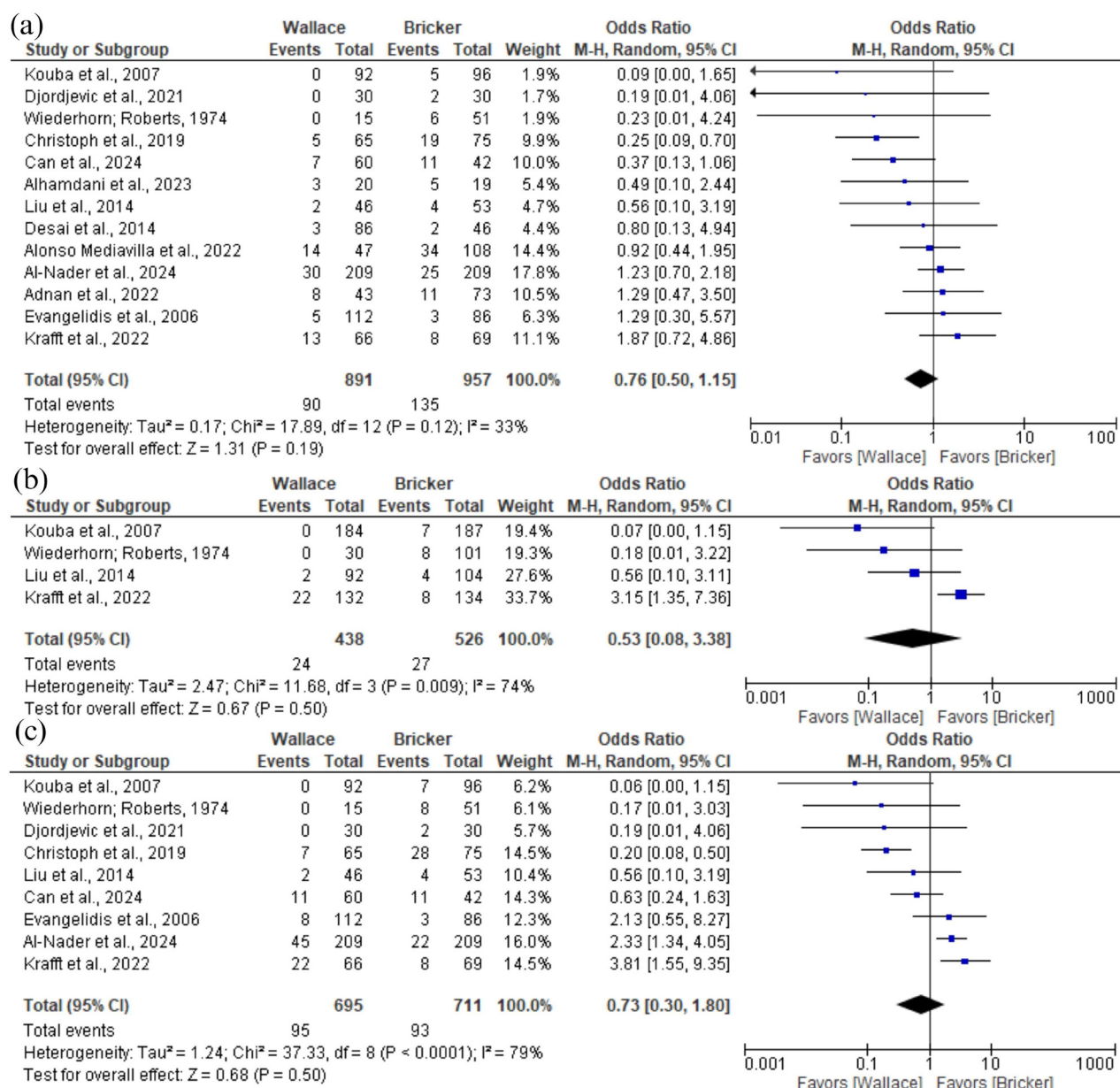
Our findings indicated that there was no significant difference in urinary leakage between the Bricker group and the Wallace group (OR 1.97; 95% CI 0.93 to 4.17; $p = 0.08$; $I^2 = 3\%$; Figure-4a). Likewise, LOS presented no significant difference between the techniques (MD 0.13; 95% CI -0.50 to 0.76; $p = 0.69$; $I^2 = 0\%$; Figure-4b). A pooled analysis of four studies, including 256 patients, showed that the Wallace group had a reduced operative time than the Bricker group (MD -19.98; 95% CI -39.76 to -0.20; $p = 0.05$; $I^2 = 64\%$; Figure-4c).

Table 1 - Baseline characteristics of included studies (Wallace / Bricker).

Study (Year)	Sample	Surgical indication	Male sex no. (%)	Mean / Median* age $\pm$ SD	Mean / Median* FU $\pm$ SD (months)	BMI $\pm$ SD	XRT pelvic history (%)
Adnan et al., 2022 (15)	43 / 73	RC for Bladder Cancer	33 (76.7) / 64 (87.7)	55 ($\pm$ 11) / 63.66 ($\pm$ 10.9)	48* (24-94) ^R	25.86 ($\pm$ 4.89) / 26.31 ($\pm$ 4.66)	8 (18.6) / 5 (6.8)
Al-Nader et al., 2021 (16)	209 / 209	RC for Bladder Cancer, cystectomy for others benign conditions or pelvic malignancies	172 (83.1) / 178 (86)	66.72 ($\pm$ 9.3) / 66.9 ($\pm$ 9)	25* (3-197) ^R / 25* (3-85) ^R	26.2 ($\pm$ 4.49) / 26.23 ($\pm$ 4.62)	16 (7.7) / 13 (6.2)
Alhamdani et al., 2023 (28)	20 / 19	Radical cystectomy and radical cystoprostatectomy for bladder cancer	13 (65) / 18 (94.7)	67.5* (61.5-71) ^{IR} / 67* (63-74) ^{IR}	12* (6.3-36) ^{IR} / 19* (4-33.8) ^{IR}	NA	2 (10) / 0
Can et al., 2024 (17)	60 / 42	RC for Bladder Cancer	52 (86.7) / 37 (88.1)	66* (32-81) ^R / 65* (40-75) ^R	20* (10-71) ^R / 18* (10-31) ^R	27 / 26	Exclusion criteria
Christoph et al., 2019 (18)	65 / 75	RC for Bladder Cancer	46 (70.8) / 50 (66.7)	71* / 71*	17* / 36.5*	26.4 / 26.2	Exclusion criteria
Desai et al., 2014 (19)	86 / 46	RC for Bladder Cancer	114 (86.4)	60 ($\pm$ 10)	25.1 ($\pm$ 25.9)	26.8 ($\pm$ 5.1)	NA
Djordjevic et al., 2021 (20)	30 / 30	RC with standard pelvic lymph node dissection	24 (80) / 22 (73.3)	68 ($\pm$ 6.6) / 63 ($\pm$ 7.2)	24	26.1 ($\pm$ 3.2) / 27.2 ($\pm$ 2.6)	Exclusion criteria
Evangelidis et al., 2006 (21)	112 / 86	Any patient undergoing Radical Cystectomy	78 (69.6) / 55 (64)	62 / 66	18.6 / 21.3	NA	14 (12.5) / 19 (22.1)
Kadoriku et al., 2024 (22)	32 / 23	Patients undergoing robotic-assisted intracorporeal ileal conduit urinary diversion	21 (65.6) / 18 (78.3)	73* (69-76) ^{IR} / 77* (75-81) ^{IR}	12	22.8* (20.7-25.3) ^{IR} / 24.2* (21.9-25.4) ^{IR}	0
Kouba et al., 2024 (23)	92 / 96	Cystectomy for bladder cancer	69 (75) / 75 (78.1)	66.7 ($\pm$ 12.2) / 66.3 ($\pm$ 11.9)	32.5 ($\pm$ 21.4) / 34.3 ($\pm$ 20.5)	25.9 ($\pm$ 5.4) / 29.0 ($\pm$ 6.3)	9 (10) / 15 (16)
Krafft et al., 2022 (24)	66 / 69	Cystectomy for any reason	48 (72.7) / 55 (69.7)	67.6 ($\pm$ 9) / 66.6 ($\pm$ 10.8)	16* (6-58) ^R / 14* (6-39) ^R	27 ($\pm$ 4.4) / 26.7 ($\pm$ 5.4)	6 (9.1) / 3 (4.3)
Liu et al., 2014 (25)	46 / 53	Radical cystectomy for transitional cell carcinoma	38 (82.6) / 44 (83)	62.7 ($\pm$ 8.6) / 61.9 ($\pm$ 9.0)	26.3 ($\pm$ 10) / 26.4 ($\pm$ 10.2)	23.5 ($\pm$ 1.3) / 23.3 ($\pm$ 1.9)	6 (13) / 5 (9.4)
Alonso Mediavilla et al., 2022 (26)	47 / 108	Patients undergoing urinary diversion employing small bowel	NA	NA	NA	NA	NA
Wiederhorn; Roberts, 1974 (27)	15 / 51	Patients with malignant or benign disease undergoing urinary diversion	NA	NA	29.8 / 34.17	NA	19 (28.79)

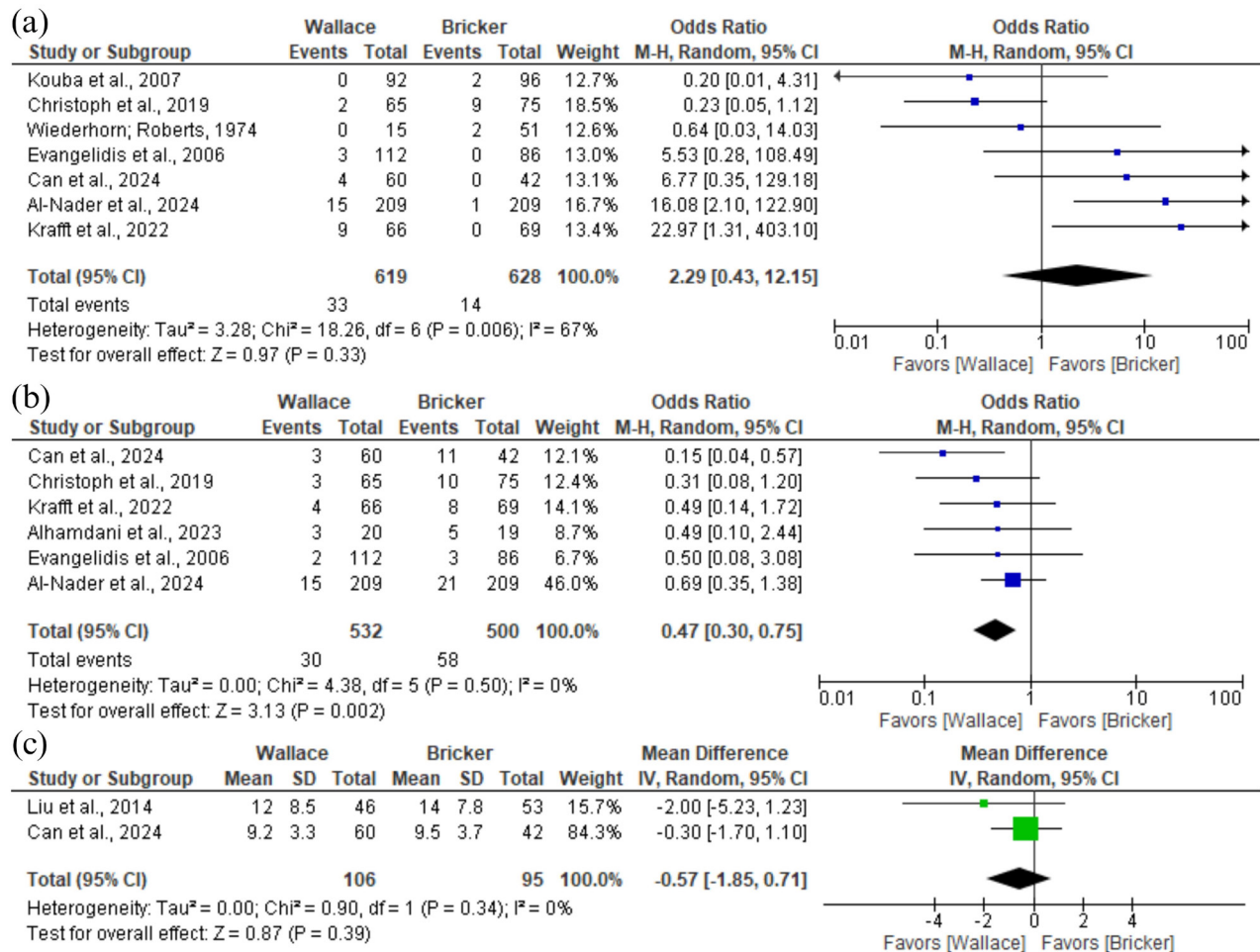
NA = not available; RC = Radical Cystectomy; SD = Standard deviation; Xrt = Radiation therapy; * = Median; ^R = Range; ^{IR} = Interquartile Range; FU = follow-up period

Figure 2 - Forest plot of stricture rates.



Forest plot for stricture rates in (a) patients with stricture per total patients, (b) ureteral stricture per total ureter units and (c) ureteral stricture per total patients.

Figure 3 - Forest plot of bilateral stricture, unilateral stricture and time to stricture (in months).



Forest plot for (a) patients with bilateral stricture per total patients, (b) patients with unilateral stricture per total patients and (c) median time to stricture, in months.

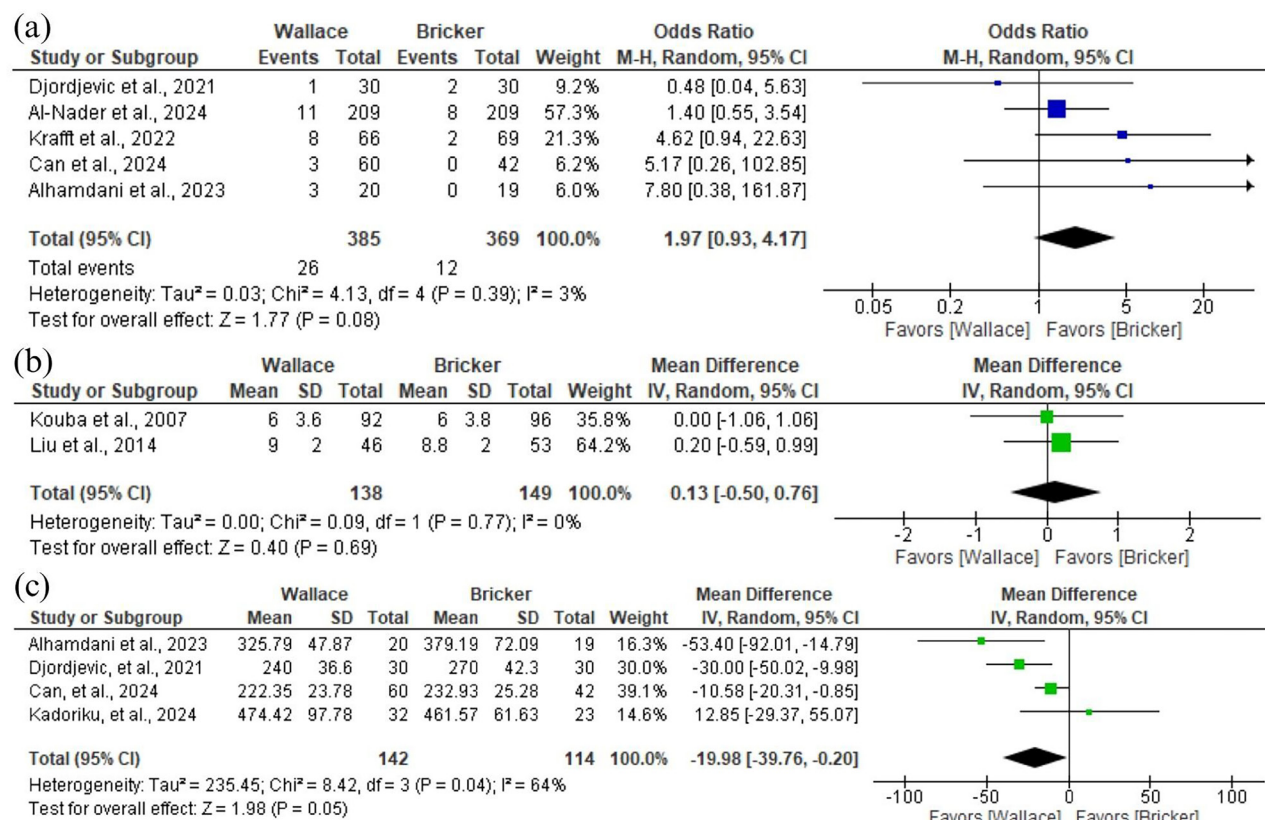
Safety outcomes

We also examined safety outcomes related to surgery and postoperative complications such as electrolyte disturbance (OR 0.72; 95% CI 0.26 to 1.97; $p = 0.52$; $I^2 = 48\%$; Figure-5a), blood transfusion (OR 0.80; 95% CI 0.55 to 1.16; $p = 0.24$; $I^2 = 0\%$; Figure-5b), ileus (OR 0.77; 95% CI 0.35 to 1.73; $p = 0.53$; $I^2 = 11\%$; Figure-5c). All of these analyses showed no significant difference between Wallace or Bricker groups.

However, the meta-analysis of three studies regarding hydronephrosis showed better results for the Wallace group (OR 0.37; 95% CI 0.17 to 0.79; $p < 0.05$; $I^2 = 0\%$; Figure-5d).

Subgroup analyses of Stricture rates

We conducted a subgroup analysis comparing stricture on different populations. Furthermore, the Wallace technique revealed significantly lower

Figure 4 - Forest Plot of Urinary Leak, LOS and Mean Operative Time.

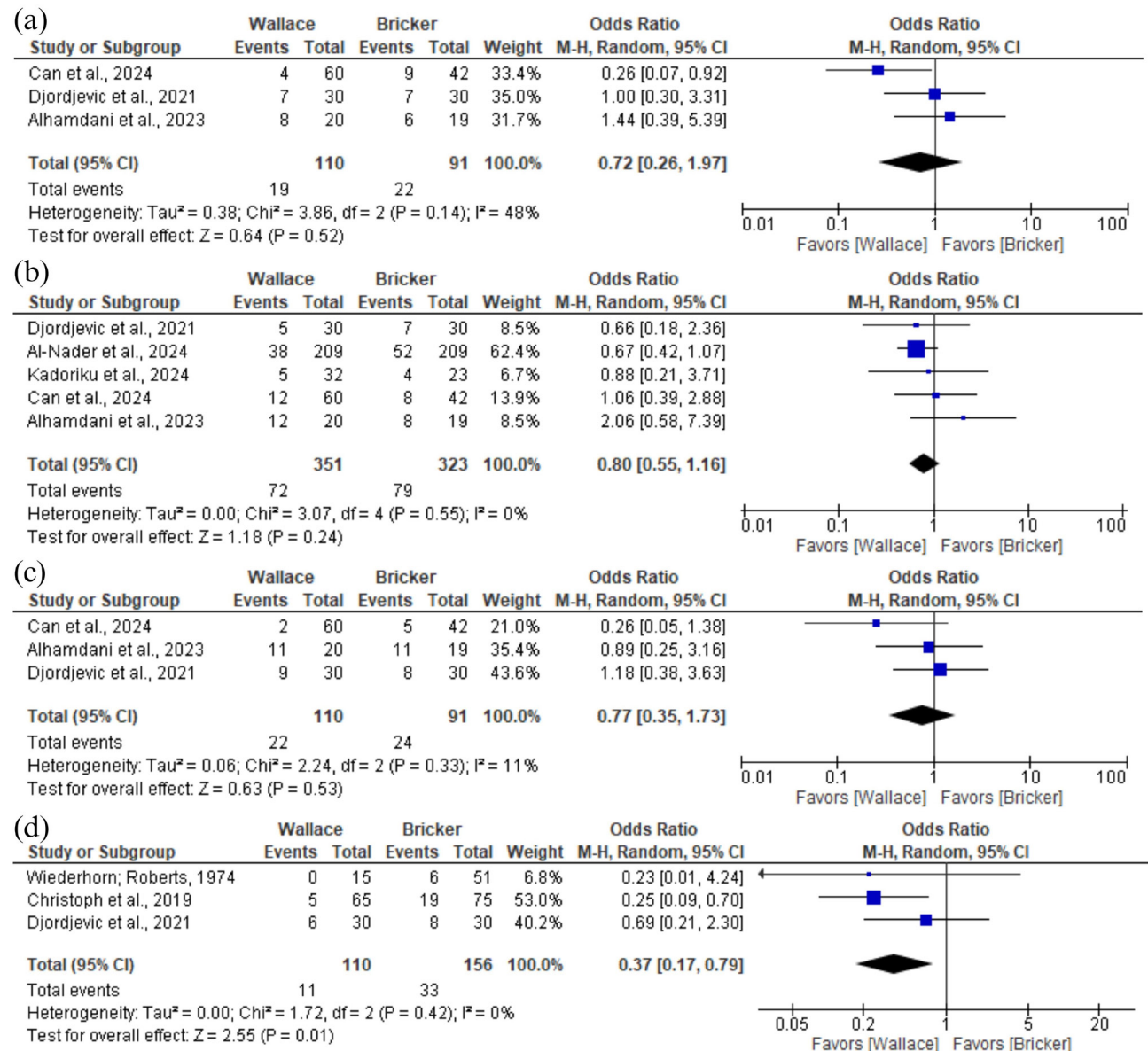
Forest plot for (a) urinary leakage occurrence, (b) LOS and (c) mean operative time, in minutes.

stricture rates compared to Bricker on patients who underwent ileal-conduit urinary diversion (OR 0.35; 95% CI 0.19 to 0.64; $p < 0.001$; $I^2 = 0\%$; Figure 6a), in those not previously subjected to radiotherapy (OR 0.29; 95% CI 0.14 to 0.61; $p < 0.001$; $I^2 = 0\%$; Figure-6b), and a combined analysis of both these subgroups (OR 0.30; 95% CI 0.14 to 0.64; $p < 0.01$; $I^2 = 0\%$; Figure-6c). There was no significant difference between these techniques in the patients diagnosed with bladder cancer (OR 0.59; 95% CI 0.34 to 1.04; $p = 0.07$; $I^2 = 40\%$; Figure-6d), and in patients who underwent neobladder urinary diversion (OR 0.55; 95% CI 0.11 to 2.62; $p = 0.45$; $I^2 = 0\%$; Figure 6e). The summary of findings in this meta-analysis are shown in Table-2.

Sensitivity analyses

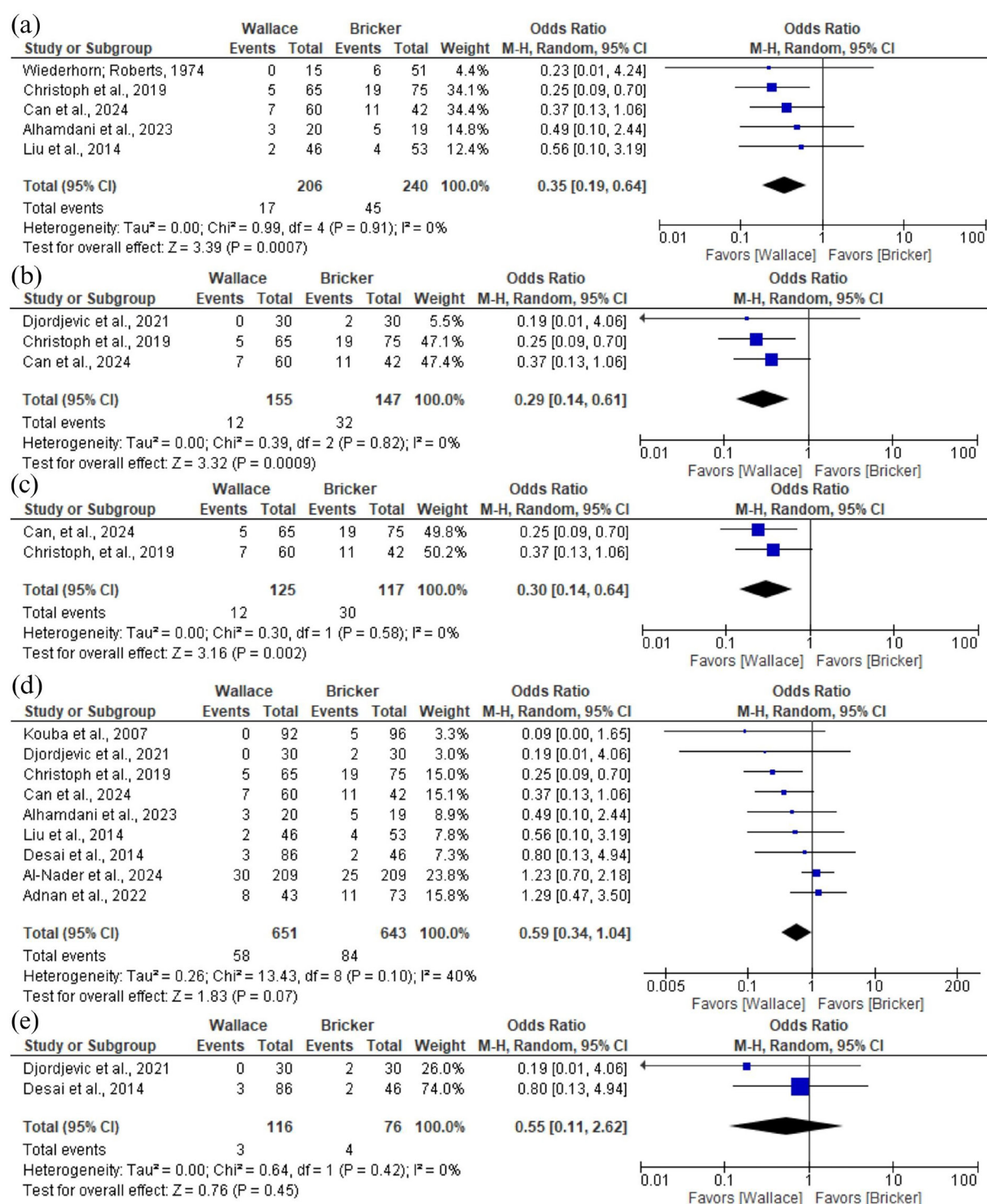
The occurrence of ureteral strictures relative to the total number of ureteral units presented a high heterogeneity. The heterogeneity was resolved after excluding Krafft et al. ($I^2 = 0\%$), with a significant result favoring the Wallace group (Supplementary Methods 4). Even after the leave-one-out approach, heterogeneity remained high when considering the occurrence of ureteral strictures relative to the total patient count ($I^2 = 65\%$) (Supplementary Methods 5). For the bilateral stricture rates, the omission of the study Christoph et al. reduced the heterogeneity present to 40% (Supplementary Methods 6), yet the out-

Figure 5 - Forest plot of safety outcomes.



Forest plot for (a) electrolyte disturbance rates, (b) blood transfusion rates, (c) ileus rates and (d) hydronephrosis rates.

Figure 6. Forest plot of subgroup analysis.



Forest plots for patients with stricture per total patients in (a) patients who underwent ileal-conduit urinary diversion, (b) those not previously subjected to radiotherapy, (c) patients without previous radiotherapy who underwent ileal conduit urinary diversion, (d) patients diagnosed with bladder cancer and (e) patients who underwent neobladder urinary diversion.

Table 2 - Pooled outcomes of Wallace urinary diversion compared to Bricker urinary diversion.

Outcomes and subgroup analysis	Effect Size (95% CI)	P value	I ²	No. of Studies	No. of Patients (Wallace vs Bricker)
Stricture rates (patients with stricture relative total patients)	OR 0.76 (0.50-1.15)	0,19	33%	13	891 vs 957
Stricture rates (ureteral stricture relative total ureter units)	OR 0.53 (0.08-3.38)	0,5	74%	4	438 vs 526
Stricture rates (ureteral stricture relative total patients)	OR 0.73 (0.30-1.80)	0,5	79%	9	695 vs 711
Bilateral stricture	OR 2.29 (0.43-12.15)	0,33	67%	7	619 vs 628
Unilateral strictures	OR 0.47 (0.30-0.75)	<0,01	0%	6	532 vs 500
Median time to stricture (in months)	MD -0.57 (-1.85-0.71)	0,39	0%	2	106 vs 95
Urinary leakage occurrence	OR 1.97 (0.93-4.17)	0,08	3%	5	385 vs 369
Length of Stay	MD 0.13 (-0.50-0.76)	0,69	0%	2	138 vs 149
Mean operative time (in minutes)	MD -19.98 (-39.76--0.20)	0,05	64%	4	142 vs 114
Electrolyte disturbance rates	OR 0.72 (0.26-1.97)	0,52	48%	3	110 vs 91
Blood transfusion rates	OR 0.80 (0.55-1.16)	0,24	0%	5	351 vs 323
Ileus rates	OR 0.77 (0.35-1.73)	0,53	11%	3	110 vs 91
Hydronephrosis rates	OR 0.37 (0.17-0.79)	<0,05	0%	3	110 vs 156
Stricture rates in patients who underwent ileal-conduit urinary diversion	OR 0.35 (0.19-0.64)	<0,001	0%	5	206 vs 240
Stricture rates in patients not previously subjected to radiotherapy	OR 0.29 (0.14-0.61)	<0,001	0%	3	155 vs 147
Stricture rates in patients without previous radiotherapy who underwent ileal conduit urinary diversion	OR 0.30 (0.14-0.64)	<0,01	0%	2	125 vs 117
Stricture rates in patients diagnosed with bladder cancer	OR 0.59 (0.34-1.04)	0,07	40%	9	651 vs 643
Stricture rates in patients who underwent neobladder urinary diversion	OR 0.55 (0.11-2.62)	0,45	0%	2	116 vs 76

OR = odds ratio; MD = Mean difference; No. = Number.

come still showed no difference between Wallace and Bricker groups. Finally, after performing a leave-one-out sensitivity analysis, the Wallace technique no longer maintained its superiority over Bricker, while heterogeneity remained considerable ($I^2 = 55\%$) (Supplementary Methods 7).

Quality assessment

A summary of the risk of bias assessment is provided in Supplementary Methods 3. Of the fourteen included studies, seven had a low risk of bias, six were evaluated as moderate, and one had a high risk of bias. The outcome domain showed strong performance, with most studies employing robust methods to assess outcomes and ensuring sufficient follow-up time. Overall, the studies exhibited high or moderate scores across all domains.

DISCUSSION

In this systematic review and meta-analysis of 14 studies and 1,903 patients, we evaluated the comparative efficacy and safety between patients who underwent urinary diversion using the Wallace or Bricker technique. One of the key findings was that: (I) both techniques demonstrated similar results regarding main analyses of stricture rates (patients with stricture relative total patients; ureteral stricture relative total ureter units; and ureteral stricture relative total patients). Additionally, to our knowledge, this is the first meta-analysis to compare efficacy and safety outcomes, excluding stricture rates, between the Bricker and Wallace techniques. The findings listed below represent novel contributions to the field: (I) there were fewer occurrences of unilateral strictures, and the operative time was shorter in the Wallace group; (II) we showed no significant differences between the techniques in terms of bilateral stricture, urinary leakage, median time to stricture, LOS, ileus, hydronephrosis, electrolyte disturbance, blood transfusion; (III) the subgroup analysis showed that the Wallace technique was favored in patients who underwent ileal-conduit urinary diversion and patients not previously subjected to radiotherapy, and

patients with both conditions simultaneously; (IV) no significant differences were observed between the techniques in patients diagnosed with bladder cancer or patients who underwent neobladder urinary diversion.

Bladder replacement with an ileal conduit is a common procedure following cystectomy for bladder cancer (29). Bricker (7) standardized this technique, while Wallace (8) later proposed a modification that involves joining the ureters into a single confluence before attaching them to the conduit. Although Wallace's approach is considered more time-efficient (16), the Bricker technique remains the preferred choice for many surgeons, largely due to familiarity and personal preference (6). A previous meta-analysis, however, has not demonstrated a clear advantage of one technique over the other (10). One of the first comparative studies, conducted in 1974, suggested a lower risk of postoperative complications with Wallace's technique, though potential bias exists due to imbalanced sample sizes (27). However, to this day, the lack of randomized studies on the subject remains a significant limitation, hindering a reliable comparison between these techniques, as retrospective studies are inherently more prone to bias (11).

Although the pathophysiology of strictures remains unclear, it is a critical factor in determining postoperative outcomes, as it can significantly impact patient quality of life (30). The etiology of strictures varies, with technical errors and tissue edema being common causes (31). In addition, a previous meta-analysis (10), suggested that the choice of technique may not significantly influence its specific outcome. Similarly, our analyses revealed no statistically significant differences in the overall stricture rates between the Bricker and Wallace techniques, consistent across various metrics. First, the proportion of patients with strictures offers a clear and straightforward interpretation of the frequency of complications. Second, the incidence of ureteral strictures relative total ureter units allows for a more detailed evaluation by considering the number of ureteral units at risk. Lastly, the occurrence of ureteral strictures relative to total patients offers a global perspective of the

techniques impact of the entire patient population. The use of three distinct metrics strengthens the evidence by offering a more comprehensive analysis.

Nevertheless, the equivalence in overall stricture rates reinforces the notion that the choice of technique should be primarily guided by the surgeon's preference and expertise, as well as tailored to the clinical features of each individual patient (25). However, despite the persistence of high heterogeneity in the sensitivity analysis of ureteral strictures relative to total patients, the analysis based on total ureter units showed significantly lower stricture rates in the Wallace group. While this finding suggests a potential advantage of the Wallace technique, the observational design of the included studies limits the ability to draw firm conclusions regarding causality.

The analysis of the laterality of stenosis highlights the importance of understanding the fundamental principles of each technique. While earlier concerns regarding bilateral strictures in the Wallace technique (24) or higher unilateral stricture rates in the Bricker technique have been noted in smaller studies (23), our results showed the slightly higher incidence of unilateral strictures observed in Bricker compared to Wallace. These findings align with the results of previous retrospective studies, as all studies included in this analysis reported a higher number of patients with unilateral strictures in the Bricker group than Wallace group (17, 18, 21, 24, 28). In the analysis of bilateral strictures, some studies suggest that the Wallace technique might result in a higher incidence of bilateral strictures compared to the Bricker technique (16, 22-25). However, we found no significant difference in the incidence of bilateral strictures between the two techniques, including in the sensitivity analysis. Furthermore, our study demonstrated no significant difference in the median time to stricture formation between the groups, consistent with findings reported in the literature (17, 32).

Urinary leakage is recognized as a risk factor for the development of ureteroenteric strictures (UES) and is one of the primary postoperative complications associated with urinary diversion (33). In our study, no significant difference in urinary leak-

age rates was observed between the techniques. Electrolyte disturbances and urine stasis may be associated with modified Bricker techniques or other approaches that involve a larger intestinal segment in an attempt to reduce UES rates (17). In addition, patients undergoing urinary diversion, and with advanced pelvic malignancies, appear to experience greater surgical complexity, a higher incidence of hydronephrosis, and an increased risk for UES development (16). Likely, in our analysis, the Wallace technique demonstrated significantly greater safety for hydronephrosis, aligning with findings from a study conducted in 1974 (27).

Regarding the complexity of selecting the UEA type, the studies included in this analysis consistently showed that the choice of technique was strongly influenced by the surgeon's personal preference and expertise, a pattern also supported by previous meta-analysis (10). Additionally, when performing cystectomies and urinary diversions, institutional factors specific to each center may impact operative outcomes (34, 35). In this context, one of the outcomes known to be influenced by institutional volume and experience is operative time (34), which, in relation to the choice of UEA technique, was shorter in the Wallace group according to our analysis (17, 20, 22, 28). Furthermore, the sensitivity analysis of this outcome revealed no significant difference between the techniques (17, 20, 22), with consistently high heterogeneity remaining unresolved. On the other hand, in the current study, the LOS was comparable, with no significant differences between the two techniques across all included studies (17, 23, 25, 28). Similarly, other outcomes, such as blood transfusion rates (16, 17, 20, 22, 28) and ileus incidence (17, 20, 28), showed no significant differences.

Additionally, our subgroup analyses provide a more in-depth examination of patient-specific factors, such as the influence of prior radiotherapy history, previous diagnoses, and the type of urinary diversion, which were not explored in previous meta-analysis (10). Despite the absence of clear recommendations regarding the ideal type of urinary diversion following cystectomy for bladder cancer (17) and the

two established UEA techniques (10, 17) discussed in this study, our findings suggest no advantage of one technique over the other in these patients. Regarding urinary diversion types, the ileal conduit has been recognized for decades as one of the most widely adopted gold-standard techniques worldwide (22, 36). When analyzing this subgroup in the present study, our results found a lower likelihood of UES development when the Wallace technique was used in association with the ileal conduit. This finding holds critical importance, as the ileal conduit remains one of the most performed urinary diversions in clinical practice and is closely associated with patient outcomes (37). Conversely, in patients undergoing neobladder urinary diversion, a technique known for providing superior functional outcomes and quality of life (1), despite its more complex surgical execution and higher complication rates (19); in our analysis no significant differences were observed between the Bricker and Wallace techniques.

Moreover, a prior meta-analysis reported no difference in UES rates among patients with or without history of radiation therapy (10). Our results found that studies excluding patients with a history of radiotherapy demonstrated significantly lower UES rates when using the Wallace technique for UEA, with more stricture rates in the Bricker group. Additionally, supporting this observation, the subgroup analysis restricted patients without previous radiotherapy who underwent ileal conduit urinary diversion also favored the Wallace group. These findings underscore the importance of tailoring surgical techniques to a patient's specific needs and clinical context; more precisely, the selection of the method should consider the planned urinary diversion and the patient's prior radiotherapy, rather than applying a one-size-fits-all approach.

This systematic review and meta-analysis have limitations that should be acknowledged: (I) the absence of RCTs among the included studies represents a significant limitation, as observational and retrospective cohort designs are more susceptible to bias; (II) among the included studies, we identified differences in patient populations, including varia-

tions in diagnoses, disease severity and preoperative conditions, which may have influenced the reported outcomes; (III) small sample size in specific subgroups, such as patients undergoing neobladder urinary diversion, reduced the robustness of subgroup analyses; (IV) differences in surgical outcomes may reflect variability in surgeon expertise or institutional protocols, factors that were not consistently reported or controlled; (V) the criteria for allocating participants to the Wallace and Bricker groups varied among the included studies, potentially influencing reported outcomes; and (VI) late complications might have been underrepresented, given the relatively short follow-up of many included studies.

CONCLUSIONS

Our findings indicate no significant differences in main analyses of stricture rates, median time to stricture, LOS, urinary leakage, bilateral stricture, electrolyte disturbances, blood transfusion, and ileus between the techniques examined, suggesting that the choice of approach should primarily be guided by the surgeon's judgment, experience, and the patient's unique clinical profile. However, in the laterality analysis, unilateral strictures appear to be more commonly associated with the Bricker technique, since the Wallace technique exhibited lower rates of UES. The Wallace technique also demonstrated advantages, including lower rates of UES in patients who underwent ileal conduit urinary diversion, without a history of radiotherapy and reduced rates of hydronephrosis.

For clinical practice, our subgroup results provide valuable information for individualized surgical selection. Therefore, beyond surgeon preference, the choice of technique should consider the patient's history of radiotherapy, and the type of urinary diversion planned, aiming to optimize postoperative outcomes and minimize the risk of specific complications. Recognizing the limitations of this study, larger and higher-quality randomized trials are necessary to more comprehensively evaluate the efficacy and safety of the Bricker and Wallace techniques.

ABBREVIATION LIST

BMI = Body Mass Index

CI = Confidence Interval

LOS = Length of Stay

MD = Mean Differences

OR = Odds Ratio

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO = International prospective register of systematic reviews

RC = Radical Cystectomy

RCT = Randomized Clinical Trials

SD = Standard deviation

UEA = Ureteroenteric Anastomosis

UES = Ureteroenteric Stricture

ADDITIONAL INFORMATION

Any additional information is available upon request from the corresponding author.

CONFLICT OF INTEREST

None declared.

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APPENDIX

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Supplementary Methods 1 - Details of the search strategy according to the database.

Database	Search strategy
PubMed/ MEDLINE	("Wallace" AND "Urinary Diversion"[mh]) OR ("Bricker" AND "Urinary Diversion"[mh]) OR ("Wallace" AND "Bricker")
Embase	('wallace'/exp OR 'wallace') AND ('urinary diversion'/exp OR 'urinary diversion') OR ('bricker' AND ('urinary diversion'/exp OR 'urinary diversion')) OR (('wallace'/exp OR 'wallace') AND 'bricker')
Cochrane	("Wallace" AND "Urinary Diversion") OR ("Bricker" AND "Urinary Diversion") OR ("Wallace" AND "Bricker")

Supplementary Methods 2 - Baseline characteristics of included studies (Wallace / Bricker).

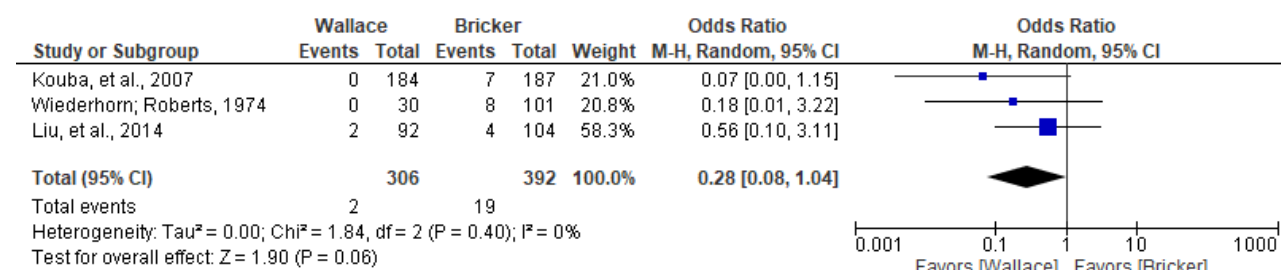
Study (Year)	Country	Sample	Surgical indication	Types of urinary diversion	Male sex no. (%)	Mean / Median* age $\pm$ SD	Mean / Median* FU $\pm$ SD (months)	BMI $\pm$ SD	XRT pelvic history (%)
Adnan et al., 2022 (15)	Pakistan	43 / 73	RC for Bladder Cancer	Ileal conduit and Orthotopic neobladder	33 (76.7) / 64 (87.7)	55 ($\pm$ 11) / 63.66 ($\pm$ 10.9)	48* (24-94) ^{IR}	25.86 ($\pm$ 4.89) / 26.31 ($\pm$ 4.66)	8 (18.6) / 5 (6.8)
Al-Nader et al., 2021 (16)	Germany	209 / 209	RC for Bladder Cancer, cystectomy for others benign conditions or pelvic malignancies	Ileal conduit, Orthotopic bladder substitution or Continent cutaneous diversion	172 (83.1) / 178 (86)	66.72 ($\pm$ 9.3) / 66.9 ($\pm$ 9)	25* (3-197) ^{IR} / 25* (3-85) ^{IR}	26.2 ($\pm$ 4.49) / 26.23 ($\pm$ 4.62)	16 (7.7) / 13 (6.2)
Alhamdani et al., 2023 (28)	Australia	20 / 19	Radical cystectomy and radical cystoprostatectomy for bladder cancer	Ileal conduit	13 (65) / 18 (94.7)	67.5* (61.5-71) ^{IR} / 67* (63-74) ^{IR}	12* (6.3-36) ^{IR} / 19* (4-33.8) ^{IR}	NA	2 (10) / 0
Can et al., 2024 (17)	Turkey	60 / 42	RC for Bladder Cancer	Ileal conduit	52 (86.7) / 37 (88.1)	66* (32-81) ^{IR} / 65* (40-75) ^{IR}	20* (10-71) ^{IR} / 18* (10-31) ^{IR}	27 / 26	Exclusion criteria
Christoph et al., 2019 (18)	Germany	65 / 75	RC for Bladder Cancer	Ileal conduit	46 (70.8) / 50 (66.7)	71* / 71*	17* / 36.5*	26.4 / 26.2	Exclusion criteria
Desai et al., 2014 (19)	Sweden/ USA	86 / 46	RC for Bladder Cancer	Robotic intracorporeal ileal neobladder	114 (86.4)	60 ($\pm$ 10)	25.1 ($\pm$ 25.9)	26.8 ($\pm$ 5.1)	NA
Djordjevic et al., 2021 (20)	Serbia	30 / 30	RC with standard pelvic lymph node dissection	Hautmann neobladder with single chimney and Bricker / Hautmann neobladder with chimney modification and Wallace	24 (80) / 22 (73.3)	68 ($\pm$ 6.6) / 63 ($\pm$ 7.2)	24	26.1 ($\pm$ 3.2) / 27.2 ($\pm$ 2.6)	Exclusion criteria
Evangelidis et al., 2006 (21)	USA	112 / 86	Any patient undergoing Radical Cystectomy	Ileal conduit, Continent urinary reservoir or Neobladder	78 (69.6) / 55 (64)	62 / 66	18.6 / 21.3	NA	14 (12.5) / 19 (22.1)
Kadoriku et al., 2024 (22)	Japan	32 / 23	Patients undergoing robotic-assisted intracorporeal ileal conduit urinary diversion	robot-assisted intracorporeal ileal conduit urinary diversion	21 (65.6) / 18 (78.3)	73* (69-76) ^{IR} / 77* (75-81) ^{IR}	12	22.8* (20.7-25.3) ^{IR} / 24.2* (21.9-25.4) ^{IR}	0
Kouba et al., 2024 (23)	USA	92 / 96	Cystectomy for bladder cancer	Ileal conduit or Ileal neobladder	69 (75) / 75 (78.1)	66.7 ($\pm$ 12.2) / 66.3 ($\pm$ 11.9)	32.5 ($\pm$ 21.4) / 34.3 ($\pm$ 20.5)	25.9 ($\pm$ 5.4) / 29.0 ($\pm$ 6.3)	9 (10) / 15 (16)
Krafft et al., 2022 (24)	Germany	66 / 69	Cystectomy for any reason	Ileal conduit, Orthotopic bladder substitute or Continent cutaneous diversion	48 (72.7) / 55 (69.7)	67.6 ($\pm$ 9) / 66.6 ($\pm$ 10.8)	16* (6-58) ^{IR} / 14* (6-39) ^{IR}	27 ($\pm$ 4.4) / 26.7 ($\pm$ 5.4)	6 (9.1) / 3 (4.3)
Liu et al., 2014 (25)	China	46 / 53	Radical cystectomy for transitional cell carcinoma	Ileal conduit	38 (82.6) / 44 (83)	62.7 ($\pm$ 8.6) / 61.9 ($\pm$ 9.0)	26.3 ($\pm$ 10) / 26.4 ($\pm$ 10.2)	23.5 ($\pm$ 1.3) / 23.3 ($\pm$ 1.9)	6 (13) / 5 (9.4)
Alonso Mediavilla et al., 2022 (26)	Spain	47 / 108	Patients undergoing urinary diversion employing small bowel	Ileal conduit or Neobladder	NA	NA	NA	NA	NA
Wiederhorn; Roberts, 1974 (27)	USA	15 / 51	Patients with malignant or benign disease undergoing urinary diversion	Ileal conduit	NA	NA	29.8 / 34.17	NA	19 (28.79)

NA = not available; RC = Radical Cystectomy; SD = Standard deviation; Xrt = Radiation therapy; * = Median; IR = Interquartile Range; FU = Follow-up period.

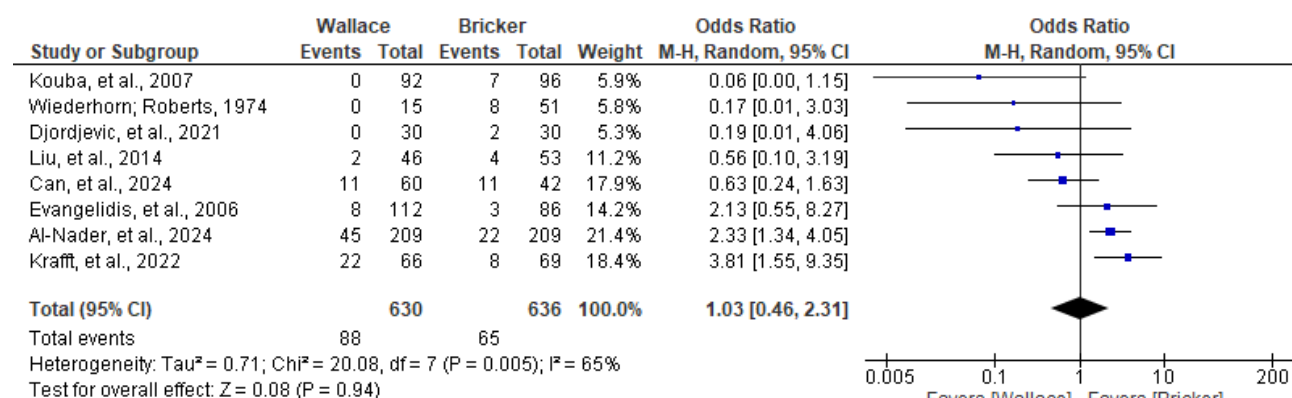
Supplementary Methods 3 - Newcastle-Ottawa Scale (NOS) assessment of non-randomized trials.

Study	Selection			Comparability			Outcome		Total (9/9)
	Representa tive of the exposed cohort	Selection of external control	Ascertain ment of exposure	Outcome of interest not present at the start of the study	Main factor	Additional factor	Assessment of outcomes	Sufficient follow- up time	
Adnan et al., 2022 (15)	*	*	*	*			*	*	5/9
Al-Nader et al., 2021 (16)	*	*	*	*			*	*	5/9
Alhamdani et al., 2023 (28)	*	*	*	*	*		*	*	6/9
Can et al., 2024 (17)	*	*	*	*	*	*	*	*	7/9
Christoph et al., 2019 (18)	*	*	*	*	*		*	*	6/9
Desai et al., 2014 (19)	*	*	*	*	*		*	*	6/9
Djordjevic et al., 2021 (20)	*	*	*	*	*	*	*	*	6/9
Evangelidis et al., 2006 (21)	*	*	*	*	*	*	*	*	8/9
Kadoriku et al., 2024 (22)	*	*	*	*	*	*	*	*	7/9
Kouba et al., 2024 (23)	*	*	*	*	*	*	*	*	7/9
Krafft et al., 2022 (24)	*	*	*	*	*	*	*	*	7/9
Liu et al., 2014 (25)	*	*	*	*	*	*	*	*	7/9
Alonso Mediavilla et al., 2022 (26)	*			*				*	3/9
Alhamdani et al., 2023 (28)	*		*	*	*	*	*	*	7/9

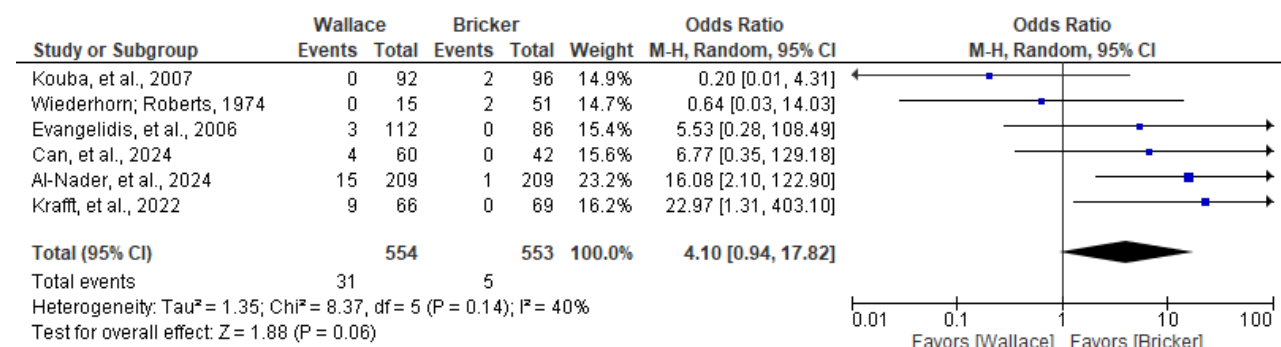
Supplementary Methods 4 - Sensitivity analysis of Ureteral strictures relative to the total number of ureteral units.



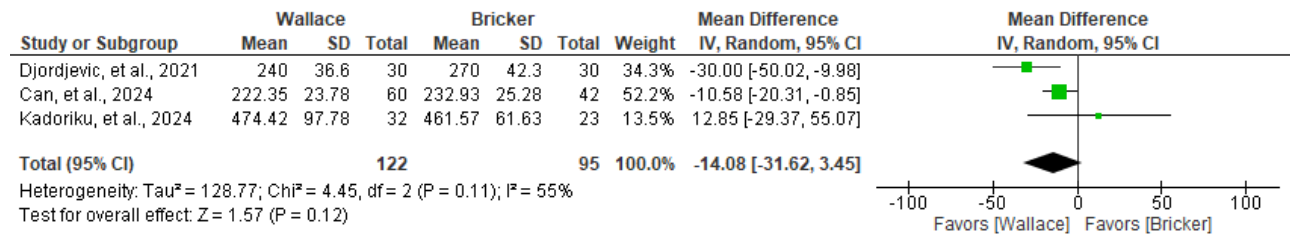
Supplementary Methods 5 - Sensitivity analysis of Ureteral strictures relative to the total patient count.



Supplementary Methods 6 - Sensitivity analysis of Bilateral stricture.



Supplementary Methods 7 - Sensitivity analysis of Mean operative time.





Infection Prophylaxis in Urological Diagnostic and Surgical Procedures – A narrative review and Recommendations

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ABSTRACT

Objectives: In this review we will provide recommendations for surgical site infection (SSI) prophylaxis in urological diagnostic and surgical procedures.

Material and Methods: We performed a narrative review of the literature in PubMed (Medline), EMBASE, LILACS, Web of Science, and Cochrane Collaboration databases using the terms "infection," "surgery," "urology," and "antibiotic prophylaxis"

Results: We suggest recommendations of prophylactic antibiotic in the follow procedures: prostate biopsy, Urethrocystoscopy, Extracorporeal Shock Wave Lithotripsy (ESWL) for Urinary Stones, endoscopic ureterolithotripsy, percutaneous nephrolithotomy, Transurethral Resection of the Prostate (TURP) and Prostatic Enucleation, Transurethral Resection of Bladder Tumor (TURBT), Intravesical Botulinum Toxin Injection, surgical correction of female stress incontinence, Surgical Correction of Pelvic Organ Prolapse, urological prosthesis implantation and Open, Laparoscopic, and Robotic Urologic Surgery

Conclusions: Consideration in SSI prophylaxis and the prophylactic antibiotic regimens in several urological procedures are show in this paper and will be useful to urologic practice.

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INTRODUCTION

Surgical site infection (SSI) affects the incision, organ, or space involved in an operative procedure. The incidence ranges from 0.5% to 15% in surgical patients and can reach up to 38% in some studies (1-3). Several factors influence the risk of SSI, including the degree of procedure contamination, preoperative hair removal, operative time, patient comorbidities, overall health status, and proper antibiotic prophylaxis. Implementing evidence-based preventive measures can prevent approximately half of SSIs (1, 4).

General preventive measures include stringent operating room hygiene, instrument sterilization, restriction of unnecessary personnel movement in the operating room, and proper surgical attire, which are beyond the scope of this manuscript. SSI prophylaxis specific to patient care includes both non-antibiotic and antibiotic measures. While antibiotics are crucial in reducing surgical infections, non-antibiotic measures—many historically adopted in surgical practice before being validated by clinical trials—remain equally essential.

A critical consideration in SSI prophylaxis is the rising rate of bacterial resistance to antibiotics, now recognized as a public health concern. This has prompted the World Health Organization (WHO) to advocate for urgent implementation of antimicrobial stewardship programs to optimize antibiotic use.

This document aims to provide recommendations for SSI prophylaxis in urological diagnostic and surgical procedures.

MATERIALS AND METHODS

Key topics were determined through a consensus meeting among the authors to develop the recommendations, followed by a literature review. PubMed (Medline), EMBASE, LILACS, Web of Science, and Cochrane Collaboration databases were searched using the terms "infection," "surgery," "urology," and "antibiotic prophylaxis." Articles published exclusively in English from 2012–2024 were initially

screened by title and abstract, and selected for full-text screening if they met inclusion criteria defined by the purpose of the review. Additional relevant publications were identified through reference list screening of the selected studies. Studies published before 2012 were included if they contained relevant concepts or data not covered by more recent studies.

The recommendations were developed following the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) system, by the Ministry of Health's guidelines. Under the GRADE framework, the level of evidence is classified as high, moderate, low, or very low, while the strength of the recommendation is categorized as strong or weak. Each recommendation is accompanied by its corresponding GRADE assessment, presented as (GRADE: level of evidence, strength of recommendation) (5). In cases where the authors disagreed about the strength of a recommendation, the majority consensus was adopted. The lowest grade was chosen when the literature provided varying grades of recommendation for different aspects of a procedure.

RESULTS

General Aspects of Surgical Infection Prophylaxis

Non-Antibiotic Measures for Surgical Infection Prophylaxis

Glycemic Control: Preoperative glycemic control is one of the most critical parameters for reducing the risk of SSIs. The U.S. Centers for Disease Control and Prevention (CDC) recommends maintaining blood glucose levels below 200 mg/dL in both diabetic and non-diabetic patients (1, 6, 7). A meta-analysis proposed a stricter threshold of 150 mg/dL for both groups, although this approach carries a higher risk of hypoglycemia (8). Compared to conventional glycemic control protocols, intensive perioperative insulin regimens have been shown to reduce SSI incidence in cardiac and abdominal surgeries (7).

Preoperative Bathing: Among antiseptic practices aimed at reducing infection risk, bathing with soap and water effectively removes transient mi-

crobiota and inactivates skin flora, lowering the risk of SSI by threefold (9). However, the effectiveness of a 4% chlorhexidine gluconate antiseptic solution in preoperative bathing has not been demonstrated when compared to placebo, non-medicated soaps, or the absence of bathing (4, 10). Therefore, full-body washing with a soap-based solution—whether or not it contains an antimicrobial agent or antiseptic—is considered good practice and is widely encouraged in the literature. It is recommended at least on the night before surgery. Studies have yet to determine the precise benefits, the optimal time interval between bathing and surgery, or the ideal number of preoperative baths (1).

Hair Removal: There is no formal recommendation regarding hair removal at the surgical incision site, despite its routine use in clinical practice (11). A meta-analysis by the Cochrane Collaboration found no significant difference in SSI risk between no hair removal, chemical depilation, and clipping (12). However, shaving with a razor was associated with a higher risk of infection (13). Another meta-analysis found no significant differences between shaving, clipping, no hair removal and depilatory cream in the frequency of surgical site infections (14). Regarding the timing of hair removal, no difference in infection risk was observed whether it was performed the day before or on the day of surgery (12).

Antisepsis: The risk of SSI in clean surgeries ranges from 0.6% to 5%. The primary source of contamination in clean procedures is the patient's skin microbiota. There are no comparative studies evaluating the effectiveness of performing antisepsis versus omitting it. A meta-analysis comparing alcohol-based solutions with aqueous solutions of chlorhexidine and iodine-based agents demonstrated superior performance for alcohol-based solutions (1). Among alcohol-based solutions, 0.5% chlorhexidine was more effective than povidone-iodine, although this conclusion was based on a single study with a high risk of bias (15). No evidence supports the reapplication of the antiseptic solution at the end of the procedure or the use of antimicrobial sealants on the skin after intraoperative antisepsis (1, 16). System-

atic reviews and meta-analyses have found no benefit in using adhesive incise drapes, whether coated with povidone-iodine (PVPI) or not, compared to their omission (17, 18).

Surgical Site Irrigation: There is no significant difference in SSI rates with or without irrigation of the incised surgical site (19). The use of iodophor-based aqueous solutions for peritoneal lavage is not necessary in cases where there is no local contamination or infection (1). The application of plastic adhesive wound drapes, with or without antimicrobial properties, over a primarily closed surgical wound does not reduce the risk of SSI (1).

Body Temperature Regulation: Perioperative warming and maintenance of normothermia are recommended to reduce the risk of surgical infections (1, 20, 21). However, there are no randomized studies establishing the lower acceptable limit of body temperature, the optimal strategy for thermal maintenance, or the ideal duration of normothermia.

Recommendations:

- Maintain preoperative blood glucose levels below 200 mg/dL; use insulin therapy when necessary. (GRADE: moderate, strong)
- Perform a full-body wash with a soap-based solution, with or without antiseptics, at least the night before surgery. (GRADE: low, strong)
- Hair removal is not mandatory. Clipping is the preferred method for hair removal at the surgical incision site. (GRADE: high, strong)
- Apply a 0.5% alcohol-based chlorhexidine solution for preoperative skin antisepsis. (GRADE: low, strong)
- There is no recommendation for irrigation of the incised surgical site or the abdominal cavity without contamination or infection. (GRADE: low, weak)
- The use of antibiotic-containing sealants or adhesive drapes (whether coated with povidone-iodine or not) following antisepsis, surgical site irrigation, or abdominal cavity irrigation in the absence of contamination or infection is not recommended. (GRADE: low, weak)

- Implement perioperative warming and maintain normothermia. (GRADE: moderate; strong)

Antibiotic Prophylaxis Measures for Surgical Infection Prevention

Perioperative antibiotic prophylaxis is administered to individuals without active infection, aiming to achieve serum and tissue drug concentrations above the minimum inhibitory concentration of potential infectious agents, thereby preventing the development of clinical infection (22). In urological surgeries, the involvement of potentially colonized structures or organs (e.g., the urinary tract or intestines), as well as the use of catheters and drains, increases the risk of infection due to contamination of the surgical site by endogenous microorganisms, bacterial dissemination from a possible septic focus, or contamination of sterile urine (22-24).

The decision to administer prophylactic antibiotics in urological procedures—whether open or endoscopic—should be individualized, weighing the risks and benefits of prophylaxis versus no prophylaxis (22).

Preoperative detection of bacteriuria aims to reduce infection risk and optimize the effectiveness of prophylactic antibiotic coverage. Urine culture is the preferred diagnostic method for detecting bacteriuria. Comparative studies with alternative diagnostic techniques, including some with faster turnaround times, have shown that none are suitable replacements for urine culture (25).

Patients with asymptomatic bacteriuria should only receive antibiotic treatment if they are undergoing procedures that involve breaching the urothelium (26, 27). Antibiotics for prophylaxis can be administered via parenteral (most common), oral, or topical irrigation routes. The antibiotic must be administered before the surgical incision. The timing of parenteral administration should be guided by the drug's pharmacokinetic and pharmacodynamic properties to ensure adequate bactericidal serum and tissue concentrations during incision or at the start of a non-incisional procedure, with levels maintained

throughout the surgery (28). Initially introduced in the CDC's 1999 guidelines, this recommendation was reaffirmed in an updated publication by the same regulatory body in 2017 (1). There are no randomized studies, systematic reviews, or meta-analyses directly comparing different timing intervals for prophylactic antibiotic administration. However, multiple international guidelines recommend administration within 60 minutes before incision for most antibiotics and 60 to 120 minutes prior for vancomycin and fluoroquinolones (1, 18).

A retrospective study comparing no prophylaxis versus different antibiotics with different administration regimens demonstrated that antibiotic prophylaxis effectively reduces surgical site infections, favoring agents with a half-life exceeding four hours and showing that single-dose prophylaxis is as effective as a three-day regimen, with a lower risk of selecting resistant bacterial strains (22). Short half-life antibiotics may fail to maintain adequate serum levels for minimum bacterial inhibitory concentrations throughout surgery. However, there is limited evidence on the benefits and risks of intraoperative antibiotic re-administration. Based on expert opinion and guideline reviews, a repeat dose is recommended for prolonged surgeries (>3–4 hours or exceeding two half-lives of the antibiotic) or in blood loss greater than 1,500 mL (1, 29). A recent meta-analysis found no difference in infection risk between single-dose and multiple-dose prophylactic antibiotic regimens in orthopedic surgeries involving implants (30). No randomized studies have evaluated this comparison in urological procedures.

There are no controlled studies supporting the need for antibiotic dose adjustments based on patient weight or body mass index. Current recommendations for weight-based dose adjustments are based on guideline reviews and expert opinion (1).

After skin closure or completion of an endoscopic procedure, there is no indication for additional antibiotic doses, even if surgical drainage is maintained for clean or potentially contaminated surgeries. This recommendation is supported by randomized studies across multiple surgical special-

ties, including cardiac, thoracic, vascular, orthopedic, head and neck, gynecological, and gastrointestinal procedures (1).

Recommendations:

- Asymptomatic bacteriuria should be treated (based on antibiotic susceptibility testing) ONLY for diagnostic or surgical procedures that breach the mucosal barrier of the urinary tract. Urine culture is the method of choice for diagnosing bacteriuria. (GRADE moderate, strong)
- Parenteral antibiotic administration should be timed to ensure adequate tissue concentration before surgical incision or endoscopic intervention. For most antibiotics, the recommended administration window is within 60 minutes before incision and between 60 and 120 minutes for vancomycin and fluoroquinolones. (GRADE low, strong)
- A repeat antibiotic dose should be administered in procedures exceeding two antibiotic half-lives or when blood loss exceeds 1,500 mL. (GRADE low, strong)
- There is no recommendation for antibiotic dose adjustment based on body weight in adults. (GRADE very low, weak)
- No additional antibiotic doses should be administered after skin closure or completion of an endoscopic procedure, even if surgical drainage is maintained for clean or potentially contaminated surgeries. (GRADE moderate, strong)

Specific Measures for Surgical Infection Prophylaxis in Urological Surgeries

Urodynamic Study

Urinary tract infection (UTI) is the most common complication of urodynamic studies, although its exact incidence remains unclear due to variations in definitions across studies (31-36). While antibiotic prophylaxis has been shown to reduce the incidence of asymptomatic bacteriuria, its clinical impact and the cost-effectiveness of antimicrobial prophylaxis in preventing UTIs are not fully established (37-40). As a result, most scientific society guidelines recommend

reserving antibiotic prophylaxis for patients at higher risk of developing UTIs, including neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury, age over 70 years, asymptomatic bacteriuria, immunosuppression, use of urinary catheters (indwelling, cystostomy, or clean intermittent catheterization), total orthopedic prosthesis implantation with risk factors for local infection due to bacteremia (e.g., inflammatory arthritis, diabetes mellitus, HIV infection), and patients with post-void residual volume exceeding 50 mL. (31, 33, 41-54)

Due to the globally high resistance rates of uropathogens to fluoroquinolones, we recommend avoiding this class of antibiotics for urodynamic prophylaxis (55-59). Single-dose antibiotic prophylaxis before the urodynamic study has been described using the following regimens: fosfomycin-trometamol (3g, 2 hours before the procedure), nitrofurantoin (100 mg, 2 hours before the procedure), sulfamethoxazole-trimethoprim (800 mg/160 mg, 1 hour before the procedure), or cephalexin (500mg, 1hr. before the procedure) (31, 60).

Considering the latest recommendations for managing acute and recurrent cystitis, the susceptibility profile of uropathogens, and the efficacy of different agents against urinary tract microorganisms, fosfomycin-trometamol or nitrofurantoin should be the first-choice prophylactic regimen (61-63).

Recommendations:

- Administer antibiotic prophylaxis for patients undergoing urodynamic studies who have risk factors for UTI development. (GRADE moderate, strong)
- Avoid the use of fluoroquinolones. (GRADE high, strong)
- Use fosfomycin-trometamol (3g, 2 hrs. before the procedure) or nitrofurantoin (100mg, 2 hrs. before the procedure) as the first-choice prophylactic regimen. (GRADE low, weak)

Prostate Biopsy

Prostate biopsy is considered a high-risk, contaminated, invasive procedure and therefore re-

quires antibiotic prophylaxis (64). Risk factors for post-biopsy infection include prior antibiotic use within the last six months, the presence of an indwelling urinary catheter, and a history of recurrent prostatitis (65, 66).

There is evidence that non-antibiotic measures can effectively reduce infection-related complications. A meta-analysis of eight randomized studies including 1,786 patients evidenced a 50% reduction in infection rates with rectal cleansing using povidone-iodine (67).

The necessity and efficacy of antibiotic prophylaxis were demonstrated in a Cochrane Collaboration review of nine randomized studies with 3,599 patients, comparing those who received antibiotics to a control group prior to transrectal prostate biopsy (68). The study showed a 63% reduction in infectious events in the prophylaxis group: bacteriuria (14.8% vs. 3.9%), bacteremia (8.6% vs. 2.1%), fever (10.8% vs. 4.0%), urinary tract infection (9.0% vs. 3.3%), and hospitalization (3.3% vs. 0.3%). Another meta-analysis of 11 studies with 1,753 patients reported a 44% reduction in post-transrectal biopsy infection rates with antibiotic prophylaxis (69). Based on these findings, international consensus guidelines strongly recommend antibiotic prophylaxis for all patients undergoing a transrectal prostate biopsy, with a high level of evidence and a strong grade of recommendation (65, 66, 70).

Although there is a consensus that antibiotic prophylaxis is necessary, there is significant variability in clinical practice regarding the choice of antibiotics (64). The selected antibiotic should target gram-negative bacteria (*Enterobacteriaceae*), achieve good penetration into prostate tissue, and reach the minimum inhibitory concentration at the time of the procedure. It is also essential to consider local resistance patterns of *Enterobacteriaceae* to commonly used antibiotics. The most frequently recommended antibiotics are fluoroquinolones and cephalosporins (66, 71).

Although most studies have utilized fluoroquinolones, there has been a progressive global increase in *Enterobacteriaceae* resistance to this class

of antibiotics, with reported resistance rates ranging from 18% to 83% in patients undergoing prostate biopsy. For instance, there has been a rise in post-biopsy infectious complications from 1% in 1996 to 4.1% in 2002 in Canada (68, 69). A prospective study conducted in São Paulo, Brazil, analyzing 623 transrectal biopsies, reported an infectious complication rate of 6.4%, with 92% of infections caused by *E. coli*, of which 94% were fluoroquinolone-resistant (72). In light of these findings, the American Urological Association (AUA) recommends avoiding fluoroquinolone use in regions where resistance rates exceed 20% (66). Similarly, the European Medicines Agency and the European Association of Urology (EAU) contraindicate fluoroquinolones for transrectal biopsy prophylaxis, not only due to increasing resistance rates but also because of their musculoskeletal side effects (65, 73, 74).

A systematic review found similar infection complication rates between fluoroquinolones, cephalosporins, and aminoglycosides, while fosfomycin significantly reduced infection complications compared to fluoroquinolones (69). A review and meta-analysis of five studies—three randomized and two retrospective—comparing 1,447 patients who received fosfomycin versus fluoroquinolones showed a significant 80% reduction in post-biopsy infection rates with fosfomycin, therefore confirming fosfomycin's role as an alternative (75).

Extended prophylaxis refers to the use of two antibiotics. Although this approach contradicts the principle of using a single agent for prophylaxis, its rationale lies in providing broader coverage against potential resistance to a single antibiotic class (73). A meta-analysis of three randomized studies demonstrated that adding an aminoglycoside to a fluoroquinolone or cephalosporin reduced the risk of infectious complications by 65% (71). Similarly, a review of nine studies involving 2,597 patients confirmed extended prophylaxis's superiority (69).

A meta-analysis involving 12,320 individuals evaluated the use of rectal swab cultures to guide targeted antibiotic prophylaxis. The analysis demonstrated that targeted prophylaxis significantly re-

duced infection rates from 3.4% to 0.8% compared to empirical antibiotic therapy. However, only one of the nine included studies was randomized, with the remaining being retrospective series (76). Another meta-analysis of six studies involving 1,511 prostate biopsies found that empirical fluoroquinolone therapy was inferior to targeted antibiotic prophylaxis (69).

A systematic review, along with European and American consensus guidelines on transrectal biopsy prophylaxis, concluded that in regions with high fluoroquinolone resistance rates, extended prophylaxis, targeted prophylaxis, or the use of alternative antibiotics such as fosfomycin is recommended (66, 69, 77). The lowest effective dose and shortest duration should be used to minimize antibiotic-related side effects and reduce the risk of resistance. There is ongoing controversy regarding the optimal duration of prophylaxis and the timing of its initiation for transrectal biopsy.

There is no consensus or standardized regimen for antibiotic prophylaxis in transrectal biopsy. However, a meta-analysis found that single-dose prophylaxis was inferior to a one-day regimen (69). A Cochrane review comparing one-day versus three-day prophylaxis reported similar infection rates, fever, and hospitalization but a lower incidence of bacteriuria in the three-day prophylaxis group (68). A meta-analysis of 17 studies including 3,999 patients found that short-term prophylaxis (ranging from a single dose to three days) was associated with a higher incidence of infectious complications than long-term prophylaxis (one to seven days) using fluoroquinolones. The study also evidenced that the administration route and the antibiotic initiation timing (ranging from 12 to 2 hours before biopsy) did not influence infection rates (69). Another systematic review and meta-analysis, including 13 randomized studies with 3,389 patients, compared longer prophylaxis durations (three, five, and seven days) to a one-day regimen and found a 39% lower infection rate in favor of more extended prophylaxis (71). Subgroup analyses showed that while three-day prophylaxis was superior to one day, extending prophylaxis to five or seven days did not provide additional benefits (71).

In settings with high fluoroquinolone resistance rates, alternative prophylactic regimens are recommended. These include fosfomycin (3g orally, 3 hours before biopsy, followed by a second 3g dose 24 hours after the procedure); aminoglycosides such as amikacin (15 mg/kg IV) or gentamicin (3 mg/kg IV), administered 30 to 60 minutes prior to biopsy; or ceftriaxone (1g IV, 30 minutes before biopsy) followed by a second-generation cephalosporin for three days (69).

The most effective strategy for preventing infection after prostate biopsy is transitioning to the transperineal approach. A meta-analysis of 11 studies comparing 1,644 transperineal and 1,634 transrectal biopsies found a 74% lower infection rate with the transperineal route (77). A systematic review including 165 studies and 162,577 patients reported sepsis rates of 0.1% for transperineal biopsies and 0.9% for transrectal biopsies (78).

The European Association of Urology (EAU) recently updated its meta-analysis, now including 11 studies with 3,131 patients comparing infectious complications following transperineal versus transrectal prostate biopsy. Incorporating randomized trials published in 2024, the analysis concluded that the transperineal approach is significantly associated with lower rates of infectious complications ($p = 0.03$) (79).

Transperineal prostate biopsy is considered a clean procedure, as it avoids needle passage through the rectum and thus requires only antibiotic coverage for skin flora of the perineal region (65, 70, 73, 74). There are no randomized studies evaluating different antibiotic regimens for transperineal biopsy prophylaxis. Most available data come from single-center case series, which commonly used first- or second-generation cephalosporins, such as cefazolin or cefuroxime, with reported infectious complication rates below 1% (65, 80-83).

Two recently published meta-analyses evaluated the feasibility of performing transperineal prostate biopsy without antibiotic prophylaxis. Basourakos et al. reviewed 106 studies comparing 37,805 patients who received prophylaxis to 4,772 who did not and found no significant difference in sepsis

rates between the groups (0.05% vs. 0.08%, $p = 0.2$). However, when considering minor complications, antibiotics had a significant advantage (0.55% vs. 1.22%, $p < 0.01$) (80). Another review of eight studies—four retrospective and four prospective non-randomized—compared 3,662 transperineal biopsies performed with or without antibiotic prophylaxis. This analysis found no significant difference in the incidence of fever (0.69% vs. 0.47%) or urinary tract infection (0.13% vs. 0.31%) (81). A key limitation of this review was the moderate to high risk of bias in seven of the included studies. Supporting the potential for transperineal biopsy without antibiotics, Hu et al. published a multicenter randomized trial in 2024, in which 742 patients were assigned to undergo either transperineal biopsy without antibiotics or transrectal biopsy with standard antibiotic prophylaxis. The study found no infectious complications in the transperineal group, compared to a 1.6% infection rate in the transrectal group ($p = 0.015$) (84).

Consensus guidelines still recommend administering a single intravenous dose of 1 gram of cefazolin immediately before transperineal biopsy to provide coverage against skin flora. Additionally, perineal skin antisepsis with povidone-iodine or chlorhexidine is advised (65, 80, 81). For patients with beta-lactam allergy, oral sulfamethoxazole-trimethoprim is recommended as an alternative prophylactic option (85).

Recommendations:

- Rectal cleansing with povidone-iodine immediately before transrectal biopsy is recommended. (GRADE high, strong)
- Antibiotic prophylaxis for transrectal prostate biopsy should be administered for 1 to 3 days, starting between 12 and 2 hours before the procedure. (GRADE high, strong)
- Fluoroquinolones (only if local bacterial resistance is $<20\%$) and cephalosporins are recommended for transrectal biopsy prophylaxis. (GRADE high, strong)
- Fosfomycin, cephalosporins, and aminoglycosides should be considered alternatives to fluoroquinolones. (GRADE high, strong)
- In place of fluoroquinolones, extended pro-

phylaxis with the addition of a broad-spectrum parenteral antibiotic (GRADE moderate, strong) or targeted antibiotic therapy based on rectal swab cultures (GRADE high, strong) is recommended.

- Perineal skin antisepsis with povidone-iodine or chlorhexidine is recommended before biopsy. (GRADE low, strong)
- For transperineal prostate biopsy, single-dose antibiotic prophylaxis with intravenous cefazolin is recommended. For patients with beta-lactam allergy, single-dose oral sulfamethoxazole may be used as an alternative. (GRADE low, weak)

Urethrocystoscopy

Antibiotic prophylaxis during urethrocystoscopy has been shown to reduce the risk of urinary tract infection (UTI) but does not lower the incidence of UTIs with systemic manifestations (41, 86, 87). However, existing studies are of low methodological quality, which limits the ability to support a recommendation for routine prophylaxis in all patients. Therefore, antibiotic prophylaxis is not recommended in asymptomatic patients with sterile urine cultures (77, 64). In contrast, antibiotic prophylaxis is indicated for patients with risk factors for developing bacteremia, such as immunosuppression, the presence of an indwelling urinary catheter, heavy smoking history, malnutrition, prolonged hospitalization, pregnancy with asymptomatic bacteriuria, diabetes mellitus, neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury, and advanced age. Antibiotic prophylaxis should also be considered in cases where extensive mucosal trauma is expected during the procedure (64).

Due to the global rise in bacterial resistance of uropathogenic enterobacteria to fluoroquinolones, this class of antibiotics should be avoided for prophylaxis in urethrocystoscopy (55-58, 88, 89). As alternatives, several prophylactic regimens have been described and may be administered before or after the procedure. These include amoxicillin combined with potassium clavulanate (500 mg + 125 mg, single dose, 2 hours before the procedure), cephalexin (500 mg, single dose, 2 hours before the procedure), fosfomycin trometamol (3 g, 3 hours before the procedure, with a second 3 g

dose 24 hours later), and nitrofurantoin (50 mg immediately after the procedure, then every 6 hours for 2 days). These regimens are associated with mild and infrequent adverse effects (64, 90, 91).

Recommendations

- Antibiotic prophylaxis is not recommended for asymptomatic patients with a negative urine culture undergoing urethrocystoscopy. (GRADE moderate, strong)
- Antibiotic prophylaxis is recommended for patients undergoing urethrocystoscopy with risk factors for developing bacteremia. (GRADE moderate, strong)
- Fluoroquinolones are not recommended for antibiotic prophylaxis in urethrocystoscopy. (GRADE high, strong)

Extracorporeal Shock Wave Lithotripsy (ESWL) for Urinary Stones

Regarding antibiotic prophylaxis in patients undergoing ESWL, two meta-analyses—Lu et al. (2012) and Mrkobrada et al. (2015)—evaluated nine and eight randomized clinical trials, respectively, including data from 1,364 and 940 patients. Neither study demonstrated the benefit of prophylactic antibiotic use in preventing fever, bacteriuria, or any infectious outcomes following ESWL (92, 93, 70). During the same period, although with lower evidence strength, an ecological study based on a New Zealand database including over 10,000 cases also found no significant benefit from the routine use of prophylactic antibiotics to prevent urinary tract infections after lithotripsy (94). More recently, a meta-analysis evaluating 16 randomized clinical trials and including 2,442 patients—incorporating several newer trials with stronger methodological quality—showed no benefit of antibiotic prophylaxis in preventing UTIs, even in patients with prior urinary tract manipulation (95).

Recommendation

Antibiotic prophylaxis is not recommended for patients without bacteriuria undergoing ESWL. (GRADE high, strong)

Endoscopic Ureterolithotripsy

A recent meta-analysis including 11 randomized clinical trials and 4,591 patients found that preoperative antibiotic prophylaxis did not reduce the risk of febrile urinary tract infection after endoscopic ureterolithotripsy. However, a single dose of antibiotic was effective in reducing pyuria and bacteriuria. The authors suggested that a single oral dose of prophylactic antibiotic was preferable due to its cost-effectiveness. These findings support the notion that, while prophylaxis may reduce subclinical infection, its clinical impact in preventing serious complications such as sepsis remains uncertain (96). Another study evaluating the incidence of systemic inflammatory response syndrome (SIRS) in patients receiving different types of antibiotics found no significant difference in serious complication rates between those who received no prophylaxis, a single dose, or two doses. Subgroup analysis, however, indicated a higher likelihood of SIRS in patients with stone burdens larger than 200 mm² who did not receive antibiotic prophylaxis (97). A cohort study compared extended antibiotic prophylaxis to standard single-dose prophylaxis in patients undergoing flexible ureteroscopy with negative urine cultures. Those who received extended prophylaxis had twice the risk of developing cystitis and isolating multidrug-resistant organisms, with no difference in the rates of pyelonephritis or urosepsis. These findings reinforce the recommendation for single-dose preoperative prophylaxis (98).

The adoption of personalized prophylactic strategies—such as the use of preoperative urine cultures, selection of antibiotics based on local bacterial resistance profiles, and the application of technologies like next-generation sequencing (NGS) to guide antibiotic choice—has been shown to reduce the incidence of clinically significant UTIs (99).

Recommendation

- Single-dose antibiotic prophylaxis should be administered preoperatively for endoscopic ureterolithotripsy, guided by local antibiotic resistance patterns. (GRADE high, strong)

Percutaneous Nephrolithotomy

A meta-analysis including 1,549 patients from 13 randomized clinical trials demonstrated that preoperative antibiotic prophylaxis in PCNL significantly reduces postoperative rates of sepsis and fever. Prolonged use of antibiotics after the procedure showed no additional benefit in preventing sepsis and was associated with an increased incidence of fever (100). Another meta-analysis, which included seven randomized clinical trials with 649 patients, found no benefit to extended antibiotic prophylaxis—whether postoperatively or continued until nephrostomy tube removal—further reinforcing the concept that prophylaxis should be limited to the anesthetic induction period (101).

In high-risk patients—such as those with staghorn calculi, indwelling catheters or stents, or known preoperative colonization—a meta-analysis of 10 randomized clinical trials found that prolonged antibiotic regimens may also be beneficial while single-dose prophylaxis is effective (102). Another meta-analysis, which included five studies (three randomized clinical trials and two observational studies), evaluated extended preoperative prophylaxis and found that combining a one-week preoperative antibiotic course plus a dose of intravenous antibiotics at the time of surgery reduced the risk of infection and sepsis in high-risk patients. This regimen also lowered the rates of positive intraoperative urine and stone cultures without increasing the incidence of postoperative fever (103). Comparisons between different antibiotic regimens did not reveal significant differences in infection rates associated with the procedure (104).

Recommendations

- Single-dose antibiotic prophylaxis should be administered preoperatively in patients undergoing PCNL. (GRADE high, strong)
- In high-risk patients, extended preoperative antibiotic prophylaxis (7 days) and one dose of intravenous antibiotics at the time of surgery is recommended. (GRADE high, strong)

Transurethral Resection of the Prostate (TURP) and Prostatic Enucleation

A meta-analysis by Dahm et al., initially published in 2009 and updated in 2017, evaluated 39 randomized clinical trials and demonstrated that antibiotic prophylaxis in TURP significantly reduces the risk of postoperative infections. Specifically, it showed a 50% relative risk reduction for sepsis (95% CI: 27–96%), a 64% reduction in febrile complications (95% CI: 55–75%), and a 37% reduction in bacteriuria (95% CI: 32–41%) (105). Regarding the duration of antibiotic use, patients with sterile urine cultures in the preoperative period showed similar infection rates regardless of whether they received a single dose or extended antibiotic regimens when undergoing prostatic enucleation (106). More recently, Baten et al. observed that patients without preoperative catheters or pyuria had low rates of febrile infectious complications, suggesting that antibiotic prophylaxis may not be necessary in such cases (107).

Recommendations

- Preoperative antibiotic prophylaxis is recommended for men without bacteriuria undergoing TURP or enucleation of the prostate. (GRADE high, strong)

Transurethral Resection of Bladder Tumor (TURBT)

A meta-analysis by Bausch et al., which included seven studies and 1,725 participants, did not demonstrate significant benefits from antibiotic prophylaxis in patients undergoing bladder tumor resection. The incidence of symptomatic bacteriuria (OR = 1.55 [0.73–3.31], 95% CI) and asymptomatic bacteriuria (OR = 0.43 [0.18–1.04], 95% CI) did not differ significantly between the groups analyzed (108).

However, antibiotic prophylaxis was found to be beneficial in specific high-risk populations, including patients with a history of pelvic radiotherapy, advanced age, prolonged preoperative hospital stay, tumors larger than 2 cm, and those with preoperative pyuria or bacteriuria (109, 110).

A randomized clinical trial evaluating high-risk patients demonstrated the non-inferiority of oral fosfomycin administered the day before the procedure compared to intravenous cefoxitin given peri-operatively (111).

Recommendation

- Antibiotic prophylaxis is recommended for high-risk patients undergoing TURBT. (GRADE high, strong)

Intravesical Botulinum Toxin Injection

No randomized clinical trials are available to guide antibiotic prophylaxis for intravesical botulinum toxin injection. Current evidence suggests a trend toward omitting prophylactic antibiotics, even in asymptomatic bacteriuria (112-115). An important exception involves patients undergoing botulinum toxin treatment for neurogenic lower urinary tract dysfunction secondary to suprasacral spinal cord injury (113-115). In this population, antibiotic prophylaxis is recommended on the day of the procedure, with continuation for 1 to 3 days following the injection (115). A retrospective study conducted in a Brazilian cohort demonstrated that a single antibiotic dose at the time of anesthesia induction was associated with a UTI rate of only 1.8%, supporting the efficacy of this approach (113).

Among the available antibiotics, cefazolin is recommended as the first-line option, with ciprofloxacin reserved for exceptional cases (113). Although there is currently no clinical data supporting the prophylactic use of fosfomycin trometamol in this specific patient group, a recent epidemiological study showed that urinary pathogens isolated from neurologic patients undergoing intravesical botulinum toxin injections generally do not exhibit resistance to fosfomycin, in contrast to the resistance patterns seen with other antibiotic classes (116).

Recommendations

- Antibiotic prophylaxis is recommended for patients with asymptomatic bacteriuria and suprasacral spinal cord injury undergoing in-

travesical botulinum toxin injection. (GRADE moderate, strong)

- When antibiotic prophylaxis is indicated, a single intravenous dose of cefazolin during anesthesia induction is recommended as the first-line option for intravesical botulinum toxin procedures. (GRADE moderate, strong)

Surgical Correction of Female Stress Urinary Incontinence

In general, there is a growing tendency not to recommend routine antibiotic prophylaxis for surgical correction of female stress urinary incontinence, primarily due to the low postoperative infection rates associated with current surgical techniques (117-120). A retrospective controlled study from Norway involving more than 9,000 patients found a reduction in infections with antibiotic prophylaxis; however, the overall infection rate was only 1.2% (117). Supporting these findings, a case series of 174 patients who did not receive prophylaxis reported no surgical site infections and only an 8% rate of asymptomatic bacteriuria (119). The only available double-blind, randomized controlled trial on the topic, which compared a single 1 g dose of intravenous cefazolin administered at anesthesia induction to a placebo, was terminated early due to the very low infection rates observed (120).

Recommendation

- Antibiotic prophylaxis is not recommended for mid-urethral sling surgeries in women. (GRADE moderate, strong)

Surgical Correction of Pelvic Organ Prolapse

In general, antibiotic prophylaxis is recommended for surgical correction of pelvic organ prolapse (64, 121-123). For procedures performed via the vaginal or abdominal route without the use of synthetic mesh, postoperative infection rates are reduced with a single intravenous dose of cefazolin 2 g (or 3 g for patients over 120 kg), administered one hour before the surgical incision (64, 121, 124).

In cases involving synthetic mesh placement, there is no standardized protocol; however,

better efficacy has been observed using at least two combined intravenous antibiotics, administered one hour before the incision and continued for the first 24 hours postoperatively. Commonly used combinations include clindamycin and gentamicin, aminoglycoside and vancomycin, aztreonam and vancomycin, aminoglycoside and a second-generation cephalosporin, or aztreonam and a second-generation cephalosporin (64, 122).

Recommendations

- For pelvic organ prolapse repair surgeries without synthetic mesh, cefazolin is recommended as the first-line agent for antibiotic prophylaxis. (GRADE moderate, strong)
- For pelvic organ prolapse repair surgeries with synthetic mesh, combined antibiotic prophylaxis is recommended. (GRADE moderate, strong)

Urologic Prosthesis Implantation

To date, no randomized placebo-controlled trials have directly compared preoperative antibiotic administration with no prophylaxis in urologic prosthesis implantation. Nevertheless, the benefits of antibiotic prophylaxis in this setting are widely accepted based on evidence from other surgical fields. Studies in closed fracture repair and inguinal hernia repair with mesh have shown that appropriate prophylaxis with broad-spectrum, long-acting antibiotics significantly reduces the incidence of surgical site infections and early postoperative complications (125-127). For skin incisions where prosthetic devices are to be implanted, as well as for groin and perineal incisions—where the risk of surgical site infection may be higher—recent guidelines recommend preoperative antibiotic prophylaxis (64, 128-137). In surgeries involving prosthesis implantation, the use of meticulous surgical techniques combined with appropriate antibiotic prophylaxis against both Gram-positive and Gram-negative bacteria has been shown to reduce infection rates (129). A recommended prophylactic regimens consists of aminoglycosides (or aztreonam in cases of renal insufficiency) combined

with a first- or second-generation cephalosporin or vancomycin. This combination is aimed at covering skin flora, particularly coagulase-negative staphylococci and Gram-negative bacilli, including *Pseudomonas* spp (64, 128). Identifying and decolonizing patients colonized with nasal *Staphylococcus aureus* using mupirocin and chlorhexidine prior to surgery has been shown to reduce surgical site infection rates from 4.4% to 0.9% (131). Although recent studies have demonstrated a general decline in prosthetic infection rates, relatively high rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and fungal infections have been increasingly reported in cultures from explanted infected penile prostheses (136). Regarding antifungal prophylaxis in prosthetic surgery, a recent retrospective study showed it reduced the risk of infection, and a recent systematic review has also highlighted the likely importance of antifungal prophylaxis (134, 135). Nonetheless, further comparative studies are needed to justify the routine inclusion of antifungal agents in prophylactic protocols.

An analysis of explanted prostheses identified a wide range of pathogens, including Gram-positive and Gram-negative bacteria, *Candida* species, anaerobic bacteria, *Staphylococcus aureus*, and polymicrobial infections. These findings suggest that, even when following current antibiotic recommendations aimed at covering the majority of skin flora, the microorganisms isolated in this study were not adequately covered by AUA guideline-recommended regimens in 14% to 38% of cases (136).

Contemporary literature has also shown a reduction in penile prosthesis infection rates of approximately 50%, mainly attributed to the introduction of antibiotic-impregnated devices and antibiotic-coated implants, therefore, great importance is given to the topical solution to be used in prostheses (139-142). The most commonly used devices among penile prosthesis and artificial urinary sphincter incorporate various technologies for antibiotic delivery—either through pre-impregnation with antibiotics or surface coatings that allow the surgeon to soak the device in an antibiotic solution of choice prior to implantation, enhancing localized antimicrobial activity (143-145). In a large-cohort,

multicentre, retrospective study of men with diabetes who received a Coloplast Titan™ implant, different solutions for implant dipping were evaluated, and the combination of vancomycin and gentamicin proved to be the most effective in preventing postoperative infection, explantation, and revision (143). In contrast, for artificial urinary sphincters, the presence of InhibiZone coating has not demonstrated a significant impact on infection rates or explantation risk, according to findings from a retrospective cohort study (144).

Although there are no systematic reviews or prospective studies supporting the effectiveness of antibiotic prophylaxis specifically for artificial urinary sphincters, AUA guidelines recommend a similar approach to that used for penile prostheses. Prophylaxis should consist of an aminoglycoside combined with either a first- or second-generation cephalosporin, or vancomycin (64, 144).

For testicular prostheses, a review has suggested the use of pre-incision antibiotics, including vancomycin and gentamicin, although the level of evidence supporting this recommendation is low (64, 132, 146).

Regarding the postoperative extension of antibiotic prophylaxis, a survey of prosthetic surgeons in the United States revealed that 90% of respondents routinely prescribed postoperative oral antibiotics, with an average duration of 7 days. This practice prompted the publication of a consensus in which all panel experts reported prescribing oral antibiotics postoperatively for 5 to 14 days despite well-documented evidence in surgical literature highlighting the risks associated with prolonged postoperative antibiotic use (144, 147). A 2020 consensus statement recommended that postoperative antibiotic use should be discontinued within 24 hours unless specific antimicrobial prophylactic regimens are justified for particular patient populations. In such cases, postoperative prescribing is often based on the individual surgeon's clinical judgment and aligned with local institutional guidelines (124). Current evidence suggests that routine postoperative antibiotic administration is unlikely to benefit patients undergoing implant surgery, and more randomized controlled trials are needed to inform stronger recommendations (148).

Recommendations

- Intravenous antibiotic prophylaxis is recommended for urologic prosthesis implantation. (GRADE low, strong)
- The recommended antibiotic regimen includes an aminoglycoside combined with a first- or second-generation cephalosporin, or vancomycin. (GRADE low, strong)
- There is currently no recommendation to include antifungals or to broaden the spectrum of antibiotic coverage beyond standard prophylaxis. (GRADE low, weak)
- Antibiotic irrigation of prostheses is recommended, particularly for devices with hydrophilic coatings, using gentamicin alone or combined with rifampin or vancomycin. (GRADE low, weak)
- No current evidence supports the routine use of postoperative antibiotics. (GRADE low, strong)

Open, Laparoscopic, and Robotic Urologic Surgery

Antibiotic prophylaxis in abdominal or pelvic urologic surgeries should be guided by the patient's clinical condition, the type of procedure, and the expected microbial flora encountered during surgery (1). The classification of the surgical wound, based on its contamination risk, in combination with the local antimicrobial resistance profile and the nature of the intervention, should inform the choice of prophylactic antibiotics (1, 149). The duration of antibiotic prophylaxis should not exceed 24 hours, with most procedures requiring only a single parenteral dose (64, 150). There are no differences in prophylactic antibiotic regimens between open, laparoscopic, or robot-assisted techniques. All approaches follow the same principles with respect to antibiotic type, dosing, and duration.

Classification Based on Surgical Wound Type

Surgical wounds are classified into four categories, adapted for urologic procedures, and used to determine the need and type of prophylaxis (64, 151).

Class I/Clean Procedures

These are surgeries that do not involve entry into the gastrointestinal or genitourinary tracts. For low-risk clean procedures in patients without significant comorbidities and with expected operative times under three hours—such as vasectomy, circumcision, and varicocelectomy—antibiotic prophylaxis is not indicated (64, 152). For clean procedures with higher infectious potential—such as adrenalectomy, lymphadenectomy (pelvic or retroperitoneal), hydrocelectomy, and inguinal or scrotal orchiectomy—antibiotic prophylaxis should be considered with coverage targeting skin flora (64, 153-155). A single parenteral dose of cefazolin is preferred, with clindamycin as an alternative in cases of beta-lactam allergy. Procedures involving prosthetic implantation require broader prophylactic strategies, which are addressed in a separate section.

Class II/Clean-contaminated procedures

These involve controlled entry into the genitourinary tract, such as radical or partial nephrectomy, pyeloplasty, prostatectomy, and partial cystectomy (64). Antibiotic prophylaxis is recommended for all cases, targeting gram-negative rods and *Enterococcus*. The recommended regimen is a single intravenous dose of cefazolin or trimethoprim-sulfamethoxazole. Alternative regimens include ampicillin/sulbactam; an aminoglycoside plus metronidazole; aztreonam plus metronidazole; an aminoglycoside plus clindamycin; or aztreonam plus clindamycin.

Class III/Contaminated procedures

These include surgeries involving bowel segments (e.g., colonic urinary diversions) or those performed in the presence of infected stones, such as percutaneous nephrolithotomy for struvite calculi (64). Antibiotic prophylaxis is recommended for all contaminated procedures due to the high risk of SSI or even systemic infection. For colorectal diversions, preoperative mechanical bowel preparation combined with oral antibiotics is recommended as it is linked to lower complication rates (156-158). The recommended oral agents include neomycin plus metro-

nidazole or erythromycin base (64). These should be used in addition to systemic antibiotics that provide both aerobic and anaerobic coverage. A single dose of a first-generation cephalosporin, combined with metronidazole for anaerobic coverage, is considered first-line parenteral prophylaxis for colorectal diversions or any surgery involving the large bowel (64). Carbapenems (eg, ertapenem) are also a first-line option and should be reserved for multi-drug resistant bacteria. Third or higher generations of cephalosporins are not routinely recommended due to their association with increased rates of multidrug-resistant bacterial infections (159, 160). Alternative regimens may include ampicillin/sulbactam, piperacillin/tazobactam, or ticarcillin/clavulanate.

In contrast, using small bowel segments for diversion does not require bowel preparation (161, 162). The upper gastrointestinal tract harbors a less dense and less diverse microbial flora compared to the colon. Therefore, for non-obstructed small bowel procedures—such as cystectomy with small bowel urinary diversion—a single dose of cefazolin is generally recommended for prophylaxis (64, 163). Alternative regimens include a single dose of clindamycin combined with an aminoglycoside, a second-generation cephalosporin, or a combination of an aminopenicillin with a β -lactamase inhibitor and metronidazole. (64).

A randomized, single-center, non-blinded, non-inferiority trial compared 24-hour versus extended (>48 hours, median 8 days) perioperative antibiotic prophylaxis in patients undergoing cystectomy with urinary diversion (164). The study found no significant differences between the two groups in terms of surgical site infections, all-cause mortality, febrile urinary tract infections, or length of hospital stay—supporting the non-inferiority of the shorter regimen.

Class IV/Dirty procedures

Class IV, or dirty procedures, include surgeries involving open trauma, abscesses, or extensive debridement—such as in cases of Fournier's gangrene—where infection is already present at the time of the procedure. By definition, all Class IV proce-

dures are considered infected (64). In these cases, intraoperative cultures should be obtained to guide therapy. Until culture results are available, empiric antibiotic therapy should be initiated or continued, tailored to the likely pathogens based on the surgical site and clinical context.

Recommendations

- Prophylactic antibiotic regimens should not differ between open, laparoscopic, and robot-assisted urologic surgeries, as all follow the same evidence-based principles regarding agent selection, dosing, and timing. (GRADE very low, strong)
- Antibiotic prophylaxis is not routinely recommended for Class I (clean) procedures, except in cases involving prosthetic implantation or where surgical site infection risk may be increased. In such cases, single-dose antibiotic prophylaxis targeting skin flora is recommended. (GRADE low, strong)
- Antibiotic prophylaxis is recommended for all Class II (clean-contaminated) procedures, with single-dose coverage targeting gram-negative bacilli and *Enterococcus*. (GRADE very low, strong)
- Antibiotic prophylaxis is recommended for all Class III (contaminated) procedures (GRADE low, strong)
- For colorectal diversions, combined mechanical bowel preparation and oral antibiotics should be used in conjunction with parenteral agents providing both aerobic and anaerobic coverage. (GRADE low, strong)
- In small bowel urinary diversions, where bowel preparation is not required, a single preoperative dose of cefazolin is recommended. (GRADE low, strong)
- Antibiotic prophylaxis duration should not exceed 24 hours for patients undergoing cystectomy with urinary diversion. (GRADE moderate, strong)
- For Class IV (dirty) procedures, such as abscess drainage or debridement in the setting

of active infection, empiric broad-spectrum antibiotics should be initiated or continued based on the expected pathogens. Intraoperative cultures should be obtained to guide therapy. (GRADE low, strong)

CONCLUSIONS

The standardization of replicable prophylactic protocols in diagnostic and therapeutic urological procedures is a key component for ensuring patient safety and effective care. However, both the use of non-antibiotic measures and the prescription of antimicrobials for prophylactic purposes are often based on outdated information, empirical practice, or commercial motivations, lacking the necessary scientific support. Notably, antibiotic prophylaxis in urological surgical procedures remains an area with a paucity of high-level evidence studies. The definition of prophylactic strategies must consider not only the characteristics of the procedure itself but also patient-related factors such as prior bacterial colonization, a history of recurrent urinary tract infections, catheter use, previous urological manipulation, urinary tract malformations, and the patient's overall clinical and immunological status. Additionally, aspects related to the underlying disease and potential functional interference with other organs must be integrated into the decision-making process. Thus, evidence-based and risk-adapted prophylaxis is essential for reducing infectious complications in the urological setting.

CONFLICT OF INTEREST

None declared.

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Portrait of a Series of Patients with Pheochromocytoma/Paraganglioma from a Reference Center in Brazil: Relevance of Prior Background Features

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ABSTRACT

Purpose: Pheochromocytomas (Pheo) and paragangliomas (PGL) are catecholamine-secreting tumours, whose functionality is confirmed by elevated plasma (PI) and/or 24-h urinary (Ur) metanephrines (MN). Relevance of prior background features were reviewed in a large cohort of patients with Pheo and PGL.

Material and Methods: We reviewed clinical, hormonal, and imaging aspects of 116 patients studied prospectively: 93 Pheo; 22 PGL; one Pheo plus PGL.

Results: Twenty-five % PPGL were discovered incidentally. Systemic arterial hypertension (SAH) was present in 81% (43% on stage 3), whereas 9.5% were prehypertensive and 9.5%, normotensive. SAH plus paroxysms occurred in 31 (32.9%) patients, being exclusively sustained in the remaining; 26 (28%) had resistant SAH. Orthostatic hypotension was seen in 65% of patients. PI/Ur MN and normetanephrine (NMN) were compared to those of a positive (56 functioning PPGL) and a negative control group (654 subjects with normal MN/NMN). Total and fractionated Ur MN were elevated in 94% PPGL patients. Cut-off values of 885 mcg/24-h for Ur MN, and of 1.5 nmol/L for PI MN identified functioning lesions with 100%/100% sensitivity and 93%/97% specificity, respectively. MRI detected 56% right-side Pheo, 25% on the left, and 19% bilateral; PGL were 56.5% (13/23) retroperitoneal and 43.5%, cervical (10/23). Right-side Pheo were larger (5.8 cm) than left-side ones (3.7 cm), but retroperitoneal (6.5 cm) and neck PGL (6.9 cm) were similar. Tumour size positively correlated with total Ur MN.

Conclusions: in this large cohort of PPGL patients we highlighted relevant aspects of SAH, the frequently overlooked manifestation of orthostatic hypotension, common incidental presentation, significant tumour size/hormonal production.

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INTRODUCTION

Pheochromocytomas (Pheo) and paragangliomas (PGL) are uncommon catecholamine-secreting tumors of the adrenal medulla and extra-adrenal chromaffin tissue, respectively. PGL usually develops from the sympathetic paraganglia of the chest and abdomen. Both are derived from ectodermal neural crest cells and are grouped under the term Pheo/PGL (PPGL) syndrome (1). Recently, the WHO recommended the single name paraganglioma to designate both adrenal and extra-adrenal pheochromocytomas (2, 3).

The incidence of PPGL is between 500 and 1,600 cases per year, with an equal sex distribution and the highest frequency in the 4th and 5th decades of life. PPGL has a prevalence of 0.1 to 0.6% among the hypertensive population (4-6).

PPGL manifests clinically as sustained arterial hypertension that is usually accompanied by paroxysms (headache, palpitation, and sweating) and refractoriness to antihypertensive medications. Silent PPGL may be found as adrenal incidentalomas. With more genetic discoveries and detection tools, hereditary syndromes will become more common, whereas sporadic disease was the rule in the past (6-10).

Laboratory confirmation is based on elevated levels of plasma and/or urinary fractionated metanephrines. Plasma and urinary catecholamines can also be used, but are less sensitive, as is urinary vanillylmandelic acid (VMA), which was used in the past (11-16). The imaging location of unilateral or bilateral Pheo and cervical (head and neck), thoracic and pelvic PGL can be found by both CT and MRI, which may be functionally complemented by scintigraphy with ¹³¹I-MIBG (meta-iodobenzylguanidine) and ⁶⁸Ga-DOTATATE (DOTA-octreotate) (6, 8, 13, 17-20).

This article will focus on the major clinical, hormonal, and imaging aspects of a large series of PPGL patients studied in a single endocrine reference center in São Paulo, state of São Paulo, Brazil.

MATERIAL AND METHODS

Study population

From 2001 to 2019, we prospectively studied 137 patients ranging in age from 12 to 82 years in whom a diagnosis of Pheo and/or PGL was clinically considered and later confirmed by (i) hormonal assessment, (ii) specific imaging procedures, (iii) genetic evaluation for germline variants, (iv) surgery, and (v) pathological examination. Twenty-one patients were later excluded: 18 declined further participation, and three were under 14 years, the limit age per our protocol. The remaining 116 were 75 females (64.7%) and 41 males, with a median age of 45 years (ranging from 14 to 79 years). All patients were referred to the Adrenal and Hypertension Outpatient Clinic of the Division of Endocrinology and Metabolism, Department of Medicine at EPM/UNIFESP for 1) evaluation of a possible secondary form of hypertension; 2) the presence of a suspicious adrenal or extra-adrenal mass; and 3) the existence of first-degree relatives with PPGL.

Control groups

To analyse and compare values of plasma and urinary metanephrines, we used two control groups, both extracted from an uncharacterized database registry of the Fleury Group, São Paulo, Brazil, after formal authorization: one consisted of data from patients with elevated plasma and/or urinary metanephrines in whom a diagnosis of PPGL was unequivocally established (positive control group); the other comprised data from a large cohort of subjects who had been evaluated for different disorders and included a panel of plasma and/or urinary metanephrines that were all normal. None of those patients were diagnosed with a PPGL at that time (negative control group); non-functioning PPGL could not be excluded.

Positive controls included 56 subjects: 33 females (58.9%) and 23 males ranging in age from 26 to 82 years (median of 54). Fifty of them had Pheo and six had PGL. They were all "functioning" PPGL (hormone-secreting) by definition.

The negative control were 654 subjects: 412 females (63%) and 242 males ranging in age from 16 to 82 years (median of 51). All had plasma and urinary

metanephrines within the Fleury laboratory's reference ranges. "Nonfunctioning" PPGL could not be excluded in them.

All 116 patients from this study cohort (and/or their parents or liable) signed a written informed consent form for all investigational procedures and therapeutic decisions, which were previously approved by the Committee of Ethics in Clinical Research of the Institution. Patients from the positive and negative control groups were individually investigated by their respective physicians. Authorization to use the biochemical data employed in this manuscript, plus sex, age and information that led to the final diagnosis, was provided by the responsible Board of Directors of Fleury Group without personal patient identification.

STUDY DESIGN

The following data were obtained from all patients at the time of admission: sex and age, height and weight (and body mass index, BMI), systolic and diastolic blood pressures and heart rate (HR), specific manifestations of the disease (such as sustained hypertension and/or paroxysms, tachyarrhythmia, orthostatic hypotension, cardiogenic shock), impaired glucose tolerance (prediabetes or diabetes mellitus), presence of comorbidities, family history of PPGL and specific conditions suggesting the presence of germline pathogenic variants (PVs, see below), and current or past use of antihypertensive medications. We used the 2020 Brazilian Guidelines of Hypertension to grade the patient's arterial hypertension (21).

Conditions suggesting the presence of germline PVs were as presented elsewhere (22-24).

LABORATORY EVALUATION

Urinary and blood collections

All patients clinically suspected underwent hormonal evaluation directed towards the hormonal detection of PPGL. Up to 2014, we employed 24-h urinary collections to measure 1) catecholamine excretion: norepinephrine [NE], epinephrine [E],

and dopamine [Dp], 2) fractionated metanephrines: normetanephrine [NMN], metanephrine [MN], and 3-methoxy-tyramine [3MT], and 3) vanillylmandelic acid (VMA). In addition, we simultaneously withdrew blood to measure plasma catecholamines (NE, E, and Dp). From 2014 on, as per the Endocrine Society's PPGL Guideline (8), we started measuring plasma NMN and MN in addition to 24-h urinary metanephrines and discontinued urinary and plasma catecholamines.

In several patients, we also measured plasma chromogranin A by immunoassay or targeted proteomics, and when indicated, we performed a clonidine test (0.3 mg PO with blood collected before and after 3h) and measured plasma catecholamines or metanephrines.

Hormonal measurements

We measured plasma catecholamines, 24 h urinary catecholamines and metanephrines, and VMA by high-performance liquid chromatography (HPLC) using the Chromsystem Commercial Kit. [Chromsystems Instruments & Chemicals, GmbH].

Plasma metanephrines were determined by HPLC coupled to tandem mass spectrometry (LC-MS/MS) through an in-house method developed and validated at the Fleury Group in 2010 [unpublished], in consonance with other protocol (25).

Radiological/Imaging evaluation

We performed the following imaging procedures, as indicated and available: 1) abdominal (adrenal) and pelvic computerized tomography (CT) and/or magnetic resonance imaging (MRI); 2) cervical and/or chest MRI for patients with a suspected head/neck or thoracic tumor; 3) ¹³¹I-mIBG full body scintigraphy; and 4) ¹⁸F-FDG and/or ⁶⁸Ga-DOTATATE or DOTATOC PET-CT.

We analysed the following CT and MRI data: topography, size, and characteristics of the lesion.

We performed whole-body ¹³¹I-mIBG scintigraphy if the image was uncertain, dubious, or suggestive of the presence of metastases (on clinical or hormonal grounds) and in cases of confirmed metas-

tasis to evaluate the possibility of radiopharmaceutical therapy.

We analysed the following data: moderate/strong uptake in adrenal and/or extra-adrenal topographies and uptake in target organs of metastasis (bones, liver, lungs, and lymph nodes).

Not all biochemical and imaging diagnostic procedures were necessary for each patient. We requested specific hormonal and topographic tests only for diagnostic purposes, mainly 24-h urinary NMN/MN and adrenal MRI or CT and/or ^{131}I -mIBG and ^{18}F FDG PET-CT, whenever necessary and available.

Genomic evaluation

Genetic analysis was performed in 115 patients to determine the familial (hereditary) or sporadic nature of their respective diseases using a panel that had the following 23 PPGL-related genes: ATM, ATR, CDKN2A, EGLN1, FH, HRAS, KIF1B, KMT2D, MAX, MDH2, MERTK, MET, NF-1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TP53, VHL, and PIK3CA. The results of the genomic studies are reported elsewhere (22).

Statistical Analysis

All patient variables were deposited in a computer program database (Microsoft Excel) and updated at each follow-up visit. For statistical purposes, all nondetectable values were arbitrarily considered equal to the limit of sensitivity for the assay divided by the square root of 2 (26). We performed parametric and nonparametric statistical tests according to the nature of the variable, which were tested for normality by the Kolmogorov-Smirnov test. Descriptive analysis included absolute (n) and relative (%) frequencies and bar graphs of qualitative variables and summary measures (mean, standard deviation, median, minimum, and maximum). Inferential analysis included the association test using Chi-square or Fisher's exact test and the logistic regression-stepwise forward method and ROC curve analysis to evaluate possible cutoff points for quantitative variables, complemented by calculation of sensitivity and specificity. Cut-

off points were established by ROC curve analysis as recommended (27). $P < 0.05$ was significant.

RESULTS

Among the 116 PPGL patients in the present series, 102 were index cases (probands), and 14 were relatives from 8 families.

Anthropometry and clinical presentation

Table - 1 depicts anthropometric and clinical features of the 116 PPGL patients, separated into Pheo (n= 94) and PGL (n= 22). Among the 94 Pheo patients, one patient also had a neck PGL (thus, in Table-2 and Figure-1, total PGL are 23). The sex ratio was approximately 2 F:1 M. PGL patients were younger (35.5 vs. 45 years, $p < 0.01$) and comprised significantly more subjects ≤ 20 years of age than Pheo (18.2% vs. 6.4%; $p < 0.01$). Median BMI and heart rate were similar between groups.

Patients were referred for investigation mainly owing to systemic arterial hypertension (SAH; 81%) (see below), but also due to a previous positive genetic screening (26.7%), the presence of an adrenal incidentaloma (23.4%), and other reasons (11.2%).

Virtually all Pheo (98.9%) (including the one combined with a neck PGL) and 59.1% of PGL were functioning lesions, in the sense that they produced excessive catecholamines that resulted in clinical manifestations. At presentation, 64.7% of the patients had two clinical manifestations, 25% had only one, and 13.8% had three or more. The most common clinical manifestation was SAH in its various forms.

Blood pressure

Table-1 and Figure-2 show the results related to hypertension. SAH was present in 94 of the 116 PPGL patients (81%), whereas 11 (9.5%) were prehypertensive and 11 (9.5%) had normal blood pressure. Among the 94 hypertensive patients, 28 (29.8%) were in stage 1, 25 (26.6%) were in stage 2, and 41 (43.6%) were in stage 3. Stage 3 SAH prevailed over stages 1 and 2 in the whole PPGL group, especially among the PGL patients. Overall, systolic and diastolic blood

Table 1. Anthropometric and clinical data from all 116 PPGL patients, divided into pheochromocytoma (Pheo) and paraganglioma (PGL). Data are mean $\pm$ SEM, median and range, and absolute and percent values.

	Pheochromocytoma	Paraganglioma	All PPGL	p
N=	94*	22	116	
F (%) / M	60 (64%) / 34	15 (68%) / 7	75 (65%) / 41	NS
Age, y (range)	45 (14-72)	35.5 (14-79)	45 (14-79)	<0.001
Age $\leq$ 20y (%)	6 (6.4%)	5 (22.7%)	11 (9.5%)	<0.001
BMI (kg/m ²)	25.0 $\pm$ 0.4	25.5 $\pm$ 1.0	25.1 $\pm$ 0.4	NS
median [range]	24.5 [17.7-42.0]	25.3 [16.5-36.6]	24.6 [16.5-42.0]	
Functioning PPGL	93 (98.9%)	13 (59.1%)	106 (91.3%)	<0.05
Metastatic	4 (4.3%)	7 (31.8%)	11 (9.5%)	<0.001
Heart rate (bpm)	85.0 $\pm$ 1.0	86.7 $\pm$ 2.8	85.3 $\pm$ 1.0	NS
median [range]	88 [64-100]	88 [68-120]	88 [64-120]	
Normal BP	9 (9.6%)	2 (9.1%)	11 (9.5%)	NS
Pre-hypertension	7 (7.5%)	4 (18.2%)	11 (9.5%)	
Hypertension	78 (83%)	16 (72.7%) ^φ	94 (81%)	
Paroxysms only	6 (6.4%)	1 (4.6%)	7 (6.0%)	
Post. hypotension	65 (69.1%)	10 (45.5%)	75 (64.7%)	<0.05
Witht Htn (%)	59 (90.8%)	10 (100%)	69 (92%)	
Without Htn (%)	6 (9.2%)	0 (0%)	6 (8%)	
Only hypertensives:				
– Stage 1 Htn	25 (32.1%)	3 (18.8%)	28 (29.8%)	NS
– Stage 2 Htn	21 (26.9%)	4 (25%)	25 (26.6%)	
– Stage 3 Htn	32 (41%)	9 (56.3%)	41 (43.6%)	
SBP (mmHg)	168.3 $\pm$ 2.9	173.4 $\pm$ 8.0	169.1 $\pm$ 2.8	
median [range]	165 [135-270]	170 [130-250]	170 [130-270]	
DBP (mmHg)	99.6 $\pm$ 1.7	110.0 $\pm$ 5.5	101.4 $\pm$ 1.7	
median [range]	95 [70-150]	100 [80-150]	100 [70-150]	
Sustained BP only	31 (39.7%)	8 (50.0%)	39 (41.5%)	NS
Sustained + Paroxysms	47 (60.3%)	8 (50.0%)	55 (58.5%)	
Difficult control	20 (25.6%)	6 (37.5%)	26 (27.7%)	

* includes one pt. with both a right pheo and a neck PGL;

φ hypertensive neck PGLs were possibly essential.

Table 2 - Imaging data from all 117 PPGL lesions (116 patients*), divided into pheochromocytoma (Pheo) and paraganglioma (PGL). Data are mean $\pm$ SEM, median and range, or n (%).

	Pheochromocytoma	Paraganglioma	All PPGL lesions
N	94*	23*	117
Imaging data			
MRI / CT	87 / 10	23 / 1	110 / 11
Incidentaloma	22 / 94 (23.4%)	0 / 23	22 / 117 (18.8%)
Unilateral Pheo (R/L)	53 (56.4%) / 23 (24.5%)	----	76 (65.5%)
Bilateral	18 (19.2%)	----	18 (19.2%)
Size [#] R/L (cm)	5.8 $\pm$ 0.4 / 4.5 $\pm$ 0.5	----	5.3 $\pm$ 3.3
median [range]	5.8 [1-24] / 3.7 [0.6-12]	----	5.0 [6-24]
Retroper/Neck*	----	13 (56.5%) / 10 (43.5%)	23 (19.6%)
Size Retr/Neck (cm)	----	7.2 $\pm$ 1.0 / 6.3 $\pm$ 0.7	6.8 $\pm$ 6.2
median [range]	----	6.5 [2.2-14] / 6.9 [3-9]	6.8 [2.2-14]
Functional imaging			
¹³¹ I-mIBG	77	14	91
Unilateral Pheo (R/L)	40 (52.0%) / 21 (27.3%)	----	61 (67.0%)
Bilateral	16 (20.7%)	----	16 (17.6%)
Retroper/Neck*	----	9 (64.3%) / 5 (35.7%)	14 (15.4%)

* = includes one pt. with both a right pheo and a neck PGL; # = includes bilateral lesions (all right side = 71; all left side = 41).

Figure 1 - Individual values of fractionated plasma and 24-h urinary catecholamines (epinephrine, norepinephrine, and dopamine) from 15 patients with PPGL. Shaded areas represent reference laboratory values. Note the semilogarithmic scale; horizontal bars denote means.

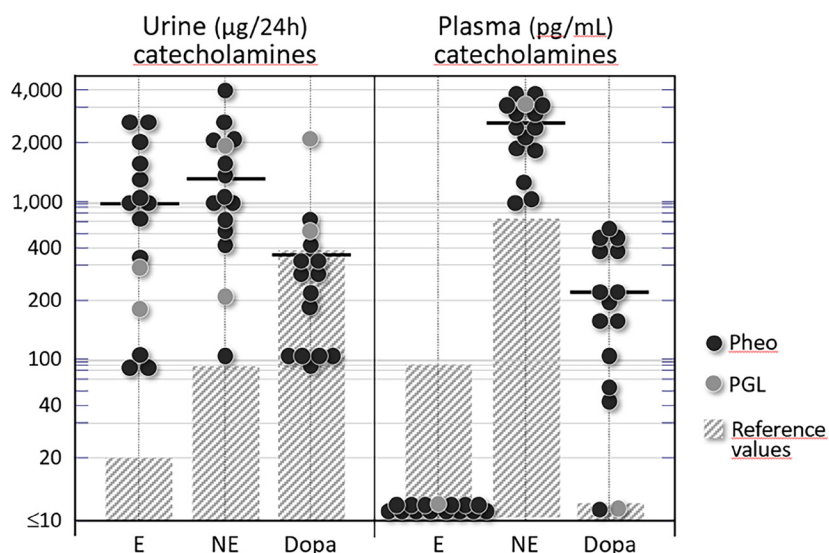
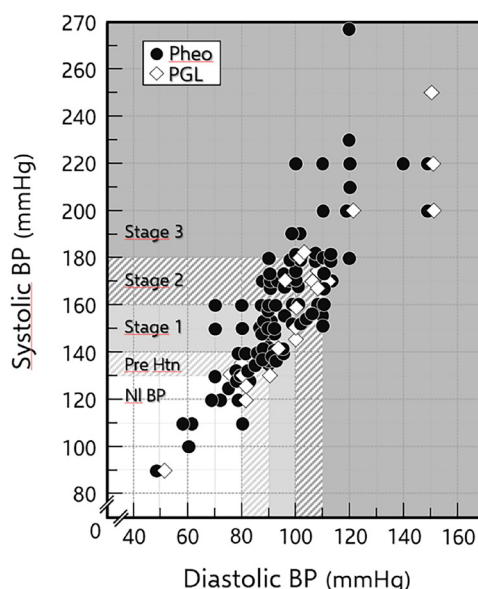


Figure 2 - Individual paired values of systolic and diastolic blood pressure from the 116 PPGL patients studied. Background shaded grades define areas of normal blood pressure (NI BP), prehypertension (pre-Htn), and stages 1 to 3 hypertension. Solid circles denote pheochromocytomas; open lozenges denote PGL.



pressure (BP) were higher in hypertensive PGL than in Pheo, albeit not significantly.

High BP was found alone in 29 (37.2%) hypertensive PPGL patients (29 Pheo) and was accompanied by paroxysms in the remaining 31 (32.9%) (29 Pheo). Hypertension that was difficult to control (resistant SAH) was present in 26 (27.7%) PPGL patients (20 Pheo) presented paroxysmal and combined hypertension. Seventy-five (64.7%) patients (65 Pheo) had orthostatic hypotension, six of whom (8%, all Pheo) did not have hypertension of any form (all genetic [cluster 2], hormonally secretory, and generally smaller in size).

The estimated median time for presentation of SAH (with or without paroxysms) was 24 month (ranging from 1 to 480 months).

PPGL-associated comorbidities

Impaired glucose tolerance was the most frequently associated comorbidity, present in 18.1% of cases. These other comorbidities were mostly associated with genetic disease: medullary thyroid carcinoma (15%), type 1 neurofibromatosis (7.8%), primary hyperparathyroidism (4.3%), retinal angioma and central

nervous system (CNS) hemangioblastomas (3.4%), and clear cell renal carcinoma (3.4%).

Metastases

Recurrence of PPGL and metastasis occurred in 11 (9.5%) patients (Table-1): seven PGL (six with germline PVs in the SDHB gene and one in the VHL gene) and four Pheo (one with a PV in the NF1 gene). Metastases involved lymph nodes in all, blood vessels in eight, bone (spine and pelvis) and liver in five each, lungs in three, and CNS (head and neck PGL) in two.

Two patients relapsed after 12 months, five after 36 months, and one each after 5, 28, and 33 years. The last two patients have already been discharged from their respective medical services after 10 years of uncomplicated follow-up. Nevertheless, paroxysmal hypertension and a syndrome of weight loss/sarcopenia manifested in them after another 18 and 23 years, respectively.

Hormonal presentation

Urinary and plasma metanephrines

With the large negative control population (n= 654) as reference, we defined our own reference ranges

for total and fractionated 24-h urinary and plasma MN as follows (results in mean $\pm$ SE, and [range]): 24-h urinary NMN: 214.8 ± 4.0 mcg/24 h [15-784]; MN: 81.9 ± 1.6 mcg/24 h [3.5-326], and total metanephrines: 296.7 ± 4.7 mcg/24 h [33-878]. Plasma NMN: 0.45 ± 0.01 nmol/L [0.14-1.0] and MN: 0.18 ± 0.01 nmol/L [0.14-0.6], and total metanephrines: 0.63 ± 0.01 nmol/L [0.28-1.5].

As shown in Table-3, 88 PPGL patients from the present study and, especially, 56 from the positive control group had significantly higher levels of NMN, MN, and total MN than the negative controls. The individual values of 24-h urinary MN from these subjects are shown in Figure-3.

A cut-off value of 885 mcg/24 h for total urinary MN, determined by ROC curve analysis, had 100% sensitivity and 92.5% specificity at separating functioning from nonfunctioning PPGL (study cases and positive controls vs. negative controls). In fact, 67.4% of the 24-h urinary total MN values were above 885 mcg/24 h in the subgroup of functioning PPGL from this study and the positive control groups, compared to none in the negative controls (Figure-3).

Table-3 also shows that plasma metanephrines (NMN and MN) from the study group ($n = 20$) and the positive control group ($n = 56$) were significantly higher than those from the negative control group ($p < 0.01$). A cut-off value of 1.5 nmol/L for total plasma MN determined by ROC curve analysis had 100% sensitivity and 97.3% specificity to separate functioning from nonfunctioning PPGL lesions (study cases and positive controls vs. negative controls).

Urinary and plasma catecholamines

The following results were obtained for 24-h urinary catecholamines from 13 patients with Pheo and two with PGL: epinephrine: 906 ± 216 mcg/24 h (800; range: 70-2,500); norepinephrine: $1,275 \pm 263$ mcg/24 h (900; range: 100-3,900); and dopamine: 360 ± 123 mcg/24 h (250; range: 70-2,000). Figure-1 depicts all the individual values.

None of the PPGL patients had detectable values for plasma epinephrine, whereas plasma norepinephrine was $2,373 \pm 221$ pg/mL (2,500; range:

900-3,500) and dopamine was 215 ± 42 (180; range: 28-500). Individual values are shown in Figure-1.

Clonidine test and chromogranin A

Clonidine tests were performed in seven PPGL patients (six Pheo) and were positive in all.

Plasma chromogranin A was above 800 ng/mL (reference values < 93 ng/mL) in three patients with metastatic PPGL.

Topographic distribution and tumor size

Most PPGL patients (93.9%) were initially imaged by MRI instead of CT (given the ease of performing it in our service). Imaging features from all patients are shown in Table-3: 53 Pheo (56.4%) were located on the right side, 23 (24.5%) on the left, and 18 (19.2%) were bilateral. Among the 23 PGL, 13 (56.5%) were retroperitoneal and 10 (43.5%) were cervical.

Table-2 also shows tumor sizes (larger diameter). Note that the Pheo located on the right side were significantly larger than those on the left (including the bilateral ones) (median of 5.8 vs. 3.7 cm, respectively) ($p < 0.01$). Retroperitoneal and neck PGL had similar sizes (medians of 6.5 and 6.9 cm, respectively). The individual sizes of all PPGL lesions are depicted in Figure-4. Note that 70% of all 117 PPGL lesions were larger than 3 cm in diameter (and 61% were larger than 4 cm).

High signal intensity on the T2-weighted sequence was observed in 108 of the 109 patients (99.1%) who underwent MRI. Among the 11 PPGL patients who underwent CT imaging, all typically had pre-contrast attenuation values above 10 HU, above 20 HU in the portal phase, and a contrast washout $< 60\%$.

¹³¹I-mIBG whole-body scintigraphy

As shown in Table-2, 91 PPGL patients underwent ¹³¹I-mIBG scintigraphy: 77 in the Pheo group (40 right-side, 16 bilateral) and 14 in the PGL group (nine retroperitoneal).

Fifty-seven PPGL patients (52.3%) underwent both MRI and ¹³¹I-mIBG scintigraphy: 29 (50.9%) had right-side and 17 (29.8%) left-side Pheo (including one with a neck PGL), six (10.5%) had retroperitoneal and three (5.3%) neck PGL, and two (3.5%) had bilateral

Table 3 - Urine and plasma total and fractionated metanephrines from 88 PPGL study patients and the positive and negative control groups. Their laboratory upper reference values are written (see text for explanation). Data are mean $\pm$ SEM, median and range, or n (%).

	Pheochromocytoma	Paraganglioma	All PPGL	Positive Controls (Pheo)	Positive Controls (PGL)	Positive Controls (All PPGL)	Negative Controls	Reference
24h-Urine data ($\mu\text{g}/24\text{h}$)	N= 71	N= 17	N= 88	N= 50	N= 6	N= 56	N= 654	
NMN (mean $\pm$ SE)	1,354 $\pm$ 158	1,748 $\pm$ 554	1,430 $\pm$ 165	4,860 $\pm$ 2,026	437 $\pm$ 65	4,387 $\pm$ 1,817	214.8 $\pm$ 4.0	< 800
median [range]	971 [21-5,800]	600 [48-7,543]	892 [21-7,543]	697 [150-72,768]	425 [217-716]	639 [150-72,768]	201 [15-784]	
MN (mean $\pm$ SE)	1,076 $\pm$ 168	112 $\pm$ 47	890 $\pm$ 142	911 $\pm$ 350	82 $\pm$ 22	822 $\pm$ 315	81.9 $\pm$ 1.6	< 400
median [range]	580 [3.5-6,572]	50 [3.5-800]	277 [3.5-6,572]	147 [37-15,453]	85 [4-170]	145 [4-15,453]	76 [3.5-326]	
Total MN (mean $\pm$ SE)	2,430 $\pm$ 239	1,860 $\pm$ 540	2,320 $\pm$ 219	5,771 $\pm$ 2,048	519 $\pm$ 87	5,208 $\pm$ 1,840	296.7 $\pm$ 4.7	< 1,200
median [range]	1,950 [28-10,300]	675 [112-7,547]	1,882 [28-10,300]	859 [258-72,835]	497 [221-886]	822 [221-72,835]	286 [33-878]	
Plasma data (nmol/L)	N= 14	N= 6	N= 20	N= 50	N= 6	N= 56	N= 654	
NMN (mean $\pm$ SE)	29.9 $\pm$ 7.3	71 $\pm$ 5.6	23.0 $\pm$ 5.8	19.1 $\pm$ 10.4	1.5 $\pm$ 0.2	17.2 $\pm$ 9.3	0.45 $\pm$ 0.01	< 0.9
median [range]	21.9 [0.6-80.2]	1.6 [0.6-35]	8.6 [0.6-80.2]	2.3 [1-502]	1.5 [1-2.3]	2 [1-502]	0.4 [0.14-1.0]	
MN (mean $\pm$ SE)	11.4 $\pm$ 4.5	0.5 $\pm$ 0.1	9.0 $\pm$ 3.4	1.5 $\pm$ 0.5	0.2 $\pm$ 0.0	1.4 $\pm$ 0.4	0.18 $\pm$ 0.001	< 0.5
median [range]	2.2 [0.2-45.0]	0.4 [0.2-0.9]	1.0 [0.2-45.0]	0.3 [0.1-17.2]	0.2 [0.1-0.3]	0.3 [0.1-17.2]	0.14 [0.14-0.6]	

MN = metanephrines; NMN = normetanephrines

Figure 3 - Individual values of total and fractionated 24-h urinary metanephrines from 89 patients with PPGL and 56 positive controls (see text for explanation). Shaded areas represent the normal ranges (minimum and maximum values from the negative control group). Note the semilogarithmic scale; horizontal bars denote means. Boxed numbers atop each series represent the percentage of values above the upper limit of normal (ULN).

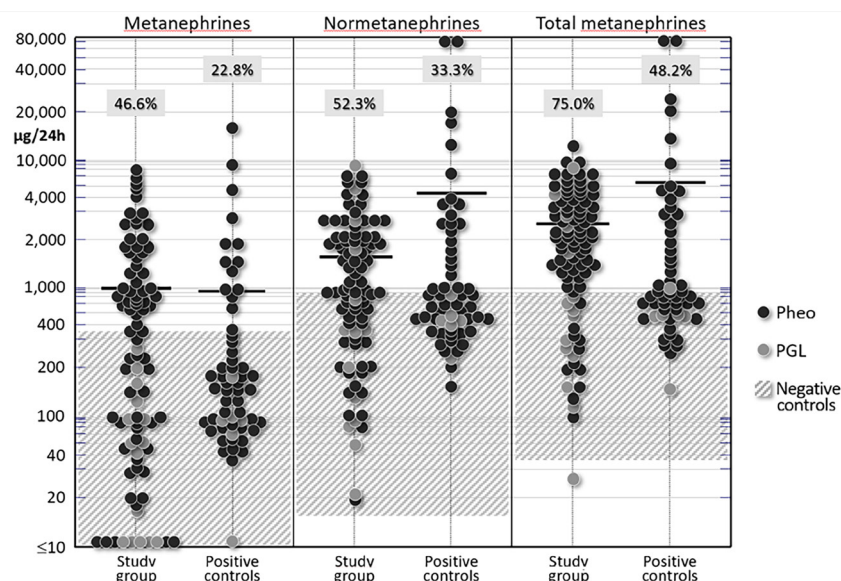
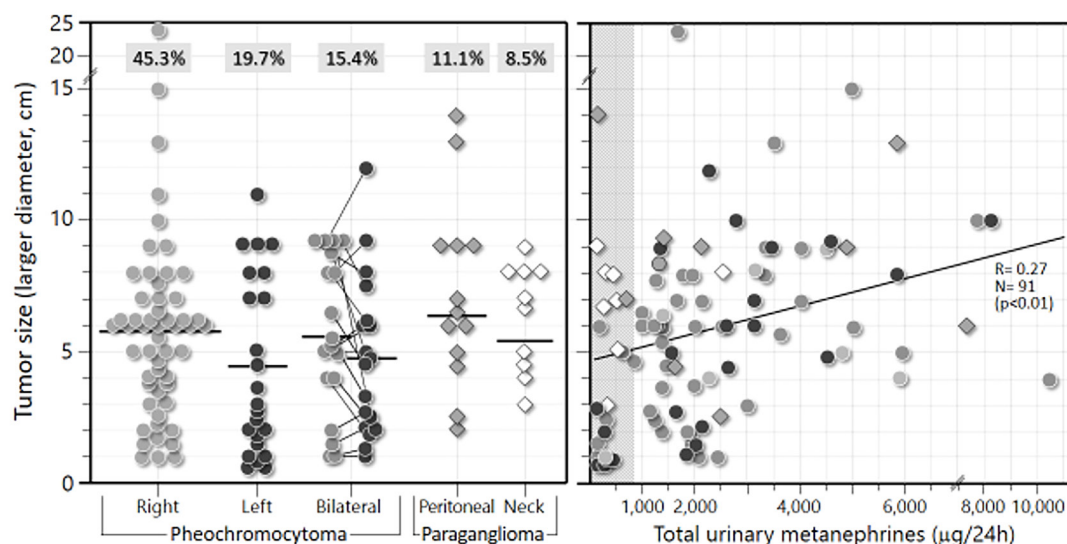


Figure 4 - Individual location and size of lesions from 116 PPGL patients. Size is the largest diameter (in cm) obtained by CT or MRI. A) Horizontal bars denote means. Boxed numbers atop each series represent percentages of total PPGL. B) Correlation between lesion size and 24-h urinary excretion of total metanephrines from 89 patients with PPGL. Represented are either unilateral pheochromocytomas or the larger lesion of the bilateral ones.



Pheo. The concordance between both procedures was 98.2%. The only discordance occurred in the patient with adrenal Pheo and neck PGL, in whom uptake was observed only in the left adrenal Pheo. ^{131}I -mIBG scintigraphy was done in 30 (63.8%) of the 47 patients carrying PVs: uptake was observed in 29 of them (22).

In eight PPGL patients (two Pheo with an SDHB gene PV), metastases were present or developed during follow-up. Lesions were identified in the spine and pelvis by ^{68}Ga -DOTATATE PET-CT.

Metanephrines and tumor size

A significant positive correlation was observed between tumor size (larger diameter, in cm) and total urinary MN (in mcg/24 h) for 91 functioning PPGL (74 Pheo and 17 PGL): $r = 0.27$; $p < 0.01$ (Figure-4). Nonfunctioning PPGL, especially head and neck PGL, presented 24-h urinary MN within the normal range.

DISCUSSION

PPGL is a rare neuroendocrine tumor that is potentially metastatic and fatal if this diagnosis is not promptly suspected and treatment is not started soon. Its incidence has been increasing recently due to improvements in the measurement of catecholamine metabolites and a greater demand for imaging tests. Unfortunately, there is still a significant diagnostic delay, some diagnosis only coming postmortem (2, 3).

This diagnostic delay was confirmed in our population sample: most patients took two or more years to seek medical assistance, and one of them took almost 40 years to be diagnosed. Hence, major complications related to hypertension are to be expected.

PPGL is one of the main diagnostic possibilities in the investigation of secondary and/or resistant forms of SAH, regardless of the presence of paroxysms. Clinical scores are available to help define an individual's risk of having PPGL. Features such as hyperhidrosis, palpitations, pallor, tremors, and nausea are 30-90% more prevalent in the PPGL population than in other hypertensive patients. These characteristics plus a heart rate above 85 bpm and BMI $< 25 \text{ kg/m}^2$ guarantee scores close to the maximum of 7 points, a score that makes

PPGL 5.8 times more likely than lower scores do (14).

The main manifestation in our patients that led to the suspicion of PPGL was sustained SAH. Other common ones were paroxysms, genetic screening, difficult-to-control SAH and adrenal incidentalomas, consistent with the medical literature (7, 13, 19). When first investigated, most patients were already taking two or more classes of antihypertensive drugs. Orthostatic hypotension was a mostly relevant finding, often associated with SAH but also found in normotensive patients who were initially referred for genetic screening or evaluation of adrenal incidentaloma. This finding is important in the initial evaluation, as it is often present whether the individual has SAH or not.

Normotensive and prehypertensive patients (almost 20% of our sample) were referred for evaluation of PPGL due to a positive family history or presence of adrenal incidentaloma (22%), as has been reported (19, 22-24, 28, 29, 31, 32). These data also help to dismiss the outdated "rule of 10%" for PPGL.

Investigation of PPGL is recommended for recent-onset diabetes mellitus in a young, lean, hypertensive patient since catecholamine excess favours hepatic gluconeogenesis and less degranulation of insulin by pancreatic beta cells (13). Eighteen percent of our patients had impaired glucose tolerance, raising the question whether diagnosis and treatment of PPGL could change some subjects' DM history, even leading to a "cure".

The landscape of PPGL germline gene variants from 115 of our patients had many pathogenic and likely pathogenic variants, most often in the RET gene, followed by the VHL and SDHB genes (22, 34, 35).

Total plasma MN are considered the gold standard for the diagnosis of functioning PPGL, with slight superiority over 24-h total urinary MN. In the past, the combination of urinary MN with plasma/urinary catecholamines was recommended because of its lowest false negative rate; however, plasma MN alone is diagnostically better than any of the combined tests. Negative plasma MN virtually excludes functional PPGL, but in its absence, 24-h urinary MN can replace them. Thus, the current laboratory diagnosis of PPGL must include plasma and/or 24-h urinary MN (6-9, 13, 15, 30, 33).

Both our PPGL study patients and the positive control group presented very high values of 24-h urinary and plasma MN compared to our large reference negative control group, even when nonfunctioning PPGL (especially those located in the neck) were included. The cut-off value of 885 mcg/24 h had a sensitivity and specificity of 100% and 92.5%, respectively, for total urinary MN. Thus, 24-h urinary MN alone is likely a sensitive and good marker of PPGL functionality, useful for screening patients for the disease.

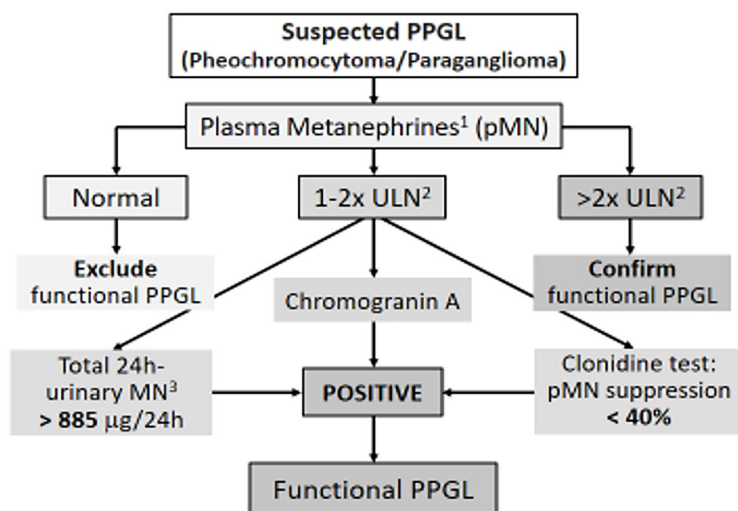
Plasma MN values twice above the upper limit of normal are strongly suggestive of PPGL, whereas values between 1X and 2X are considered suspect, requiring diagnostic complementation with 24-h urinary MN and/or chromogranin A measurement and/or a suppression test with clonidine. Based on our findings and others, we suggest a simple and direct algorithm (Figure-5) to diagnose functioning PPGL. The measurement of 3-methoxy-tyramine can help in the diagnosis of PPGL, especially in dopamine-producing, metastatic, and neck PGL (13).

The topographic diagnosis of PPGL should initially be made with CT of the adrenals and pelvis,

whereas MRI would be reserved for specific cases such as carriers of PV in PPGL-related genes, intracardiac and head/neck PGL, pregnant women, children, tumor recurrence and metastatic PPGL. Both imaging procedures have good sensitivity and specificity for the diagnosis of PPGL. The characteristics of PPGL on CT are attenuation values in the pre-contrast phase greater than 10 HU, usually above 20, with a contrast washout <60% and high signal intensity ("light-bulb" bright) on the T2-sequence and out-of-phase sequence of MRI, with no loss of signal (8, 9, 13).

The ready availability of MRI over CT in our group prompted us to study 109 of our 116 patients with MRI at first, which was able to identify the high signal intensity on T2 in 108 of them; seven of the patients who underwent adrenal/pelvis CT had characteristics of a nonadenomatous lesion. The tumor diameter in our patients was mostly in the range of 5 to 6 cm. We identified three micropheochromocytomas (the smallest measuring 3 mm in diameter), none of hereditary origin, whose images disclosed only adrenal thickening, but their adrenergic clinical picture was exuberant. Increased hormonal levels were detected during adrenergic episodes.

Figure 5 - Suggested algorithm for laboratory investigation of functioning pheochromocytoma/paraganglioma (PPGL). 1 Measured by HPLC coupled with tandem mass spectrometry (LC-MS/MS); 2 ULN= upper limit of normal; 3 Measured by HPLC or LC-MS/MS.



The largest Pheo in our series was 24 cm in diameter and was initially suspected to be a primary adrenal carcinoma.

We found a significant positive correlation between tumor size and total 24-h urinary MN. Functioning PPGL with a diameter greater than 5 cm tend to produce total urinary MN above 1,000 mcg/24 h.

Whole-body scintigraphy with ^{131}I -mIBG was employed in 57 of our patients for the following reasons: to search for PGL foci (mainly in hereditary cases) and to investigate metastases, dubious MRI or CT images and the possibility of treatment with radiopharmaceuticals. In all, scintigraphy had excellent agreement with MRI, in addition to accurately mapping hereditary cases and metastases. One patient with a PV in the NF1 gene underwent an exam that was able to identify metastases following tumor recurrence, which made treatment with ^{131}I -mIBG possible.

In advanced and aggressive metastatic PPGL cases and in those with PV in the SDHB gene, ^{131}I -mIBG scintigraphy was not able to identify all foci of metastasis, unlike ^{68}Ga -DOTATATE PET-CT and ^{18}F FDG PET-CT. Therefore, in these situations, we suggest initially performing ^{68}Ga -DOTATATE PET-CT and later performing ^{18}F FDG PET-CT.

In summary, we present the clinical, hormonal, and imaging picture of a representative cohort of PPGL patients studied in a single reference center in São Paulo, Brazil, whose data mostly agree with other series reported worldwide. Of note, nearly 25% of the Pheo were discovered incidentally. Sustained SAH was present in more than 80% of cases (especially PGL patients), mostly severe and treatment-resistant and typically accompanied by paroxysms. Two-thirds of patients had orthostatic hypotension, an important but generally overlooked diagnostic clue. Diagnostic confirmation of a functioning PPGL strongly relies on the finding of elevated metanephrines (plasma and/or 24-urinary), complemented by chromogranin A and/or a clonidine test, as necessary. MRI was particularly valuable to identify PPGL and to investigate patients with germline variants: the right adrenal gland was more frequently affected than the left, and bilateral masses were present in 20% of cases. The average mass diameter was 5-6 cm, and

the larger the mass, the more marked its total urinary metanephrine excretion. ^{131}I -mIBG was virtually 100% concordant with MRI. Although uncommon, the diagnosis of PPGL should be considered in young, lean, treatment-resistant hypertensive patients with an impaired glucose tolerance or new-onset diabetes mellitus.

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CONFLICT OF INTEREST

None declared.

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First Brazilian Series of Urologic Surgeries Using Versius Robotic Multiport Platform

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ABSTRACT

Purpose: This is the first series of urological conditions using the Versius Surgical System® platform in Brazil. We evaluated perioperative results, and surgeons' learning curve in Brazilian hospitals.

Materials and Methods: This prospective, multicenter study included urological surgeons certified on the Versius® platform and their respective procedures from May 2022 to August 2024. Perioperative variables included type of surgery, docking time, console time, number of bedside units (BSUs), complications according to the Clavien-Dindo classification, readmission and reoperation rates within 30 days after surgery. Surgeons were stratified according to experience in laparoscopy and robotic surgery.

Results: Nineteen surgeons and 302 urological procedures were included. There was no statistically significant difference between docking time and console time when comparing obese patients (BMI > 30, p=0.507) and non-obese patients (BMI < 30, p=0.733). One hundred thirty-seven (45.4%) surgeries were performed by surgeons with experience in laparoscopy and robotics (> 5 years), and 238 surgeries (78.8%) were performed by surgeons who had more than 10 Versius® procedures. Docking time was 13.4 (SD 7.23) minutes. Nephroureterectomy was the procedure with the shortest docking (8.7 minutes, 6–13 min) and console (83.3 minutes, 38–152 min) times. Of the 10 surgeons with 10 or more procedures, 6 had shorter docking times, and 4 had shorter console times. There were four Clavien-Dindo III-IV complications within 30 days postoperatively (1.3%), and six (2%) patients required reoperation. Mean hospital stay was 2 days.

Conclusion: This study is the largest Brazilian and worldwide case series of urological surgeries performed using the Versius® robotic platform. Our results demonstrate the safety and efficacy of the Versius® platform and provide real-world evidence of the surgeons' learning curves and performance based on their prior expertise in laparoscopic and/or robotic surgery.

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INTRODUCTION

The field of minimally invasive surgery, particularly in Urology, evolved significantly during the early 2000s when the Da Vinci® robotic platform (Intuitive Surgical, Sunnyvale, CA, USA) was approved by the Food and Drug Administration (FDA) in the United States. Despite the benefits demonstrated by the robotic technique for patients, over the last 20 years, the Da Vinci® platform has been used in a still limited number of patients globally (1, 2). However, several new multiport and single-port robotic platforms have been developed, and some are now clinically available (2).

The Versius Surgical System® (CMR, Cambridge, United Kingdom) has innovative features that differ from the original Da Vinci® concept. It is a new teleoperated surgical robotic system intended for use of robotic assisted surgery with an ergonomic open console and modular configuration of arms. Moreover, the open design of the console has the advantage of facilitating communication between the team, and the manual controls provide all functions, including cutting and coagulation energies, without pedals attached to the console (3, 4). The Versius® arm is designed to mimic the human arm and wrist. Instruments reach up to seven degrees of freedom, which results in a better dissection and surgical approach than laparoscopy. The operating room does not require specialized infrastructure to accommodate the system, and the instruments are sterilized in a standard autoclave (5).

In Brazil, Versius® was registered for clinical use with ANVISA (National Health Surveillance Agency) in July 2021 (Registration 81346500064), and the first surgery was performed on April 19, 2022. Currently, there are 10 Versius® platforms installed in eight Brazilian states [Rio Grande do Sul (2), Santa Catarina (2), São Paulo (1), Rio de Janeiro (1), Bahia (1), Espírito Santo (1), Mato Grosso (1) and Federal District/Brasília (1)]. More than 1500 patients underwent Versius® surgical procedures by different surgical specialties, including Urology (cmrsurgical.com). Our hypothesis is Versius® a safe platform and the

learning curve is feasible for Brazilian surgeons? This is the first Brazilian series of urological surgeries using the Versius® platform and evaluates this platform's perioperative results, learning curve and safety in the Brazilian reality.

MATERIALS AND METHODS

This prospective, multicenter study describes the clinical experience of Brazilian urological surgeons qualified and certified on the Versius® system, according to CMR surgical's training. These surgeons were located at six private institutions located in the South and Southeast regions of Brazil (São Paulo, Santa Catarina and Rio Grande do Sul). Urological surgeons were invited to participate in the study as soon as they were qualified and certified on this robotic platform. If accepted, they signed the Free and Informed Consent Form and received guidance on completing the data collection instrument. Data collection took place between May 2022 and August 2024. This study was approved by the Research Ethics Committee of Instituto Presbiteriano Mackenzie, CAAE no. 80018524.0.0000.0103.

This Versius® system comprises the surgeon's console with hand controllers to manipulate the arms and camera of the four robotic arms [bedside units (BSUs)] (Figure-1).

The modular configuration is independent of the BSUs, providing several docking options depending on the patient's characteristics and the surgical team's needs as well as a high flexibility in port-placement following the surgeon to replicate as far as possible the setup of conventional laparoscopic surgery. The surgeon receives three-dimensional high-definition video-feedback from the camera via head-up display (Figure-2). As a disruptive system due to the difference of Da Vinci system, the docking with modular arms and docking with an open console without pedals (Figure-2) could impact in the learning curve.

A prospective, non-consecutive database was developed, including pre-, intra-, and postoperative variables completed by the surgeons responsible for

Figure 1 - Console and bedside units.



Figure 2 - Open Console with no pedals and docking of modular arms (BSUs).



each surgical case, which were obtained through the CMR Surgical data manager system. The variables of interest included type of surgery, docking time, console time, number of BSUs used, complications according to the Clavien–Dindo classification, readmission within 30 days and reoperation within 30 days.

Surgeons were stratified according to their experience in laparoscopy and robotic surgery (laparoscopy < and > 5 years, robotics < 5 years, laparoscopy and robotics < and > 5 years) to assess the impact of prior experience on the learning curve.

STATISTICAL METHODS

The data were cataloged in Excel and later exported to IBM SPSS statistics version 20.0 for statistical analysis. The normality of the variables was verified using the Kolmogorov–Smirnov test. The variables with a normal distribution were described using the mean and standard deviation, and those with asymmetric distribution were described by the median and interquartile range. The qualitative variables were described by frequencies and percentages.

RESULTS

Of the 24 qualified and certified surgeons at these locations, 19 (79.1%) agreed to participate in the study, reporting 302 urological procedures from May 2022 to August 2024. The hospital A included 4 (20%) surgeons and 143 (47.4%) procedures, B included 7 (35%) surgeons and 109 (36.1%) procedures, C included 5 (25%) surgeons and 32 (10.6%) procedures, D included 1 (10%) surgeon and 10 (3.3%) procedures, E included 2 (5%) surgeons and 6 (2%) procedures, F included 1 (5%) surgeon and 2 (0.7%) procedures. One surgeon performed surgery at institutions E and F.

Table-1 shows the distribution of surgeons according to their previous experience in laparoscopy and/or robotics, the number of surgeries per surgeon, the different robotic procedures performed in this case series and the distribution of procedures performed according to docking time and console time.

The study sample included 259 (85.8%) male and 43 (14.2%) female patients, with a mean age of 63.8 years (SD 12.6; 21–86) and mean BMI of 27.3 (SD 4.6; 16.6–43.4). There was no statistically significant difference between docking time and console time when comparing surgeries on obese (BMI > 30, $p=0.507$) and non-obese (BMI < 30, $p=0.733$) patients.

Regarding the number of BSUs utilized, four were used in 270 (89.4%), and three were used in 32 (10.6%) cases. The most common BSU arrangement was three on the left and one on the patient's right side. This configuration was used in 78 pelvic procedures (25.85%). It was also found that in 240 (79.5%) cases, five access points (four for the robotic forceps and one for the auxiliary laparoscopic) were utilized.

As shown in Table-1, the mean time for BSU docking was 13.4 (SD 7.23) minutes. Moreover, the nephroureterectomy procedure had the shortest docking (mean 8.7 minutes, 6–13 min) and console (mean 83.3 minutes, 38–152 min) times.

Since 10 (52.6%) surgeons had performed ≥ 10 procedures, we performed statistical analyses to verify whether there was a correlation between the reduction in docking time and console time as the surgeon progressed along the robotic platform learning curve (Table-2). The surgeon's previous experience was not considered in the correlation test, but it is described in the table to explain these results. The values presented after the p-value refer to the magnitude, which, when negative, indicates that as surgeons gain experience with each procedure, the time reduces; greater than 0.6 is strong, and 0.4–0.6 is considered moderate. Among the 10 surgeons with ≥ 10 procedures, docking time decreased for six and console time decreased for four as the learning curve developed.

Concerning postoperative complications within 30 days, according to the Clavien–Dindo classification, there were 285 (94.4%) classified as I, 12 (4.0%) as II, 1 (0.3%) classified as III, and 3 (1.0%) classified as IV. Of the 302 patients, only 8 (2.6%) were readmitted to the hospital in less than 30 days post-operatively, and 6 (2%) required reoperation within

Table 1 - Distribution of surgeons according to previous experience, number of procedures per surgeon, types of procedure performed, and procedures performed according to docking time and console time.

Variables		
Surgeons Experience	N	%
Laparoscopy and robotics > 5 years	137	45.4
Laparoscopy and robotics < 5 years	55	18.2
Robotics < 5 years	57	18.9
Laparoscopy > 5 years	43	14.2
Laparoscopy < 5 years	10	3.3
Number of procedures per surgeon	N	%
2-5	8	42.1
6-10	4	21.1
11-20	4	21.1
> 21	3	15.7
Types of Procedures	N	%
RARP*	183	60.6
Partial nephrectomy	53	17.5
RASP#	11	3.6
Radical nephrectomy	9	3.0
Adrenalectomy	8	2.6
Colpopromontofixation	8	2.6
Nephroureterectomy	7	2.3
Pyeloplasty	7	2.3
Radical cystectomy	3	1.0
Retroperitoneal lymphadenectomy	3	1.0
Others	10	3.3
Procedure	Docking Time Average/SD [Min-Max]	Console Time Average/SD [Min-Max]
RARP	12.99 ±7.3 [4-45]	196.7 ±74.2 [49-540]
RASP	13.8 ±5.4 [7-23]	160.2 ±54.3 [104-243]
Partial nephrectomy	13.0 ±5.9 [4-30]	110.5 ±46.8 [38-234]
Total nephrectomy	15.0 ±4.7 [9-21]	126.0 ±43.8 [80-223]
Nephroureterectomy	8.7 ±2.8 [6-13]	83.3 ±40.4 [38-152]
Pyeloplasty	13.3 ±5.4 [6-20]	116.4 ±42.7 [65-189]
Adrenalectomy	15.6 ±8.7 [7-35]	113.1 ±42.9 [50-175]
Colpopromontofixation	22.6 ±15.4 [12-60]	151.2 ±49.2 [90-236]
Radical cystectomy	14.0 ±4.0 [10-18]	238.7 ±3.5 [235-242]
Lymphadenectomy	14.0 ±7.0 [9-22]	128.3 ±119.9 [30-262]
Others	13.3 ±5.5 [5-23]	121.4 ±114.8 [23-420]

Table 2 - Distribution of the correlation between the reduction in docking time and console time according to the surgeon's experience for each procedure.

Surgeon	Experience	N surgeries	Docking Time		Console Time	
			r_s	p	r_s	p
11	LAP < 5 years	10	-0.162	0.678	-0.400	0.286
4	LAP > 5 years	10	-0.163	0.653	-0.167	0.668
7	LAP > 5 years	17	-0.648	0.007	-0.557	0.020
17	LAP > 5 years	15	-0.869	0.0001	0.084	0.766
18	ROB < 5 years	51	-0.700	0.0001	-0.90	0.540
2	LAP and ROB < 5 years	14	-0.691	0.006	-0.130	0.659
10	LAP and ROB < 5 years	23	0.341	0.112	-0.541	0.008
15	LAP and ROB < 5 years	12	0.836	0.001	-0.719	0.008
19	LAP and ROB < 5 years	10	-0.948	0.0001	-0.236	0.511
6	LAP and ROB > 5 years	106	-0.292	0.002	-0.207	0.034

LAP = laparoscopy; ROB = robotic surgery.

Only surgeons with > 10 surgeries were included in the analysis

*Spearman correlation coefficient between variables

30 days. The mean hospital stay was 2 (median 2.23) days. There was one conversion to open surgery due to intraoperative bleeding caused by the release of a hemostatic clip near the aorta.

DISCUSSION

The Versius® platform had its first clinical case performed in India in March 2019, and currently, there are approximately 170 platforms installed in more than 30 countries, with 29,000 surgeries performed worldwide. In Brazil, there are approximately 1500 surgeries performed in different specialties (cmrsurgical.com); however, since the beginning of its clinical use, no urological case series have been reported to date, making this the largest case series of urological surgeries described with the Versius® platform reported in the literature. Soumpasis et al. (6) recently published a cohort of 2083 patients operated on with Versius® in an international multicenter study covering several surgical specialties; however, there were only 169 urological cases. Other previously published urological case series included only 18

(7), 53 (8) and 58 (9) patients, making our case series quite relevant in the literature.

The most frequently performed procedure in this case series was RARP (183 procedures), accounting for 60.6% of the total. The mean docking time for this procedure was 12.99 minutes, and for console time, it was 196.7 minutes. These results were similar to the case series by De Maria et al. (7) and Polom et al. (9) but lower when compared to that of Soumpasis et al. (6). The nephroureterectomy procedure required the shortest docking time (8.7 minutes, SD 2.8). This result was possibly due to the similarity of the arrangement of the Versius® trocars with the pure laparoscopic approach, which is widely known by surgeons, and to the greater ease of performance of this procedure due to the greater spacing between the trocars in nephroureterectomy compared to nephrectomy, easily adapting to any patient biotype.

The Versius®, being modular, allows for using three or four BSUs during the surgical procedure. Both possibilities of BSUs with different trocar arrangements have been validated in preclinical studies, including for RARP and nephrectomies, spe-

cifically (10, 11). In this case series, 270 (89.4%) procedures used four BSUs, which is of great value since the fourth arm is one of the advantages of robotic over laparoscopic surgery. The Versius® adapts to the patient and the team, and our results show no difference between docking and console time for obese ($p=0.507$) and non-obese ($p=0.733$) patients. Due to be modular, a fast undocking of the BSUS in case of emergency was observed in the only conversion to open surgery described. We considered a great advantage of robotic modular platforms.

Regarding the arrangement of the BSUs, the most prevalent was three on the left and one on the right of the patient (25.85%) when in pelvic procedures. This result demonstrates that the teams mostly preferred the third robotic arm in the surgeon's left hand and the bedside assistant on the patient's right side, as in the first description of docking by Rocco B et al. (12).

It is important to point out that properly evaluating robotic surgical techniques is complicated by robots being a "disruptive" technology, changing every aspect of the work environment. Indeed, clinical evaluation of safety and efficacy is only one of many dimensions that must be included in a comprehensive assessment of their overall value (13). In broad alignment with the Idea, Development, Exploration, Assessment, Long-term study- Devices framework, evidence detailing the development of the device has been reported in previous studies validating the usability and operational safety of Versius® (3, 5, 6). Pre-clinical studies have reported the successful use of the device in multispecialty including urological procedures in cadaver and porcine specimens (10, 11). Subsequently, live human clinical studies have evaluated the safety and effectiveness of the device for use in various multispecialty procedures (6-9, 12, 14). We report the largest analysis of urologic cases across a range of surgical indications. Data were reported as a measure of device and surgeon performance and the unprecedented real-world data presented here provide evidence of the safe implementation of a next-generation surgical robot into clinical practice, especially in Brazil.

Previous studies have identified a correlation between surgeons' prior experience and their performance in training on robotic surgical systems (9, 11, 14-17). Butterworth et al. (15) demonstrated that surgeons with extensive experience in robotic surgery performed better in the Versius® training program than surgeons without experience, especially in the depth perception and robotic control domains. On the other hand, some metrics provided by studies using the Versius® simulator suggest that surgeons with prior experience in robotic surgery may take longer to adapt to certain specific Versius® techniques than those without any robotics experience. This result is mainly due to the features of the Versius® that differ from other platforms, such as the hand controller grip and the lack of foot pedals for electrocautery control (6, 8, 15).

Regarding the learning curve, this study demonstrated a decrease in docking time as the curve developed for 6 of the 10 (60%) surgeons who performed 10 or more procedures, while console time decreased for 4 of these same 10 (40%) surgeons. Notably, the type of surgery and the surgeon's previous experience were not considered, which may elucidate why docking time showed a greater reduction with statistical significance than console time. Butterworth et al. (15) suggested that adapting Versius® training to the surgeons' previous experience may facilitate and reduce the learning curve since previous routine with other platforms may have contributed to a longer path in adaptation and learning curve with this platform. On the other hand, the similarity of some aspects, such as the arrangement of the trocars and the grip of the hand controllers, facilitate surgeons with experience in laparoscopy.

Concerning professional experience, 180 (59.6%) procedures were performed by surgeons who reported having experience in laparoscopy and/or robotic surgery for at least 5 years before using Versius®. Although only 7 of the 19 surgeons (36.7%) had performed more than 10 surgeries, the vast majority of the total surgeries (238 surgeries, 78.8%) were performed by these surgeons. In this sense, surgeons experienced in laparoscopy and/or robot-

ics adapt more easily to this platform, as described by other authors (3, 15). Furthermore, this result corroborates the validation of our results regarding the learning curve for using the Versius® platform.

Our study has some limitations: a) the surgeries included does not represent 100% of surgeries performed with Versius® in the period of this study because a small number of surgeons did not include their surgeries in the database, b) our study is not a comparable trial head-to-head with Da Vinci® platform, c) difficulty of comparison to the literature because the few and small urological series published with Versius®.

Versius® exhibited efficacy and safety with comparable results to other robotic platforms in a systematic review that included publications on pre-clinical use in different series with human cadavers and swine models (18) and also included several clinical case series in humans (6-9, 19). Notably, our results concerning complication rate, length of hospital stay, reoperation rate and hospital re-admission are consistent with the literature, specially according to new platforms (20-24). Thus, given the scarcity of publications of urological case series with the Versius® platform, we can conclude that these perioperative results are similar and comparable to those already published with other multiport platforms (2). In addition to being the largest global urological case series with Versius®, it is worth mentioning that this study includes most of the urological procedures that can be performed with robotic technology with outcomes similar to those reported in the literature.

CONCLUSIONS

This study reports the largest Brazilian and global series of urological surgeries performed with the Versius® robotic platform. The perioperative outcomes reported here, including a wide range of uro-oncological surgeries, demonstrate this platform's safety and efficacy and provide real-world evidence of the learning curve and performance of the surgeons according to their prior expertise in laparoscopic and/or robotic surgery.

ABBREVIATIONS

BMI = Body Mass Index

RALP = Robotic Assisted Laparoscopic Prostatectomy

RASP = Robotic Assisted Simple Prostatectomy

MAS = Minimal Access Surgery

BSU = Bedside Units

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CONFLICT OF INTEREST

None declared.

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Impact of Partial Penectomy and Glansectomy on Couples' Sexual Function

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ABSTRACT

Objective: To evaluate the sexual function of couples after surgeries to treat penile cancer.

Material and Methods: Patients who underwent partial penectomy or glansectomy at a cancer center, between April 2014 and January 2024, and their partners were interviewed only once, at least six months after surgery, through individually conducted interviews. We used a semi-structured questionnaire, the Six-Item Female Sexual Function Index Scoring (FSFI-6) questionnaire to assess feminine sexual function and the Erection Hardness Score (EHS) and The International Index of Erectile Function-5 (IIEF-5) questionnaire to evaluate erectile function.

Results: Fourteen couples were included in this study. Five patients underwent glansectomy and nine underwent partial penectomy. All of male patients remained sexually active post-procedure. Of the ten who completed the IIEF-5, five (50%) experienced mild erectile dysfunction. Among partners, twelve (85.7%) continued sexual activity. Of the ten partners who completed the FSFI-6, five (50%) had sexual dysfunction. The size of the penile stump was not correlated with satisfaction of the couples. Four (28.6%) patients adopted adaptive strategies, as engaging in sexual activity in a dark environment and use of silicone penile substitutes. All participants expressed dissatisfaction with the medical information provided by their doctors regarding sexuality after penile surgery.

Conclusions: Many couples described sexual dysfunctions after PC surgeries. However, the majority of couples reported maintaining an active sexual life and the majority of the partners reported achieving orgasm. Unfortunately, counseling by healthcare professionals of these couples about sexual health after surgery to treat PC is inadequate.

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INTRODUCTION

Penile cancer (PC) is rare in industrialized countries, with a higher incidence in regions of Africa, Asia, and South America (1). In Brazil, the incidence varies from 2.9 to 6.8 per 100,000, affecting 5.7% of male neoplasms in populations residing in the Northeast region (2, 3). Squamous cell carcinoma is the most common histological type, accounting for over 95% of malignant penile neoplasms (4).

Early-stage PC (T1-T2) can be conservatively treated with 5-FU, laser, circumcision, or organ-sparing surgery like glans resurfacing and local excision with grafting recommended for glans tumors <4 cm without deep invasion. Invasive PC requires tumor excision with clear margins. T2 glans tumors are treated with glansectomy and grafts. Larger or deeper lesions may need partial penectomy, while total penectomy with perineal urethrostomy is reserved for extensive or advanced cases (5). Prophylactic lymphadenectomy is a viable procedure for selected patients at high risk of metastasis. However, no definitive predictive biomarker of inguinal lymph node metastasis has yet been established and there are many challenges to achieve this goal (6).

Penile surgeries offer good cancer control but impact body image, self-esteem, sensitivity, and sexual function (7, 8). Partial penectomy often leads to erectile dysfunction (ED) and shame over penile size and glans loss, hindering return to sexual activity (9). However, literature is scarce regarding the impact on the sexual life of couples after penectomy or organ sparing surgery, especially concerning the quality of sexual life for partners.

We believe that majority of couples maintain satisfactory sexual function after penectomy or glansectomy and counseling by healthcare professionals of these couples about sexual health is inadequate.

The objective of this study was to assess the impact of partial penectomy or glansectomy on sexual function in patients and partners.

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of our university (IRB 66905623.0.0000.5243).

In this cross-sectional study, patients who underwent partial penectomy or glansectomy at a cancer center, between April 2014 and January 2024, and their partners were invited to participate. They were interviewed only once, at least six months after surgery, through individually conducted interviews. Each participant responded to a semi-structured questionnaire. Demographic and clinical data were retrospectively collected from interviews and medical records. Men were queried about erectile function using validated questionnaires: Erection Hardness Score (EHS) (9), regarding penile rigidity and The International Index of Erectile Function-5 (IIEF-5) (10) concerning the post-operative period. No patients reported the continuous use of phosphodiesterase-5 inhibitors. Additionally, the length of the flaccid penile stump from the pubic symphysis to the distal end of the penis was measured using a ruler by a single observer (11). The partners of these patients had their sexual function evaluated using the Six-Item Female Sexual Function Index Scoring (FSFI-6) questionnaire (12). Exclusion criteria included partners with painful urogenital disease, ongoing incurable cancer, prior extensive pelvic treatment, male partners, couples with less than one year of relationship at the time of surgery, and cases of total penectomy or glans resurfacing.

Data were analyzed using means, standard deviations, frequencies, and percentages. Spearman's correlation was applied, with $p < 0.05$ considered significant. Analyses were performed in MedCalc software® (MedCalc software Ltd, Belgium), version 20.006.

RESULTS

This study included 14 couples in which the man had undergone partial penectomy ($n = 9$) or glansectomy ($n = 5$) for PC surgical treatment. The duration of the relationships ranged from 3 to 50 years, with an average of 22.3 ± 12.9 years. All the couples were married and reported being heterosexual. The average age of the men was 58.8 ± 13.4 years while the average age of the female partners was 56.4 ± 11.6 years. Table-1 details sociodemographic and clinical characteristics of couples and their sexual function scores.

Table 1 - Sociodemographic and Clinical Characteristics of Couples Affected by Penile Cancer and Their Sexual Function Scores.

Couple	Duration of relationship (y)	Patient			Partner			Post-operative time of interview (months)	Surgery type	Pre-operative EHS	Post-operative EHS	IIEF-5	FSFI-6	Penile length (cm)
		Age	Education	Religion	Age	Education	Religion							
1	15	53	HS	E	48	PS	E	22	PP	4	2	20	25	6.5
2	50	74	PS	E	52	PS	E	90	PP	4	3	19	22	5
3	22	45	PS	E	46	PS	E	23	G	4	4	24	25	7
4	3	62	PS	C	59	HS	C	45	G	4	4	24	24	8.5
5	40	66	PS	C	67	PS	C	41	G	4	3	NA	NA	4
6	40	86	HS	C	87	HS	C	29	PP	2	2	10	24	5
7	20	52	PS	E	53	PS	E	24	PP	4	1	9	15	6
8	21	48	PS	C	48	PS	C	75	PP	3	2	NA	NA	4
9	20	50	PS	C	55	HS	E	25	PP	4	4	NA	NA	3.5
10	20	60	PS	C	56	PS	C	25	PP	4	4	NA	NA	7
11	15	41	HS	A	43	CO	C	78	G	3	3	23	9	9
12	10	47	HS	E	62	PS	C	30	PP	3	3	17	8	8.5
13	12	61	PS	A	47	PS	S	18	G	4	4	20	19	6.5
14	24	41	PS	E	43	PS	E	15	PP	3	3	18	18	4
General mean±SD								38.5±24.5		3.6±0.6	3.0±1.0	18.4±5.3	18.9±6.4	6.0±1.8
Glansectomy (G) mean±SD										3.8±0.4	3.6±0.5	22.75±1.9	19.25±7.3	7.0±2.0
Partial penectomy (PP) mean±SD										3.4±0.7	2.7±1.0	15.5±4.8	18.7±6.4	5.5±1.6

SD = standard deviation; HS = high school; PS = primary school; CO = college; E = evangelical; C = catholic; A = atheist; S = spiritualist; NA = not applicable; G = glansectomy; PP = partial penectomy

Of the cases, 13 (92.9%) were localized PC and 1 (7.1%) had advanced PC. Localized PC refers to tumors that are confined to the penis without evidence of lymphatic or distant metastasis, typically classified as T1 and T2 lesions in the TNM staging system. Advanced PC includes tumors that have extended beyond the primary site, involving deeper structures such as the corpora cavernosa or urethra (T3, T4), regional lymph nodes (N1-N3), or distant metastasis (M1) (13). The surgical and anatomopathological findings are better detailed in Table-2.

Nine patients underwent partial penectomy (64.3%) and five underwent glansectomy (35.7%) with split-thickness skin grafts utilized for neoglans reconstruction. Among the 6 patients classified as primary tumor T1, 4 underwent partial penectomy and 2 underwent glansectomy.

Regarding penile size in the flaccid state, the length of the penile stump among these patients ranged from 3.5 to 9 cm (mean $\pm$ SD: 6.0 $\pm$ 1.8cm). Only one patient of the cohort (7.1%) presented with a stump <4 cm, while the patient with the largest penile stump in the series had undergone glansectomy. All the men reported maintaining sexual activity after the surgery. Of the 14 patients in this study, four of them (28.6%) do not engage in penetrative sexual intercourse, opting instead for digital and oral stimulation. Among these four patients, three (75%) underwent partial penectomy and one (25%) underwent glansectomy. Nine patients of this study (64.3%) exhibited a degree of good satisfaction according to the semi-structured questionnaire data, with only one (7.1%) man who underwent partial penectomy reporting an inability to achieve orgasm. The mean reported sexual frequency was 4.8 $\pm$ 4.1 encounters per month. One (7.1%) patient disclosed engaging in extramarital relations post-glansectomy. Of the 14 patients, 10 completed the IIEF-5 questionnaire, as it is applicable exclusively to those engaging in penetrative sexual activity. Of these, five (50%) developed mild ED (IIEF-5 between 17 and 21 points), two (20%) developed moderate ED (IIEF-5 between 8 and 11 points), and three others (30%) did not exhibit ED (IIEF-5 $\geq$ 22). When analyzing the surgery subgroup,

glansectomy did not exhibit ED (mean IIEF-5 $\pm$ SD 22.75 $\pm$ 1.9) while partial penectomy group developed mild ED (mean IIEF-5 $\pm$ SD 15.5 $\pm$ 4.8). Eleven (78.6%) out of 14 patients undergoing reported satisfactory penile rigidity according EHS (score 3 or 4), independently of the specific surgical technique employed. However, EHS score was higher in the glansectomy group (3.6 $\pm$ 0.5) than in the partial penectomy group (2.7 $\pm$ 1) (Table-1).

In regard to the sexual function of their partners, twelve women (85.7%) reported continuing to engage in sexual activity, with discrepancies noted in the male responses in two cases. The average frequency of intercourse reported by them was 3.2 $\pm$ 3.0 times a month. Only four (33.3%) women reported not achieving orgasm, and 6 (50%) exhibited a degree of regular satisfaction according to the semi-structured questionnaire data. Of the 12 women with an active sexual life, 3 (25%) reported good sexual satisfaction, 6 (50%) reported regular satisfaction, and 3 (25%) reported poor sexual satisfaction. Only 2 women reported experiencing pain during sexual intercourse. Despite the pain, both women reported achieving orgasm. Among the 10 women who engaged in vaginal intercourse and were able to respond to the FSFI-6 questionnaire, 5 (50.0%) experienced sexual dysfunction (FSFI-6 $\leq$ 20), primarily related to low sexual satisfaction and difficulty achieving orgasm. The degree of female sexual dysfunction was similar between the surgical type groups (Table-1).

Vaginal intercourse was the preferred type of sexual activity reported by men (35.7%) and their partners (25%). Regarding preferred sexual positions for vaginal intercourse, of the 10 men engaging in this practice, 6 (60%) reported a preference for the man-on-top position, 2 (20%) for the woman-on-top position, 1 (10%) for the doggy-style position, and 1 (10%) for the side position. Although 10 patients reported engaging in penetrative sexual intercourse, 8 partners reported the same. Among the 8 women reporting vaginal sexual activity, 5 (62.5%) preferred the man-on-top position, 1 (12.5%) preferred the woman-on-top position, 1 (12.5%) preferred the doggy-style position, and 1 (12.5%) preferred the side position.

Table 2 - Description of Surgical and Pathological Results in Penile Cancer and Postoperative Sexual Behavior of the Couple.

Surgery type	N (%)
Glansectomy	5 (35.7%)
Partial penectomy	9 (64.3%)
Histological Subtype	
Squamous	13 (92.9%)
Verrucous	1 (7.1%)
Histological Grade	
I (well-differentiated)	4 (28.6%)
II (moderately differentiated)	9 (64.3%)
III (undifferentiated)	1 (7.1%)
TNM Classification	
Primary Tumour	
T1	5 (35.7%)
T2	8 (57.2%)
T3	1 (7.1%)
Regional Lymph Nodes	
N0	12 (85.7%)
N1	2 (14.3%)
Distant Metastasis	
M0	14 (100%)
M1	0
Lymphadenectomy	
Yes	7 (50%)
No	7 (50%)

Sexual intercourse		Patient/Partner
Yes		14 (100%)/12 (85.7%)
No		0/2 (14.3%)
Preferred type of sexual intercourse		
Vaginal		5 (35.7%)/3 (25%)
Digital stimulation		1 (7.1%)/1 (8.3%)
Vaginal/Anal		1 (7.1%)/1 (8.3%)
Vaginal/Oral/Digital Stimulation		3 (21.5%)/2 (16.7%)
Oral / Digital Stimulation		3 (21.5%)/1 (8.3%)
Oral		0/2 (16.7%)
Vaginal/Digital Stimulation		1 (7.1%)/2 (16.7%)
Preferred vaginal sex position		
Man on top		6 (60%)/5 (62.5%)
Woman on top		2 (20%)/1 (12.5%)
Doggy-style position		1 (10%)/1 (12.5%)
Side position		1 (10%)/1 (12.5%)
Orgasm		
Yes		13 (92.9%)/8 (66.7%)
No		1 (7.1%)/4 (33.3%)
Extra-marital relationship		
Yes		1 (7.1%)/0
No		13 (92.9%)/14 (100%)

Four men (28.6%) adopted adaptive strategies. Two of them (50%) started having sexual relations in a dark environment, and the other 2 (50%) began using a silicone penile substitute for vaginal penetration. There was no statistically significant correlation

between penile stump size and sexual satisfaction ($p=0.44$) or type of sexual activity ($p=0.81$). Moreover, there was no significant association between the type of surgical technique (e.g., glansectomy vs. partial penectomy) and either sexual satisfaction or

penile stump length. Data on the couple's sexual behavior after the surgeries are described in Table-2.

In this study, all patients and their partners reported not having been adequately informed about post-surgical sexuality, as answered in the semi-structured questionnaire.

DISCUSSION

PC treatment may be conservative or surgical. Organ-sparing methods preserve function and appearance, with surgical choice based on stage, margins, and patient preference (5, 13, 14). In this study, partial penectomy was the most frequently performed surgical procedure (64.3%), followed by glansectomy (35.7%).

Surgery and cancer affect body image, confidence, sensitivity, and sexual activity, often causing performance anxiety, especially after penectomy, with rates up to 90% (7-9, 15, 16). Despite this impact, few studies assess male sexuality, and only one includes both partners (17).

PC is a disease that usually affects patients aged 50 and over (18-20). In this study, the mean age of the patients was 58 years and of the partners was 56 years. Considering the 14 men who have an active sexual life, the level of sexual satisfaction was deemed good for 9 (64.3%) of them, regular for 4 (28.6%), and poor for only one (7.1%). All of the men reported maintaining sexual activity after surgery, with an average reported sexual frequency of 4.8 encounters per month. According to a literature review involving 128 penectomized patients using 13 different quality of life assessment instruments, an incidence of 36% of cases without sexual activity was observed (8).

Partial penectomy often leads to fewer orgasms and greater concern with penile appearance, especially due to glans absence, even without ED or partner issues (9, 21, 22). In our study, only one man, unable to perform penetration, reported not having orgasms. Within our series, no differences in sexual satisfaction were observed based on the specific surgical technique employed. Nonetheless, Falcone

et al. reported that glans resurfacing seems to provide better sexual outcomes when compared to other organ sparing approaches (14). ED is common after partial penectomy. Monteiro et al. found a 62% incidence, linked to shorter shaft, positive nodes, and age (16). Psychological factors like shame over penile size and glans loss also hinder sexual activity (17).

Penetration influences female sexual satisfaction, with pain or discomfort reducing it (23). Strong pelvic floor muscles are linked to better sexual function (24). In our study, most partners showed a preference for sexual intercourse with penetration, with a preference for the man-on-top position. However, we know that penetrative sex is not the only aspect of a satisfactory sexual relationship (17). Nevertheless, measuring the degree of sexual satisfaction in women is challenging due to biological, psychological, physiological, and cultural variables that can influence the final satisfaction level (25). Therefore, we applied the validated FSFI-6 questionnaire with the aim of using a simpler and reliable assessment tool. In our sample, five women had scores indicative of sexual dysfunction. The partner with the highest level of sexual dysfunction has a partner with of the longest penile stump, measuring 8.5 cm. These findings in this small cohort support the literature that larger penis size and penetration are not unique of female sexual satisfaction (17). Interestingly, the partners who achieved the highest scores on the FSFI-6 questionnaire were those whose partners underwent partial penectomy and glansectomy, with penile stumps measuring 6.5 cm and 7 cm, respectively.

According to a study that applied the FSFI-6 questionnaire to 737 women aged 40 to 55, a prevalence of 53.5% of female sexual dysfunction was observed. Older age, menopausal symptoms, and age at menopause onset were inversely correlated with sexual function (12). Additionally, four women reported not having orgasms, all with a regular satisfaction level. Despite not achieving orgasm, the average sexual frequency was 3.2 encounters per month.

Adaptive measures are often utilized by these couples. A very common condition, which was also observed in our study, is engaging in sexual activ-

ity in a dark environment, indicating protection from visual exposure to the mutilated genitals. Adopting a more favorable position for penetration proved to be a simple and effective action for one of the couples. However, in general, the use of penile stretching sleeves or external penile prostheses was a common tactic employed, including in patients after total penectomy (7, 26). On the other hand, some couples reported engaging in non-penetrative sexual relations, using alternative stimulation techniques, discovering new erogenous zones, and developing new forms of intimacy and emotional connection. Previous studies have shown that, with the maintenance of the partnership, there is a high possibility that post-penectomy sexual relations will be of similar quality to pre-penectomy relations (17, 27, 28). Bhat et al. evaluated the sexual lives of 12 couples after penectomy, including two cases of total penectomy. The authors observed that one patient experienced orgasm through stimulation of the penectomy scar at the base of the penis. Additionally, patients and their partners reported accepting masturbation as a means of achieving sexual satisfaction (17).

PC is a rare tumor, and few urologists have personal experience with the postoperative sexual life of these patients. The lack of data in the medical literature in this area leads physicians to underestimate the sexual performance of patients, who often retain the same ability for intercourse as before surgery (29). In this study, all patients and their partners reported not being adequately informed about post-surgical sexuality. Adequate preoperative counseling by the treating physician can assist in post-treatment adjustment regarding sexuality, for both patients and their partner (17). Additionally, medical support before surgery and the continuity of professional support can improve sexual satisfaction rates for couples who have undergone penectomy (30, 31).

This study has some limitations. Self-reported data may include omissions, and lack of preoperative IIEF-5 limits ED assessment. The small sample size is our main limitation. However, to our knowledge, this is the second study published in the literature evaluating the impact on couple's sexual function

after penectomy with a larger sample and deeper partner analysis. Moreover, the purpose of this study was achieved, and we identified that the majority of couples maintain an active sexual life with satisfactory sexual function, highlighting an important information for the field of Onco-sexology.

CONCLUSION

Many couples described sexual dysfunctions after PC surgeries. Mild to moderate ED was common. However, the majority of couples reported maintaining an active sexual life and the majority of the partners reported achieving orgasm and the ability to maintain satisfactory sexual function. The size of the penile stump was not correlated with satisfaction of the couples. Adaptive behaviors were used with the goal of ameliorating the impact of the masculine mutilation and improving the sexual satisfaction.

Counseling by healthcare professionals of these couples about sexual health after surgery to treat PC is inadequate. Therefore, it is important to develop programs with a multi-professional approach about sexual health to meet unsatisfied needs of couples. Finally, multicentric studies and larger sample sizes are needed to improve the understanding of the impact of penectomy on couples' sexual function.

CONFLICT OF INTEREST

None declared.

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Performance of ChatGPT and DeepSeek in the Management of Postprostatectomy Urinary Incontinence

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ABSTRACT

Purpose: Artificial intelligence (AI) continues to evolve as a tool in clinical decision support. Large language models (LLMs), such as ChatGPT and DeepSeek, are increasingly used in medicine to provide fast, accessible information. This study aimed to compare the performance of ChatGPT and DeepSeek in generating recommendations for the management of postprostatectomy urinary incontinence (PPUI), based on the AUA/SUFU guideline.

Materials and Methods: A total of 20 questions (10 conceptual and 10 case-based) were developed by three urologists with expertise in PPUI, following the AUA/SUFU guideline. Each question was submitted in English using zero-shot prompting to ChatGPT-4o and DeepSeek R1. Responses were limited to 200 words and graded independently as correct (1 point), partially correct (0.5), or incorrect (0). Total and domain-specific scores were compared.

Results: ChatGPT achieved 19 out of 20 points (95.0%), while DeepSeek scored 14.5 (72.5%; $p = 0.031$). In conceptual questions, scores were 9.0 (ChatGPT) and 8.0 (DeepSeek; $p = 0.50$). In case-based scenarios, ChatGPT scored 10.0 versus 6.5 for DeepSeek ($p = 0.08$). ChatGPT outperformed DeepSeek across all guideline domains. DeepSeek made critical errors in the treatment domain, such as recommending a male sling for radiated patients.

Conclusion: ChatGPT demonstrated superior performance in providing guideline-based recommendations for PPUI. However, both models should be used under expert supervision, and future research is needed to optimize their safe integration into clinical workflows.

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INTRODUCTION

Artificial intelligence (AI) has emerged as a transformative force in healthcare, particularly through large language models (LLMs) capable of processing and generating complex medical content. ChatGPT, developed by OpenAI, has become one of the most widely used tools, designed to simulate human-like dialogue and provide accurate, contextually relevant responses (1). Since its release in 2022, ChatGPT has shown substantial potential in supporting healthcare professionals by enabling rapid access to clinical information, assisting in medical decision-making, and improving patient care workflows (2-5).

More recently, other LLMs such as Perplexity, Gemini 2.0 and Copilot have entered the field, offered unique features and expanded the landscape of AI in medicine (6). In mid-January 2025, DeepSeek-R1, an innovative open-source LLM that has rapidly gained prominence worldwide, is an open-source and cost-free platform with strong performance and broad accessibility (7). Its disruptive potential lies in combining high-quality outputs with zero user cost, making it especially appealing in low-resource settings or for professionals seeking efficient, freely available AI solutions.

As the use of these tools becomes more widespread in clinical and academic settings, their evaluation is essential to ensure safe and practical application in real-world scenarios. For instance, recent studies have evaluated the accuracy and reproducibility of ChatGPT in answering questions related to various urological diagnoses, highlighting areas where its responses can be incomplete or misleading (8). Physicians increasingly turn to LLMs such as ChatGPT, DeepSeek, and Gemini to answer questions across medical specialties, including disease management strategies (4-6, 8). These platforms offer structured, on-demand access to medical knowledge, assisting with treatment algorithms, diagnostic decisions, and drug information retrieval during clinical routines (9, 10).

Urinary incontinence after prostate surgery – particularly postprostatectomy urinary incontinence (PPUI) – remains a common and challenging condi-

tion (11). Its management often requires individualized approaches based on various patient factors, and may prompt complex clinical questions. To support clinicians, the Incontinence After Prostate Treatment guidelines developed by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) provide structured, evidence-based recommendations (12).

Our group previously assessed the performance of ChatGPT versions 3.5 and 4 in delivering guideline-based recommendations for PPUI management, using the AUA/SUFU document as a reference standard (5). Building on this foundation, we postulated that ChatGPT-4.0, given its advanced development and optimization, would outperform the recently introduced open-source model DeepSeek R1 in delivering recommendations consistent with established clinical guidelines. Consequently, the present study compares the most recent version of ChatGPT (4o) with DeepSeek (R1), focusing on their ability to deliver accurate and clinically relevant guidance for evaluating and treating PPUI.

MATERIALS AND METHODS

This research presents a comparative assessment of two widely utilized large language models – ChatGPT-4.0 and DeepSeek R1 – focusing on their capacity to deliver recommendations aligned with established guidelines for managing PPUI. To accomplish this, a set of questions was constructed by three urologists, each possessing over two decades of clinical experience and specialized expertise in PPUI. The questions were derived from the Incontinence After Prostate Treatment: AUA/SUFU Guideline, ensuring that each inquiry corresponded to a well-defined and non-controversial answer (12). The guideline itself is structured into several key domains: (a) considerations before prostate treatment, (b) management following prostate treatment, (c) evaluation strategies for post-treatment incontinence, (d) therapeutic interventions, (e) surgical complications, and (f) complex scenarios, including compromised urethral integrity, bladder neck strictures, and approaches to complications arising from surgical management of PPUI (12).

Test 1 – Conceptual questions: Ten conceptual questions were prepared based on the Guideline recommendations, divided into pre-prostate treatment (two questions), post-prostate treatment (two questions), evaluation of incontinence after prostate treatment (three questions), and treatment options (three questions).

Test 2 – Case-based questions: To analyze the ability of ChatGPT and DeepSeek to apply knowledge and critical thinking skills, 10 questions were created using real or hypothetical clinical cases and grounded in the concepts and recommendations provided by the AUA guideline. These questions were divided into post-prostate treatment (one question), evaluation of incontinence after prostate treatment (two questions), treatment options (four questions), surgical complications (two questions), and special situations (one question). A list of the questions used in tests 1 and 2 can be found in the *Supporting Information*.

All questions were open-ended and descriptive. They were entered individually and anonymously (without IP tracking) into ChatGPT-4o and DeepSeek R1 in February 2025. A single investigator submitted all prompts in English, who instructed the AI engines to provide specific, concise answers limited to 200 words. The AI models were not prompted to incorporate any particular guidelines. Each question was submitted independently using the "New Chat" function to ensure a zero-shot format, meaning no prior context or sequential prompting was used.

The same three expert urologists who formulated the questions independently evaluated the AI-generated responses. Each answer was graded using the following system:

- (A) Correct (1 point)
- (B) Mixed: includes correct and incorrect or outdated information (0.5 points)
- (C) Incorrect (0 points)

The overall performance of each model—ChatGPT and DeepSeek—was assessed for both conceptual (Test 1) and case-based (Test 2) questions, with a maximum score of 10 points per test.

This study was exempt from IRB review as no patient-level data were used.

Statistical analysis

Quantitative variables were expressed as absolute values, percentages, or proportions. We compared categorical variables using the Chi-square test or Fisher's exact test. All tests were two-sided, and statistical significance was $p < 0.05$. The analysis was performed using GraphPad Prism, version 10.0.01 for Windows.

RESULTS

ChatGPT scored 19 out of 20 points (95.0% accuracy). In comparison, DeepSeek scored 14.5 out of 20 points (72.5%; $p = 0.031$). Tables 1 and 2 show examples of errors and differences in performance between the two AI models. They also show the domains and reasons for all incorrect or partially correct responses from ChatGPT and DeepSeek.

Test 1: In the conceptual questions, ChatGPT provided accurate answers to eight questions and partially correct answers to two, resulting in a final score of 9.0. No incorrect responses were recorded. In contrast, DeepSeek provided six correct answers and four partially correct responses, with a final score of 8.0 ($p = 0.50$).

Test 2: ChatGPT provided fully correct answers to all ten case-based questions, achieving a perfect score of 10.0. In contrast, DeepSeek provided five correct answers, three partially correct responses, and two incorrect answers, resulting in a final score of 6.5 ($p = 0.08$).

Tables 2 and 3 show the differences in performance between ChatGPT and DeepSeek, according to the different domains of the guideline. ChatGPT outperformed DeepSeek in all domains. Its two partially correct responses occurred in the *Evaluation* and *Treatment Options* domains. One of ChatGPT's partially correct answers was in response to a question about the need for urethrocystoscopy. It stated that the exam *should be considered* in patients being evaluated for surgical treatment of PUI and correctly listed its principal utilities in this context; however, it did not classify the procedure as mandatory. The other partially correct response in-

Table 1 - Sample Questions Showing Divergent Performance Between ChatGPT-4 and DeepSeek in PPUI Recommendations.

Question	Guideline recommendation*	ChatGPT answer	DeepSeek answer
Conceptual question*			
What are the known preoperative risk factors for PPUI?	Advanced age, radiotherapy, larger prostate, and shorter membranous urethra increase risk. Surgical approach has little impact, except for preserving neurovascular bundles. BMI may affect short-term, but not long-term, continence.	Risk factors for incontinence include advanced age, high BMI, LUTS, poor baseline continence, short membranous urethra, weak sphincter or pelvic floor, large prostate, aggressive cancer, comorbidities, and prior pelvic surgery or radiation.	Preoperative risk factors include advanced age, high BMI, LUTS, diabetes, weak pelvic floor muscles, and poor physical fitness. Surgical experience and technique also influence outcomes. Psychological factors like anxiety may affect recovery.
		CORRECT	PARTIALLY CORRECT: <i>It doesn't mention urethral length or radiotherapy</i>
Question based on clinical case*			
A 66-year-old man with mild SUI, two years post-prostatectomy and unresponsive to conservative treatment, seeks surgery. He has no urgency and underwent salvage radiotherapy. Is a male sling appropriate?	Male slings should not be routinely performed in patients with severe stress incontinence.	No, a male sling is generally not the preferred surgical option for this patient due to his history of salvage radiotherapy.	Yes, surgical treatment with a male sling is a reasonable option for this patient.
		CORRECT	INCORRECT: <i>Considers a sling an option in this post-radiotherapy patient</i>

This table provides a comparison of responses from ChatGPT-4 and DeepSeek for selected conceptual and case-based questions related to PPUI, highlighting instances where their performance differed from guideline recommendations.

BMI = body mass index; LUTS = lower urinary tract symptoms; SUI = stress urinary incontinence; PPUI = postprostatectomy urinary incontinence.

* Questions, answers, and recommendations in this table are abbreviated

Table 2 - Performance of ChatGPT and DeepSeek according to guideline domains.

Domain (number of questions)	ChatGPT			DeepSeek		
	Correct	Partial	Wrong	Correct	Partial	Wrong
Preprostate treatment (2)	2			1	1	
Postprostate treatment (3)	3			2		1
Evaluation (5)	4	1		3	2	
Treatment options (7)	6	1		4	2	1
Complications (2)	2			1	1	
Special situations (1)	1				1	
Total (20) ^a	95.0% ^b			72.5% ^c		

This table summarizes the performance of ChatGPT and DeepSeek across various guideline domains, indicating the number of correct, partially correct, and incorrect responses for both conceptual and case-based questions.

a. Ten conceptual and ten are case-based questions.

b. Eighteen correct; two partially correct.

c. Eleven correct; seven partially correct.

Table 3 - Wrong answers from ChatGPT and DeepSeek.

Guideline domains	ChatGPT	DeepSeek
Pre-prostate treatment	-	It does not mention urethral length or radiotherapy ^a
Post-prostate treatment	-	Failed to recognize the ideal time to treat PPUI ^a
Evaluation of PPUI	Did not consider cystoscopy mandatory in the preoperative evaluation ^a	Did not consider cystoscopy mandatory in the preoperative evaluation ^a
	-	Considered urodynamic study as one of the mandatory tests in the preoperative evaluation ^a
Treatment options	Does not mention the time from surgery to PPUI treatment; considers urodynamics mandatory in the preoperative evaluation ^a	Considers urodynamics mandatory to confirm urethral mobility and function ^{a,b}
	-	Offers a sling as a reasonable option for a man with a history of radiotherapy ^c
Complications after PPUI surgery	-	Considers urodynamics essential in a patient with clearly defined pure SUI based on history and physical exam; does not mention cystoscopy ^a
Special situations	-	Fails to acknowledge the need to treat BNC prior to AUS implantation ^a

This table details the specific errors made by ChatGPT and DeepSeek, categorized by guideline domain, including instances of partially correct and incorrect answers.

^a. Partially correct; ^b. An error was made in two different questions; ^c. Wrong answer.

PPUI = post-prostatectomy urinary incontinence; SUI = stress urinary incontinence; BNC = bladder neck contracture; AUS = artificial urinary sphincter.

involved selecting patients with PPUI for sling placement. Although ChatGPT appropriately identified the incontinence as *mild to moderate* and noted the absence of prior pelvic radiotherapy, it failed to mention the time interval between surgery and treatment. It is considered mandatory in the preoperative evaluation.

DeepSeek presented partial or complete errors across all six guideline domains. Its poorest performance was in *Treatment Options*, where it provided two partially correct answers and one incorrect response. The other incorrect answer occurred in the *Pre-prostate Treatment* domain. Additionally, two partially correct answers were given in the *Evaluation* domain, and one partially correct response was observed in each of the following domains: *Pre-prostate Treatment*, *Complications*, and *Special Situations*.

Neither chatbots informed users that their answers may be based on general training data rather than specific, up-to-date, high-quality medical content, nor did they provide warnings about the limitations of

their training data or the potential for inaccuracies. In a few responses (one conceptual and two case-based), DeepSeek highlighted the importance of shared decision-making, noting that surgical treatment involves risks and requires realistic expectations regarding outcomes. It also recommended early referral to a specialist in male incontinence to optimize the timing and appropriateness of the intervention. ChatGPT did not include explicit recommendations to consult a physician or healthcare professional. Some responses advised that a thorough discussion of risks, benefits, and the potential need for lifelong device management is essential to support better outcomes.

DISCUSSION

This study aimed to evaluate and compare the accuracy of two LLMs, ChatGPT-4o and DeepSeek R1, in generating guideline-concordant recommendations for the management of PPUI, using the AUA/SUFU guide-

line (12) as a benchmark. This direct, head-to-head comparison of these two contemporary LLMs in a specialized urological context provides novel insights into their relative clinical utility and potential safety implications. ChatGPT outperformed DeepSeek, achieving an overall accuracy of 95.0% versus 72.5%, respectively ($p = 0.031$). This performance gap was especially pronounced in case-based scenarios, where ChatGPT scored a perfect 10/10, while DeepSeek obtained 6.5/10. These results reinforce previous findings from our group (5) and from an independent study (13), where ChatGPT-4 significantly surpassed version 3.5 in similar clinical contexts.

ChatGPT demonstrated consistently high performance across all evaluated guideline domains, particularly in complex areas such as treatment selection and surgical complication management. In contrast, DeepSeek produced partially or fully incorrect responses in every domain, with its weakest performance in the "treatment options" section. Notably, many of these inaccuracies were critical rather than minor; for example, recommending a male sling for a radiated patient represents a potentially hazardous clinical decision, not a trivial factual slip, thereby heightening safety concerns. While DeepSeek occasionally incorporated ethical elements, such as promoting shared decision-making and specialist referral, these did not offset its factual inaccuracies. This divergence likely reflects differences in training architecture, particularly reinforcement learning with human feedback, which has been associated with improved factual reliability in newer LLMs (1).

Both models were tested under a zero-shot prompt configuration without prior context or instruction to follow a specific guideline. This design was intentional, simulating real-world interactions where users input spontaneous questions. Under these conditions, ChatGPT's strong contextual alignment with evidence-based recommendations suggests real-world utility in clinical support or educational use. Nonetheless, performance was not flawless. For instance, ChatGPT failed to state that cystoscopy is mandatory in the preoperative workup and incorrectly portrayed urodynamic testing as universally required, demonstrating that even high-performing LLMs may falter in nuanced or infrequently referenced scenarios.

The study methodology included domain-stratified question design by experienced urologists and structured, independent evaluation. Although the assessment framework was rigorous, the absence of a blinded review may have introduced bias. Additionally, as all prompts were in English, the findings may not generalize to other languages or cultural contexts.

ChatGPT's high accuracy in guideline-based PPUI scenarios supports its potential as a supplementary tool in urologic clinical practice. While not a substitute for clinical judgment, it may aid physicians in patient education, draft preparation, or as a second opinion generator. Similar performance advantages have been noted in other urologic conditions – including benign prostatic hyperplasia, prostate cancer, and urolithiasis – where ChatGPT-generated materials have been favorably rated compared to traditional resources (14).

These findings also underscore the broader potential of LLMs to improve healthcare delivery across diverse settings (15). In resource-limited environments, where access to trained specialists is constrained but digital connectivity is increasingly available, LLMs may serve as a valuable tool to support triage and immediate clinical decision-making (16). Beyond access, these models may enhance healthcare system efficiency by organizing and synthesizing complex clinical information, facilitating the monitoring of patients with multiple comorbidities, and reducing the administrative workload that often burdens clinicians (1).

Nonetheless, current LLMs lack key capabilities for individualized care. They do not reliably account for patient-specific variables such as comorbidities, psychosocial context, or long-term treatment trajectories. Moreover, neither model provided disclaimers regarding the scope or limitations of their training data, nor did they express uncertainty or confidence levels in their outputs. These omissions pose risks, particularly in unsupervised or low-resource environments. As static systems, LLMs that do not incorporate real-time updates may become outdated or misleading, further underscoring the need for continuous monitoring and recalibration (17).

The limitations observed in this study align with the broader literature on LLM performance in Medicine.

Recent evaluations in pediatric urology have demonstrated that while ChatGPT offers general knowledge, its responses can be incomplete, ambiguous, and even misleading, particularly when compared to formal guidelines for conditions like phimosis (18). While ChatGPT generally outperforms models such as Gemini and Bard in urologic domains, all tend to simplify or misrepresent complex clinical cases (4, 6). Moreover, our comparison involved the premium version of ChatGPT and the free version of DeepSeek, which may have influenced the overall performance gap. Another limitation is the potential language bias, as both AI models were evaluated exclusively in English. DeepSeek's performance may differ – and possibly improve – in Chinese, the language in which it was originally developed and likely optimized. Future studies should explore multilingual evaluations, particularly in Chinese, to more accurately assess each model's full capabilities and real-world applicability across diverse linguistic contexts.

Another significant limitation is the relatively small sample size, which utilizes only 20 questions to assess model performance. Although the questions were carefully developed based on established clinical guidelines and reviewed by experienced urologists, this limited number may not fully represent the wide spectrum of real-world clinical decision-making scenarios. Small differences in interpretation or phrasing could disproportionately influence the results.

CONCLUSIONS

While ChatGPT demonstrates superior performance over DeepSeek in the context of PPUI, both models currently lack the ability to autonomously guide clinical decision-making. Our findings support the view that AI can effectively augment – but not replace – physician expertise in Urology, highlighting the need for transparent, continuously updated, and supervised integration of LLMs into clinical workflows to ensure their safe and effective use.

CONFLICT OF INTEREST

None declared.

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APPENDIX

QUESTIONS WITH ANSWERS

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Question 1	What are the known preoperative risk factors that could affect the chance of developing urinary incontinence in patients undergoing radical prostatectomy? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Preoperative risk factors for urinary incontinence following radical prostatectomy include advanced age, higher body mass index (BMI), preexisting lower urinary tract symptoms (LUTS), and poor baseline continence. Anatomical and functional factors such as a shorter membranous urethral length, decreased urethral sphincter function, and reduced pelvic floor muscle strength also contribute. Larger prostate volume and more aggressive prostate cancer (high Gleason score, extracapsular extension) may necessitate extensive dissection, increasing the risk of sphincter damage. Comorbidities like diabetes mellitus, cardiovascular disease, and neurological disorders can impair nerve and muscle function, further predisposing patients to postoperative incontinence. Additionally, prior pelvic surgeries or radiation therapy may compromise sphincter integrity and urethral support. Understanding these risk factors is crucial for patient counseling and prehabilitation strategies, such as pelvic floor muscle training before surgery, to improve postoperative outcomes.
DeepSeek 0,5	Several preoperative risk factors have been identified that may increase the likelihood of developing urinary incontinence (UI) following radical prostatectomy. Advanced age is a significant predictor, as older patients often have reduced pelvic muscle tone and slower recovery. Higher body mass index (BMI) is also associated with increased UI risk due to added pressure on the pelvic floor. Pre-existing lower urinary tract symptoms (LUTS), such as urgency or weak stream, can exacerbate postoperative incontinence. Additionally, a history of diabetes or other conditions affecting nerve function may impair bladder control. Surgical factors, such as the surgeon's experience and the surgical technique used (e.g., nerve-sparing vs. non-nerve-sparing), also play a role, though these are not strictly preoperative. Preoperative pelvic floor muscle strength and the patient's overall physical fitness level can influence recovery, with weaker muscles correlating with higher UI risk. Lastly, psychological factors, such as anxiety or depression, may indirectly affect outcomes by impacting adherence to rehabilitation exercises. Identifying and addressing these risk factors preoperatively can help tailor interventions to mitigate the risk of UI post-surgery.
Question 2	In patients undergoing radical prostatectomy, is incontinence expected in the short-term following surgery? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, urinary incontinence is expected in the short-term following radical prostatectomy, primarily due to the disruption of the anatomical structures responsible for continence, including the external urethral sphincter and supportive pelvic tissues. The immediate postoperative period often involves stress urinary incontinence (SUI), characterized by leakage during activities that increase intra-abdominal pressure. Contributing factors include sphincteric dysfunction, loss of urethral length, and temporary neuropraxia affecting the pelvic floor muscles. Most patients experience significant improvement within the first year as sphincter function recovers and pelvic floor muscles strengthen. Early recovery is influenced by preoperative continence status, surgical technique (e.g., nerve-sparing approaches), and adherence to pelvic floor muscle training. While the majority regain continence within 6 to 12 months, a subset may have persistent incontinence requiring additional interventions such as pelvic floor therapy, pharmacologic treatment, or surgical management with slings or artificial urinary sphincters.

DeepSeek 1,0	Yes, incontinence is a common short-term complication following radical prostatectomy, affecting a significant proportion of patients initially. The surgery involves removing the prostate gland, which can disrupt the urinary sphincter mechanism and surrounding structures responsible for urinary control. In the immediate postoperative period, many patients experience stress urinary incontinence (leakage with coughing, sneezing, or exertion) or urge incontinence (sudden, uncontrollable need to urinate). Studies suggest that up to 50-80% of patients may experience some degree of incontinence shortly after surgery, though the severity varies. Pelvic floor muscle exercises, behavioral modifications, and time often lead to gradual improvement, with many patients regaining continence within 3 to 12 months. However, a small percentage may continue to experience persistent incontinence, necessitating further interventions such as physical therapy, medications, or surgical options like artificial urinary sphincter placement. Factors such as age, surgical technique, preoperative urinary function, and surgeon experience can influence the likelihood and duration of incontinence. Patients should be counseled preoperatively about this risk and the expected recovery trajectory to manage expectations and encourage adherence to postoperative rehabilitation strategies.
Question 3	In patients who have undergone radical prostatectomy, do pelvic floor muscle exercises or pelvic floor muscle training help recovering urinary continence in the early post-operative period? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, pelvic floor muscle exercises (PFME) or pelvic floor muscle training (PFMT) can aid in the recovery of urinary continence in the early post-operative period after radical prostatectomy. Studies have shown that structured PFMT improves continence rates and shortens the duration of post-prostatectomy incontinence by enhancing the strength and coordination of the pelvic floor muscles, which compensate for the loss of urethral sphincter function. Early initiation, ideally preoperatively or within the first few weeks post-surgery, appears to be beneficial in accelerating continence recovery. Supervised programs by physiotherapists or trained specialists tend to yield better outcomes compared to unsupervised exercises. However, the magnitude of benefit varies, and some patients may continue to experience incontinence despite training. While PFMT is generally recommended as a first-line conservative approach, its efficacy should be evaluated in the context of individual patient factors, including baseline pelvic floor function and adherence to the exercise regimen.
DeepSeek 1,0	Yes, pelvic floor muscle exercises (PFME) or pelvic floor muscle training (PFMT) have been shown to aid in the recovery of urinary continence in the early post-operative period following radical prostatectomy. Studies indicate that structured PFMT programs, when initiated soon after catheter removal, can significantly improve the rate and speed of regaining urinary control compared to no intervention or general advice alone. These exercises strengthen the pelvic floor muscles, which are often weakened or damaged during surgery, thereby enhancing urethral sphincter function and reducing urinary leakage. Early and consistent PFMT, often guided by a physiotherapist, helps patients regain continence more quickly, with some evidence suggesting improved outcomes within the first 3-6 months post-surgery. However, the extent of benefit may vary based on individual factors such as preoperative continence status, surgical technique, and adherence to the exercise regimen. While PFMT is generally recommended as a non-invasive and effective approach, it is often most beneficial when combined with other strategies like behavioral modifications and patient education. Overall, early initiation of PFMT is a valuable component of post-prostatectomy rehabilitation for improving urinary continence outcomes.
Question 4	In patients with bothersome stress urinary incontinence after radical prostatectomy, when should surgical treatment be offered? Your answer must be in one paragraph and a maximum of 200 words.

GPT 4o 1,0	Surgical treatment for bothersome stress urinary incontinence (SUI) after radical prostatectomy should be considered at least 12 months postoperatively to allow for maximal spontaneous recovery of continence. However, earlier intervention may be appropriate in cases of severe incontinence significantly impacting quality of life. Before surgery, patients should undergo a thorough evaluation, including urodynamic studies and cystoscopy, to assess sphincter function, bladder compliance, and rule out anastomotic strictures or detrusor dysfunction. Conservative measures, such as pelvic floor muscle training and behavioral modifications, should be optimized before proceeding with surgery. The artificial urinary sphincter (AUS) remains the gold standard for moderate to severe SUI, while male slings are an option for patients with mild to moderate incontinence and adequate sphincter function. Patient preference, comorbidities, and prior treatments should guide decision-making.
DeepSeek 1,0	Surgical treatment for bothersome stress urinary incontinence (SUI) after radical prostatectomy should be considered after a thorough evaluation and a period of conservative management. Typically, surgical intervention is offered if significant incontinence persists beyond 6 to 12 months post-surgery, as spontaneous improvement may occur during this time. Prior to considering surgery, patients should undergo a comprehensive assessment, including urodynamic studies, to confirm the diagnosis of SUI and rule out other causes of incontinence, such as detrusor overactivity or bladder outlet obstruction. Conservative measures, including pelvic floor muscle training, lifestyle modifications, and possibly pharmacotherapy, should be attempted first. If these measures fail to provide adequate symptom relief and the patient's quality of life remains significantly impacted, surgical options such as an artificial urinary sphincter (AUS) or male sling can be considered. The choice of procedure depends on factors such as the severity of incontinence, patient preferences, and surgeon expertise. Shared decision-making is essential, as surgical treatment carries risks and requires realistic expectations regarding outcomes. Early referral to a specialist in male incontinence is recommended to optimize timing and appropriateness of intervention.
Question 5	In patients being considered for surgical treatment for stress urinary incontinence following radical prostatectomy, should cystourethroscopy be performed? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 0,5	Yes, cystourethroscopy should be considered in patients being evaluated for surgical treatment of stress urinary incontinence (SUI) after radical prostatectomy. This examination helps assess urethral integrity, the presence of anastomotic strictures, bladder neck contractures, or residual sphincteric function, which can impact surgical planning and outcomes. Identifying urethral pathology preoperatively allows for appropriate management, such as treating strictures before artificial urinary sphincter (AUS) implantation or selecting an alternative surgical approach. Additionally, cystourethroscopy can help determine whether there is significant bladder dysfunction, which may affect the choice between an AUS and a male sling. While not always mandatory in straightforward cases, it provides valuable anatomical and functional insights that contribute to optimal surgical decision-making and improved patient outcomes.

DeepSeek 0,5	In patients being considered for surgical treatment for stress urinary incontinence (SUI) following radical prostatectomy, cystourethroscopy is generally recommended as part of the preoperative evaluation. This procedure allows for the direct visualization of the lower urinary tract, helping to identify potential anatomical abnormalities, urethral strictures, bladder neck contractures, or other pathologies that could contribute to incontinence or affect surgical planning. Additionally, cystourethroscopy can assess the integrity of the urethral sphincter and bladder neck, which are critical for determining the most appropriate surgical intervention, such as an artificial urinary sphincter or male sling. It also helps rule out other causes of urinary symptoms, such as bladder stones or tumors, which may require alternative management. While cystourethroscopy is not mandatory in all cases, it provides valuable diagnostic information that can optimize patient selection, improve surgical outcomes, and reduce the risk of complications. Therefore, it is considered a useful and often necessary component of the preoperative workup for post-prostatectomy SUI.
Question 6	In patients being considered for surgical treatment for stress urinary incontinence following radical prostatectomy, should urodynamic testing be performed? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, urodynamic testing should be considered in patients undergoing surgical treatment for stress urinary incontinence (SUI) following radical prostatectomy, though its routine use remains debated. Urodynamics can help differentiate between true sphincteric insufficiency and other contributing factors such as detrusor overactivity, reduced bladder compliance, or impaired bladder contractility, which may influence treatment decisions. Identifying detrusor overactivity may prompt consideration of conservative or pharmacologic management before proceeding with surgery. Additionally, confirming adequate bladder contractility is crucial, particularly in patients at risk for post-surgical voiding dysfunction, such as those with detrusor underactivity. However, some studies suggest that clinical evaluation alone, including history, physical examination, and pad test, may be sufficient in straightforward cases, as urodynamic findings rarely alter surgical planning when intrinsic sphincter deficiency is the predominant cause. Therefore, while not mandatory in all cases, urodynamic testing is particularly useful in patients with atypical symptoms, prior radiotherapy, previous incontinence surgeries, or suspected concomitant bladder dysfunction, helping to optimize patient selection and improve surgical outcomes.
DeepSeek 1,0	In patients being considered for surgical treatment for stress urinary incontinence (SUI) following radical prostatectomy, urodynamic testing (UDS) is not universally mandatory but can provide valuable insights in specific cases. While clinical evaluation, including history, physical examination, and bladder diaries, often suffices to diagnose SUI, UDS may be warranted when the diagnosis is unclear, when mixed urinary symptoms (e.g., urgency or obstruction) are present, or when prior surgical interventions have failed. UDS helps differentiate between intrinsic sphincter deficiency (the primary cause of post-prostatectomy SUI) and other contributing factors, such as detrusor overactivity or bladder outlet obstruction, which could influence surgical planning and outcomes. However, routine use of UDS in straightforward cases of SUI may not significantly alter management or improve results, as surgical decisions are often based on clinical findings. Therefore, UDS should be selectively employed based on individual patient complexity and the need for additional diagnostic clarity to optimize treatment strategies.
Question 7	What is the ideal patient profile for the implantation of an artificial urinary sphincter in men with stress urinary incontinence after radical prostatectomy seeking for surgical treatment? Your answer must be in one paragraph and a maximum of 200 words.

GPT 4o 1,0	The ideal candidate for artificial urinary sphincter (AUS) implantation in men with stress urinary incontinence (SUI) following radical prostatectomy is one with moderate to severe SUI persisting for at least 12 months despite conservative measures, such as pelvic floor muscle training. He should have good cognitive function and manual dexterity to operate the device, or a reliable caregiver if assistance is needed. A stable bladder with adequate capacity, compliance, and the absence of detrusor overactivity or significant post-void residual volume is crucial to prevent complications. Patients should have no evidence of active infection, urethral stricture, bladder neck contracture, or prior pelvic radiation with severe fibrosis, as these conditions increase the risk of erosion and device failure. Good general health, with the ability to tolerate anesthesia and surgery, is also important. Psychological readiness and realistic expectations regarding potential complications, device longevity, and the need for future revisions should be assessed preoperatively. Proper patient selection optimizes outcomes, ensuring satisfactory continence restoration and quality-of-life improvement.
DeepSeek 0,5	The ideal patient profile for the implantation of an artificial urinary sphincter (AUS) in men with stress urinary incontinence (SUI) after radical prostatectomy includes individuals with persistent, bothersome SUI that significantly impacts their quality of life, typically after a minimum of 6-12 months of conservative management (e.g., pelvic floor exercises) without sufficient improvement. Candidates should have adequate manual dexterity and cognitive function to operate the device, as well as realistic expectations regarding outcomes, including the potential need for revisions or explantation. They should be in good overall health with no active urinary tract infections, untreated bladder dysfunction, or severe detrusor overactivity, as these conditions may compromise surgical success. Urodynamic studies are often recommended to confirm SUI and rule out other contributing factors. Patients with prior radiation therapy or urethral strictures may still be candidates but require careful evaluation due to higher risks of complications. A thorough assessment of urethral integrity and bladder capacity is essential. The AUS is particularly suitable for patients seeking a durable, effective solution for SUI who are willing to accept the risks of mechanical failure, infection, or erosion, and who are committed to long-term follow-up.
Question 8	What is the ideal patient profile for the implantation of sling in men with stress urinary incontinence after radical prostatectomy seeking for surgical treatment? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 0,5	The ideal candidate for male sling implantation to treat stress urinary incontinence (SUI) after radical prostatectomy is a patient with mild to moderate incontinence, typically defined as requiring ≤ 3 pads per day, with preserved or mildly compromised detrusor contractility. Candidates should have an intact external urethral sphincter without significant fibrosis or scarring, confirmed through clinical evaluation and urethroscopy. The patient should not have a history of pelvic radiation therapy or previous urethral surgery, as these conditions increase the risk of failure. Urodynamic studies should demonstrate adequate bladder compliance and the absence of significant detrusor overactivity. The ideal candidate is motivated, has realistic expectations regarding surgical outcomes, and understands that slings are less effective for severe incontinence compared to artificial urinary sphincters.

DeepSeek 0,5	The ideal patient profile for male sling implantation in post-radical prostatectomy stress urinary incontinence (SUI) includes men with mild to moderate incontinence (typically defined as 1-2 pads per day), who have failed or declined conservative management such as pelvic floor exercises or behavioral therapy. Candidates should have a stable or improved urinary condition for at least 6-12 months post-prostatectomy, ensuring no further recovery of continence is expected. They should have adequate urethral mobility and function, confirmed through urodynamic studies, and no significant detrusor overactivity or reduced bladder compliance. Additionally, patients should be in good general health, without untreated bladder outlet obstruction, recurrent urethral strictures, or prior radiation therapy, as these factors can compromise outcomes. Realistic expectations regarding the potential for improvement rather than complete continence are essential, as sling procedures aim to reduce leakage rather than fully restore pre-surgery function. A thorough evaluation, including pad tests, cystoscopy, and patient-reported symptom severity, is crucial to confirm suitability for the procedure.
Question 9	In men with stress urinary incontinence after primary, adjuvant, or salvage radiotherapy who are seeking surgical management, what is the most appropriate treatment alternative? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	In men with stress urinary incontinence (SUI) following primary, adjuvant, or salvage radiotherapy, the artificial urinary sphincter (AUS) remains the gold-standard surgical treatment due to its proven efficacy in restoring continence. Radiotherapy-induced fibrosis and tissue atrophy increase the risk of complications, such as urethral atrophy and erosion, making AUS a preferred choice over male slings, which require preserved urethral integrity and sufficient sphincteric function. In select cases of mild-to-moderate SUI with adequate urethral compliance, an adjustable balloon device may be considered as an alternative, offering modulation of continence control postoperatively. However, the risk of infection, erosion, and device malfunction is higher in radiated patients, necessitating careful patient selection and counseling. Multidisciplinary evaluation, including urodynamic studies and endoscopic assessment, is crucial to guide surgical planning.
DeepSeek 1,0	In men with stress urinary incontinence (SUI) following primary, adjuvant, or salvage radiotherapy, the most appropriate surgical treatment is typically the implantation of an artificial urinary sphincter (AUS). The AUS is considered the gold standard for managing moderate to severe SUI in this population due to its high efficacy and durability. It consists of a cuff placed around the bulbar urethra, a pressure-regulating balloon in the retroperitoneum, and a pump in the scrotum, allowing the patient to manually control urination. While other options, such as male slings, may be considered for mild to moderate SUI, they are generally less effective in post-radiation patients due to compromised tissue integrity and reduced urethral mobility caused by radiation-induced fibrosis. The AUS, however, is better suited to address the complex pathophysiology of SUI in this context. Careful patient selection, preoperative counseling, and management of expectations are crucial, as complications such as infection, erosion, or mechanical failure can occur. Despite these risks, the AUS offers significant improvements in quality of life and continence rates, making it the preferred surgical option for post-radiation SUI in men.
Question 10	Prior to implantation of an artificial urinary sphincter as surgery for stress urinary incontinence after radical prostatectomy, what should clinicians evaluate to ensure that patients will have the ability to operate the device? Your answer must be in one paragraph and a maximum of 200 words.

GPT 4o 1,0	Before implanting an artificial urinary sphincter (AUS) for stress urinary incontinence following radical prostatectomy, clinicians must evaluate the patient's cognitive function, manual dexterity, and motivation to ensure they can properly operate the device. Cognitive assessment is crucial to confirm the patient understands how to manipulate the control mechanism and adhere to postoperative care instructions. Manual dexterity must be sufficient to locate, squeeze, and release the control pump, typically positioned in the scrotum. Conditions such as arthritis, neuropathy, or prior hand surgery should be considered. Additionally, assessing the patient's motivation and expectations is essential, as successful use requires active participation in device operation. Urodynamic studies should confirm adequate bladder compliance and capacity, ruling out detrusor overactivity or reduced compliance that could compromise AUS function. <u>A thorough discussion of the risks, benefits, and potential need for lifelong device management is necessary to ensure patient commitment.</u>
DeepSeek 1,0	Prior to implantation of an artificial urinary sphincter (AUS) for stress urinary incontinence following radical prostatectomy, clinicians must evaluate the patient's physical and cognitive ability to operate the device effectively. This includes assessing manual dexterity, as the device requires manipulation of a scrotal or labial pump to control urine flow. Patients with conditions such as arthritis, neuropathy, or other impairments affecting hand strength or coordination may struggle to use the device. Cognitive function should also be evaluated to ensure the patient can understand and follow the necessary steps to operate the AUS, particularly in cases of dementia or other cognitive disorders. Additionally, clinicians should consider the patient's motivation and willingness to comply with the device's operation and maintenance. A thorough discussion of the device's mechanism, potential complications, and the patient's expectations is essential to confirm their ability and commitment to using the AUS. If the patient is deemed unable to operate the device, alternative treatments for incontinence should be explored. This comprehensive evaluation ensures the AUS is a suitable and effective option for the patient's specific needs.
Question 11	A 65-year-old male patient who is bothered with severe stress urinary incontinence after radical prostatectomy and considering surgical treatment presents for preoperative evaluation. The patient has no complaints of urgency or urgeincontinence, has a good urinary flow and stress urinary incontinence is demonstrated on physical examination. What further tests are needed before surgery? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0 .	In the preoperative evaluation of this 65-year-old male with severe stress urinary incontinence (SUI) after radical prostatectomy, key additional tests are needed to optimize surgical planning. A 24-hour pad test or pad weight test quantifies urine loss severity. Uroflowmetry and post-void residual (PVR) measurement confirm adequate emptying. Cystoscopy assesses urethral integrity, the presence of anastomotic strictures, and bladder neck competence. Urodynamic testing (optional but recommended in select cases) helps rule out detrusor dysfunction, impaired compliance, or occult detrusor overactivity, especially if prior radiation therapy was received. A videourodynamic study may be particularly useful if there is concern about bladder dysfunction. Finally, assessment of manual dexterity and cognitive function ensures the patient can manipulate a device like an artificial urinary sphincter (AUS), if chosen. These evaluations guide surgical decision-making, ensuring appropriate treatment selection and minimizing postoperative complications.

DeepSeek 0,5	Before proceeding with surgical treatment for stress urinary incontinence (SUI) post-radical prostatectomy, further evaluation should include urodynamic studies to confirm the diagnosis of pure SUI, assess bladder capacity, compliance, and detrusor function, and rule out detrusor overactivity or poor compliance that could affect surgical outcomes. A 24-hour pad test can quantify the severity of incontinence, while cystoscopy may be performed to evaluate the urethral sphincter integrity, bladder neck, and urethral anatomy, ensuring no obstruction or other abnormalities. Post-void residual urine measurement should be done to confirm complete bladder emptying. Additionally, a urinalysis and urine culture are necessary to exclude infection. If the patient has a history of radiation therapy or complex pelvic surgery, imaging such as a retrograde urethrogram or MRI may be considered to assess tissue quality and anatomy. These tests help ensure the patient is an appropriate candidate for surgery, such as an artificial urinary sphincter or male sling, and optimize the likelihood of a successful outcome.
Question 12	A 78-year-old male patient who is bothered with severe stress urinary incontinence after radical prostatectomy and considering surgical treatment presents for preoperative evaluation. The patient has Parkinson's disease and complains of both stress and urge incontinence. He has a good urinary flow and stress urinary incontinence is demonstrated on physical examination. Cystourethroscopy is normal. Should other tests be obtained before surgery? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, additional tests should be obtained before proceeding with surgery, given the patient's Parkinson's disease and mixed urinary incontinence (stress and urge incontinence). A urodynamic study is essential to assess detrusor function, given the high likelihood of detrusor overactivity or impaired compliance in neurogenic conditions, which could impact surgical outcomes. If significant detrusor overactivity or poor bladder compliance is present, stress incontinence might not be the sole contributor to his symptoms, and surgery alone may not provide satisfactory results. Additionally, a post-void residual (PVR) measurement should be performed to evaluate potential bladder dysfunction, especially given his neurological condition. If PVR is high, this may indicate underlying detrusor underactivity, which could lead to postoperative urinary retention. Finally, a careful neurological assessment should be conducted to evaluate the severity of Parkinson's disease, as advanced disease may increase the risk of postoperative complications and affect the patient's ability to manage a device such as an artificial urinary sphincter. These evaluations will help guide surgical decision-making and optimize outcomes.
DeepSeek 1,0	Before proceeding with surgical treatment for stress urinary incontinence (SUI) in this patient, additional tests are warranted to ensure an accurate diagnosis and appropriate management. Given his Parkinson's disease, which can contribute to both stress and urge incontinence due to detrusor overactivity and impaired bladder control, a urodynamic study (UDS) is essential. UDS will help differentiate between the components of his incontinence, assess bladder capacity, detrusor function, and urethral sphincter competence, and rule out detrusor overactivity or poor bladder compliance, which could influence surgical outcomes. Additionally, a 24-hour pad test can quantify the severity of incontinence, providing objective data to guide treatment decisions. Since he has a good urinary flow and normal cystourethroscopy, obstruction is unlikely, but UDS will confirm this. Given his age and Parkinson's disease, a comprehensive geriatric assessment may also be beneficial to evaluate his overall fitness for surgery and identify any factors that could impact postoperative recovery. These tests will ensure that the chosen surgical intervention, such as an artificial urinary sphincter or male sling, is appropriate and likely to provide optimal results while minimizing risks.
Question 13	A 67-year-old male patient with severe stress urinary incontinence persisting 3 months after radical prostatectomy, who have already undergone pelvic floor muscle exercises, desires surgical treatment for his condition. Should the implantation of an artificial urinary sphincter be considered in this scenario? Your answer must be in one paragraph and a maximum of 200 words.

GPT 4o 1,0	No, the implantation of an artificial urinary sphincter (AUS) should not be immediately considered in this scenario, as severe stress urinary incontinence (SUI) persisting at only three months post-radical prostatectomy is still within the expected recovery period. While early severe SUI may predict long-term incontinence, conservative management, including pelvic floor muscle training, is typically continued for at least 6 to 12 months before considering surgical intervention. Most guidelines recommend waiting at least 6 months post-prostatectomy to allow for potential spontaneous improvement. However, in select cases of severe, bothersome incontinence with minimal improvement over time, earlier intervention may be considered, particularly if quality of life is significantly impacted. If symptoms persist beyond 6–12 months, the patient could be evaluated for AUS implantation, which remains the gold standard for moderate-to-severe post-prostatectomy incontinence. A thorough assessment, including urodynamics if necessary, should confirm sphincteric deficiency without bladder dysfunction before proceeding.
DeepSeek 0	Yes, the implantation of an artificial urinary sphincter (AUS) should be considered in this scenario. AUS is a well-established and effective surgical treatment for severe stress urinary incontinence (SUI) in men, particularly after radical prostatectomy when conservative measures like pelvic floor muscle exercises have failed. The device, typically placed around the bulbar urethra, allows the patient to manually control urination by inflating or deflating a cuff. Studies have shown significant improvement in continence rates and quality of life for patients with post-prostatectomy SUI who undergo AUS implantation. However, the decision should be made after a thorough evaluation, including urodynamic studies to confirm SUI severity and exclude other causes of incontinence. The patient should also be informed about potential risks, such as infection, erosion, or mechanical failure, and the need for possible future revisions. Given the patient's age and persistent symptoms, AUS remains a viable and often preferred option for achieving long-term continence.
Question 14	A 63-year-old male patient with urinary incontinence two years after radical prostatectomy, presents with lower urinary tract symptoms characterized predominantly by urgency and urgeincontinence. He complains of occasional stress urinary incontinence when coughing or sneezing. He has a normal urinary flow, low post-void residual volume and a normal urinalysis. Should surgical treatment with a male sling be offered? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	No, surgical treatment with a male sling is not the best option in this case. Male slings are typically indicated for mild to moderate stress urinary incontinence (SUI) with preserved sphincter function, but this patient's predominant symptoms are urgency and urge incontinence, which suggest detrusor overactivity rather than significant sphincteric deficiency. The occasional stress incontinence episodes do not justify a male sling, as it would not address his primary complaint. Given his normal urinary flow, low post-void residual volume, and absence of infection, further evaluation with urodynamic studies may be warranted to confirm detrusor overactivity. First-line treatment should focus on behavioral modifications and pharmacologic therapy with antimuscarinics or β-agonists. If symptoms persist despite conservative management, advanced therapies such as intradetrusor botulinum toxin injection or neuromodulation may be considered.
DeepSeek 1,0	In this 63-year-old male with mixed urinary incontinence (predominantly urge incontinence with occasional stress incontinence) two years post-radical prostatectomy, surgical treatment with a male sling may be considered but is not the first-line option. His symptoms suggest a combination of detrusor overactivity (urgency, urge incontinence) and mild stress urinary incontinence (SUI). Given his normal urinary flow, low post-void residual volume, and normal urinalysis, there is no evidence of obstruction or infection. Initial management should focus on behavioral modifications, pelvic floor muscle training, and pharmacologic therapy (e.g., anticholinergics or β-3 agonists) for urge incontinence. If SUI persists and significantly impacts his quality of life after conservative measures, a male sling or artificial urinary sphincter could be considered. However, the male sling is typically more effective for mild to moderate SUI, and its success may be limited if urge symptoms remain predominant. A thorough urodynamic evaluation is recommended to confirm the diagnosis and guide treatment. Shared decision-making is essential, weighing the risks and benefits of surgery against the patient's symptoms and preferences.

Question 15	A 66-year-old male patient with stress urinary incontinence two years after radical prostatectomy, and who failed conservative treatments for his condition, presents for surgical treatment. His stress urinary incontinence is mild and he has no complaints of urgency or urgeincontinence. His past medical history includes salvage radiotherapy for biochemical prostate cancer recurrence. Should surgical treatment with a male sling be offered? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	No, a male sling is generally not the preferred surgical option for this patient due to his history of salvage radiotherapy. While a male sling can be effective for mild stress urinary incontinence (SUI), its success is significantly lower in patients with prior pelvic radiation. Salvage radiotherapy can cause fibrosis, compromising urethral compliance and increasing the risk of failure or complications, such as urethral erosion. The artificial urinary sphincter (AUS) remains the gold standard for post-prostatectomy SUI, especially in radiated patients, as it provides better long-term outcomes and continence rates. However, given his mild incontinence, a thorough discussion should be conducted to assess the risks and benefits of AUS implantation versus ongoing conservative management, particularly considering the potential for worsened outcomes due to radiation-related tissue changes.
DeepSeek 0,0	Yes, surgical treatment with a male sling is a reasonable option for this patient. The male sling is particularly suitable for patients with mild to moderate stress urinary incontinence (SUI) following radical prostatectomy, as it provides a less invasive alternative to an artificial urinary sphincter (AUS) with potentially fewer complications. Given that the patient has failed conservative treatments and has mild SUI without urgency or urge incontinence, he fits the profile of a good candidate for this procedure. The male sling works by compressing the bulbar urethra to improve continence, and studies have shown favorable outcomes in appropriately selected patients. However, the patient's history of salvage radiotherapy should be considered, as radiation can affect tissue quality and healing, potentially impacting surgical outcomes. While the male sling is generally effective, the patient should be counseled about the possibility of needing additional interventions, such as an AUS, if the sling does not provide adequate relief. Shared decision-making is essential, weighing the benefits, risks, and patient preferences. Overall, the male sling is a viable and appropriate surgical option for this patient.
Question 16	A 79-year-old male patient with bothersome severe stress urinary incontinence five years after radical prostatectomy presents for the medical visit accompanied by his wife interested in surgical treatment. He uses more than 6 pads/day, and his urodynamics confirms pure stress urinary incontinence. He is under investigation with a neurologist for a progressive complaint of memory loss. Should surgical treatment with an artificial urinary sphincter be offered? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	No, surgical treatment with an artificial urinary sphincter (AUS) should be approached with caution in this patient due to his ongoing evaluation for progressive memory loss. While he has severe stress urinary incontinence (SUI) confirmed by urodynamics and is highly symptomatic, cognitive decline can significantly impact his ability to understand, operate, and comply with the AUS mechanism, increasing the risk of device-related complications and failure. The decision should involve a thorough assessment by his neurologist to determine the extent and progression of cognitive impairment. If his cognitive function is preserved or the decline is minimal, AUS implantation may still be considered with strong caregiver support, particularly from his wife. However, if significant cognitive impairment is confirmed, alternative approaches such as absorbent products or, in select cases, a male sling may be more appropriate. A shared decision-making process, including discussions about the risks and long-term management, is essential.

DeepSeek 1,0	In this case, the 79-year-old male patient with severe stress urinary incontinence (SUI) following radical prostatectomy is a potential candidate for an artificial urinary sphincter (AUS), given his significant symptom burden (≥ 6 pads/day) and urodynamic confirmation of pure SUI. However, his progressive memory loss, currently under neurological investigation, raises concerns about his ability to manage the device postoperatively, as AUS requires manual dexterity and cognitive understanding to operate the pump mechanism. A thorough assessment of his cognitive function and manual dexterity, along with caregiver support (e.g., his wife's involvement), is essential before proceeding. If he is deemed unable to operate the device independently, alternative treatments such as a male sling or continued conservative management may be more appropriate. Shared decision-making with the patient and his wife is crucial, weighing the benefits of improved continence against the risks and complexities of AUS implantation in the context of his cognitive decline.
Question 17	A 81-year-old male patient with bothersome severe stress urinary incontinence five years after radical prostatectomy presents in consideration for surgical treatment. He uses more than 8 pads/day, and his urodynamics confirms pure stress urinary incontinence. His past medical history is significant for rheumatoid arthritis which significantly hampers his manual dexterity. Should surgical treatment with an artificial urinary sphincter be offered? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, surgical treatment with an artificial urinary sphincter (AUS) can be considered for this patient, given his severe stress urinary incontinence (SUI) significantly affecting his quality of life. AUS is the gold standard for post-prostatectomy SUI, particularly in patients with high pad usage and confirmed urodynamic stress incontinence. However, his rheumatoid arthritis, which severely limits manual dexterity, raises concerns about his ability to manipulate the AUS activation mechanism. Alternative strategies include selecting a larger, easier-to-operate control pump, involving a caregiver for device activation, or considering alternative treatments such as male slings, though their efficacy is lower in severe SUI. A thorough preoperative discussion is essential to assess the patient's ability to use the device effectively and to explore support systems. If he cannot reliably operate the AUS, surgical intervention may not be beneficial, and other options, including external devices or catheterization, should be discussed.
DeepSeek 1,0	Yes, surgical treatment with an artificial urinary sphincter (AUS) should be offered to this patient. He has severe stress urinary incontinence (SUI) following radical prostatectomy, significantly impacting his quality of life, as evidenced by his use of more than 8 pads/day. Urodynamic studies confirming pure SUI support the diagnosis and appropriateness of AUS, which is the gold standard for managing severe SUI in men post-prostatectomy. While his rheumatoid arthritis may complicate manual dexterity, the AUS can still be a viable option with proper patient education and support for device management. Alternative treatments, such as male slings, are less effective for severe incontinence, and bulking agents offer only temporary relief. Preoperative counseling should address the need for manual dexterity to operate the AUS and involve caregivers if necessary. Given the patient's age and medical history, a thorough evaluation of surgical risks and benefits is essential, but the AUS remains the most effective long-term solution for his condition.
Question 18	A 67-year-old male patient with stress urinary incontinence two years after radical prostatectomy, and who failed conservative treatments for his condition, presents for surgical treatment. His stress urinary incontinence is severe and he has no complaints of urgency or urgeincontinence. His cystourethroscopy reveals a bladder neck contracture. Should surgical treatment with an artificial urinary sphincter be offered? Your answer must be in one paragraph and a maximum of 200 words.

GPT 4o 1,0	No, an artificial urinary sphincter (AUS) should not be immediately offered without first addressing the bladder neck contracture. The presence of a bladder neck contracture can compromise the function of the AUS by affecting urethral dynamics and increasing the risk of obstruction or failure. The contracture should be treated first, typically through endoscopic incision or dilation, followed by a period of observation to ensure resolution and stable voiding. Persistent or recurrent contracture may necessitate additional interventions before considering AUS implantation. Once the bladder neck is adequately treated and the patient demonstrates a stable urethral patency without significant voiding dysfunction, AUS placement can be reconsidered. This stepwise approach optimizes the success of AUS implantation and minimizes complications such as obstruction or erosion.
DeepSeek 0,5	Yes, surgical treatment with an artificial urinary sphincter (AUS) should be offered to this patient. He has severe stress urinary incontinence (SUI) following radical prostatectomy, which has persisted despite conservative treatments, making him a suitable candidate for surgical intervention. The AUS is considered the gold standard for managing post-prostatectomy SUI, particularly in cases of severe incontinence, as it provides effective and durable continence outcomes. The presence of a bladder neck contracture (BNC) does not preclude AUS implantation but must be addressed prior to or during the procedure. BNC can be managed with bladder neck incision or dilation to ensure proper device function and urethral coaptation. Importantly, the patient's lack of urgency or urge incontinence is favorable, as these symptoms can negatively impact AUS outcomes. Preoperative urodynamic studies may be considered to confirm the diagnosis of pure SUI and rule out detrusor overactivity. Shared decision-making is essential, as the patient must understand the risks (e.g., infection, erosion, mechanical failure) and the need for device manipulation. Overall, given his severe SUI and failure of conservative measures, an AUS is an appropriate and effective treatment option.
Question 19	A 70-year-old male patient underwent artificial urinary sphincter implantation five years ago. He remained continent for three years but he has recurrent stress urinary incontinence for the past two years. Proper evaluation confirmed that his incontinence is due to pure stress urinary incontinence. Should surgical revision of the artificial urinary sphincter be offered? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	Yes, surgical revision of the artificial urinary sphincter (AUS) should be offered to this patient. Given his history of successful continence for three years followed by recurrent stress urinary incontinence, the most likely causes are urethral atrophy or mechanical failure of the device. Proper evaluation, including physical examination, cystourethroscopy, and radiographic assessment, should confirm the integrity of the AUS components and rule out erosion or infection. If the device remains intact, urethral atrophy is the most probable etiology, which may be managed by downsizing the cuff or translocating it to a proximal location. If mechanical failure is identified, complete device replacement is warranted. Since the patient has previously benefited from the AUS and his incontinence is due to stress urinary incontinence alone, revision surgery can restore continence and improve quality of life.
DeepSeek 0,5	Yes, surgical revision of the artificial urinary sphincter (AUS) should be considered for this patient. Recurrent stress urinary incontinence (SUI) after initial success with an AUS is often due to device-related issues such as mechanical failure, urethral atrophy, or cuff erosion. Given that the patient has pure SUI and previously experienced three years of continence, it is likely that the current incontinence is related to a malfunction or degradation of the AUS components. Surgical revision typically involves replacing or repositioning the cuff, pump, or pressure-regulating balloon, depending on the underlying cause. Revision surgery has been shown to restore continence in a significant proportion of patients, with success rates comparable to primary implantation. However, the decision should be individualized, considering the patient's overall health, surgical risk, and preferences. Preoperative evaluation, including urodynamic studies and imaging, is essential to confirm the diagnosis and guide the surgical approach. If the patient is a suitable candidate, revision surgery offers a reasonable chance of restoring continence and improving quality of life.

Question 20	A 58-year-old male patient underwent removal of an artificial urinary sphincter due to urethral erosion six weeks ago. He is bothered with severe stress urinary incontinence and desires reimplantation of the device. Cystourethroscopy does not reveal urethral abnormalities. Should artificial urinary sphincter reimplantation be offered at this moment, considering that the patient is miserable with his incontinence? Your answer must be in one paragraph and a maximum of 200 words.
GPT 4o 1,0	No, artificial urinary sphincter (AUS) reimplantation should not be performed at this moment. Although the patient is experiencing severe stress urinary incontinence and is eager for reimplantation, a minimum waiting period of 3 to 6 months after AUS explantation due to urethral erosion is generally recommended to allow adequate tissue healing and reduce the risk of recurrent erosion. Early reimplantation may increase the likelihood of complications, including poor tissue integration and repeat erosion. The absence of visible urethral abnormalities on cystourethroscopy is encouraging but does not guarantee complete mucosal and submucosal healing. During the waiting period, the patient should be counseled on temporary management strategies, such as external collection devices or incontinence clamps, to improve quality of life. If severe bother persists, a discussion regarding alternative interventions, such as an adjustable male sling, may be warranted. However, if the patient remains a strong candidate for AUS, reassessment after the appropriate healing period should be performed, including repeat cystourethroscopy, before proceeding with reimplantation.
DeepSeek 1,0	Reimplantation of an artificial urinary sphincter (AUS) should be approached cautiously in this patient, despite his severe stress urinary incontinence and desire for the device. Urethral erosion, which led to the initial removal, indicates compromised urethral integrity, and reimplantation too soon could risk recurrent erosion or infection. Although cystourethroscopy shows no current abnormalities, the urethra may still be healing, and a minimum waiting period of 3–6 months is typically recommended to ensure adequate tissue recovery. Additionally, the patient's history of erosion suggests potential risk factors such as poor tissue quality or compromised vascular supply, which must be carefully evaluated. Alternative management options, such as pelvic floor physiotherapy or a temporary male sling, could be considered to alleviate symptoms while allowing further healing. If reimplantation is pursued, a thorough assessment of urethral health, including urodynamic studies and possibly imaging, is essential to minimize risks. Shared decision-making with the patient, emphasizing the balance between his quality of life and the potential for complications, is crucial. If the urethra is deemed healthy and sufficient time has passed, reimplantation may be appropriate, but premature intervention should be avoided.



The Path to Global Equity in Surgical Care: Clinical and Technical Results of Cross-Border, Ultra-Long-Distance, Asia to Middle East Human Telesurgery

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ABSTRACT

Purpose: To demonstrate the feasibility and reproducibility of Ultra-long-distance, Asia to Middle East human telesurgery using low latency connectivity on multiple patients and different procedures.

Methods: Five human telesurgeries were performed over six months using a multiport robotic platform with fiber-optic and 5G connection. Remote surgeon (SA) was in Shanghai, China, and patients were in Kuwait City, Kuwait 7,000 kilometers (Km) apart.

Results: Case 1 was performed in December 2024. Cases 2 – 5 were performed consecutively over four days in April 2025. Three robotic assisted radical prostatectomies and two robotic assisted partial nephrectomies were performed. There were no clinical or technical issues encountered during any of the procedures. The average round-trip latency for all procedures was 166.6 milliseconds (ms) using fiber-optic broadband network with 5G network as back-up. Enhanced cybersecurity was employed with no recorded threats. There was an experienced robotic surgeon (AA) present in the operating room in Kuwait with a clear criteria for console take-over in case of emergencies. There were no reported complications. Patients were discharged on post-operative day two and three. Final pathology showed low grade, low stage disease in all patients and no evidence of disease at eight weeks follow-up.

Conclusion: This study demonstrated the feasibility and reproducibility of multiple human telesurgical procedures through successful collaboration between two countries using a robotic system with telecommunication capabilities, with good outcomes and without complications. However, there is a need to establish robust international guidelines to allow globalization of telesurgery.

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INTRODUCTION

Telesurgery, an innovation that allows surgeons to perform procedures remotely using advanced robotic technology, has revolutionized the way surgical care is delivered (1). From a concept born in the military, telesurgery has progressed over the past two decades with the aim to provide expert surgical care to distant and underserved locations by overcoming geographical barriers, improving global education and mentorship, and increasing surgical accuracy and safety (2). Its application could also help in delivering surgical care in extreme clinical setting such as battlefields, natural disasters, humanitarian assistance missions, underwater missions, and even space missions (3).

Since the groundbreaking Lindbergh Operation in 2001 where Marescaux et al. and his group demonstrated the feasibility of transatlantic human cholecystectomy from New York City (USA) to Strasbourg (France) spanning a distance of 6200 kilometers (Km), the widespread adoption of remote surgery remained limited due to issues relating to network reliability for long distances, lack of training, poor robotic precision, high cost, and cybersecurity concerns (4, 5). However, recent developments in high speed 5G and fiber-optic networks, surgeons experience, audiovisual communications, secure data transmission, and cost-effective robotic platforms with built-in remote connectivity capabilities allowed us to overcome many of the challenges that previously limited telesurgery (6). Prior to globalization of telesurgery, there exists a need for standardized guidelines to address the grey areas surrounding it including critical ethical concerns, liability issues, infrastructure requirements, and training and certification protocols (7).

In recent years, several published trials have described telesurgery in human and animal models between continents and different time zones (1, 6, 8-12). Those were considered promising progressive steps forward towards universal healthcare access, providing a template for the telesurgical community to benefit from. In December 2024, our group demonstrated the feasibility of performing ultra-long distance Asia to Middle East human robotic assisted radical prostatectomy (RARP)

marking the first telesurgery in the Middle East (12). The surgeon (SA) was in Shanghai, China, using an immersive surgeon console to control a multiport robotic platform docked on a patient 7,000 Km away in Kuwait City.

Telesurgery provides the context for global medical collaboration and telementoring (13, 14). Through advanced communication technologies, surgeons from various geographical locations can consult or jointly conduct surgeries in real-time. This has been shown using animal models, spanning the longest recorded distance of 13,000 Km (Orland, USA to Shanghai, China) with a mean latency of 139 milliseconds (ms) and the ability to switch console control multiple times during surgeries. Surgeons could communicate and discuss cases in real-time and transfer control when needed (15).

Robotic assisted surgery is expanding in the Middle East and the Gulf Cooperation Council (GCC), fueled by investments in technology and growing expertise. Telesurgery fits perfectly with this expansion to address disparities in access to advanced surgical care by connecting surgeons in remote or poorly equipped areas with experts across the region and enhance skill and confidence by providing tele-mentoring. The current study had two primary endpoints. First, pilot demonstration of the feasibility and reproducibility of multiple ultra-long-distance human telesurgeries over different urological procedures with optimal network latency and acceptable outcomes. Secondly, to demonstrate the feasibility of transcontinental tele-proctoring in human model. To our knowledge this is the largest report of telesurgery cases with short-term outcomes in the Middle East, with demonstration of tele-mentoring in human model.

MATERIALS AND METHODS

Patient and hospital details

A telesurgery review committee was established at our center to ensure readiness and optimization of our project (12). Members of this committee include: hospital director, head of department of surgery, anesthesiology, nursing, and biomedical engineering including remote and local telecommunication special-

ists. Patients' demographics and pre-operative clinical data are shown in Table-1. The robot used in the present study was the MicroPort Toumai robotic system® (MTRS). It was capable with fiber-optic, 5G, and wireless network connections. It had national medical products administration (NMPA) and Conformite European (CE) approvals (13, 16). The MTRS was very similar to the Da Vinci Xi® in terms of the console and patient cart design making an easy transition for the surgeons using it (17-20). RARP and RAPN were performed according to our previously described technique (12, 21). The hospital in Kuwait was a tertiary urology referral center with experience in robotic surgery since 2014 where the first robotic procedure was performed in the country, and more than 2000 local robotic urological procedures

(mostly oncological) performed at the center to date. Both the remote and local surgeons were North American board certified, fellowship trained uro-oncologists. The remote surgeon (SA) was located at MTRS headquarters in Shanghai, China, and the local robotic surgical team lead by the local surgeon (AA) were located in the operating room in Kuwait. The team was capable of inserting trocars, docking the robot, and inserting/exchanging instruments. The contingency plan was set for the local team to take over and finish the case if any of the following were to happen: patient hemodynamic instability, latency > 300 ms lasting for > 5 minutes, network failure with loss of video/audio feeds, suspected or proven cyber-attack, intraoperative complications, and/or technical problems with the robotic surgical system.

Table 1 - Patient demographics and pre-operative data.

	Dec 20 th , 2024, RARP/Case 1	April 10 th , 2025, RAPN/Case 2	April 11 th , 2025, RAPN/Case 3	April 12 th , 2025, RARP/Case 4	April 13 th , 2025, RARP/Case 5
Age	68	56	51	57	59
Sex	M	F	M	M	M
BMI (kg/m²)	30.1	36.7	32.9	31.5	29.6
PIRADS	3	N/A	N/A	5	5
PSA (ng/mL)	6.8	N/A	N/A	7.2	7.69
Prostate size (grams)	55	N/A	N/A	37	41
PSA density (ng/mL²)	0.08	N/A	N/A	0.18	0.18
Clinical T stage	cT1c	cT1a	cT1a	cT1c	cT1c
ISUP-GG	10 cores of 3+3 GG1	N/A	N/A	4 cores of 3+4 2 cores of 3+3 GG2	6 cores of 3+4 6 cores of 3+3 GG2
Briganti score	4.1%	N/A	N/A	4.9%	6%
Decision to do lymph node dissection	No	N/A	N/A	Yes	Yes
SHIM score	<7	N/A	N/A	<7	<7
RENAL nephrometry score	N/A	5a	6p	N/A	N/A

RAPN = robotic assisted partial nephrectomy; RARP = robotic assisted radical prostatectomy; BMI = body mass index; PIRADS = prostate imaging reporting and data system; N/A = not applicable; PSA = prostate specific antigen; ISUP-GG = international society of uro-pathology grade group; SHIM = sexual health inventory for men

In case there was a need to take-over due to any of the aforementioned criteria, the local surgeon has the ability to immediately assume full control of the MTRS away from the remote surgeon using the local console. In the event of technical problems with the MTRS, the local surgeon could exchange to the local Da Vinci Xi® robotic system or convert to laparoscopy or open approach if they deemed necessary (12).

Informed consent and ethical approval

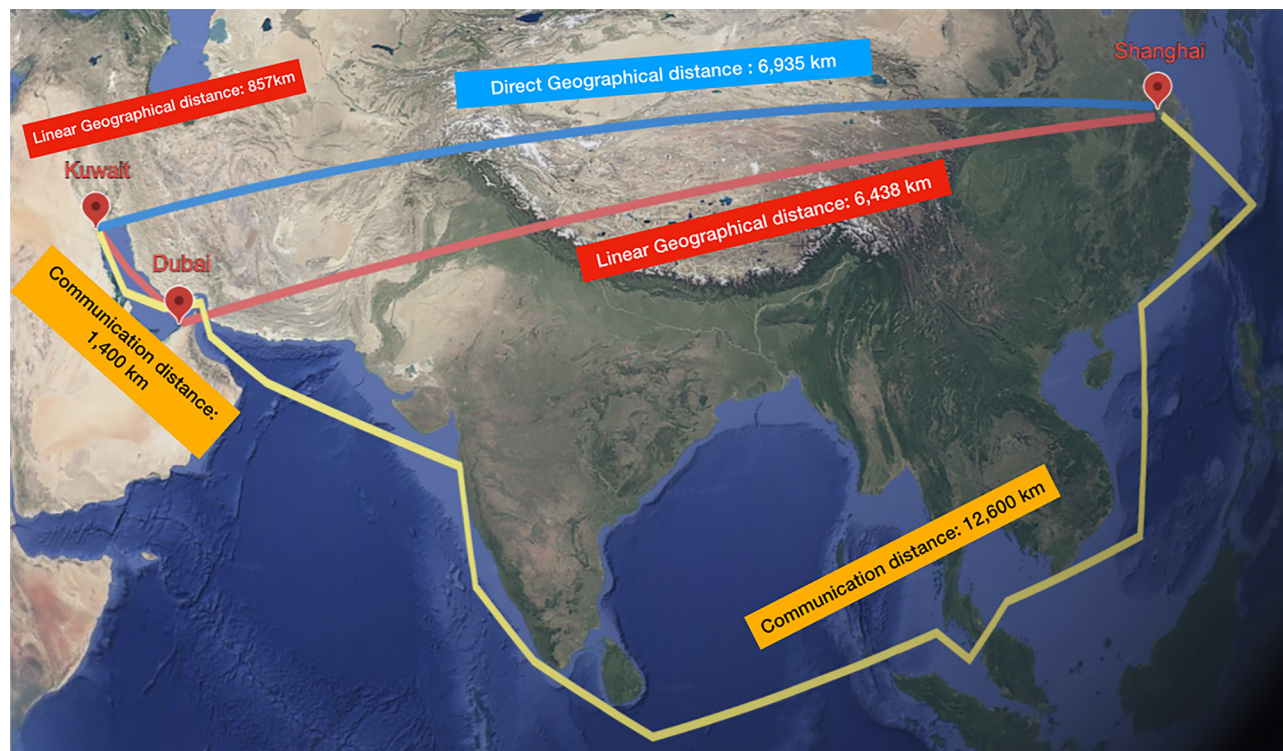
The research project received institutional review board (IRB) approval. A detailed informed consent was obtained from all patients in this study with clear discussion of risks, possible complications, and alternatives. All patients met with telesurgery review committee members and fully understood the role of the remote and local teams. In case of adverse events the responsibility falls on the Kuwaiti team including the remote surgeon (SA) who was the primary urologist for all the patients (10).

Telesurgery and network details

On the Kuwaiti end, a primary dedicated fiber-optic broadband network was used with a redundancy 5G network as back-up. We added next generation firewall and high-end load balancer for added cybersecurity. On the Shanghai end, two dedicated fiber-optic broadband networks, a primary and a back-up, were employed to secure a redundancy network in case of primary network failure (22). Multiple connectivity testing was performed on a regular basis prior to commencing the project to ensure an acceptable Round-trip latency (RTL) between Shanghai and Kuwait. This averaged at 164 ms which was well within the acceptable range not to interfere with the smooth going of the procedure (23, 24).

The exact linear geographical distance between the hospital in Kuwait City and MTRS headquarters in Shanghai was 6,935 Km (Figure-1). A local relay server was setup in Shanghai, China, and both ends communicated with each other by connecting to this relay server. Based on the international ethernet private line (IEPL)

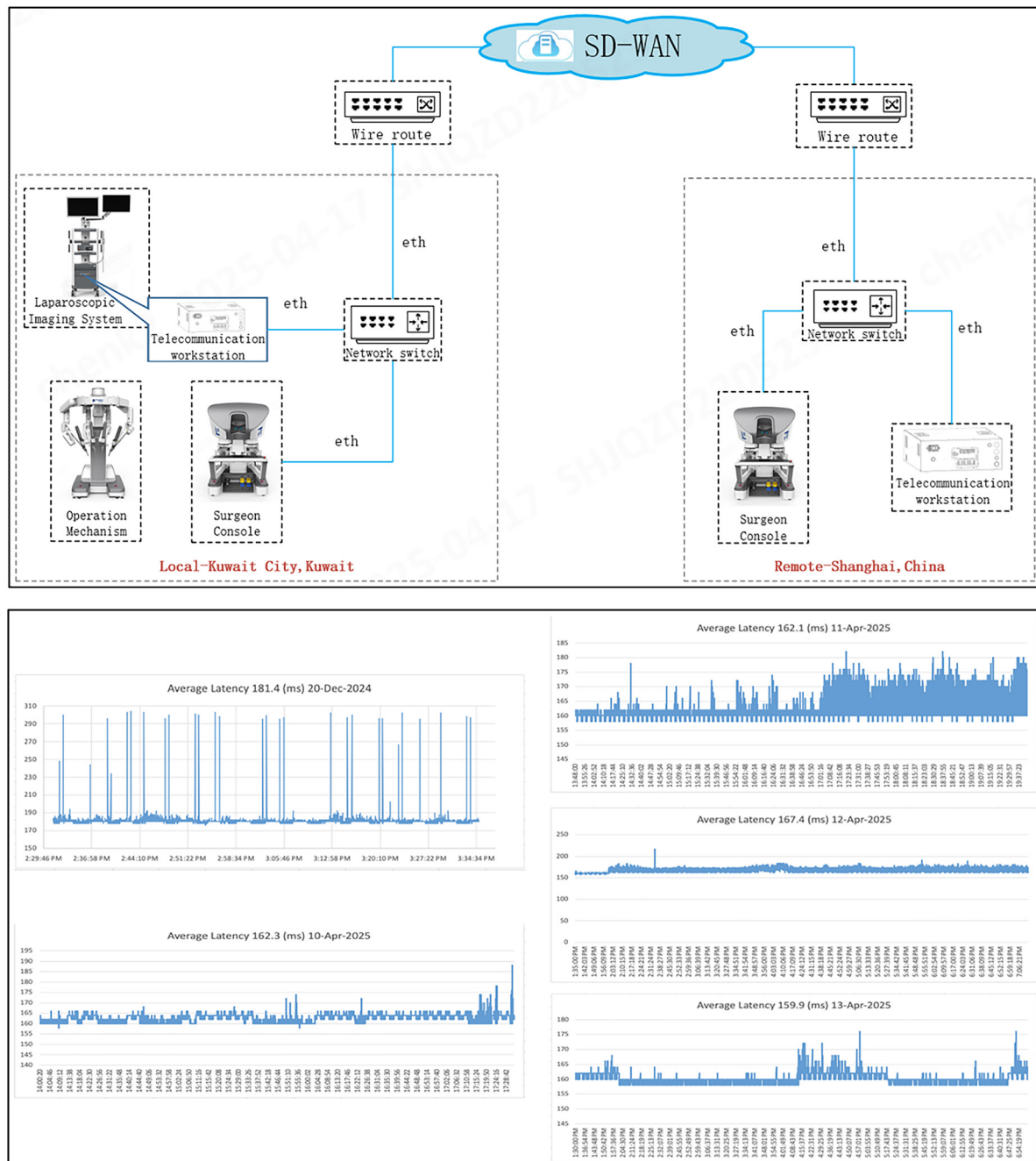
Figure 1 - Round trip communication distance from Shanghai to Kuwait. Relay server was in Shanghai and connected to Dubai using international ethernet private line.



dedicated fiber-optic between Dubai, United Arab Emirates and Shanghai, China, a software-defined wide-area-network (SD-WAN) technology (a virtual cloud ar-

chitecture with its own firewall) was adopted to reduce network delay, add more security, and stabilize network communication (Figure-2) (7). Communications between

Figure 2 - Schematic network setup between Kuwait and Shanghai showing ethernet in the hospital connected to software-defined wide-area-network cloud server in Shanghai. One-hour delay display in milliseconds for the five cases, with whole procedure average latency for each procedure.



SD-WAN = software-defines wide-area-network; eth = ethernet. ms = milliseconds

both sides of the connection were encrypted. A control request with the correct access code from the remote surgeon (SA) in Shanghai, China, was required with approval from the local surgeon (AA) in the operating room in Kuwait City. A separate line of audio-visual communication between the remote surgeon and the local team in Kuwait was created as well (1). Both teams had access to the patient's clinical information. Communication was in the English language. This set up was essential to allow evaluation of surgical safety, latency performance, and network stability which was the main objectives of the current study.

RESULTS

Peri-operative data

Post-operative clinical and network data are shown in Table-2. There were two RAPN and three RARP. Case 1 was performed on a Friday, and cases 2 – 5 were performed on Thursday, Friday, Saturday, and Sunday which resulted in the avoidance of network congestion (Figure-2). Each procedure started at seven o'clock in the morning Kuwait standard time (equivalent to noon Shanghai standard time). There were no peri-operative complications recorded. None of the patients required a blood transfusion. All patients were discharged on the second post-operative day, except one of the RAPNs, where the patient was discharged on the third post-operative day for blood pressure monitoring as she was known to have hypertension with no interventions needed. The Foley catheter was removed for the RARP patients on the 10th post-operative day. Resection surgical margins were negative for all patients. Patients were seen at eight weeks post-operatively with no evidence of disease on imaging, a stable renal function (RAPN patients), an undetectable PSA (RARP patients), and no short-term complications.

During cases 4 and 5 (RARP), we conducted a tele-mentoring experience where a local robotic fellow (SB) in Kuwait performed unilateral right standard pelvic lymph node dissection under supervision of the remote surgeon (SA) (Figure-3). The duration of the telementoring was 25 and 30 minutes, respectively. There was smooth switching of the console between the proctor

and the fellow multiple times for directions only without take-over, with clear and direct communication and discussion in real-time. The time taken to switch console control from the remote site to the local site and vice versa was under five seconds. The fellow (SB) performed the lymph node dissection independently under remote proctoring. There was a local experienced robotic surgeon (AA) present next to the fellow for safety and he did not have to take-over either. No significant delays were encountered during the switching to cause interference with the mentoring. Average latency during the exercise was 170 and 167 ms, respectively.

Data transmission and network details

Despite the significant round-trip communication distance of 28,000 Km, the overall average latency for the consecutive cases 2 – 5 was 164 ms (minimum 158.9, maximum 196.8) with no delays to impact any of the steps in any of the procedures (Table-2). There were no network failures encountered and the local surgeon (AA) did not have to take-over control from the remote surgeon (SA).

DISCUSSION

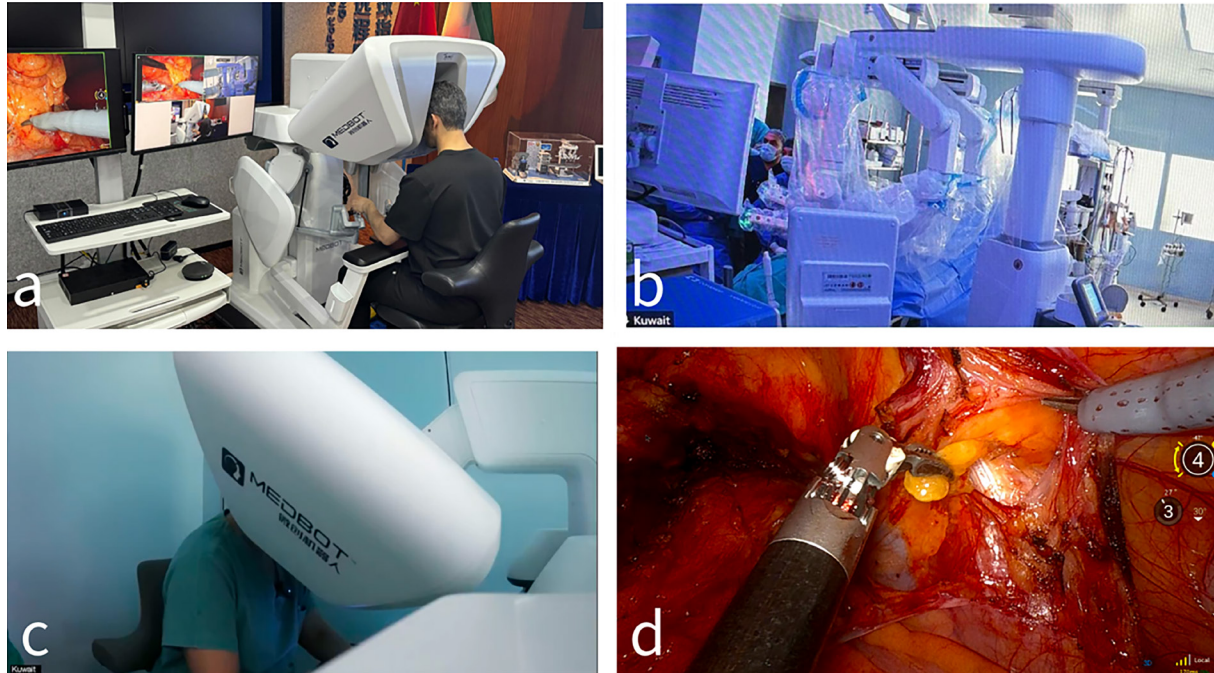
Telesurgery holds significant global healthcare benefits by providing advanced surgical care to underserved and remote areas with limited access (6, 25). Furthermore, it holds immense potential for advancing education and training (15). Over the past two decades, telesurgery progressed from experiments and trials to a real-time surgical option coinciding with the emergence of cost-effective robotic platforms with telecommunication capabilities (26). However, widespread adoption remains limited, especially for cross-border and trans-continental telesurgery, due to challenges relating to network reliability, legal liability, cybersecurity, ethical concerns, cost, and credentialing (27). If expert surgeons, engineers, telecommunication specialists, surgical societies, law makers, company executives, and hospital administrators from around the World get together and establish standardized international guidelines, this could pave the way for safe and effective global implementation of telesurgery (7). The individual publications

Table. 2 - Post-operative clinical and telecommunication data.

	Dec 20 th , 2024, RARP/Case 1	April 10 th , 2025, RAPN/Case 2	April 11 th , 2025, RAPN/Case 3	April 12 th , 2025, RARP/Case 4	April 13 th , 2025, RARP/Case 5
Surgeon to patient distance	6,935 km	6,935 km	6,935 km	6,935 km	6,935 km
Latency					
Average (ms)	181.1	162.3	162.1	167.4	159.9
Highest (ms)	304	188	182	216	176
Lowest (ms)	176	158	158	158	158
Console time (min)	210	180	250	180	300
Warm ischemia time (min)	N/A	25	22	N/A	N/A
Hemoglobin (g/dL)					
Pre-operative	12.9	12.8	15.1	13.4	12.5
Post-operative	12	11.1	15	12.5	11.9
PSA ng/mL (8 Weeks post-operative)	<0.01	N/A	N/A	<0.01	<0.01
Creatinine μmol/L (eGFRmL/min/1.73m²)					
Pre-operative	N/A	53 (102)	78 (98)	N/A	N/A
Post-operative	N/A	58 (98)	80 (97)	N/A	N/A
ICU admission	No	No	No	No	No
Estimated blood loss (mL)	70	100	120	20	100
Blood transfusion	No	No	No	No	No
Post-operative fever	No	No	No	No	No
Readmission	No	No	No	No	No
Complications (Clavien-Dindo grade)	None	None	None	None	None
Pathological stage (TNM)	pT2 Nx Mx	pT1a Nx Mx	pT1a Nx Mx	pT3a N0 M0	pT3a N0 M0
ISUP-GG	GG 2	N/A	N/A	GG 2	GG 2
Extracapsular extension	Yes	N/A	N/A	Yes	Yes
Fuhrman grade	N/A	1	2	N/A	N/A
Histology	Adenocarcinoma	Clear cell renal cell carcinoma	Clear cell renal cell carcinoma	Adenocarcinoma	Adenocarcinoma
Follow-up imaging	N/A	U/S: No evidence of disease	U/S: No evidence of disease	Cystogram Day 10: No leak	Cystogram Day 10: No leak

RAPN = robotic assisted partial nephrectomy; RARP = robotic assisted radical prostatectomy; ms = milliseconds; min = minute; PSA = prostate specific antigen; GFR = glomerular filtration rate; ICU = intensive care unit; mL = millilitres; ISUP-GG = international society of uro-pathology grade group; N/A = not applicable; U/S = ultrasound abdomen and pelvis

Figure 3 - a) Remote surgeon using the MedBot Toumai console while performing hilar dissection during right sided RAPN. b) Patient-side cart docked during right sided RAPN. c) Robotic fellow using the local console (Kuwait) while being tele-mentored by the remote surgeon (Shanghai). d) right sided standard pelvic lymph node dissection during tele-mentoring showing a round-trip latency of 170 ms.



RAPN = robotic assisted partial nephrectomy; ms = milliseconds

of human and animal telesurgery experiences contributed significantly to the expansion of telesurgery by allowing societies and hospitals around the World to benefit from it, ultimately leading to the establishment of clear operational frameworks (4, 12). The present study demonstrated the feasibility and reproducibility of different urological telesurgeries performed consecutively with good clinical and technical results. To our knowledge, this is the first cross-border, transcontinental human telesurgery experience in the Middle East, including the first reported telesurgery human RAPN.

Prior to embarking on telesurgery, several elements need to be ensured to guarantee patient safety and successful execution, especially when multiple procedures are planned. A stable network with secure and optimal latency, a fully functional robotic platform with multiple connectivity options, clear and direct audiovisual communication between the local and remote site, compliance with informed consent and legal site-spe-

cific protocols, readiness and orientation of the operating room personnel, and clear-cut emergency take-over criteria by the local surgical team (13). In the present study, a telesurgery review committee was responsible for coordinating all the aforementioned in collaboration with the remote team. Their role includes periodic audits of the telesurgery program to ensure safety, reproducibility, and consistency of the outcomes. Telesurgery in the Middle East can help centralize advanced surgical care to reach areas lacking both the expertise and technology and ultimately saving the travel expenses on patients and physicians.

Patel et al. and his group demonstrated the feasibility of telesurgery in animal model across the longest recorded distance between Orlando, Florida, United States of America (USA), and Shanghai, China (approximately 13,000Km) with optimal low-latency connectivity (mean 296 ms) using both 5G and fiber-optic broadband networks (10). They also described telesurgery ap-

plication in Africa performing two RARPs over two consecutive days using a dedicated fiber-optic connection with a distance of one Km between the surgeon and the patient with a latency < 10 ms (6). In another study, they explored the tele-proctoring potential of telesurgery in a bidirectional manner using porcine models with frequent switching of console control between Shanghai and Orlando with an average latency of 139 ms (15).

The present study between Shanghai and Kuwait sets a compelling example of real-time collaboration between teams from different countries, highlighting how remote surgery can overcome geographical limitations. The successful outcome was the result of extensive connectivity testing achieving an average latency of 166.6 ms and 164 ms for all five cases and for the four consecutive cases 2 to 5, respectively, using a dedicated fiber-optic broadband connection outside peak hours of network congestion. The SD-WAN cloud server played a crucial role in reducing network delay and adding more security and stability (7). Redundancy networks were 5G and dedicated fiber-optic line in Kuwait and Shanghai, respectively (22). During case 1 (December 2024), the average RTL was 181.4 ms with few delays exceeding 300 ms that lasted a second or two. They were not noticeable and did not interfere with any of the steps of the procedure due to instant switching to the redundancy back-up network. During cases 2 – 5 (April 2025), the highest latency obtained was 216 ms and we believe part of the reason for this improvement was using a local server (Shanghai) which helped obtain better latencies (Figure-1). Low RTL minimizes the “move and wait” nature of the procedure. The remote surgeon should be able to synchronize command of an action with visualization of the action on console screen. There was no existing reference value in terms of maximum RTL that is considered optimal for telesurgery, with a range from 100 to 300 ms considered safe to perform the procedure (28). The remote surgeon (SA) adapted well and was not affected by any perceivable delay that could compromise the optimal quality of telesurgery.

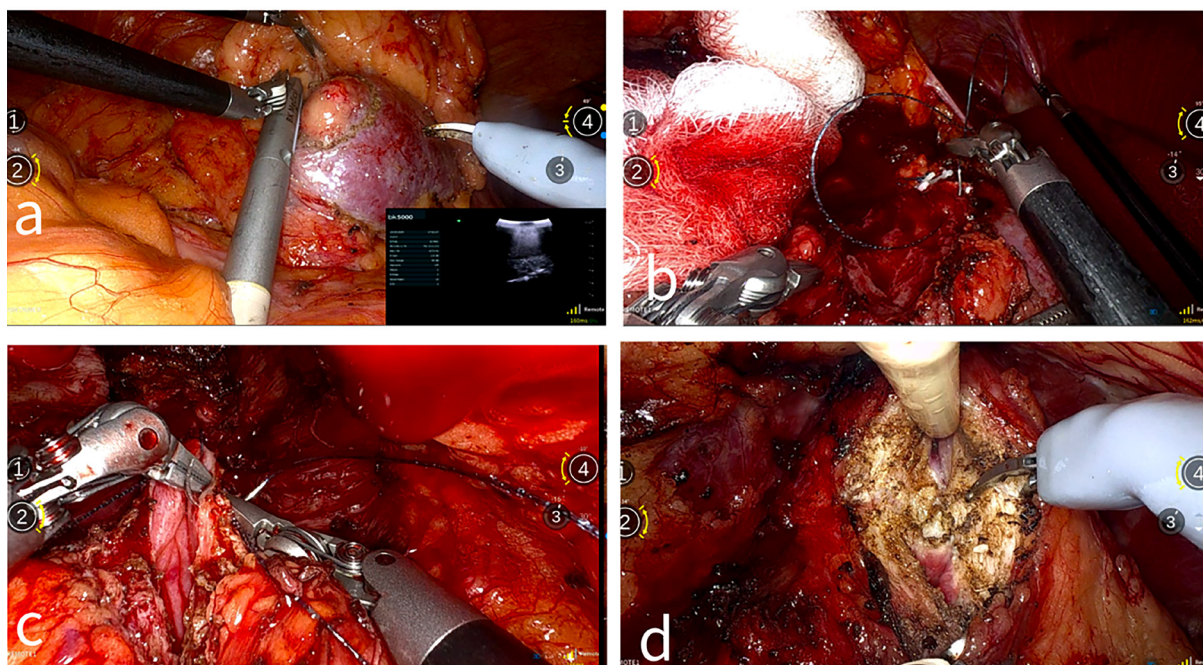
Telesurgery can provide the perfect medium for tele-mentoring and tele-proctoring in medical education, emergency situations, areas with restricted access to surgical care, conflict zones, and resource limited

setting (3, 15). Traditionally, training has been limited by geographical proximity and expert availability. Now experts can mentor and assist in complex procedures remotely. Employing augmented reality tele-mentoring was described previously for COVID-19 positive surgical patients using the Proximie™ platform (29). Moschovas et al. demonstrated robotic tele-mentoring in animal model (15). The present study demonstrated it in human model showing how the remote surgeon (SA) supervised and guided the training fellow (SB) in performing pelvic lymph node dissection during RARP. However, Tele-proctoring requires more trials and clinical validation of the remote site before being accredited as a telesurgery remote training site.

Another valuable demonstration in the present study was showing the feasibility of displaying the real-time intra-operative ultrasound image from a portable ultrasound machine at the patient's location (Kuwait) onto the remote surgeon console display (Figure-4). This was performed during the tumor marking step of the RAPN. This allowed the procedure to feel like local surgery for the remote surgeon, but due to the associated increased risk of bleeding during RAPN, several precautionary steps were taken to ensure patient safety during the telesurgery. A first assistant sparing technique was used where all the sutures and laparoscopic bulldogs were placed inside the peritoneal cavity prior to clamping. After dissection and exposure of the tumor with the aid of intra-operative ultrasound, the renal arteries were clamped using laparoscopic bulldogs to start warm ischemia time. Tumor excision was carried out sharply using the robotic scissors. The tumor bed was over-sewn using 3-0 absorbable barbed suture, 26 mm taper needle with a non-absorbable clip at its tail. Early unclamping and a sliding clip renography were performed using 0 absorbable barbed suture, 37 mm taper needle with a non-absorbable clip at each needle entry and exit on the renal capsule.

The present study had several limitations. First, the study design with only five patients' limits generalizing the results on a larger group of patients. Second, the short follow-up prevents assessment of long-term oncological outcomes and comparison with local robotic results. Third, the present study featured selecting

Figure 4 - a) Laparoscopic ultrasound drop-in probe used to mark the tumor during right sided RAPN showing real-time ultrasound image at the bottom right corner of the console display. b) Suturing the tumor bed during the final steps of right sided RAPN. c) Urethro-vesical anastomosis during RARP. d) Posterior bladder neck dissection during RARP.



RAPN = robotic assisted partial nephrectomy; RARP = robotic assisted radical prostatectomy.

non-complex and relatively easy cases which could have introduced selection bias and limited the extrapolation of the findings to patients with more advanced disease. Finally, there was no cost-effective analysis performed which could have been very useful especially when considering the application in resource-limited areas. Despite the aforementioned limitations, the present study achieved an important milestone. The present study demonstrated the concrete achievement of safe and successful execution of multiple human telesurgeries across continents without complications, representing a real-world demonstration of technical feasibility of RARP and RAPN. By continuing to explore and refine this technology we have the opportunity to democratize healthcare. Lessons learned from real-world case studies, including the present study, have provided insights into potential challenges in country to country telesurgery and how to overcome them.

CONCLUSIONS

The present study demonstrated the feasibility of multiple human telesurgical procedures performed through successful collaboration between two countries from different continents and time zones using a robotic surgical system compatible with fiber optic and 5G connectivity without intraoperative complications and excellent short-term outcomes. Highly reliable, low latency connectivity, and dual network redundancy were essential for the success of the present study. Nevertheless, Telesurgery is still not widely adopted, and one should be aware of the complexity and challenges of applying it to a larger group of patients. There are no specific laws governing international telesurgery, and additional efforts are necessary to further guarantee the safety of large-scale telesurgery in the future. Further improvements in telecommunications are required before larger trials can be carried out with longer follow up. This calls

for establishing standardized guidelines and operational framework for cross-border telesurgery.

ABBREVIATIONS

RARP = Robotic-assisted radical prostatectomy
 RAPN = Robotic-assisted partial nephrectomy
 MTRS = MicroPort Toumai robotic system
 NMPA = National medical products administration
 CE = Conformite European
 RTL = Round-trip latency
 IEPL = International ethernet private line
 SD-WAN = Software-defined wide-area-network
 COVID-19 = Coronavirus disease 2019
 BMI = Body mass index
 PIRADS = Prostate imaging reporting and data system
 PSA = Prostate specific antigen
 ISUP GG = International society of uro-pathology grade group
 SHIM = Sexual health inventory for men
 GCC = Gulf Cooperation Council
 IRB = institutional review board
 Km = kilometer
 ms = milliseconds
 mL = milliliters
 GFR = Glomerular filtration rate
 ICU = Intensive care unit

ETHICAL APPROVAL

All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

INFORMED CONSENT

Informed consent was obtained from all patients included in the study.

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CONFLICT OF INTEREST

None declared.

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Transition: The Patient in a No-Man's Land

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ABSTRACT

Introduction: The need for transition from pediatric to adult health services developed from better survival rates of congenital diseases. Quality of life, Independence, and health preservation are to be considered. Perspectives on transition differ between patients, families, health professional and administrators.

Methods: Non-systematic review and discussion of transition dilemmas in a structured format.

Results: Medical transition occurs during late adolescence/ early adulthood. Patients are expected to have increased longevity, need lifeterm follow-up and present varying degrees of complexity. Patients' fundamental wishes may conflict with caregivers' considerations. Technical decisions must be balanced, taking into account patient's social, cognitive, motor and psychological conditions, and the needs of their family caregivers. Difficulties by pediatric healthcare professionals in mastering adult diseases, and challenges encountered by adult-specialized physicians in managing sequelae or ensuring continuity of care for pediatric conditions, are the rule. Patients afflicted by with chronic complex conditions may prove financially challenging. For families, transitioning from from paediatric care to adult-oriented medicine is destabilizing and distressing. The idealization of an unattainable normality is prevalent and detrimental, leading to the abandonment of therapeutic strategies deemed socially undesirable.

Discussion: Transition care urgently requires planning by health administrators. Patients should be transferred to adult care only after clinical stabilization. Three models of transition have been suggested (direct transfer, protocol and age-driven; permanence under pediatric assistants control with eventual consultation with adult experts and gradual transition, permeated by a period of conjoint assistance). The last format is considered ideal.

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INTRODUCTION

The need for a transition mechanism for patients with congenital diseases or their sequelae (DCS) from pediatric care to adult specialist services is, in a sense, a recent development, and has quickly become a significant issue. Several general reference websites have been made available, all from high-income countries (e.g., <http://www.gotttransition.org>, <http://www.med.unc.edu/transition>), as well as some guidelines, most of which are directed at populations with spina bífida (1).

The increase in survival rates—and, more importantly, the possibility of autonomous living with a full social life, including a paid job—has provided these patients with a perspective of adulthood, expectations of better quality of life and, at least to some extent, independence, depending on individual cases. Beyond preserving physical health, enabling the best possible quality of life on a case-by-case basis and encouraging independence and self-confidence are priorities (2).

Transition

From a medical point of view, is the formal process that allows an adolescent or young adult (AYA) with a DCS to assume management of their health condition and to move from specialized pediatric care to sector-specific adult care. The goal is to provide assistance with appropriate perspectives and expertise tailored to mature and self-responsible individuals and to the health needs of the adult population. For healthcare managers and system infrastructure, this process enables optimal resource management, including equipment and logistics, the creation of new slots for high-complexity pediatric patients, planning for AYA DCS treatment, and monitoring long-term complex congenital diseases treatment outcomes.

Transition is a process

Not merely an administrative age-based moment. The simple formal transfer of AYAs to adult services—accompanied by a break in the pediatric

healthcare relationship—often proves ineffective, frequently resulting in informal returns to initial providers, therapeutic abandonment, refusal of acceptance by adult sectors, or loss to follow-up, with potentially serious health consequences (3). A recent paper reported that 2/3 of a cohort of North-American AYA with DCS reported difficulties to access medical care, and circa ¼ were not enrolled in adult clinics after 21 years of age (4).

Remaining under pediatric care without a proper transition is not without problems either. AYAs have clinical needs beyond the usual scope of pediatric specialists, including issues related to sexual and reproductive health, surveillance and treatment of adult and elderly diseases—often exacerbated or accelerated by their pediatric condition (e.g., tumor surveillance, cardiovascular and renal diseases, orthopedic issues, osteopenia). For example, children cured of pediatric tumors after chemotherapy and/or radiotherapy may have long-term sequelae, secondary tumor risks, high infertility risk, and, whenever gametes were preserved before treatment, a predicted need for reproductive specialist care.

An effective transition process requires:

1. Planning and assessing the patient/family's readiness for the change in healthcare sources.
2. Availability of mechanisms for control and monitoring after transfer to detect issues and prevent therapeutic abandonment—potentially affecting up to half of patients with chronic diseases (2).
3. Adaptation of receiving services to meet the logistical and practical needs of AYAs with DCS, involving multidisciplinary care, social support, financial assistance, and accessibility—fundamentally different from adult treatment models designed for isolated diseases in mature age.

In this paper we propose to discuss the challenges involved for transition from different perspectives:

METHODS

Non-systematic review and discussion of transition dilemmas in a structured format, regarding:

1. Relational Aspects Between Patients with Congenital Diseases, Their Families, and the Healthcare Teams Throughout Life Until Adulthood;
2. Technical Aspects Related to the Sequelae of Congenital Diseases and Their Treatments, Often Unfamiliar to Adult Medicine Experts;
3. Structural Aspects of Public and Private Healthcare Systems Concerning the Care of These Patients.

RESULTS

Typically, medical transition occurs during late adolescence/ early adulthood (between 14 and 21 years of age). This population is expected to have increased longevity and necessitates long-term follow-up, often throughout their entire lives to manage current and potential health issues.

For the same underlying condition, different needs may arise. Individuals with congenital diseases exhibit varying degrees of complexity, diverse therapeutic outcomes, and frequent associations with comorbidities and syndromes. The results and needs can differ depending on the timing of diagnosis (antenatal versus early versus late), previous treatment strategies, modifications in the standard of care during the patient's growth, treatment choice for the specific patient conditions (including social and familiar issues), and the feasibility of therapeutic planning within the social context, availability of resources, and technological advancements.

As an example, an 18-year-old patient post-treatment for posterior urethral valves may be a clinically stable young adult requiring renal and cardiovascular monitoring; a young man facing fertility issues; a stable young individual dependent on intermittent clean catheterization; a renal transplant recipient; or a person on dialysis with severe hyperten-

sion. Also, the management of patients with urinary incontinence varies depending on access to costly hygiene supplies and the patient's motor capacity. In other words, the needs of individuals with Congenital Urological Conditions are highly individualized and variable, defying a single standardized guideline—"one size fits all", and this is true for life.

Social and cognitive factors influence the timing of transition, which cannot be based solely on age.

The evolution of each adolescent through maturity differs, especially in the context of chronic illness. Chronological age may not suffice to classify patients with DCS as adults. Patients with significant physical dependence or severe cognitive limitations require tailored approaches and often have different future prospects compared to others. Some professionals suggest that certain adults with DCS and high dependency—particularly those with syndromic conditions involving cognitive and growth deficits—might need to remain under pediatric care, given their strict and permanent reliance on family caregivers and their inability to assume personal care responsibilities.

In the Brazilian context, social and logistical support for dependent patients within public health services remain very limited in practice, despite inclusive legislation. Similarly, most private health assistance institutions provide minimal ongoing support in terms of supplies, medications, and home care assistance. Consequently, the ongoing influence of close family members on therapeutic decisions persists long-term, sometimes involving ethically complex or conflicting choices, alongside the practical involvement of caregivers in daily needs.

Considerations regarding the quality of life of family members and caregivers, including financial commitments, must be integrated into the transition process.

Patients' fundamental wishes may conflict with their caregivers' considerations. For instance,

what should be done if parents of an adolescent with severe cognitive limitations request sterilization? Or when a teenage girl with spina bifida requests contraception, while her family refuses to acknowledge the possibility of an active sexual life? How can we balance the constant and lifetime need for support for children with DCS with the relational and financial needs of parents and siblings, aiming for fairness and justice?

Technical decisions must be carefully balanced, taking into account social, cognitive, and psychological conditions of the patients, their degree of dependence, and the needs of their family caregivers. Some decisions are particularly challenging, requiring a delicate balance between clinical needs, ethical considerations (such as ableism and social prejudices), the disproportionate and ongoing sacrifices of caregivers, and legal aspects. Practical circumstances must be considered realistically, including logistical and financial factors. Occasionally, the ideal outlined by technical guidelines may be unattainable, necessitating case-by-case decision-making. A common example among urological patients is the preferential choice of incontinent diversions for individuals with severe cognitive limitations, limited social expectations, or inability to perform self-care—particularly when family members need to work and lack adequate support structures.

Dysmorphia, social isolation, and unrealistic expectations are frequent among DCS patients. Suicidal ideation is not uncommon. Psychosexual concerns related to the penis following surgeries for hypospadias and epispadias are typical, as are distress regarding genital aesthetics and dyspareunia in female patients after genital reconstruction surgeries. Questions about fertility and the adoption of erroneous perspectives concerning the genetic transmission of diseases are also prevalent within this patient group. These issues typically emerge during adolescence and early adulthood, requiring integrated multidisciplinary care, including consultations with mental health and quality of life specialists, as well as social workers—services that are rarely available within pediatric or adult healthcare systems.

Technical Aspects Related to the Sequelae of Congenital Diseases and Their Treatments, Often Unfamiliar to Adult Medicine Specialists:

The difficulties faced by pediatric healthcare professionals in mastering adult diseases, as well as the challenges encountered by adult-specialized physicians in managing sequelae or ensuring continuity of care for pediatric conditions, are remarkable. The increasing sophistication and expansion of medical knowledge have led professionals to focus predominantly on technical content within their usual domains or specific patient populations. This trend is evident even among generalists and emergency physicians specialized in adult medicine. The rarity and variability of many congenital diseases further complicate matters, as do the multidisciplinary aspects typical of patients with high-complexity conditions. Another significant issue is the scarcity of reliable guidelines for the treatment of patients with DCS (3).

In the current landscape of medical practice and training curricula, the education of physicians specialized in adult medicine regarding pediatric and congenital diseases remains limited to foundational knowledge. This can be particularly challenging for physicians which primarily or exclusively treat adults to care for patients with DCS, especially those with rare conditions.

A recent study revealed that only 5% of gynecologists in a U.S. healthcare facility had received formal training in pediatric and adolescent gynecology, and merely 7% of the institutions employing these professionals offered outpatient services for children and adolescents. Within this cohort, approximately one-third of physicians reported having performed a perineal examination on a patient with anorectal malformation, and only 12% and 5% had previously managed patients with appendicovesicostomy or appendicocolostomy, respectively. Moreover, 80% of these gynecologists expressed discomfort, and 82% considered themselves incompetent to treat adult patients with anorectal anomalies. Additionally, 22% explicitly indicated no interest in such patients, and 34% reported lacking the time to care for women with

anorectal malformations. When responding to a basic questionnaire on anorectal and related anomalies and their implications in adult patients, approximately half of the professionals answered correctly only up to two out of seven questions (5). The knowledge and recognition of sequelae stemming from congenital diseases, as well as the possible adaptations and prognoses, are not easily accessible among adult medicine specialists, that often show limited interest in working with this population (6).

On the other side, pediatric experts do not master certain aspects of adult care, particularly concerning degenerative or aging-related diseases, reproduction and sexuality, as well as early detection and prevention of neoplasms.

As a consequence, lack of training regarding chronic illnesses and sequelae of congenital diseases care is a common complaint among both adult and pediatric physicians (2) and situate DCS patients in a “no-man’s land”.

The structure of healthcare and logistical considerations for the care of adult patients with congenital and developmental syndromes (DCS) requiring ongoing treatment.

DCS patients often exhibit some degree of dependency and are frequently outside the labor market, especially in low- and middle-income countries. Many have had limited education due to logistical challenges, multiple hospitalizations, or cognitive impairments. These adults have been managed throughout their lives within pediatric care frameworks that focus on family involvement and the direct protection of immature patient’s incapable of fully consenting or managing their needs.

Often, families adopt a protective role that permanently infantilizes the patient, impeding their assumption of responsibilities and fostering expectations of lasting dependence or subordination. This situation may be accepted by the patient, which then behaves passively, refraining from direct participation in their healthcare responsibilities. Conversely, it can lead to complete rejection of parental and medical

guardianship once the individual attains legal adulthood, often resulting in abandonment of therapeutic guidelines. In ideal circumstances patients and families develop a co-participatory approach, balancing patient’s needs and limitations with the aspiration for maximum autonomy.

The transition to care tailored for autonomous adult patients presents immediate adaptive challenges, which has led to the recommendation of gradual transition algorithms as ideal solutions. For patients with DCS, the structure of outpatient medical services for adults—often fragmented among various specialists without a centralized “overall coordination” (which, in pediatric cases, is typically managed by the pediatrician)—complicates multidisciplinary care. Frequently, patients must travel to different locations on separate days, to see various professionals, involving logistical arrangements that are both complex and costly for patients and their caregivers. From the patient’s perspective, the structure of care for adults often appears worse in quality than the structure they previously relied on for treatment.

The philosophy of care aimed at autonomous adults demands that patients assume individual responsibilities—an expectation that patients with DCS are generally unaccustomed to. The numerous healthcare professionals involved in their care often struggle to communicate effectively among themselves, especially when working in different institutions or on different schedules. Emergency visits tend to become common, even when inappropriate, as these patients are highly complex, often with conditions beyond the full technical expertise of adult emergency physicians, and frequently use multiple medications and present serious comorbidities. Urgent care typically involves symptomatic treatment and recommendations to consult their primary clinicians. Patients often find themselves caught between the limitations of emergency services and difficulties to get immediate access to their usual healthcare providers, showing another version of the “no man’s land” dilemma.

In general hospitals equipped with pediatric surgical services, contact between the pediatric

team and adult specialists is straightforward. However, for patients “graduated” from exclusively pediatric hospitals to adult care services, this process can be more challenging, due to institutional transfers. Well-founded technical reports and direct thorough access to the patient’s medical records help, but they do not fully replace direct communication among professionals—discussions that include opinions, planning, updates on previously impractical schedules, and assessments of the relational dynamics between the patient, their family, and healthcare providers. There are practical difficulties in conveying a comprehensive account of a complex, multifaceted clinical trajectory, which may involve multiple professionals and a vast amount of documentation accumulated over what is conventionally an 18-year lifespan (7).

Some issues faced by these patients have deeply personal implications—such as erectile dysfunction, infertility, or contraception in highly dependent individuals—necessitating a strong doctor-patient relationship, which is often lacking between DCS patients and their new clinician post-transition, and sometimes raising difficult ethical questions. Confidentiality can be particularly critical, especially for minors without full legal responsibility capacity or adults with cognitive limitations. There is often a conflict between unsupervised meetings between the patient and the attending physician—allowing greater privacy and more personal discussions initiated by the patient—and the legal right of guardians to be present during consultations, alongside healthcare professionals’ concerns about potential accusations of abuse or misconduct involving minors or unaccompanied adults.

Ethical and legal quandaries are commonplace: Is sterilization ethically justifiable in highly dependent young patients or those afflicted with severe, genetically transmissible diseases? Ought patients carrying genetic disorders or with possible genetic determination be referred for assisted reproductive technologies? When is advising patients at high risk against desired pregnancies defensible? Can requests for vaginal delivery be reasonably ac-

commodated in women with complex pelvic reconstructions, given the currently available substandard evidence favoring caesarean sections? What is the true risk of malignancy in young patients undergoing augmentation cystoplasty?

From a cost perspective view, patients afflicted with chronic complex conditions may prove financially disadvantageous to institutions. They require lifelong, often highly complex, periodic care, frequently encompassing expensive and repetitive routine procedures (dialysis, post-transplant management, physiotherapy, social and psychological support). Regrettably, they may become “undesirable” patients, rejected by some institutions or practitioners.

Families of adult patients bearing permanent sequelae of their condition.

For families, the transition of AYA from paediatric care to adult-oriented medicine is a destabilizing and distressing juncture. The prospect of readjusting to new treatment methodologies and new medical teams after eighteen years of frequent contact with paediatric specialists is, at the very least, unsettling and challenging. A constant relationship of profound trust and intimacy, painstakingly built over time, will be inevitably superseded, irrespective of the wishes of patients and families. The proposed approach entails the progressive independence of patients where feasible, which is emotionally challenging for many families of DCS patients.

The recognition of genuine, imagined, or exaggerated risks (depending on the case) is common. As previously mentioned, the families of these patients are often overprotective. Also, family ties frequently fracture during the course of these children’s development, and the incidence of only-children is elevated, leading to exceptionally strong bonds between mothers (typically the primary caregivers in cases of marital dissolution) and DCS patients. Often, a highly solid mother-child dyad is a form of survival under these circumstances, for the patient, that really needs intensive care, and also to the carer, that dedicates him-herself to the child, in disregard of other

personal needs and projects. However, such a powerful relationship may impede the independence of DCS young adults. For the caregiver this kind of "empty nest syndrome" can be intensely acute and painful.

Normality versus best possibility

The trials of adolescence, challenging for all children, are more arduous and protracted for DCS AYA, compounded by physical, social, and psychological issues. The idealization of an unattainable normality is prevalent and directly detrimental, frequently leading to the abandonment of therapeutic strategies deemed socially undesirable (intermittent clean catheterization in cases of micturition dysfunction or augmentation cystoplasty being a typical example) or medications perceived as having socially deleterious side effects (for instance, post-transplant medications causing acne) (8).

Risky behaviours are commonplace, including permissive sexual relationships with the risk of unplanned pregnancies in female patients, substance abuse, and the adoption of inappropriate diets. Amidst fantasies of absolute normalcy, the complete abandonment of medical treatments is common, with some patients ultimately only seeking episodic emergency care during crises.

Maturation to accept the necessity of consistent treatments in exchange for improved quality of life (as opposed to a "normal" life) and health security versus the fantasy of normality of being "just like everyone else" is difficult, often delayed, and associated with episodes of depression. A harmonious family relationship and the provision of comprehensive information regarding prognosis and expected limitations by the healthcare professional are beneficial. Patient's education given to patients requires reinforcement and repetition, increasing in complexity alongside the child/AYA's cognitive maturation, including "difficult" information involving the admission of the incurability of the disease or sequelae and the expectation of lifelong treatment.

For a subset of patients, the level of dependence on caregivers/family turns to be greater than

necessary due to insecurity, overprotective parenting, immaturity, diminished personal expectations, and social and logistical challenges. Often, the patient relinquishes the autonomy that is possible, however limited.

Accessibility for individuals with disabilities can be exceedingly challenging, especially in low- and middle-income countries, diminishing the potential for autonomy. Financial dependency and the inability to enter the workforce are related problems, sometimes attributable to insufficient formal education. For some, the theoretical expectation of autonomy predicted by technical criteria is not practically attainable, and the perspectives of the Family include the forever financial dependence of the DCS Family member.

Sexuality in a no-man's land.

Sexuality is a social taboo that becomes more problematic following genital reconstructions, for patients with continence problems, those afflicted with spinal cord neurological conditions accompanied by paraplegia, and those with cognitive deficits. The evolution of society toward recognizing the expectation of active sexual lives and typical adult affective relationships in this population remains insufficient, and these young individuals are erroneously treated as persons without such prospects or desires, or who do not elicit this type of attention. For patients, insecurity regarding specific problems, exacerbated by episodes of bullying and fear of rejection by potential partners, is the norm, leading to delayed affective and sexual initiation, submission to risky behaviours/partners and episodes of violence or long-term bachelorship.

As a consequence of neglecting the potential for sexual relationships in this population, reproductive counselling is frequently omitted. Unplanned pregnancies and/or diagnoses of sexually transmitted infections are not uncommon.

In males presenting spinal neurological conditions, anorectal anomalies, and sequelae of extensive pelvic surgery, erectile dysfunction is commonplace.

In women with spina bifida, the risk of recurrence of the condition in their offspring is higher

than in the general population. Pregnancy planning necessitates the prescription of high doses of folic acid for several months prior to the cessation of contraceptive methods, a matter that must be explained with lucidity to patients from the moment they possess sufficient comprehension.

Many malformations entail specific obstetric risks, and patients require care from professionals cognizant of their previous medical history, ideally beginning from the period when a pregnancy is contemplated. In certain instances, pregnancy necessitates alterations to pre-existing, chronic, and established management protocols. An example is the need for indwelling catheterization via abdominal catheterizable channels due to increased uterine growth after the second trimester of gestation, or the cessation of medications with the potential to cause embryological anomalies or obstetric complications. Following complex reconstructive surgeries, the presence of a surgeon and/or urologist experienced in the patient's condition during caesarean deliveries is imperative.

DISCUSSION

Arising from all of these considerations, teams dedicated to the paediatric care of patients with chronic complex conditions have been seeking algorithms for the transfer of these young individuals to specialized adult care. This need urgently requires assumption by health administrators as well (2).

An initial premise is the complete stabilization of the patient prior to transfer. AYAs should be transferred in a clinical situation that presupposes the utilization of therapeutic strategies for chronic use, already accepted and assimilated, and the absence of unresolved acute problems.

The debate regarding transition mechanisms and the considerable variability among cases suggests that a single, rigid transition mechanism is untenable. Rigid healthcare management control mechanisms, including computerized guidelines that "do not accept" patient enrolment outside of the planned age range in paediatric care, are destined to perpetrate injustices that may ultimately result in loss of

follow-up and clinical deterioration of patients, who end up as outcasts of the system.

Regrettably, this type of problem has been exceedingly frequent since the adoption of computerized classification systems based on artificial intelligence, modulated by non-specialized professionals possessed of limited decisional autonomy.

The models proposed for the transfer of patients with chronic complex conditions are (Figure-1):

Direct, Protocol-Driven Transfer at a Single Point in Time:

Direct referral to specialized adult treatment services, severing the connection with paediatric care, mediated exclusively by the transfer of clinical data (detailed reports and/or copies of medical records). This is the standard procedure in most Brazilian maternal-child healthcare services not located within general hospitals, with the age range varying between 14 and 18 years. This model is the most frequently used, owing to its "automatism" and because it has, until recently, been presented as the sole alternative (with the exception of the "informal" continuation of patients under paediatric care after adulthood). The model of compulsory automatic transfer for treatment in services directed towards adults has been most strongly associated with loss of follow-up, clinical deterioration, and episodic care in emergency departments. Another issue is the non-acceptance of the transfer by the patients, who spontaneously return to the paediatric service and complain about what they judge the insufficient technical knowledge of health adult-specialized providers about their specific condition. The perpetuation of previous treatments without medical supervision by patients is another form of reaction.

Continuation under Paediatric Treatment with Occasional Consultation in Adult Medicine:

Maintenance of patients under the care of paediatric professionals specialized

in their underlying diseases, irrespective of age range, contingent upon the modulation of these professionals regarding the need for treatment of conditions typical of adults or specific circumstances (infertility treatment, obstetric treatment, contraception, for example), in a form of "shared management." This is a common format in general hospitals that houses paediatric and paediatric surgery services, and a frequent practice, especially among older professionals. Often, it is the patients who request the continuation or return to the care of the professionals with whom they have had a relationship since childhood.

Gradual Transfer to Adult Medicine with an Intermediate Period of Overlapping Care:

Gradual transition from paediatric services to adult medicine, with an intermediate period of joint outpatient treatment by the paediatric professional and the adult specialist. This format is the most recently proposed and is considered ideal, as it fosters an initial familiarity of patients with their future attending physicians in a gradual manner, and also the gradual transfer of knowledge and information between professionals. However,

it requires the confluence of medical specialists in paediatric medicine and adult medicine in the same physical environment for a prolonged period, which may present logistical difficulties, including with regard to the time availability of both professionals.

Other issues involve the inadequate adoption of approaches "approximating" adult disease management to treat conditions specific to the paediatric age range by adult specialists, and the "competition" of patients graduating from paediatric services for appointment slots that prioritize "conventional" adult patients and cases of acute urgency, particularly those with malignant neoplasms.

The survival of patients with neurological and behavioural disorders into adulthood, especially with regard to the alarming rates of autism spectrum disorder (ASD) in isolation or in association with other congenital conditions, and patients with cerebral palsy, presents a new challenge in the near future, which has been little studied and not even considered by most of the health administrators.

CONFLICT OF INTEREST

None declared.

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Histological Analysis of the Prostate During the Human Fetal Period (12 to 22 Weeks Post-Conception)

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ABSTRACT

Purpose: The aim of this study was to quantitatively analyze the stromal components of the prostate (collagen, muscle fibers and elastic system fibers) during prostate development in normal human fetuses, in order to establish normal growth patterns.

Materials and Methods: Twenty-one normal human fetuses, aged between 12- and 22-weeks post-conception (WPC), were studied. The fetuses were divided into three groups: G1, n = 7, 12 to 16 WPC; G2, n = 6, 17 to 19 WPC, and G3, n = 8, 20 to 22 WPC. The samples were fixed in 4% buffered formalin and processed for paraffin embedding for histochemical analysis. Five 5-micrometer-thick sections were taken from each sample and stained using histochemical techniques to identify the prostate stromal components. Histomorphometric analyses were carried out by evaluating the area density of the parameters analyzed, in percentage, using ImageJ software.

Results: The quantitative analysis of collagen fibers ($p = 0.0616$) and elastic system fibers ($p = 0.6049$) showed no significant difference between groups. Smooth muscle fibers were higher in G2 (+82.38%) and G3 (+108.81%) when compared to G1, $p = 0.0020$. Linear regression of the entire fetal period studied (12 to 22 WPC) showed a proportional increase in muscle fibers in relation to gestational age ($r^2 = 0.3398$; $p = 0.0056$). Linear regression revealed a strong negative correlation between collagen fibers and smooth muscle fibers in G3 (20 to 22 WPC) ($r^2 = 0.8209$; $p = 0.0019$).

Conclusions: Changes in the stromal components of the prostate are more significant from the end of the second trimester of pregnancy. Collagen fibers and elastic system fibers showed stable growth throughout the fetal period studied. The density of smooth muscle fibers increased about twofold with increasing fetal age.

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INTRODUCTION

The prostate is a fibromuscular and glandular organ, made up of approximately 70% glandular components, arranged in acini and ductules, and 30% stromal components, made up of fibromuscular tissue and a protein matrix (1, 2).

The prostate develops during the tenth week of gestation in response to the stimulus of androgenic hormones, mainly dihydrotestosterone, with complex and subsequent epithelial-mesenchymal interactions (3, 4). These hormones play an important role in prostate development and are potential stimulators of the differentiation and growth of the prostatic epithelium and stroma, being important in the structure and function of the prostate (3, 5, 6).

The human prostate undergoes numerous morphological changes from fetal development to old age (7). Prostate development takes place through several stages, ranging from the emergence of epithelial buds from the embryonic urogenital sinus to the differentiation of luminal and basal epithelial cells and secretory cytodifferentiation at the end of the second and third gestational trimesters, and is completed at puberty, in response to an increase in androgen production (8).

Previous studies have evaluated prostate growth in human fetuses, with and without congenital anomalies (9-14). However, studies evaluating the development of the stromal components of the fetal prostate are rare. Specific data on prostate growth during the human fetal period is relevant and of great importance to the urological community, as it can provide data on the biology of prostate development. Therefore, the aim of this study was to characterize, using quantitative methods, the growth and modifications of the stromal components of the prostate in normal human fetuses, from 12 to 22 weeks post-conception (WPC), in order to establish normal growth patterns.

MATERIALS AND METHODS

The study was carried out in accordance with the Research Ethics Committee of the State Univer-

sity of Rio de Janeiro on experimentation on human subjects (IRB: 6.997.014, CAAE: 17321519.0.0000.5259).

We studied twenty-one normal human fetuses aged between 12 and 22 WPC, divided into three groups: G1 (n=7; 12 to 16 WPC); G2 (n=6; 17 to 19 WPC) and G3 (n=8; 20 to 22 WPC), from the collection of the Urogenital Research Unit of the State University of Rio de Janeiro. The fetuses were macroscopically well preserved, and the deaths were not related to the urogenital tract.

The gestational age of the fetuses was determined in WPC, according to the criterion of the largest foot length, which is the most acceptable and reliable parameter for estimating gestational age (15-18).

Material and histological procedures

After gestational age determination, the fetuses were dissected using a stereoscopic lens with a magnification between 16 and 25x, and the urogenital block, containing the ureters, bladder, prostate and penis, was removed.

After collecting the samples, the prostate was separated from the other structures, fixed in 4% buffered formalin and routinely processed for paraffin embedding. After embedding, 5 µm-thick histological sections were made at 200 µm intervals to analyze the stromal components of the prostate. The sections were stained using the following histochemical methods: Hematoxylin-Eosin to assess tissue integrity, Picrosirius red to analyze collagen fibers, Masson's trichrome to analyze smooth muscle fibers, and Weigert's Resorcin-Fuchsin with prior oxidation to analyze the fibers of the elastic system.

Histomorphometric analyses

For the histomorphometric analyses of the prostate stromal components we used the Image-J software, version 1.50i (<http://www.imagej.nih.gov/ij>). The analyses were carried out using photomicrographs taken with a microscope (BX51, Olympus America, Inc.) equipped with a digital camera (DP71, Olympus America, Inc., Melville, New York). For each analysis, the photomicrographs were captured and saved at a resolution of 2040 pixels x 1536 pixels, in TIFF format.

Quantitative analyses of the stromal components of the prostate were determined by the area densities of each component at the following magnifications: collagen fibers (400x), smooth muscle fibers (400x) and elastic system fibers (600x). For these analyses, five sections of each prostate were used and five random fields of each section were observed, totaling 25 fields in each prostate. The results for each field were obtained using the point-counting method, in which a grid of 100 points was superimposed on the photomicrographs using the "grid" tool, and the average quantification value was determined for the five sections studied from each prostate, with the results expressed as a percentage.

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normal distribution curve. The data was evaluated by analysis of variance (one-way ANOVA) with Tukey's post-test and the results were expressed as mean $\pm$ standard deviation. The mean values of each fetus were used for statistical analysis by linear regression, in which we evaluated the correlation coefficient (r) of WPC and the percentage of tissue area density of the prostatic stromal components. A p -value < 0.05 was considered statistically significant. All analyses were carried out using GraphPad Prism 5 software (GraphPad Software, San Diego, CA).

RESULTS

The prostate of fetuses with 12 WPC already presented the stromal components differentiated (Figure-1).

The results of the quantitative analyses in the three groups studied, G1 (12 to 16 WPC); G2 (17 to 19 WPC) and G3 (20 to 22 WPC), with mean and standard deviation, and the minimum and maximum values, for each group, are shown in Table-1.

A comparison of the growth of the stromal components of the prostate (collagen fibers, smooth muscle fibers and elastic system fibers) in the groups studied, showed a significant difference only in the

muscular component of G1 when compared to the other groups (G1: $19.3 \pm 9.74\%$; G2: $35.2 \pm 9.21\%$; G3: $40.3 \pm 8.54\%$; $p=0.0020$). Collagen fibers (G1: $46.0 \pm 8.24\%$; G2: $33.8 \pm 9.67\%$; G3: $35.1 \pm 9.11\%$; $p=0.0616$) and elastic system fibers (G1: $22.1 \pm 1.98\%$; G2: $20.1 \pm 3.63\%$; G3: $21.7 \pm 3.53\%$; $p=0.6049$) showed no significant difference between the groups (Figure-2).

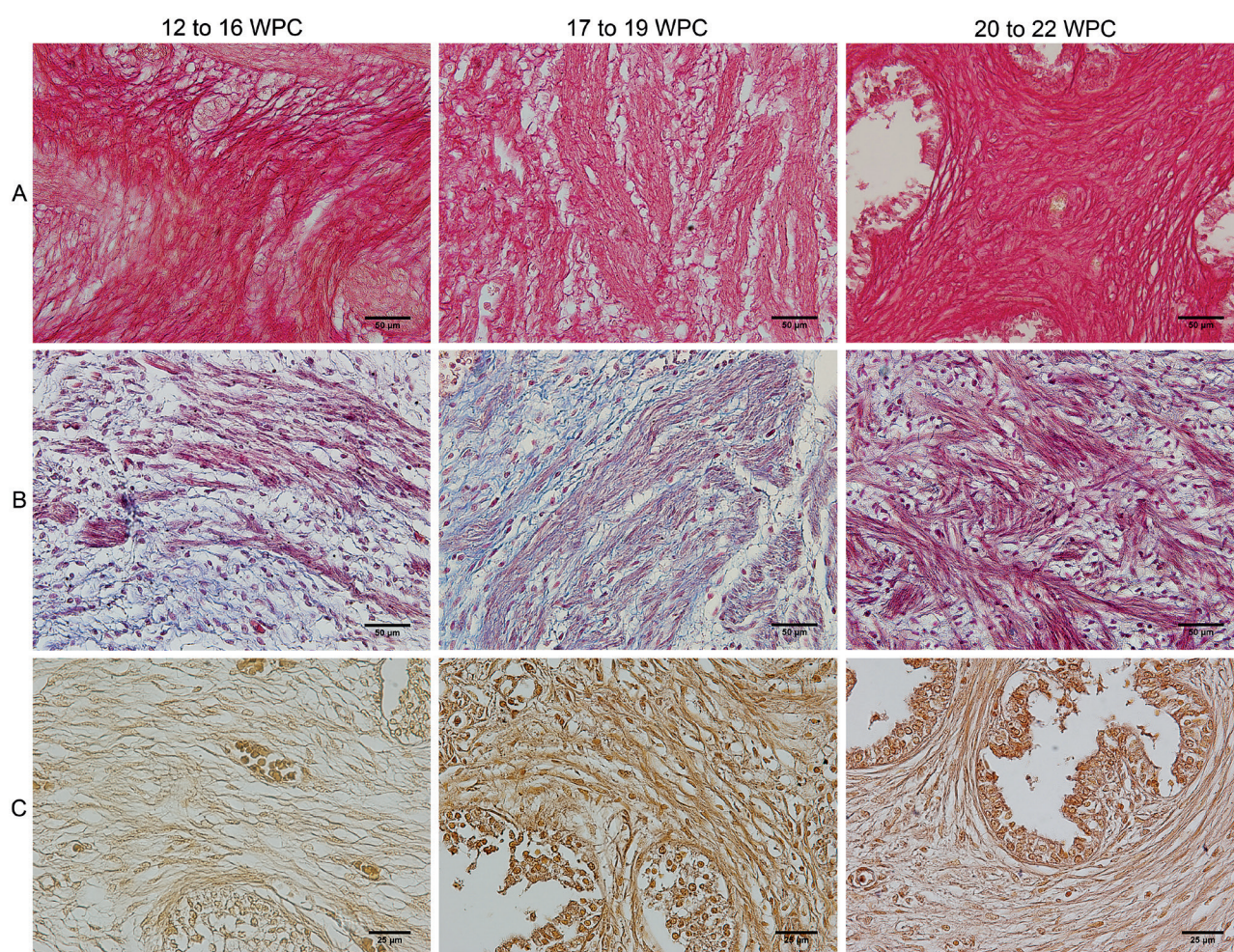
The linear regression analysis showed a significant positive correlation between muscle and gestational age throughout the fetal period studied ($r^2 = 0.3398$; $p = 0.0056$). Collagen ($r^2 = 0.07046$; $p = 0.2448$) and elastic system fibers ($r^2 = 0.02116$; $p = 0.5646$) showed no significant correlation. Linear regression analysis also revealed a strong significant negative correlation in G3 between muscle fibers and collagen ($r^2 = 0.8209$; $p = 0.0019$) (Figure-3).

DISCUSSION

The prostate is a fibromuscular and glandular organ of great clinical interest, since pathologies such as prostate cancer and benign prostatic hyperplasia are common in individuals over 40 years of age. Studies of prostate development in normal human fetuses during the second gestational trimester are rare and may be relevant due to the importance of this fetal period in the growth and development of the embryo.

As the changes during embryonic development are rapid and numerous, the fetuses were divided into three groups according to gestational age. Prostate development undergoes various differentiations, and a previous study observed intense prostate development between the 12th and 20th weeks (19).

Lunacek et al. (20) evaluated fetal prostates between 11 and 40 weeks of gestation and observed that the first signs of glandular tissue development appeared in the 11th week. A recent study evaluated the development of the urogenital tract in normal human fetuses and observed the appearance of the prostate at the 12th week with the appearance of prostatic buds (12). In the present study, we observed that the prostatic components analyzed here were already present from the 12th WPC onwards.

Figure 1 - Photomicrograph of the prostate components in normal human fetuses.

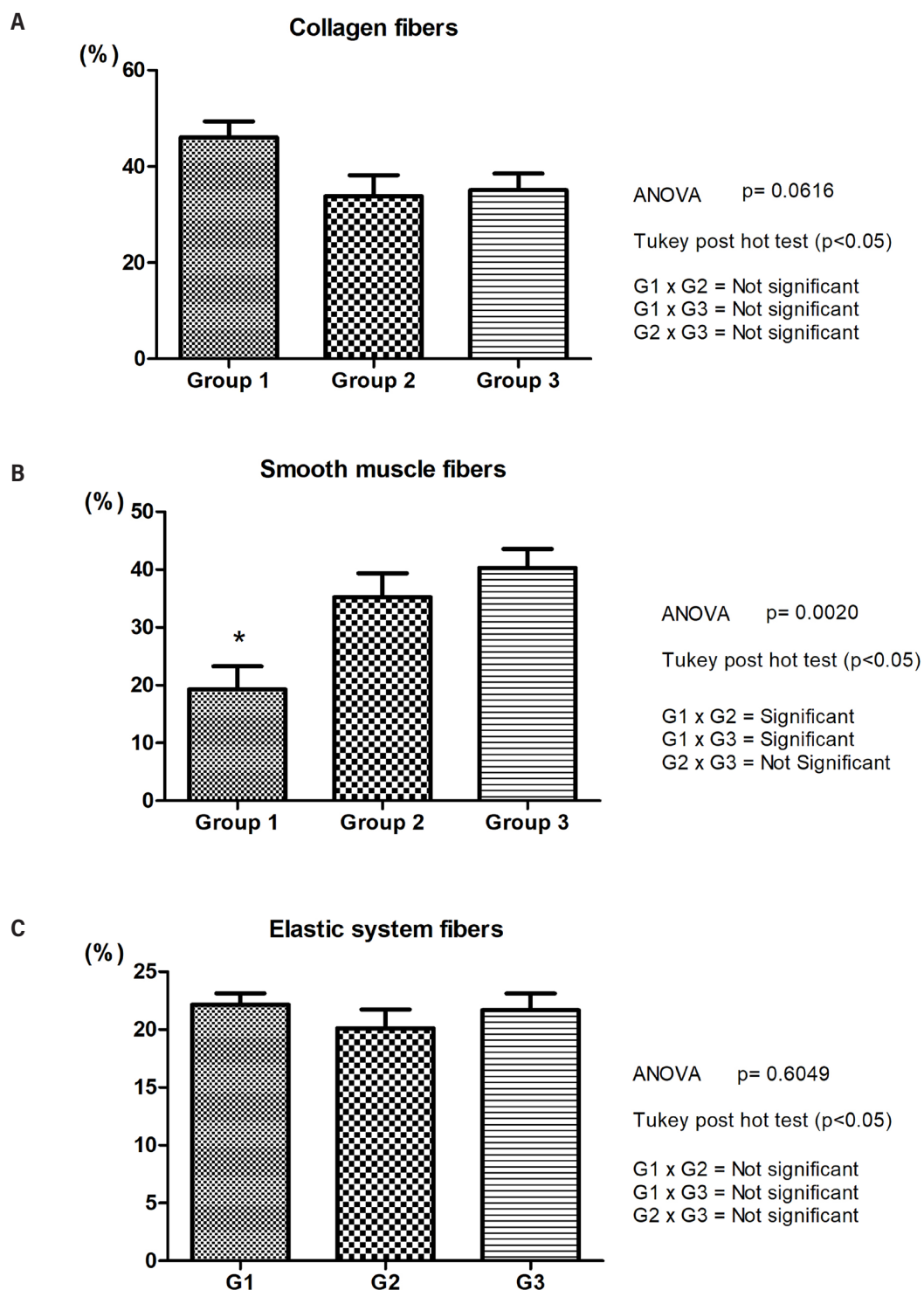
Group 1 (12 to 16 WPC), Group 2 (17 to 19 WPC) and Group 3 (20 to 22 WPC). A) Collagen fibers, Picrosirius red, 400x. B) Smooth muscle fibers, Masson's trichrome, 400x. C) Elastic system fibers, Weigert's resorcin-fuchsin, 600x.

Table 1 - The table shows the analyzed parameters in the prostate of normal human fetuses according to fetal age in weeks post-conception (WPC).

Parameter	Group 1 (12 to 16WPC)	Group 2 (17 to 19WPC)	Group 3 (20 to 22WPC)	<i>p value</i>
Collagen Fibers	32.9 to 61.8% (mean = 46/SD+- 8.2)	22.4 to 49.9% (mean= 33.8 /SD+-9.7)	17.9 to 50.5% (mean=35.1 /SD+-9.1)	p=0.0616
Smooth Muscle Fibers	8.5 to 33.8% (mean =19.3 /SD+-9.7)	17.3 to 43.7% (mean=35.2/SD+- 9.2)	26.4 to 54.3% (mean=40.3/SD+-8.5)	p=0.0020
Elastic System Fibers	18.5 to 23.7% (mean =22.1 /SD+-2)	15.7 to 25.7% (mean=20.1 /SD+-3.6)	16 to 25.2% (mean=21.7 /SD+-3.5)	p=0.6049

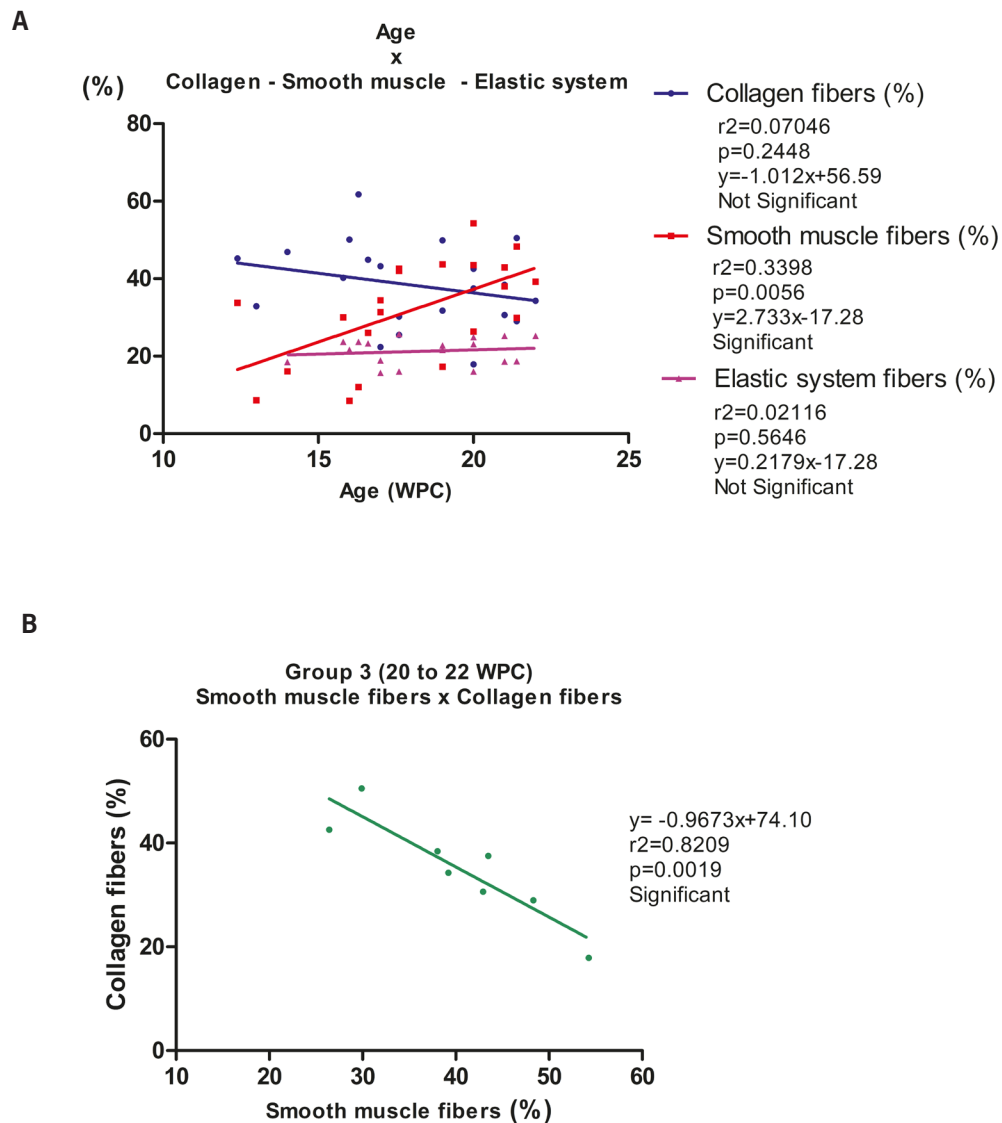
Group 1 (n = 7; 12 to 16 WPC); Group 2 (n = 6; 17 to 19 WPC) and Group 3 (n = 8; 20 to 22 WPC)
SD = standard deviation.

Figure 2 - Graphs comparing the percentage of collagen fibers, smooth muscle fibers and elastic system fibers according to weeks post-conception (WPC).



Group 1 (12 to 16 WPC), Group 2 (17 to 19 WPC) and Group 3 (20 to 22 WPC). Data were expressed as the means $\pm$ standard deviation and were compared by one-way ANOVA and Tukey post hoc test, $P < 0.05$. The symbol [*] indicates significant difference for G2 and G3.

Figure 3 - Correlation between collagen fibers, smooth muscle fibers and elastic system fibers, in percentage, with fetal age, during the fetal period studied (12 to 22 weeks post-conception - WPC).



The points plotted represent the mean values obtained for each week studied.

A) Correlation during entire fetal period studied. Linear regression indicated that the smooth muscle fibers are correlated significantly and positively with fetal age ($r^2 = 0.3398$; $p = 0.0056$).

B) Correlation during second trimester (Group 3, 20 to 22 WPC). Linear regression indicated a strong negative correlation between collagen fibers and smooth muscle fibers from 20 to 22 WPC ($r^2 = 0.8209$; $p = 0.0019$).

The prostatic stroma is made up mainly of collagen and smooth muscle.¹¹ Between 6 and 13 weeks, the amount of connective tissue around the acini increases consistently (21).

Our study showed a tendency for the percentage of collagen fibers to decrease throughout the fetal period studied (12 to 22 WPC), however, with no significant difference between the groups (Figures-1A and 2A). As during this period there is an increase in the volume of the prostate (13, 14), we can assume that there was no increase in collagen fibers during this period. On the other hand, we found that muscle fibers showed a significant increase according to the groups studied. There was a greater quantity of smooth muscle fibers than collagen up to the 22nd WPC (Figure-3).

The main and most obvious component of the normal prostate stroma are the smooth muscle fibers found around the acini (22-24). Studies suggest that the prostatic epithelium induces smooth muscle differentiation in the mesenchyme, as ductal branching is more numerous where smooth muscle cells are abundant (8, 25).

A study using alpha-actin immunomarker observed an increased expression of smooth muscle in the fetal prostate (8). In our study, the percentage of smooth muscle fibers showed a significant difference between the groups studied, being higher in groups G2 and G3, when compared to G1, with a significant increase in the percentage of this parameter with increasing of gestational age (Figures-1B and 2B). The linear regression analysis revealed a significant positive correlation between age and smooth muscle fibers when analyzed throughout the fetal period studied (12 to 22 WPC), suggesting a proportional growth of this component in relation to gestational age (Figure-3A). We observed a significant negative correlation between smooth muscle and collagen fibers around the 20th WPC, indicating that as the smooth muscle increases, the collagen fibers decrease (Figure-3B). These findings show that muscle fiber density increases proportionally with age. Gallo et al. (26) observed in the fetal penis a proportional increase in muscle in relation to age, and a relationship between muscle and collagen from the 22nd WPC onwards. It is known that the extracellular matrix is made up of various components, including collagen and elas-

tic system fibers, the latter of which are involved in the structure and organization of the prostatic tissue (27). A previous study evaluating the elastic system fibers in the penis, observed the presence of this component from the 13th WPC onwards and showed its proportional growth with gestational age (26, 28). Our study showed a stable percentage of elastic system fibers in the prostate in the different groups (Figures-1C, 2C and 3A).

CONCLUSIONS

The changes observed in the stromal components of the prostate were more significant at the end of the second gestational trimester. The density of smooth muscle fibers increased about twofold with gestational age, indicating a proportional growth to the fetal age (12 to 22 WPC) with a strong positive significant correlation. A strong negative correlation was observed between collagen fibers and smooth muscle fibers from 20 to 22 WPC.

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CONFLICT OF INTEREST

None declared.

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Male Infertility: Treatment Approach – A Committee Opinion

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*on behalf of the Andrology Committee, Brazilian Society of Human Reproduction (SBRH), 2023-2025 term

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INTRODUCTION

Male infertility is a complex and often underdiagnosed condition that contributes to nearly half of all infertility cases (1). Effective treatment requires a comprehensive and individualized approach centered around three main pillars: lifestyle modification, pharmacological intervention, and surgical treatment (1-8). These approaches must be applied individually and may be combined depending on each patient's clinical and laboratory profile. The primary

objectives are to optimize testicular and sperm function, enhance the likelihood of natural conception when feasible, and improve quality of life—given that male infertility is also a biomarker of general health (9-11). Appropriate management also seeks to improve outcomes with assisted reproductive technology (ART) when this treatment modality is indicated (9-11).

Lifestyle Modification

Increasing evidence indicates that infertile men are at higher risk for developing cardiometabolic disorders and have greater cardiovascular and all-cause mortality compared to fertile men (1). They are also more prone to chronic conditions such as obesity, metabolic syndrome, hypogonadism, and cancer.

In the context of couple infertility, an andrological assessment is essential (1). It should be carried out by an andrologist or urologist with expertise in male reproductive health, alongside a fertility specialist's evaluation of the female partner (1, 2, 4, 6-10).

The andrological consultation represents a unique opportunity to identify modifiable risk factors, relevant family history, and early-stage diseases, which may improve fertility, androgen production, and overall health. The testes consist of two main compartments—the hormonal and the spermatogenic—and their proper function directly impacts reproductive and sexual health, quality of life, and longevity (1, 12).

Adopting healthy habits is an essential part of treatment and must include guidance on avoiding or minimizing exposure to risk factors, categorized as follows (1, 4, 6-10, 13-22):

i. General factors: aging, obesity, metabolic syndrome, hypertension, autoimmune diseases, infections of viral (e.g., mumps, COVID-19) or bacterial origin, and cancer.

ii. Lifestyle factors: poor diet, excessive alcohol consumption, recreational drug use (e.g., cannabis), smoking (including electronic cigarettes and vaping), sedentary behavior, prolonged exposure to electromagnetic radiation (e.g., mobile phones and laptops near the scrotal region), and excessive heat exposure (e.g., sauna, industrial ovens).

iii. Environmental factors: exposure to pesticides, ionizing radiation, heavy metals, industrial pollutants, organic and inorganic chemicals, and xenoestrogens.

iv. Gonadotoxic medications: antidepressants, 5 α -reductase inhibitors, anabolic steroids and their precursors/metabolites, antibiotics (e.g., aminoglycosides, neomycin, gentamicin, macrolides), antifungals (e.g., ketoconazole), antivirals (e.g., ribavirin), antiretrovirals, chronic opioid use, H₂ histamine receptor blockers (e.g., famotidine, cimetidine), calcium channel blockers, and antitumor medications (e.g., colchicine).

Men undergoing gonadotoxic therapies such as chemotherapy (e.g., alkylating agents, cisplatin, methotrexate, BEP regimen, carboplatin) and radiotherapy should be warned about the risk of temporary or permanent infertility. In such cases, semen cryopreservation or, when azoospermia is already present, testicular tissue cryopreservation should be performed before treatment initiation. Cryopreservation of spermatogonia is being investigated as a fertility preservation strategy for children and adolescents, but it is not yet standard practice (23). For patients who remain azoospermic after treatment, sperm retrieval may be considered, preferably after two years, due to the potential teratogenic effects of gonadotoxic therapies. In these cases, induction of spermatogenesis with medications before retrieval may be considered.

Pharmacological Treatment

Antibiotic Therapy: It should be considered in cases of infections of the urinary or reproductive tract, including urethritis, prostatitis, orchitis, or epididymitis. Although the impact of symptomatic or asymptomatic infections on fertility remains inconclusive, clinical studies suggest that the presence of polymorphonuclear leukocytes in semen is associated with increased oxidative stress (2, 7, 24). Excessive peroxidase-positive leukocytes (>1 million/mL) indicate inflammation but do not confirm bacterial infection. Cultures and molecular tests of urethral swabs, urine, and semen may assist in pathogen identification. A threshold of >10³ colony-forming units (CFU)/mL in semen characterizes significant bacterio-

spermia. Given the variable culture positivity, collecting specimens after prostatic massage (modified Meares-Stamey test) is recommended to increase diagnostic sensitivity. Female partners should be evaluated and treated appropriately in cases of confirmed infection.

Oral Antioxidants: Selective oral antioxidants, produced from high-quality raw materials and administered at appropriate doses (e.g., acetyl-L-carnitine, zinc, selenium, vitamin C, natural isoforms of vitamin E, vitamin D), have been incorporated into the management of male infertility as adjuvant therapy (25). Studies have shown reductions in oxidative stress (OS), damage to the plasma and mitochondrial membranes, and sperm DNA fragmentation (25-29). However, the evidence remains limited and heterogeneous. Use should be individualized and maintained for at least three months (20). There is no consensus on the ideal formulation or treatment duration (1, 7, 8). Notably, over supplementation may be deleterious to semen quality (1, 7, 8, 23, 24).

Prebiotics and Probiotics Supplementation: It is under investigation but lacks robust evidence (8). Their routine use is not recommended, although they may be considered in cases requiring prolonged antibiotic treatment for genital infections.

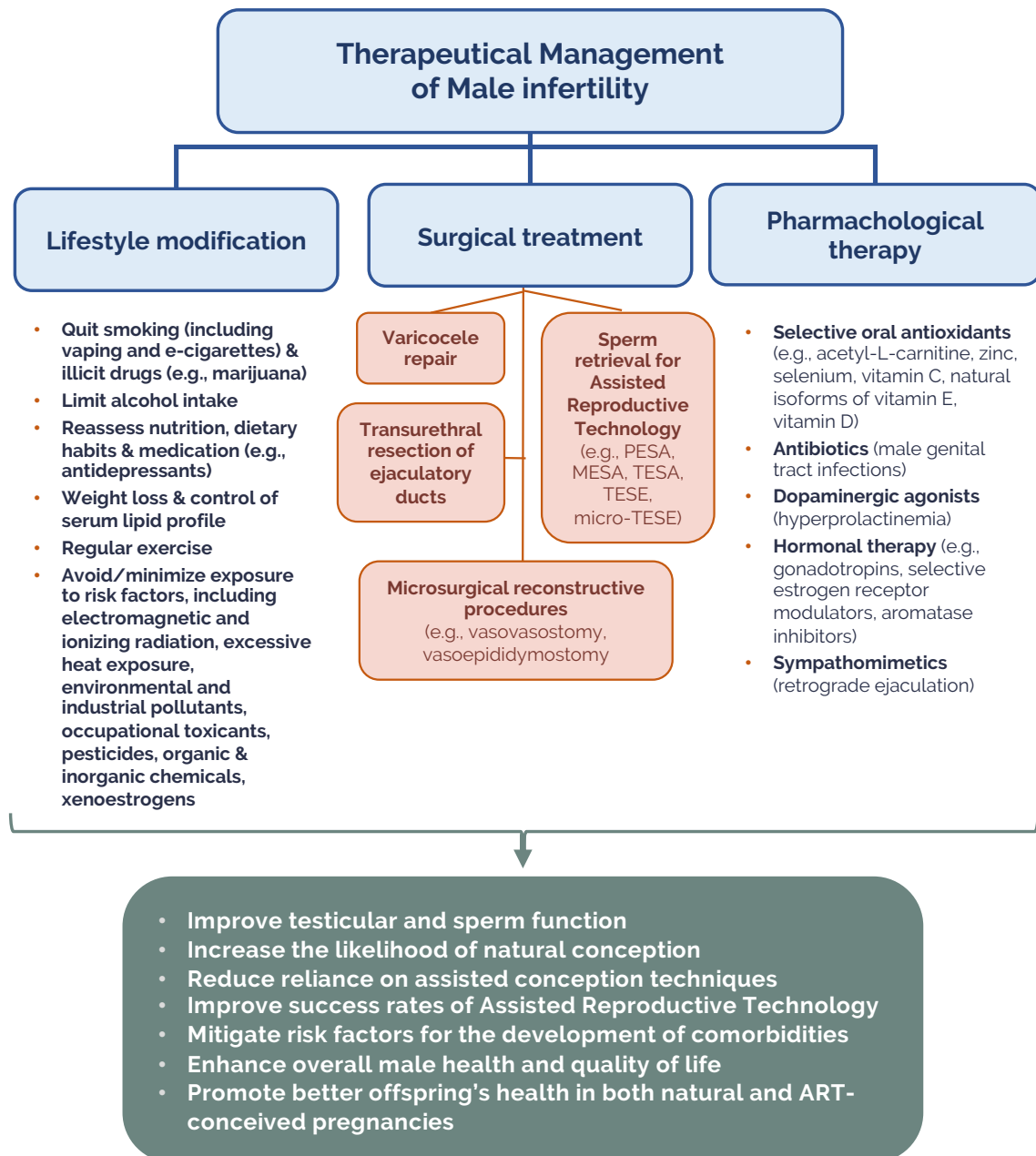
Hormonal Therapy: Recommended for specific subgroups, summarized below (1, 2, 5, 7, 8, 30, 31).

- **Hyperprolactinemia:** Dopaminergic agonists (e.g., cabergoline, bromocriptine) help normalize prolactin levels and restore reproductive function.
- **Hypogonadotropic Hypogonadism:** Gonadotropin therapy (FSH, hCG, hMG), administered in individualized regimens, induces spermatogenesis in about 75% of men.
- **Idiopathic Oligozoospermia:** FSH administration (typically 150 IU two to three times per week for at least three to four months) may be considered in eugonadal men with baseline FSH levels between 1.5–8 mIU/mL. Meta-analyses and randomized studies show significant increases in sperm concentration and total sperm count, as well as improvements in natural and ART pregnancy

rates. FSH may also improve markers such as AMH, inhibin B, and sperm DNA fragmentation. hCG alone or in combination with FSH may be used in men with biochemical hypogonadism.

- **Non-obstructive Azoospermia (NOA) with Hypogonadism:** Hormonal stimulation with hCG (alone or with FSH) may improve the likelihood of successful sperm retrieval. Although recent advances support hormonal stimulation in specific contexts, randomized clinical trials are needed before this can be recommended routinely.
- **Other Medications:**
 - Selective Estrogen Receptor Modulators (e.g., clomiphene citrate): Block estrogen receptors in the hypothalamus, increasing GnRH and consequently gonadotropin release. Meta-analyses show improvements in semen and hormonal parameters and increased pregnancy rates, though study quality is low.
 - Aromatase Inhibitors (e.g., anastrozole): Reduce peripheral conversion of testosterone to estradiol, enhancing stimulation of the hypothalamic-pituitary-gonadal axis. Though off-label, these agents improve hormonal and semen parameters with an apparent safety profile. It may be considered when the testosterone/estradiol ratio is <10 (testosterone in ng/dL and estradiol in pg/mL).
 - Sympathomimetics (e.g., pseudoephedrine): May be used in cases of retrograde ejaculation with variable efficacy.
 - Exogenous testosterone: contraindicated in men desiring fertility, as it inhibits the hypothalamic-pituitary-gonadal axis and spermatogenesis. In such cases, testosterone must be discontinued, and testicular function can be restored using hCG, FSH, selective estrogen receptor modulators, or aromatase inhibitors.

Figure 1. Therapeutic approaches to male infertility.



Management strategies include lifestyle modification, pharmacological therapy, surgical interventions, and sperm retrieval techniques for assisted reproductive technology (ART). Lifestyle changes aim to reduce modifiable risk factors such as smoking, poor diet, obesity, and environmental exposures. Pharmacological treatments involve antioxidants, antibiotics, hormonal therapies, and sympathomimetics. Surgical options include varicocele repair, microsurgical reconstructions (vasovasostomy and vasoepididymostomy), and transurethral resection of ejaculatory ducts. Sperm retrieval procedures (PESA, MESA, TESA, TESE, micro-TESE) are employed mainly for ART. These interventions collectively seek to optimize male reproductive function, enhance the chance of natural or assisted conception, and promote overall male and offspring health.

The APHRODITE criteria is a recent tool that helps identify candidates for hormonal therapy by classifying patients into clinical subgroups (e.g., hypogonadotropic hypogonadism, idiopathic infertility, NOA, unexplained infertility), thereby facilitating personalized therapeutic planning (25).

Surgical Treatment

Varicocelectomy: The surgical repair of clinical varicocele is associated with improvement in semen parameters, increased rates of natural and ART-assisted pregnancies, and reduction in oxidative stress and sperm DNA fragmentation (1-3, 7, 8, 32, 33-37). The intervention is indicated for infertile men with clinical varicocele (grades I to III with venous reflux) accompanied by semen abnormalities (concentration, motility, and/or morphology, or DNA fragmentation) or altered biochemical markers (e.g., creatine kinase, reactive oxygen species) (7, 34). The preferred surgical technique is microsurgical subinguinal varicocelectomy due to its high success rate and lower complication rate (1, 7, 8). Surgery aims to improve spermatogenesis by restoring testicular homeostasis and steroidogenesis. Approximately 70% of treated men show improvement in semen parameters, usually observed starting from the third postoperative month.

In cases of NOA, varicocelectomy may lead to the appearance of spermatozoa in the ejaculate or improve the chances of successful sperm retrieval, particularly in patients with histological findings of hypospermatogenesis or maturation arrest (38). The decision to recommend repair in NOA males should consider the couple's clinical context, given that most supporting data comes from observational studies (1, 7, 8).

Obstructive Azoospermia (OA): Management depends on the underlying etiology, site of obstruction, clinical context, and patient preferences (3, 7, 8, 38). Men with previous vasectomy benefit from microsurgical reversal (vasovasostomy or vasoepididymostomy), with high patency rates when performed by experienced microsurgeons (3). Selected cases of inflammatory or congenital obstruction (e.g., unilateral congenital absence of the vas deferens with segmental blockage) may also be eligible for reconstructive surgery. In contrast, intra-

testicular obstructions usually require surgical sperm retrieval for ART.

Reconstructive procedures may be combined with sperm collection and cryopreservation for future ART use. Ejaculatory duct obstruction, whether due to inflammation or cysts, may be treated with transurethral resection or vesiculoscopy to restore semen flow (39).

Surgical Sperm Retrieval for ART

Obstructive Azoospermia: In OA, sperm retrieval can usually be achieved using percutaneous epididymal aspiration (PESA), testicular aspiration (TESA), microsurgical epididymal aspiration (MESA), or testicular sperm extraction (TESE) (3, 7, 8, 11, 38). Each method has pros and cons regarding sperm yield and quality and the feasibility of cryopreservation for future ICSI cycles. ICSI outcomes using epididymal or testicular sperm, whether fresh or frozen, are similar, provided the laboratory is experienced.

Non-obstructive Azoospermia: In NOA men with primary spermatogenic failure, focal areas of sperm production may exist, with retrieval success rates around 50%, depending on the technique and patient population (3, 7, 8, 11). Retrieved sperm should be used for ICSI, which can result in healthy offspring (11). Microdissection TESE (micro-TESE) is the gold standard due to its superior efficacy and reduced tissue removal compared to conventional TESE, thereby minimizing testicular damage (3, 7, 8, 40). Studies show micro-TESE is about 1.5 times more effective than conventional TESE, with lower complication rates and proven success even after failed TESA or conventional TESE (3, 7, 8, 40).

Fine-needle aspiration mapping has been proposed to guide TESE prognosis. However, it requires two separate procedures (diagnostic and therapeutic) and lacks randomized trials or cost-effectiveness studies to justify routine use (7).

Factors influencing sperm retrieval success include testicular histology, hormone levels (FSH, inhibin B, AMH, testosterone), presence of varicocele, and Y chromosome microdeletions (40-42). Histological findings of hypospermatogenesis are associated with higher retrieval rates, whereas the Sertoli cell-only pattern is a poor prognostic factor. Better outcomes are observed in men with lower FSH and AMH levels and higher in-

hibin B and testosterone levels (41, 42). Clinical varicocele is a negative prognostic factor, whereas its repair is beneficial. (3, 33, 41, 42). Hormonal stimulation before retrieval may improve outcomes, although evidence is mostly from retrospective studies (7, 8, 42, 43). Complete deletions of AZFa or AZFb regions of the Y chromosome contraindicate sperm retrieval, while men with AZFc deletions have a ~50% chance of success (7, 8, 40).

Non-azoospermic men: Testicular sperm (via TESA, TESE, or micro-TESE) may be used for ICSI in non-azoospermic men with high sperm DNA fragmentation when other corrective measures (e.g., varicocelectomy, lifestyle modification, withdrawal of gonadotoxins, antioxidant therapy, treatment of hormonal imbalances), if applicable, have failed (8, 44). Testicular sperm generally have lower DNA fragmentation compared to ejaculated sperm, and emerging data suggest improved ICSI outcomes in these cases (44). The decision must be shared with the couple.

Assisted Reproduction Techniques

While ART may overcome male infertility, evaluating the male partner remains critical to identifying medically relevant conditions, providing counseling on long-term health, and directing appropriate therapy (1, 2, 10, 11). Several causes of male infertility are amenable to medical or surgical correction. Addressing treatable male factors may enhance ART success and improve offspring health (2, 10).

Conversely, indiscriminate use of ART for male factor infertility is not recommended due to potential risks such as ovarian hyperstimulation syndrome and multiple pregnancies. Furthermore, ICSI-conceived children may have higher neonatal morbidity, obstetric complications, and congenital anomalies compared to those conceived naturally (11, 45). Epigenetic alterations and impaired neurodevelopment have also been observed more frequently (11, 46). Therefore, the judicious use of ART in male infertility is essential, in alignment with evidence-based and personalized reproductive care. A call for the responsible use of ICSI is critically important to safeguard the fertility and overall health of future generations (47).

CONCLUSIONS

In at least 50% of infertile couples, a male factor is identified as a primary or contributing cause. Therefore, every infertile couple should have their male partner comprehensively evaluated. In specific cases, a multidisciplinary approach involving a nutritionist, geneticist, endocrinologist, and psychologist may be necessary to ensure comprehensive and personalized management. Interventions such as lifestyle modification, antioxidant therapy, varicocelectomy, and hormonal treatment aim to restore testicular function, improve general health, and increase the likelihood of natural and ART-assisted conception while promoting physical and metabolic well-being. All therapeutic strategies should be maintained for at least one complete spermatogenic cycle (approximately three months), with ongoing clinical and laboratory monitoring. Proper guidance, rational use of diagnostic and therapeutic resources, and active patient and partner participation are essential for optimizing outcomes and achieving biological parenthood.

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CONFLICT OF INTEREST

None declared.

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INCT UroGen and the Transformation of Brazilian Urologic Oncology: A Model for Translational Science and Health Equity

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COMMENT

There is growing momentum in Brazilian urology, driven by the rise of impactful initiatives that are reshaping the national and international landscape. Chief among them is the International Brazilian Journal of Urology (IBJU), which has achieved its highest-ever Impact Factor: 4.5, according to the 2025 Journal Citation Reports. This milestone, up from 3.7 in 2023 and ~1.0 in 2019, secures IBJU's place among the top 10 urology journals worldwide (1).

Concurrently, Brazil launched its first national translational and clinical research flagship in urology and genitourinary oncology. The National Institute of Science, Technology and Innovation in Genitourinary Cancer (INCT UroGen) is a sister ecosystem of the "UroScience: Science Beyond Borders" initiative and forms a core pillar of the Navis Mater "Immuno-Oncology Institute", a multidisciplinary, innovation-driven platform anchored at the Pontifical Catholic University of Campinas (PUC-Campinas), and associated with the newly established Comprehensive Center for Precision Oncology at the University of São Paulo (<https://c2po.usp.br/>).

Supported by a significant federal investment of R\$10.5 million (~US\$2 million) from CNPq (National Council for Scientific and Technological Development), FAPESP (São Paulo Research Foundation), and the Brazilian Ministry of Health, INCT UroGen is headquartered at PUC-Campinas and its network spans all five Brazilian macroregions, forging an un-

precedented alliance among leading universities, research centers, public hospitals, and regional stakeholders. INCT UroGen drives a comprehensive translational pipeline designed to inform national evidence-based guidelines and strengthen public health decision-making.

By embedding its scientific output within the infrastructure of the Brazilian Unified Health System (SUS), INCT UroGen is uniquely positioned to advance both scientific excellence and health equity, helping to bridge longstanding disparities in cancer care access across Brazil (2). The institute is closely aligned with the principles and trajectory of SUS, Brazil's globally recognized universal health system established in 1988. SUS is not only the backbone of public health delivery, but also a critical engine for research, surveillance, and the development of human capital (5).

To support the INCT UroGen in the SUS context, the PUC-Campinas has secured additional funding of over R\$5.7 million (~US\$1 million) through its "Immuno-Oncology Institute," leading a groundbreaking project in Brazil to develop a personalized vaccine against non-muscle invasive bladder cancer funded by Finep (Brazilian Funding Authority for Studies and Projects), through the "More Health Innovation" program.

Leveraging the SUS as a platform for innovation, INCT UroGen enhances the system's capacity to translate scientific knowledge into equitable, accessible care. This includes the validation of biomarkers and health technologies for cost-effectiveness, upholding ethical and equity-based principles, and reducing delays in diagnosis and treatment. In doing so, INCT UroGen helps build a more just and responsive health system where scientific progress directly serves public need.

Indeed, Brazil is championing a broader vision of research impact—one that moves beyond citations to encompass societal relevance, policy integration, and tangible public health outcomes. Social Impact Factor (SIF) frameworks are increasingly used to evaluate how research influences clinical guidelines, shapes health legislation, or transforms patterns of care within systems like SUS (6,7).

Long-term scientific sustainability of this initiative demands a diversified funding architecture, in which Brazil's research funders, CNPq, FINEP, and CAPES (Coordination for the Improvement of Higher Education Personnel) play

distinct, complementary, strategic, and catalytic roles in advancing health science in Brazil. INCT UroGen exemplifies how structured, transparent, and mission-driven science can effectively attract such multilateral support, engaging the private sector, philanthropic foundations, and international cooperation frameworks, increasingly essential to scale innovation, expand infrastructure, and promote institutional resilience. The establishment of shared biobanks, interoperable research databases, and co-developed translational roadmaps not only strengthens scientific productivity but also boosts donor confidence and cross-sector accountability.

Together, the Brazilian Ministry of Education, the Ministry of Health, and the Ministry of Science, Technology, and Innovation help ensure Brazil's health science ecosystem is both academically robust and innovation-driven, linking education, research, and real-world health solutions through its agencies. CNPq fosters a strong national research base and drives the generation of evidence that informs public health policies, clinical guidelines, and innovation within the SUS (8). CAPES is central to human capital development, funding graduate programs, scholarships for Master's and PhD students, and international exchange (9). Finep supports research institutions, technological development, and public-private partnerships, focusing on health technology innovation and infrastructure, funding laboratories and equipment (10).

It has been instrumental in enabling multidisciplinary consortia like INCT UroGen to emerge and thrive. Through investments in thematic projects, young investigator grants, and institutional infrastructure, the INCT UroGen amplifies national impact, enabling the institute to establish its headquarters in São Paulo while expanding collaborative nodes across all five Brazilian macroregions. As one of Latin America's most respected public funding agencies, FAPESP is known for its rigorous peer review, long-term programmatic funding, and global outlook, positioning São Paulo and Brazil more broadly as a leader in internationally visible, socially relevant science, encouraging science-industry synergy, and accelerating the real-world application of research outputs (11).

These frameworks enable Brazilian researchers to co-lead global projects, share data and infrastructure, and raise Brazil's visibility within the international scientific

community. In the INCT UroGen initiative, Brazilian Government Funding Agencies' integration and influence extend beyond funding—it provides strategic coherence, institutional legitimacy, and a long-term vision.

As a global plan of action, international collaboration is not ancillary; it is a core strategic axis of INCT UroGen's mission. Through active alignment with premier cancer centers, the institute accelerates knowledge exchange, joint discovery, and translational co-development, maintaining strategic agreements with international funding bodies such as the NIH (USA), CNRS (France), DFG (Germany), and Horizon Europe (EU).

These international partnerships allow Brazil not only to contribute meaningfully to global cancer research but also to help fill critical scientific gaps, particularly in un-

derrepresented populations and low- to middle-income settings. INCT UroGen fosters both South-to-South and South-to-North scientific pipelines, ensuring a more balanced and inclusive global research ecosystem. These collaborations are underpinned by shared clinical trials, interoperable data infrastructures, and co-governed research agendas, thereby enhancing not only scientific rigor and reproducibility but also geopolitical and ethical equity in the advancement of precision oncology.

To summarize, INCT UroGen represents a new wave of Brazilian scientific leadership: anchored in excellence, propelled by strategic collaboration, and committed to the public good (Table-1). At a time when the global cancer burden is rising and disparities in care are widening, Brazil is uniquely positioned not only to contribute to

Table 1 - Science Embedded in SUS: What Makes INCT UroGen Unique.

Feature	Description
National Reach	Active nodes across all five Brazilian macroregions, enabling inclusive research participation and addressing regional disparities in cancer care.
Public Health Integration	Research outputs are designed to inform SUS clinical guidelines, policies, and delivery protocols—ensuring direct application in Brazil's public health system.
Cost-Effectiveness Validation	Emphasis on biomarker and technology validation for economic viability within SUS, promoting sustainable innovation.
Equity-Driven Mission	Projects are aligned with SUS's foundational principles of universality, equity, and integrality—bridging gaps in access to care.
Shared Infrastructure	Creation of interoperable biobanks, research databases, and multicenter trials fosters collaboration and reproducibility.
Capacity Building	Multicenter mentorship, graduate training, and fellowships develop human capital within public universities and health institutions.
Social Impact Metrics	Tracks research translation into guidelines, legislation, and care delivery, using Social Impact Factor (SIF) frameworks.
Public-Private-Public Synergy	Facilitates cross-sector partnerships while maintaining a mission-driven, public-first agenda anchored in SUS values.
International Collaboration	Strategic alliances with global cancer centers and funding agencies enable co-developed trials and knowledge exchange.
Long-Term Vision	Backed by stable programmatic funding (e.g., CNPq, FAPESP, FINEP, CAPES) and embedded in national scientific policy frameworks.

global oncology but to lead, especially in contexts where innovation must be harmonized with equity and access.

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Complete penile disassembly for isolated penopubic epispadias repair: The “Belgrade approach”

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ABSTRACT

Introduction: Surgical treatment of epispadias has evolved significantly, from early tubularization techniques to modern penile disassembly approaches (1-3). Despite advancements, achieving urinary continence remains challenging and typically requiring multiple interventions (4).

Purpose: The objective is to present complete penile disassembly (Belgrade) technique for primary epispadias repair.

Patient and Method: We present a case of isolated penopubic epispadias and severe dorsal curvature in 18-month-old boy. Meticulous dissection is conducted ventrally and dorsally to isolate the urethral plate and spongiosal tissues. The Buck's fascia is incised ventrally to isolate the neurovascular bundles, followed by complete separation of the corpora cavernosa from each other and from the glans. The urethral plate is dissected free, transposed ventrally, and tubularized over a catheter. Penile straightening and lengthening are achieved through internal rotation of the corpora cavernosa and dorsal corporotomy with skin grafting. Glans reconstruction is done. Reassemble of all entities is performed, followed by penile skin reconstruction.

Results: At the three-month follow-up, the patient demonstrated satisfactory voiding with a good urinary stream, without evidence of urethral fistula or stricture. The cosmetic outcome was favorable, with no signs of recurrent curvature. The patient remains under vacuum device therapy, till 12 month after surgery.

Conclusion: The Belgrade approach for isolated penopubic epispadias includes radical approach with complete disassembly. This one-stage repair enables correction of all deformities – penile lengthening and strengthening, urethroplasty, glansplasty and penile skin reconstruction, with good outcomes.

CONFLICT OF INTEREST

None declared.

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Robotic Bilateral Ileal Interposition: The Total Intracorporeal Approach

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ABSTRACT

Purpose: While grafting procedures can be used to manage upper ureteric strictures (1), ileal interposition still has its role in the more complex cases with long or bilateral ureteric strictures. Ketamine-associated uropathy can mimic retroperitoneal fibrosis and give rise to long bilateral ureteric strictures (2, 3). The objective of the video is to present the total intracorporeal technique for bilateral ileal interposition with a U-configuration of small bowel loop.

Patient and methods: A 34-year-old lady with bilateral long ureteric stricture secondary to ketamine-associated uropathy was managed with robotic reconstruction. The surgical access to retroperitoneum and exposure of bilateral ureters took reference from the single-docking robotic retroperitoneal lymph node dissection technique (4). Da Vinci Xi robotic system was used. Retroperitoneal space was accessed after incision was started behind the caecum, lifting up the root of small bowel mesentery. Bilateral ureters were exposed and the segment proximal to the stricture was identified. In the literature, different techniques of small bowel isolation have been described (5, 6). In this case, a loop of small bowel in U-configuration was prepared and the end of both limbs was anastomosed to the ureters in a side-to-end manner. The apex of the bowel loop was anastomosed to the bladder, completing the procedure.

Results: The procedure took 507 minutes. Hospital stay was 8 days. Unobstructed drainage was confirmed by DTPA scan at 3 months and 15 months. UUnremarkable drainage was noted on IVU at 6 months and on CT scan at 18 months. Renal function was static at 3 years with creatinine clearance 56mL/min. The patient was symptom free at post-operative 3 years.

Conclusions: Retro-caecal exposure of the retroperitoneal plane allows a convenient access to ureters. Bilateral ileal interposition can be safely performed in a minimally invasive manner with robotic technique.

CONFLICT OF INTEREST

None declared.

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The Need for Highlevel Evidence for Genitourinary Tuberculosis (GUTB) Surgical Therapies

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To the editor,

We read with great interest the manuscript by Figueiredo et al., titled "Urogenital Tuberculosis: A Narrative Review and Recommendations for Diagnosis and Treatment" (1). We commend the authors for their comprehensive review of a topic that is often underrepresented. Notably, their focus on potential surgical therapies for genitourinary tuberculosis (GUTB) addresses one of the least explored areas in current literature.

While recent studies have provided substantial evidence regarding medical management, there remains a paucity of high-quality data on surgical interventions for GUTB. The existing literature predominantly consists of small case series and retrospective analyses, which are limited by inherent biases and lack generalizability (2). Consequently, the absence of robust clinical guidelines complicates surgical decision-making and may hinder optimal patient care (3).

An additional concern is the disparity between regions heavily burdened by GUTB and those with the resources to conduct extensive research. Countries with high incidence rates often lack the infrastructure for large-scale studies, while those with advanced research capabilities may have limited clinical exposure to GUTB cases (4, 5). This imbalance impedes the development of standardized surgical protocols and may lead to varied practices based on individual surgeon experience, potentially affecting patient outcomes.

To bridge this gap, we advocate for the establishment of international collaborative databases focused on surgical management of GUTB. Such initiatives would facilitate data sharing, enable prospective studies, and contribute to the formulation of evidence-based guidelines. By leveraging collective expertise and resources, the urological community can enhance the quality of care for patients worldwide.

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CONFLICT OF INTEREST

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Toward Precision Imaging: Commentary on the Predictive Value of T2WI and ADC in Prostate Cancer

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To the editor,

We read with great interest the recently published article entitled "[The] (Predictive Value of Multiparametric Magnetic Resonance Imaging (T2-weighted Imaging and Apparent Diffusion Coefficient) for Pathological Grading of Prostate Cancer: a Meta-Analysis)" in the International Brazilian Journal of Urology (1). This well-conducted meta-analysis highlights the increasing value of T2-weighted imaging (T2WI) and apparent diffusion coefficient (ADC) mapping in improving both diagnostic accuracy and cancer detection rates for prostate cancer, and it provides quantitative evidence supporting their integration into clinical practice. The authors are to be commended for synthesizing current evidence and drawing attention to the need for imaging-based grading in risk-adapted prostate cancer management.

However, we wish to offer a few additional observations on limitations not fully addressed in the article, along with suggestions for future research directions. First, the analysis did not stratify diagnostic performance based on tumor location within the prostate. It is well known that the detection sensitivity of T2WI and ADC varies significantly between the peripheral and transitional zones. Tumors in the transitional zone are often confounded by benign prostatic hyperplasia, which can obscure imaging interpretation. Incorporating zone-specific analyses in future studies would allow clinicians to better understand the region-specific strengths and weaknesses of mpMRI and refine biopsy targeting strategies accordingly (2, 3).

Second, the meta-analysis did not adequately address variability in MRI acquisition protocols, hardware, and ADC quantification methods. Differences in scanner vendors, field strengths (1.5T vs. 3.0T), b-values in diffusion imaging, and post-processing techniques can all influence ADC measurements, leading to inter-study inconsistency. Future investigations should advocate for standardized acquisition protocols or include scanner-specific calibration to ensure consistency in quantitative imaging.

Third, while the authors acknowledge the potential of mpMRI, we believe [that] (greater emphasis) should be placed on the integration of artificial intelligence (AI) into diagnostic workflows. AI, particularly deep learning and radiomics approaches, can extract high-dimensional imaging features beyond human perception and combine them with clinical data (e.g., PSA, age, prostate volume) to build robust predictive models. More importantly, AI can enhance reproducibility by reducing inter-observer variability in lesion segmentation and PI-RADS scoring (4, 5). Future studies should explore hybrid models that integrate T2WI, ADC, and clinical variables using explainable AI algorithms trained on large, diverse datasets. This would not only promote individualized risk stratification but may also enable real-time decision support in biopsy-naïve patients.

In conclusion, this meta-analysis provides valuable evidence supporting the diagnostic relevance of T2WI and ADC in prostate cancer grading. To further enhance the clinical utility of mpMRI, we suggest strati-

fying performance by tumor location, ensuring technical standardization of imaging parameters, and incorporating AI-driven models for improved precision and reproducibility. Such improvements will pave the way for more personalized, efficient, and accurate prostate cancer diagnostics.

Future research should include bigger and more diverse groups with thorough stratification for confounding factors (e.g., gender, baseline anxiety level, medical history) to improve the validity of the results. Furthermore, a longitudinal study assessing the long-term effects of self-visualization on anxiety, pain tolerance, and patient satisfaction over numerous cystoscopy sessions could give additional evidence of its efficacy. Alternative approaches that combine self-visualization with other pain-relieving techniques may also provide useful insights for enhancing the patient experience during cystoscopy. Finally, blinded study design may reduce bias in outcome evaluation, particularly for subjective variables like pain and satisfaction.

CONFLICT OF INTEREST

None declared.

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First Report on the use of Loop-X Image Acquisition Technology for Sacral Neuromodulation

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To the editor,

We are pleased to report the first global clinical application of the Loop-X intraoperative image acquisition system to guide sacral neuromodulation (SNM) implantation for refractory overactive bladder (OAB), carried out in Jan 2025 at Moinhos de Vento Hospital in Porto Alegre, Brazil.

As a well-established third-line treatment for OAB, SNM involves the strategic implantation of an electrode adjacent to the third sacral nerve root (S3), which plays a pivotal role in modulating bladder and urethral sphincter function (1, 2). The standard two-stage procedure includes an initial test phase lasting 1 to 2 weeks, during which patient response is evaluated using baseline bladder diaries as reference. In patients who demonstrate significant improvement, a permanent implantable pulse generator is subsequently placed to deliver chronic sacral nerve stimulation, with proven long-term benefits to quality of life.

The Loop-X system represents a novel advancement in intraoperative imaging, providing both 2D and 3D visualization capabilities (Figure-1). It enables the real-time fusion of high-definition preoperative magnetic resonance imaging with intraoperative fluoroscopy (Figures 2 to 4). This integration allows for unparalleled precision in targeting sacral nerve roots, reducing procedure time and enhancing safety and accuracy. At Moinhos de Vento Hospital, we successfully employed Loop-X technology to guide the implantation of a SureScan MRI-compatible lead (Medtronic, Minneapolis, USA). This marks the first known use of this robotic imaging platform for SNM worldwide.

Loop-X is one of several technologies comprising the Brainlab Robotic Suite, designed to support high-precision, image-guided surgical interventions. The system incorporates intraoperative 3D imaging, robotic guidance, and full digital integration. Its high degree of automation ensures procedural consistency and optimized patient outcomes.

We believe this case sets a precedent for the integration of advanced robotics and imaging technologies in functional urology. We encourage further reporting and discussion on the use of such platforms to enhance precision and outcomes in SNM and beyond.

The Authors

Figure 1 - Loop-X intraoperative image acquisition technology.

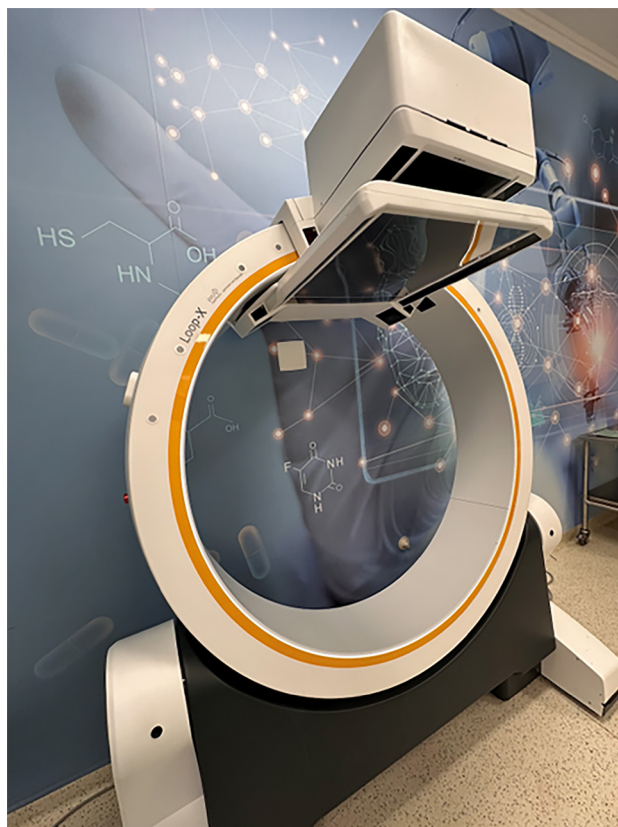


Figure 2 - Laser marks guiding the exact point of needle entry.



Figure 3 - MRI Image fusion.



Figure 4 - Electrode poles 0 and 1 demonstrated alongside the third sacral nerve (S3) in the coronal reconstruction (MRI image fusion).



CONFLICT OF INTEREST

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