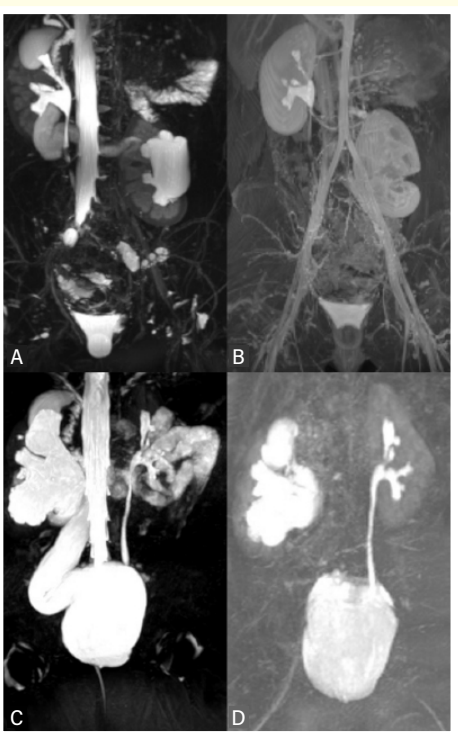
ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY and
OFFICIAL JOURNAL OF THE AMERICAN CONFEDERATION OF UROLOGY
VOLUME 51, NUMBER 3, MAY - JUNE, 2025



T1 and T2 sequences provided complimentary information in the evaluation of a ectopic left kidney in a 10-month-old girl (A, B) and of an obstructive right megaureter in a 9-month-old girl (C, D). (*e20250047*)

A) T2 MIP: left ectopic and malrotated kidney with SFU Grade 3 hydronephrosis, normal right kidney. B) T1 Gd-enhanced MIP: Markedly delayed excretion on the left with asymmetric unit pathologic differential renal function (R 65%/L 35%). C) T2 MIP: Right SFU Grade 4 hydronephrosis and hydroureter, normal right kidney. D) T1 Gd-enhanced MIP: Renal transit time is 2 minutes 9 seconds on the left, which is normal. Renal transit time is prolonged on the right, which measures greater than 10 minutes

XL Brazilian Congress of Urology
November 15 - 18, 2025 - Florianópolis - SC - Brazil

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The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.

The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development.
Editorial and Graphic Composition

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology– SBU, is published 6 times a year (bimonthly, starting in January - February).

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, PubMed/Central, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

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EDITORIAL
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Vol. 51 (3): e20250301, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.03.01

Telesurgery in Urology is the Hot Topic in this Number of International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

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The May-June number of Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Telesurgery, Prostate Cancer, Endourology, Basic Research, Penile Cancer, Bladder cancer, Urethral Cancer, Urachal carcinoma, Neurophysiology of Micturition, Testosterone replacement therapy and MRI in Pediatric Urology. The papers came from many different countries such as Brazil, Italy, China, Belgium, Turkey, Argentina, Canada and USA, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Ferreira and collegues from Brazil, presented id e20240494 (1) a nice narrative review about telesurgery in Urology to review the literature aiming at the surgical success rate as a primary objective, and secondly, the most important patient outcomes and the network system and concluded that despite its limitations, there was evidence demonstrating that robotic surgery in the genitourinary system is safe and feasible, however it is a subject that must be well discussed, and further studies must be carried out.

Dr. Suartz and Collegues from performed id e20240665 (2) an interesting narrative review about the urachal carcinoma to consolidate current evidence on the diagnosis, epidemiology, and treatment of urachal carcinoma, a rare malignancy with limited data and concluded that this study provides the most comprehensive review of urachal carcinoma to date, providing evidence to guide clinical decisions. It underscores the oncologic benefits of *en-bloc* resection with umbilectomy and specific chemotherapeutic regimens. Emerging alternative thera- pies also show potential, highlighting the need for further research to optimize patient outcomes.

Id e20250047 (3) we can observed an important review performed by Dr. Press and Dr. Kirsch from USA about the Magnetic Resonance Urogram in Pediatric Urology. This paper is the cover of this edition. Magnetic Resonance Urography (MRU) has emerged as a powerful imaging modality in pediatric urology, offering comprehensive anatomical and functional assessment of the urinary tract without exposure to ionizing radiation. The authors concluded that this review highlights the growing significance of MRU in pediatric urinary tract evaluation, emphasizing its potential to improve clinical decision-making and patient outcomes.

Dr. Basheer and collegues from USA and Brazil permorfed id e20259904 (4) a nice review about the management of Adverse Effects in Testosterone Replacement Therapy to provide the most updated knowledge regarding the treatment of adverse effects secondary to testosterone replacement therapy (TRT), such as gynecomastia, cardiovascular and

hematologic risks, prostate health risk, and liver dysfunction risks and concluded that monitoring and management of adverse effects are critical to maximize benefit and minimize the risks of TRT. Ongoing research will further elucidate the safety of TRT while advancing evidence-based practices in managing its associated adverse effects. Effective patient education and counseling are also essential to improve compliance and treatment outcomes.

Dr. Mattos and Favorito from Brazil performed id e20259907 (5) an interesting narrative review about the neurophysiology of micturition and concluded that the interplay between the complexity of LUTF, the widespread prevalence of conditions that can disrupt it, and the nonspecific nature of related symptoms frequently complicate urological decision-making. Overlooking associated neurological factors can result in suboptimal outcomes, diminished quality of life, and serious adverse consequences. A systematic approach is crucial to minimizing the risk of misdiagnosis and mismanagement, especially when considering invasive interventions.

Dr. Özbilen and collegues from Turkey performed id e20240500 (6) a nice multicentric study about the External Validation and Comparison of Current Scoring Systems in Encrusted Ureteral Stent (EUS) and concluded that the management of EUSs is often challenging for urologists. Although the current scoring systems for EUS differ somewhat, it is important to use scoring systems to guide the management of these patients.

Dr. Sighnolfi and collegues from Italy performed id e20240556 (7) a nice study about the Radical Cystectomy with Elective Indication to Cutaneous Ureterostomy (CUS): Single-Center Comparative Analysis Between Open and Robotic surgery (RARC) and concluded that RARC appears to be associated with lower morbidity and reduced incidence of complications, elements that make it particularly suitable for frail patients with an elective indication for CUS.

Dr. Villoldo and collegues from several countries of Latina America performed id e20240615 (8) an interesting multicentric study about the BCG. Use in Non-Muscle Invasive Bladder Cancer in Latin America and concluded that this study highlights critical deviations from recommended NMIBC management protocols in Latin America, including delayed BCG initiation and inconsistencies in maintenance therapy. These findings emphasize the need for standardized treatment protocols and improved adherence to international guidelines, which could enhance NMIBC patient outcomes in the region. Collaborative efforts are essential to develop region-specific strategies, improve data collection, and ultimately provide better care for bladder cancer patients in Latin America.

Dr. Fazili and collegues from Belgium and USA performed id e20259905 (9) a nice study about the role Of DSNB in Staging of Primary Urethral Cancer. The authors show the use of dynamic sentinel node biopsy (DSNB) in five patients with primary urethral squamous cell carcinoma (U-SCC) and no evidence of inguinal node disease. In the five DSNBs performed, clinically occult nodal metastasis was discovered in one patient. In this patient DSNB was performed after local recurrence and repeat imaging confirming cN0 status. Only one minor complication with DSNB was observed. Awaiting further investigations in larger series, this study highlights the feasibility of DSNB in primary U-SCC with clinically node negative disease.

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

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 51 (3): e20240494, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0494

Feasibility and Initial Outcomes of Telesurgery in Urology: a Systematic Review of the Literature

Sávio Valadares Ferreira [1], Murilo Henrique Sugai [1], Guilherme Corrêa do Nascimento [1], Antonino Caetano de Souza Netto [1], Gustavo Colombo Cabrini [2], Fernando Martins Rodrigues [1], Cleverson Luiz Rocha D' Avila [1], Geovanne Furtado Souza [1], Ricardo Vieira Zerati [1], Miguel Zerati Filho [1]

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ABSTRACT

Introduction: Telesurgery allows the procedures to be carried out over long distances, however due to lack of data, its feasibility has not been consolidated yet. Since it is a promising modality, it is important to illustrate the current scenario on this subject.
Objective: To review the literature aiming at the surgical success rate as a primary objective, and secondly, the most important patient outcomes and the network system.
Materials and Methods: In June 2024, we followed PRISMA guidelines to research trials on urological robotic surgery in humans. We used as exclusion criteria: editorials, specialist's opinions, tele-mentoring, tele-training, small procedures, non-remote surgeries, absence of interest outcomes, telesurgeries in non-humans or in cadaver.
Results: Five hundred and ninety eight studies were identified with peer review and a third reviewer for divergencies, both directed by previously established inclusion and exclusion criteria, selecting 6 studies after the exclusions. We found 54 patients who underwent urological telesurgeries; all of them were accomplished with no complications or need for conversion to open surgery. Almost all the procedures were carried out in China (98.14%) and the most used robotic model was MicroHand S (83.33%). Nephrectomy was the procedure of choice (57%). Mean surgical time was 66.2 (IQR) 56.6 minutes. Intraoperative bleeding time was 68.6 ± 76.7 milliliters. Hospital stay was 5.5 (IQR) 5 days. The distance between main surgeon and the patient was between 2,581.5 (IQR) 2,871 kilometers. 5G network was used the most (98.14%). The total network latency time was 176 (IQR) 10.9 milliseconds.
Conclusion: Despite its limitations, there was evidence demonstrating that robotic surgery in the genitourinary system is safe and feasible, however it is a subject that must be well discussed, and further studies must be carried out.

ARTICLE INFO

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Keywords:
Systematic Review [Publication Type]; Robotics; Urology

Submitted for publication: August 31, 2024

Accepted after revision: December 17, 2024

Published as Ahead of Print: January 21, 2025

INTRODUCTION

Laparoscopic surgery was at first a reason for jokes ("Mickey Mouse surgery" and "small brain-small incision.") and presented great resistance for its acceptance, since, at that time they couldn't see its huge potential. However, as time went by and due to its excellent results, it became very well accepted (1). In times of war, the military personnel tried remote medical care as an alternative to the difficulties they encountered (2). Due to COVID 19 Pandemics there was a need to communicate without close contact, this way, this concept gained momentum and intensified telemedicine in medical practice (3, 4). With the arrival of new robotic platforms and improvement in telecommunications, the association between these events became inevitable, allowing a transatlantic telesurgery to be performed successfully, becoming a landmark at that time and until today it still impacts current discussions (5-7).

In general, the definitions found show that telemedicine may be defined as an interaction among multimedia, telecommunications and robotic technologies to offer clinical or surgical care. In such telesurgery context, when there is a surgeon with active control operating the surgical instruments of a robot, the surgeon and patient don't necessarily have to be in the same place (8-10). The concept of surgical telepresence has changed the paradigms and generated major developments in laparoscopic surgery, allowing the introduction of robotic systems in daily routine. The first surgical prototype approved by the FDA was the Automated Endoscopic System for Optimal Positioning AESOP®. Then, other platforms also gained ground and currently the one that is mostly used is a model called "Da Vinci" produced by Intuitive Surgical (2, 6).

Among surgical specialties, urology stood out, and we could follow its technological evolution closely. Despite the advances in telesurgery, access to this resource is still restricted, although promising, it may generate several benefits to the world's population, especially in remote areas where specialized medical care services are not available (10, 11). In such context, it is worth reviewing the literature to illustrate the current scenario on the subject.

MATERIALS AND METHODS

Protocol and Registration

The guidelines called "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) were followed to carry out research in June 2024 combining terms on the subject with Boolean operators (Figure-1) in PubMed, Embase and Cochrane platforms to identify trials registered up to that period. We structured the study question based on PICO strategy (P: Patients who underwent urologic robotic telesurgery; I: Remotely performed surgery; C: With no comparisons with other methods; O: Primary: Surgical success rate. Secondary: Main patient clinical outcomes and the network system), registering a protocol at International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42024557337) released for online access. Search strategies, as well as figures and tables will be made available.

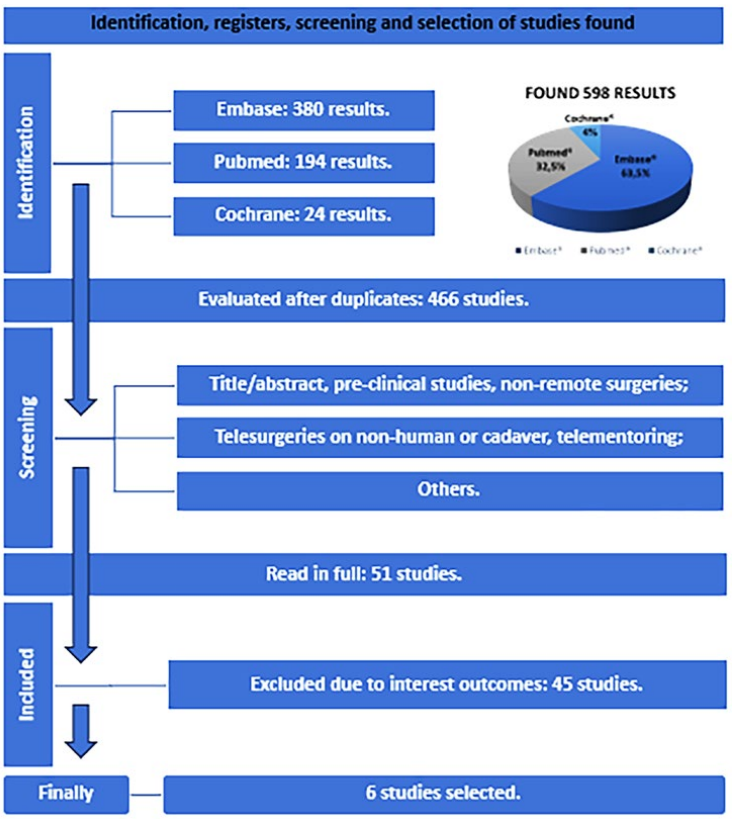
Eligibility criteria

Inclusion criteria were randomized or non - randomized, with patients who underwent urinary tract robotic telesurgery and who reported any of the outcomes of interest. Editorials, expert opinion, tele-mentoring, tele-training, minor procedures, non-remote surgeries, absence of outcomes of interest, telesurgeries on non- humans or performed on cadavers were excluded.

Trials Selection

The trials found were distributed in the Zotero® 6.0.36 program to help with duplicates and initial selection, the latter being carried out by peers (SVF and MHS), in an independent fashion and the divergencies were clarified by another researcher (MZF), both directed by previously established inclusion and exclusion criteria. References from the included trials, previous systematic reviews and meta-analysis were also manually searched for additional trials.

Figure 1 - PRISMA diagram of study screening and selection



Data collecting process and risk of bias

After final selection of the trials, data were manually collected and registered in an Excel Table – Microsoft Office Professional Plus® (2019) to organize the results, conversion and basic statistics such as frequencies and proportions, mean ± standard deviation, median with interquartile range (IQR: subtracting the third from the first interquartile interval) according to the need of how the data were reported. The trials were varied and heterogeneous as to the measurements and effect estimates (12) for samples of continuous and or categoric outcomes were acquired with the help of a calculator, available online (https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) to detect asymmetries. Besides that, we used JBI tool as critical assessments of the selected studies (13, 14).

Measures of association and subgroup analysis

The encountered outcomes of interest were worked with the help of an Excel program– Microsoft Office Professional Plus® (2019) for conversion into frequencies and proportions, mean ± standard deviation, median with calculated interquartile range, according to how they were available in selected trials. A subgroup analysis was restricted to the most used surgical robotic surgical model and the type of procedure most frequently performed in the sample.

RESULTS

Selection of trials

Five hundred and ninety-eight records of results up to June 2024 were found with 132 duplicates

excluded. After the initial analysis was reviewed by peers based on pre-established criteria, 415 studies were excluded with the help of a third investigator, both independently. The remaining 51 studies underwent a detailed analysis and 6 of them were selected (15-20) for final data collection, identifying a total sample of 54 patients who underwent telesurgery of the genitourinary system (Figure-1).

Trials characteristics

As urologic robotic telesurgery is an innovative modality, we didn't find randomized, multicentric trials, instead, a heterogeneous and small sample of patients who underwent the procedure in highly specialized centers, both represented in Table-1.

Sample results

We found a total of 54 patients that underwent urologic robotic telesurgery, both completely finished without conversion to open procedures or important intraoperative complications. Surgical time was 66.2 (IQR) 56.6 minutes, with intraoperative bleeding of 68.6 ± 76.7 milliliters, being described that, in one of the trials (17), 1 patient presented intraoperative blood transfusion as prophylaxis justified by preoperative laboratory tests results. The period of hospital stay was 5.5 (IQR) 5 days and almost all the procedures were carried out in China (98.14%). The distance between the main surgeon and patient was 2,581.5 (IQR) 2,871.7 kilometers and the most used internet network was 5G (98.14%), with total latency time of 176 (IQR) 10.6 milliseconds (Table-1).

Subgroup analysis and risk of bias

The subgroups were analyzed according to the initial guidance of PICO question. In this part of the sample, we identified that the most used robotic platform was model MicroHand S. It was used in 83% of the procedures (45 surgeries), mean age of the population was 63 (IQR) 7 years, of which 53.33% were men. Surgical time was 64 (IQR) 127.5 minutes, carried out from a distance of 199 (IQR) 988 kilometers and total latency of 215 (IQR) 39 milliseconds. Then, we realized that nephrectomy was performed in 57% of the samples (31 patients), with mean age of 57.25 (IQR) 5.75 years. 5G connection was used in all patients with total latency of 173.24 (IQR) 2.75 milliseconds, surgical time of 57.7 (IQR) 9.25 minutes and hospital stay of 6 (IQR) 2 days (Table-1).

After data collecting and analysis of estimates of sample mean values, significant asymmetries were not identified in the results. Besides, the results from the performed critical assessment (SVF and MHS) are also attached (Tables 2A-F).

DISCUSSION

Despite the limitations, we found evidence that it is possible to perform urological telesurgery with safety. The available data demonstrate that all remote procedures were concluded with safety without significant complications (Table-1). Infrastructures disparities in health and internet network associated to limitations to new technologies may be a challenge, however, a notable fact is that most of the procedures relied on a type of network that is well available worldwide, and most studies were carried out in an emerging country, albeit in specialized centers. Such fact reinforces that in appropriate places, telesurgery is feasible and may be stimulated. With the aim of providing better practical guidance, the best experts and representatives in the field came together at the First Telesurgery Consensus Conference in the United States in 2024. During the meeting a joint effort to expand the legal, ethical and financial challenges was evident and other platforms showed their interest and advances in telesurgery, such as Hinotori, Edge, Kangduo and Microport Medbot (21).

Although there are restrictions to the use of robotic platforms such as cost, specialized training, learning curve, available technological resource, appropriate material, several trials started demonstrating the possibilities of performing remote surgeries. The first urological telesurgical procedure was carried out approximately 26 years ago using a PAKY model to perform a percutaneous anal access with success (22, 23). Searching for positive results in order to prove the safety of this modality and enable it to evolve, pre-

Table 1 - Characteristics and results of the studies.

Author	Study	Sample	Robotic	Surgeon	Patient	Surgical time (min)	Blood (mL)	Hospitalization (days)	Distance (km)	Network	Total Latency (ms)
Frimberger, et al. 2022 (15)	case reports	Woman 46 years old, with cystic renal mass.	AESOP / RCM + PAKY	Baltimore	Munich	120	50	2	8000	ISDN	
Li, et al. 2023 (16)	case series	Total of 15 patients, 8 men, age 58 (IQR) 7.9, both with adrenal tumor.	MicroHand S	Qingdao	Zhucheng, Zibo, Pingyi.	45 (IQR) 22	25.69 ± 17.34		199 (IQR) 167,5	5G	31.5 (IQR) 2.32
Li, et al. 2023 (17)	case series	Total of 29 patients, 15 men, age 63 (IQR) 18, both with kidney tumor	MicroHand S	Qingdao	Shandong, Gansu.	67 (IQR) 21		8 (IQR) 2	187 (IQR) 57	5G	176 (IQR) 5
Wang, et al. 2024 (18)	case series	Total of 6 patients, all men, age 51 (IQR) 38, who presented one of the following pathologies: retrocaval ureter, adrenal tumor, kidney tumor, prostate tumor.	Edge - MP1000	Beijing, Sanya	Sanya, Beijing	65.5 (IQR) 51.5	62.5 ± 76.53	5.5 (IQR) 3	3.000	5G	171.04 (IQR) 4.23
Yang, et al. 2022 (19)	case reports	Man, 71 years old with bladder tumor	MicroHand S	Qingdao	Anshun	300	200	18	2.163	5G	254 (IQR) 12
Zhou, et al. 2022 (20)	case reports	2 men with varicocele.	Tumai	Nanjing	Xinjiang Kezhou	42.5 (IQR) 5	5	3	3.800	5G	130

clinical trials were carried out to test several procedures (24, 25). Zheng et al. performed 4 long distances laparoscopic surgeries in pigs. Although the sample accounted for only 50% of urinary tract surgeries (one nephrectomy and one cystectomy), Microhand platform and 5G technology were used and there was a mean network delay of 264 milliseconds during procedures with no complications (26). In 2023, Chu et al. used flexible ureteroscopy to fragment kidney stones with FURS robotic system remotely and transatlantic, more than 2,300 kilometers away from the operating room (27). Nguan et al. presented 18 robotic pyeloplasties, remotely with the Zeus platform, using IP-VPNe and via satellite, both successfully (28). Fan et al. im-

Table 2A - Critical appraisal checklist for case reports. (Frimberger, et al. 2022 (15))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were patient's demographic characteristics clearly described?			✓	
Was the patient's history clearly described and presented as a timeline?		✓		
Was the current clinical condition of the patient on presentation clearly described?			✓	
Were diagnostic tests or methods and the results clearly described?	✓			
Was the intervention(s) or treatment procedure(s) clearly described?	✓			
Was the post-intervention clinical condition clearly described?		✓		
Were adverse events (harms) or unanticipated events identified and described?		✓		
Does the case report provide takeaway lessons?	✓			

Table 2B - Critical appraisal checklist for case series. (Li, et al. 2023 (16))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	✓			
Was the condition measured in a standard, reliable way for all participants included in the case series?	✓			
Were valid methods used for identification of the condition for all participants included in the case series?	✓			
Did the case series have consecutive inclusion of participants?			✓	
Did the case series have complete inclusion of participants?			✓	
Was there clear reporting of the demographics of the participants in the study?	✓			
Was there clear reporting of clinical information of the participants?	✓			
Were the outcomes or follow up results of cases clearly reported?		✓		
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	✓			
Was statistical analysis appropriate?	✓			

Table 2C - Critical appraisal checklist for case series. (Li, et al. 2023 (17))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	✓			
Was the condition measured in a standard, reliable way for all participants included in the case series?	✓			
Were valid methods used for identification of the condition for all participants included inthe case series?	✓			
Did the case series have consecutive inclusion of participants?	✓			
Did the case series have complete inclusion of participants?	✓			
Was there clear reporting of the demographics of the participants in the study?	✓			
Was there clear reporting of clinical information of the participants?	✓			
Were the outcomes or follow up results of cases clearly reported?		✓		
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	✓			
Was statistical analysis appropriate?	✓			

Table 2D - Critical appraisal checklist for case series. (Whang, et al. 2024 (18))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?			✓	
Was the condition measured in a standard, reliable way for all participants included in the case series?	✓			
Were valid methods used for identification of the condition for all participants included inthe case series?	✓			
Did the case series have consecutive inclusion of participants?			✓	
Did the case series have complete inclusion of participants?			✓	
Was there clear reporting of the demographics of the participants in the study?	✓			
Was there clear reporting of clinical information of the participants?	✓			
Were the outcomes or follow up results of cases clearly reported?	✓			
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	✓			
Was statistical analysis appropriate?	✓			

Table 2E - Critical appraisal checklist for case reports. (Yang, et al. 2022 (19))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were patient's demographic characteristics clearly described?	✓			
Was the patient's history clearly described and presented as a timeline?	✓			
Was the current clinical condition of the patient on presentation clearly described?	✓			
Were diagnostic tests or methods and the results clearly described?	✓			
Was the intervention(s) or treatment procedure(s) clearly described?	✓			
Was the post-intervention clinical condition clearly described?			✓	
Were adverse events (harms) or unanticipated events identified and described?			✓	
Does the case report provide takeaway lessons?	✓			

Table 2F - Critical appraisal checklist for case reports. (Zhou, et al. 2022 (20))

JBI checklist questions	Yes	No	Unclear	Not applicable
Were patient's demographic characteristics clearly described?			✓	
Was the patient's history clearly described and presented as a timeline?			✓	
Was the current clinical condition of the patient on presentation clearly described?			✓	
Were diagnostic tests or methods and the results clearly described?			✓	
Was the intervention(s) or treatment procedure(s) clearly described?	✓			
Was the post-intervention clinical condition clearly described?	✓			
Were adverse events (harms) or unanticipated events identified and described?			✓	
Does the case report provide takeaway lessons?	✓			

Search strategy:
(robotic AND nephrectomy OR pyeloplasty OR nephroureterectomy OR cystectomy OR prostatectomy OR lymphadenectomy OR raveil OR 'ra veil' OR 'da vinci' OR urology) AND ('tele surgical' OR telesurgical OR telesurgery OR transcontinental OR 'telepresence surgery' OR toumai OR kangduo OR raven OR microport)

planted a Double J catheter, using wireless network and 5G technology with mean latency time of 272ms, with no complications (25).

There is evidence that the post-operative period can be maintained remotely enabling greater patient acceptance of the procedure. A randomized trial followed 270 patients who required hospital stay up to 72 hours comparing groups that received traditional face to face visits and groups with remote visits. The identified outcomes were similar as to morbidity rates, hospitalization, sick patient satisfaction and complications which demonstrated that virtual visits were not worse when compared to traditional face-to face model (29).

The network mode of operation utilized plays an important role in providing secure data transmission and 5G technology has its place in the spotlight although some configurations can achieve better results than others (30, 31). Aiming at only urological telesurgical procedures in humans, these studies were not included in our sample, even so, the results found in this research were compatible with the literature showing the 5G connection technology as the most widely used today (98.14%) in urological telesurgeries.

Improvement programs have been developed demonstrating that it is possible to enhance the urologist's performance in robotic surgeries (32). Remote diagnosis, tele -mentoring, live surgeries transmission, tele-training and tele-assistance, have gained room to quality education and have been used by many professionals, enabling the surgeon to become familiar with this technology (33-36). A randomized trial compared a percutaneous renal puncture performed by on-site urologists to another group carrying out the procedure controlled by a transatlantic remote robot, showing that, although the robotic puncture was slower, it was more precise and needed a smaller number of primary punctures in order for the procedure to be successful (37). The learning curve in telesurgery is continuous with the help of "medical surgical proctories", aiming at improving the quality of life of the professionals involved, optimizing costs and eliminating long periods of transportation, being able to allocate their time to other activities such as remaining closer to their families, being able to study and have leisure time, among others. Another interesting vision is the possibility of non-remote robotic surgeries being "converted" into remote ones in significantly intraoperative complications, or whenever it demands help from a more experienced professional.

There are reports of meticulous surgeries being carried out such as nephroureterectomy with as efficient results as traditional platforms (38). In this context, robotic platforms are constantly evolving to offer the surgeon the best tools, as it has been mentioned about the tactile sensitivity (24). A recent update of "Da Vinci" from Intuitive Surgical ® has made this resource available. Despite that, other companies are searching for their market share such as KangDuo Surgical Robotic®, Edge Medical Robotic®, Versius® from Cambridge Medical Robotics, and Hugotm System, RAS from Medtronic®, demonstrating their qualities, their benefits and soon they will be available at more affordable prices. Moschovas et al. performed a telesurgery robotic-assisted radical prostatectomy using Edge Medical Robotic® in a 71-year-old patient in only 60 minutes without complications and excellent patient evolution, walking in just 4 hours after the procedure (39). Because the date when this case report was published exceeded our research period, it was not included in our sample.

In a secondary analysis we identified that MicroHand S was the most used platform, accounting for 83% of the procedures, corroborating with the arrival of new robotic systems. Due to the great potential of telesurgery, demonstrating such data may alert other companies about the concentration of this modality in only one platform, fomenting new research and new projects.

More complex procedures such as partial nephrectomy and radical cystectomy, were also described as with no complications confirming how safe this modality can be. Wang et al. performed a right partial nephrectomy in approximately 48 minutes, with estimated bleeding of 10 mL, with no complication and hospital stay of 4 days 4 (18). Yang et al. performed a remote radical cystectomy with left

urethrectomy in 5 hours and cutaneous exteriorization of a ureteral stoma in a 71-year-old patient, with intraoperative bleeding of 200 mL, with a mean network delay of 254ms, without intraoperative complications (19). Analyzing the subgroups, we found that nephrectomy was the most remotely performed procedure, although it is not a complex procedure, relevant complications were not identified in these patients. Also, surgical treatment of varicocele was performed by telesurgery through a 5G network with a mean delay of 130ms, with minimal bleeding and finally a renal cyst excision, both uneventful with excellent results (15, 20).

Total latency time may be obtained through network latency with enough time for the robot to process the sign and perform movements, however, although they are similar to the values described, they can be discordant. Acceptable values to use 5G technology to carry out procedures with favorable surgical performance vary between 300 and 330 milliseconds, and the ideal ones are below 200 or 300 milliseconds (40, 41). Xu et al. proposed a network latency grading and showed that the impact is considered mild when latency values are ≤ 200 milliseconds, big when they are between 300 and 700 milliseconds and very big between 800 and 1000 milliseconds (41). As demonstrated in Table-1, total latency time in this review with 54 telesurgeries was 176 (IQR) 10.9 milliseconds. Although it is limited data, it strengthens the hypothesis that telesurgery is a viable mode. Despite the slight divergency, it is known that the greater the latency, the greater the likelihood of compromising the quality of the surgeon's movements.

Another important report is that there may exist a significant increase in the number of satellites orbiting the earth, which may reach up to a million of them (42). The combination of all these factors is a proof that within the telecommunication market there will be a relevant competition among companies, in such a way that technological improvement and lower costs will be inevitable, making access more affordable and driving the evolution of telesurgery.

There is evidence showing that not only remote surgeries can take place, but also tests can be carried out remotely. Despite its limitations, telecystoscopy was performed demonstrating that it can be done remotely (33). Tele-ultrasonography was not different. It was evaluated and found to be of diagnostic value in an intensive care unit, confirming that it is possible to identify kidney pathologies remotely (35). Therefore, tests carried out remotely may benefit many people who wait in endless queues to be attended in less favored areas.

The evolution of telehealth services has shown significant growth, exponentially, and can reach an increase of 235% per year (43). Turning our attention to the modality of telesurgery, despite being underutilized, the interest in monitoring its development has been gaining ground among urologists, since, despite the cost of the transmission equipment may reach US$70.000, such technology can be sustainable and generate huge return for the global health system (44). Although the cost of a robotic system is high and can reach 1.7 million, it is an abundant market with a potential financial turnover of US$ 5 billion (45). Since its implementation may cause a significant socioeconomical impact and influence policies for the distribution of health capital, a consideration that may seem like an insult, although very relevant, must be discussed, because this money can also be directed to other modalities that could benefit patient care (44).

Each patient must have their autonomy preserved, maintaining their right to decide based on their reasons and motives. Ethical aspects are seriously involved, such as, the risk of dehumanization, objectification of the patient, restriction of emotional connection and empathy, physician-patient relationship, medical assistance, as well as feeling satisfied with their expectations of care. That is the reason why, international guidelines and protocols need to be better established. Another aspect is that, in case of an eventual conversion to an open procedure, less and less likely these days, the local assistance team may not have the surgical expertise compared to the remote surgeon. In order to meet the patient's expectations, an informed surgical consent with precise guidance about the whole process must be

discussed (46-48). In Brazil, telesurgery has been regulated by the Federal Council of Medicine (CRM) by means of resolution n° 2.311/2022, published on March 22, 2022 (48).

Although the initial investment is considerable, although sustainable, in the long term telesurgery can reduce healthcare costs in lower income countries reducing length of hospital stay, blood transfusions, surgical and nosocomial inflections and consequently, less use of antibiotics and fewer resistant strains, higher bed turnover and early return to the patient's productive working life (49). Other benefits would be to improve the training of examinations and procedures, reduce waiting lines, optimize the time of surgical instructors, support surgeons in more complex surgeries and to avoid intraoperative complications.

Randomized trials with robust samples were not found, nor trials comparing urological telesurgeries in humans. It is known that reports of a series of cases are limited, as well as the utilization of "salami slicing", where data of a fully complete sample are not identified, there is a risk of several types of biases and may represent outcomes that are not consistent with the population to be studied. Our critical assessment indicated that the majority of the trials are limited, however, the topic in question is promising and of high scientific relevance. Another important aspect worth emphasizing is that estimates demonstrate an inefficient number of surgeons in relation to the demand for the next 10 years, since low-income countries correspond to a volume which is approximately 50% of the world's population and approximately only 20% of all available surgeons (35, 50). Therefore, it is justified to draw the attention of these professionals and organizations involved in this innovative technology and to stimulate the production of new trials and discussions on the subject since its inclusion in the surgical routine will be inevitable in a very near future.

CONCLUSION

Despite its limitations, we found evidence that performing robotic surgeries in the genitourinary system is feasible and safe, however further studies should be carried out. Telesurgery is presented as an innovative, promising modality and that is why, in a near future it may become a reality in many surgeon's practices.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 51 (3): e20240665, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0665

Urachal Carcinomas: A Comprehensive Systematic Review and Meta-analysis

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ABSTRACT

Objective: This systematic review and meta-analysis aim to consolidate current evidence on the diagnosis, epidemiology, and treatment of urachal carcinoma, a rare malignancy with limited data.

Materials and Methods: A systematic search of PubMed/MEDLINE was conducted up to September 2024 to identify studies involving patients with urachal carcinoma, reporting clinical epidemiological characteristics, diagnostic strategies, histopathological findings, tumor staging, treatment modalities, and oncological outcomes. Extracted data were systematically synthesized, and statistical analyses, including a single-arm meta-analysis, were performed to comprehensively evaluate oncological outcomes.

Results: Our study includes 1,901 cases of urachal carcinoma from 50 studies. The findings support the oncologic advantage of *en-bloc* resection with umbilectomy in localized disease, demonstrating improved survival outcomes and reduced recurrence rates. In the adjuvant setting, those receiving cisplatin-based therapy presented the best response, with 65.73% with no disease progression; similarly, in the metastatic disease, cisplatin-based regimens seem to have better responses in metastatic disease. The single-arm meta-analysis estimated a 5-year overall survival rate of 51% (95% CI: 0.49–0.54). Tumor recurrence was documented in 35% of cases (95% CI: 0.25–0.45), with local recurrence occurring in 28% (95% CI: 0.18–0.38), with the average time to recurrence of 27.6 months.

Conclusion: Our study provides the most comprehensive review of urachal carcinoma to date, providing evidence to guide clinical decisions. It underscores the oncologic benefits of *en-bloc* resection with umbilectomy and specific chemotherapeutic regimens. Emerging alternative therapies also show potential, highlighting the need for further research to optimize patient outcomes.

ARTICLE INFO

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Keywords:
Urachal cancer [Supplementary Concept]; Cystectomy; Systematic Review [Publication Type]

Submitted for publication: November 29, 2024

Accepted after revision: December 28, 2024

Published as Ahead of Print: January 21, 2025

INTRODUCTION

The urachus, a remnant of the embryonic allantois, typically becomes nonfunctional after birth. This structure forms during early development as the allantois regresses into a tubular connection between the urinary bladder and the umbilicus. By the end of gestation, it generally transforms into a fibrous cord that fuses with the obliterated umbilical arteries, creating the median umbilical ligament (1). However, a residual urachal structure remains in around one-third of adults, often presenting as a tubular or cystic formation lined by epithelium. This developmental remnant may serve as a site for urachal carcinoma (UrC) (1, 2).

UrC differs in pathological and clinical features from bladder carcinomas, highlighting their distinct origins and characteristics. It is rare, comprising less than 1% of all bladder cancer cases. Incidence estimates range from 0.022 to 0.060 per 100,000 person-years (3).

The clinical-epidemiological characteristics, surgical and clinical management, and oncological outcomes of UrC are predominantly supported by weak evidence derived from case reports, small case series, or population-based databases with incomplete information and significant missing data. When analyzed in isolation, these limitations make it challenging to apply the findings effectively to clinical practice, given the rarity of the disease.

Current controversies in the literature include the necessity of umbilical resection in conjunction with cystectomy, the indication and extent of lymphadenectomy, as well as diagnostic and prognostic criteria, all of which remain subjects of debate with conflicting results. This systematic review and meta-analysis aim to synthesize the available literature to provide more robust scientific evidence, facilitating evidence-based management for this rare malignancy.

MATERIALS AND METHODS

Literature search

The study was conducted in strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (4) statement and registered in the PROSPERO international database of prospectively registered systematic reviews (CRD42024562424).

Based on the Patient-Intervention-comparator-outcome-study design (PICOS) criteria (5), a research question was established: What is the current evidence regarding the clinical, epidemiological characteristics, management strategies, and oncological outcomes of urachal carcinoma?

The search strategy was (urachal carcinoma) OR (urachal adenocarcinoma) OR (urachal cancer), and we searched in PubMed/MEDLINE up to September 2024. We also checked the bibliographies of the included studies for further references to relevant trials. We included all case series, cohort studies, and randomized trials, all involving patients over 18 years of age with UrC without language restrictions. We excluded governmental databases, case reports, case series with fewer than eight patients or with incomplete information, editorial letters, expert opinions, and literature reviews.

Two independent authors screened all retrieved records. Discrepancies were resolved by discussion with a third review. If relevant to the present review, the full text of the screened papers was selected.

Data extraction and endpoints

All variables were entered into a spreadsheet for analysis, and another author made cross-validation. The mean and standard deviation for continuous variables were recorded from the included studies. For variables reported as median and interquartile range, the original data were converted to mean and standard deviation (6).

The variables extracted included study design, patient gender, age, comorbidities, clinical symptoms, urinary cytology results, cystoscopy utilization, preoperative oncological markers, imaging modalities employed, histological classification, clinical and pathological staging, surgical approach type, lymphadenectomy and its template, performance of umbilectomy, administration of chemotherapy for

neoadjuvant, adjuvant or salvage treatment and oncological outcomes.

RESULTS

Literature screening

The literature search retrieved 562 records, which were screened by title and abstract. Of these, 468 were excluded because they were irrelevant to the study's aim. We then reviewed the full texts of the remaining 94 studies to assess their eligibility. A total of 44 studies were excluded due to inappropriate study design, leaving 50 studies for inclusion in the final analysis (7-57), shown in the supplementary Table-1. Figure-1 presents the PRISMA flowchart summarizing the literature search and selection process.

Study characteristics

All included studies were retrospective and comprised a total of 1,901 patients. The United States had the highest number of patients in the case series (N=715; 37.61%), followed by China (N=364; 19.15%) and South Korea (N=318; 16.73%). All clinical and epidemiological characteristics of the studies are summarized in Table-1.

Epidemiology and Clinical Characteristics

The mean age at primary treatment was 51 years (±3.31), with a predominance of male patients 64%. Regarding most frequent comorbidities, 24% of patients had systemic arterial hypertension, and 13.3% had diabetes mellitus. In terms of clinical presentation, macroscopic hematuria was the most common symptom (45.5%), followed by abdominal pain (6.4%) and palpable abdominal mass (5%).

Diagnostic Methods

Concerning the prevalence of imaging modalities utilized, most patients underwent abdominal and pelvic computed tomography (CT) (69.85%). The second most performed imaging test was 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT (13.65%), while ultrasonography was used in only 9.6% of cases. The use of 18F-FDG PET CT has shown value in identifying metastatic sites that may be missed by other imaging methods, especially during follow-up. However, it does not appear to offer substantial additional insights over CT, which remains the preferred and most reliable tool for initial diagnosis and staging. Urinary cytology, when performed, had an average sensitivity of 22%, whereas cystoscopy demonstrated a higher average sensitivity of 79%. Calcification of the lesion on CT was previously reported in 50%–70% of patients, but in our systematic review was observed in only 35.5% of patients (58).

Regarding serum biomarkers, some studies utilized CEA, CA 19-9, CA 125, CA 15-3, and alpha-fetoprotein. The two markers with the highest sensitivity for UrC were CA 19-9 (84%) and CEA (80%).

Cystoscopy had a sensitivity of 0.79 (±0.19). In most cases where urachal carcinoma is detected, there is a protrusion in the bladder mucosa or a lesion that shows growth from the external region towards the bladder urothelium, contrasting with the typical tumor progression of urothelial carcinoma. A biopsy is an essential tool for diagnosis, especially in cases of atypical localization or advanced clinical staging. In these situations, it is necessary to differentiate urachal carcinoma from primary bladder adenocarcinoma and invasive adenocarcinoma originating from other sites. Specific histopathological and clinical criteria have been established to assist in this diagnosis.

Histopathological Subtypes

Histological evaluation is the cornerstone of diagnosing UrC, with the most widely used criteria being those of Sheldon et al., Gopalan et al. and Mostofi et al., more recently, (3, 19, 59). These criteria encompass four main elements: (1) the tumor must be located in the bladder dome or anterior wall; (2) the tumor's epicenter must reside within the bladder wall; (3) there should be no evidence of extensive cystitis cystica or cystitis glandularis; and (4) the absence of a known primary adenocarcinoma in any other site. We found that the most frequent histological subtype was the mucinous adenocarcinoma of the

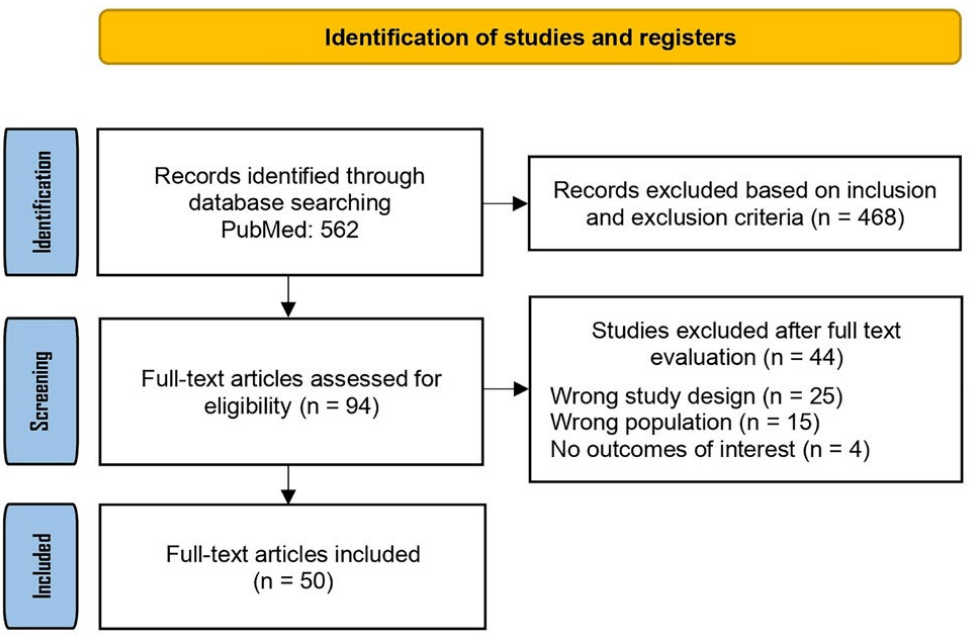
Table 1 - Clinical, epidemiological, and pathological characteristics of the included studies.

Characteristic; n (%)	Overall population
Number of patients	1,901
Age at primary treatment (Years); Mean (SD)	51 (±3.31)
Gender	1794
Male	1,148 (63.99)
Female	646 (36.01)
Smoker	200 (10.52)
Clinical signs and symptoms	1210
Hematuria	865 (45.50)
Abdominal pain	122 (6.41)
Palpable mass	95 (4.99)
Mucouria	52 (2.73)
Dysuria	36 (1.89)
Lower urinary tract symptoms	35 (1.84)
Omphalorrhoea	5 (0.26)
Diagnostic performance; Mean sensitivity (SD)	
Urinary cytology	0.22 (0.19)
Cystoscopy	0.79 (0.19)
Calcification at tomography; Prevalence (%)	35.54
Imaging exams	952
Computed Tomography Scan	665 (69.85)
18F-Fluorodeoxyglucose Positron Emission Tomography	133 (13.97)
Ultrasonography	92 (9.6)
Laparoscopy	35 (3.67)
Magnetic Resonance Imaging	27 (2.83)
Oncologic marker, nº patients positive/nº patients tested (sensitivity)	
CEA	404 / 499 (0.80)
CA19-9	403 / 476 (0.84)
CA125	20 / 66 (0.30)
Alpha fetoprotein	1/15 (0.06)
CA 15-3	3 / 50 (0.06)

Histology	1264 (100)
Mucinous	508 (40.19)
Enteric / Intestinal	426 (33.70)
Mixed	74 (5.85)
Signet Ring Cells	67 (5.30)
Urothelial	70 (5.54)
Squamous cells	11 (0.87)
Neuroendocrine	1 (0.08)
Not specified	107 (8.47)
Sheldon Classification	1,107 (100)
I	21 (1.90)
II	78 (7.05)
IIIA	262 (23.67)
IIIB	487 (43.99)
IIIC	62 (5.60)
IIID	27 (2.44)
IVA	94 (8.49)
IVB	76 (6.87)
Mayo Classification	814 (100)
I	179 (21.99)
II	385 (47.30)
III	93 (11.43)
IV	157 (19.29)
TNM Staging	579 (100)
pT0	4 (0.69)
pT1	27 (4.66)
pT2	148 (25.56)
pT3	316 (54.57)
pT4	84 (14.50)
Number of patients with metastasis at diagnosis	297 (15.62)

SD = Standard deviation

Figure 1 - PRISMA flow chart of the selected articles.



urachus (40.1%), followed by enteric urachal adenocarcinoma (33.7%) and mixed adenocarcinoma of the urachus (5.8%).

Tumoral staging

Tumor staging was reported using several classification systems. The Sheldon classification (59) was the most frequently used, with stage II being the most common (44%), followed by stage IIIa (23.6%) and stage IVa (8.5%). The Mayo classification (14) was available for 814 patients, where stage II was also the most prevalent (47.3%), followed by stage I (22%) and stage IV (19.3%). The TNM staging system was utilized in 579 patients, with stage T3 being the most common (54.5%), followed by stage T2 (25.5%) and stage IV (14.5%). Overall, only 15.6% of patients presented with metastatic disease at the time of primary diagnosis.

Surgical treatment

The earliest historical series, including the two largest single-center studies by Begg in 1931 and Mostofi et al. in 1955, advocated for treatment with radical cystectomy combined with *en-bloc* resection of the urachus and umbilical region (2, 3, 58-60).

Currently, the standard treatment is primarily surgical, consisting of extended partial cystectomy with *en-bloc* resection of the urachal mass, urachal tract, and umbilicus, combined with pelvic lymph node dissection. Although radical cystectomy has been proposed as definitive therapy in some cases, it is generally reserved for larger tumors that involve more than the superior hemisphere of the bladder. Partial cystectomy is associated with fewer postoperative complications and improved quality of life (9, 15).

In our systematic review, surgical intervention was the primary treatment in 74.5% of cases, with partial cystectomy as the predominant approach for localized disease (80.8%), followed by radical cystectomy (11.5%). Open surgery was the most frequently reported surgical technique (21.8%), followed by laparoscopic (11.9%) and robotic-assisted approaches (3.1%). However, a significant portion of studies (63.1%) did not specify the surgical approach used. The treatment characteristics of the disease are detailed in Table-2.

Sheldon et al. (3), after finding navel invasion in 7% of autopsies performed on patients who died because of urachal tumors, advocated surgical control of the urachal ligament via *en-bloc* excision of

Table 2 - Disease management of urachal carcinoma.

Characteristic; n (%)	Overall population
Primary treatment	1,901
Surgery	1,417 (74.54)
Radiotherapy	37 (1.95)
Chemotherapy	61 (3.21)
Not specified	386 (20.31)
Type of primary surgery	1,417
Partial cystectomy	1,145 (80.80)
Radical cystectomy	163 (11.50)
Transurethral Bladder Resection	50 (3.53)
Not Specified	59 (4.16)
Surgical technique	1,828
Open	349 (19.09)
Laparoscopic	192 (10.50)
Robotic	43 (2.35)
Not specified	1,244 (68.05)
Umbilectomy included	948
Yes	588 (62.0)
No	360 (37.97)
Lymphadenectomy	1,640
Yes	377 (22.98)
No	444 (27.07)
Not specified	819 (49.94)
Extent of lymphadenectomy	377
Standard: obturator nodes, external iliac nodes, internal iliac nodes	167 (44.2)
Extended: obturator nodes, external iliac nodes, internal iliac nodes, common iliac nodes, presacral nodes, and paravesical nodes.	17 (4.5)
Not specified	193 (51.2)
Lymph nodes at pathologic staging	1147
Positive	226 (19.7)
Negative	921 (80.3)
Number of lymph nodes removed; Mean (SD)	10.26 (±3.99)

SD = Standard deviation

the bladder dome, urachal ligament, posterior rectus abdominis fascia, and umbilicus (15, 59, 61). However, some authors defend that the umbilectomy may be omitted in patients with localized lesions to avoid impact on body image and quality of life (37, 62). In our systematic review, we identified 360 patients (38%) who did not undergo umbilical resection across 14 studies that reported not performing umbilectomy with urachal *en-bloc* excision (14, 15, 17, 18, 20-22, 26-28, 31, 37, 40, 44). Of the five studies comparing patients who underwent umbilectomy to those who did not, four reported worse overall survival, cancer-specific survival, and progression-free survival in patients who did not receive complete urachal remnant resection with umbilectomy. Although one study found no statistically significant difference in survival (p=0.09), the Kaplan-Meier curve suggested a trend, with 13 of the 16 long-term survivors in the group that underwent *en-bloc* resection with umbilectomy, as shown in Table-3.

Before this review, the conduct of umbilectomy with *en-bloc* resection of the urachal tract was based on the earlier study of Sheldon et al. (3). This systematic review presents five studies from the literature that highlight the oncological benefits of umbilectomy with *en-bloc* resection, further reinforcing this approach as the standard treatment for patients with localized UrC.

Table 3 - Comparison of survival outcomes between patients who underwent umbilectomy and those who did not.

Author	Year of publication	N0 of patients underwent umbilectomy	N0 of patients not underwent umbilectomy	Survival data
Yu, et al. (45)	2021	12	191	Overall survival: HR 2.491; 95% 0.980 - 6.334; p=0.005 Cancer-Specific Survival: HR 2.601; 95%CI 1.024 - 6.608; p=0.044 Recurrence-free survival: HR 2.140; 95%CI 0.918 - 4.990; p=0.078
Ashley, et al. (15)	2006	32	27	Cancer specific survival: HR 3.0; 95%CI 1.3 - 6.8 ; p=0.008
Siefker-Radtke, et al. (32)	2016	19	16	*En-bloc* resection was not statistically associated with survival (p = 0.09), but 13 of the 16 long-term survivors after resection were in the group treated with *en-bloc* resection and umbilectomy.
Jia, et al. (41)	2020	27	12	Overall survival in the umbilectomy group: HR = 0.141; 95% CI = 0.034–0.591, p=0.007. Progression-free survival: HR = 0.355; 95% CI = 0.128–0.983, p=0.046. Patients who underwent umbilectomy had significantly longer median overall survival (87 vs. 48 months, p=0.03) and progression-free survival (67 vs. 31 months, P=0.036) than those who did not.
Dhillon, et al. (29)	2015	29	11	Patients underwent umbilectomy: 10 died of cancer (34%) in a mean of 35 months (range, 13-74 months). Patients who did not undergo umbilectomy: 7 died of cancer (64%) in a mean of 31 months (range, 12-71 months).

HR = Hazard Ratio; 95%CI = 95% Confidence interval

Concerning the role of lymphadenectomy, 13 studies (14, 16-18, 21, 22,31, 37, 40, 41, 44, 49, 50) reported patients who did not undergo pelvic lymphadenectomy within the overall cohort. Still, only 3 studies compared the oncological outcomes between the two groups. Duan et al. reported that among the 35 patients who did not undergo lymphadenectomy, 7 (20%) experienced nodal recurrence, whereas 3 (11.1%) of the 27 patients who underwent lymphadenectomy had nodal recurrence (42). However, in the authors' analysis, performing pelvic lymphadenectomy was not correlated with disease-free survival (42). The second study comparing both groups included 20 patients who underwent lymphadenectomy and 40 patients who did not. The authors reported that lymphadenectomy predicted cancer-specific mortality in the univariate analysis (p = 0.02; HR 1.5, 95% CI 0.7–2.8) (14). Lastly, a third article reported 18 patients who underwent lymphadenectomy and 16 who did not. After performing a survival analysis, the authors found that lymphadenectomy had no positive effect on survival (40). The evidence in the literature remains limited, as most series have not evaluated the association between pelvic lymphadenectomy and oncological outcomes. Among the few studies that do address this, there is no clear specification regarding the extent of lymphadenectomy performed, and the results are often conflicting (63).

Systemic treatment

The NCCN recommends chemotherapy regimens for node-positive bladder adenocarcinoma that are similar to those used in colorectal cancer treatment. Specifically, the FOLFOX regimen (oxaliplatin, leucovorin, and 5-fluorouracil) and the GemFLP regimen (5-fluorouracil, leucovorin, gemcitabine, and cisplatin) are suggested as potential options (62).

For advanced disease, participation in clinical trials is strongly recommended. Although, in cases where trial enrollment is not feasible, combination chemotherapy may be an option with regimens based on 5-Fluorouracil (FOLFOX or GemFLP) or with ITP (paclitaxel, ifosfamide and cisplatin) or dual therapy with paclitaxel and a platinum compound (62-65).

In this systematic review, 16.2% of patients presented with metastatic disease at the initial diagnosis, and 16% experienced tumor recurrence after primary treatment. The primary site of tumor recurrence was the lung (22.8%), followed by the bladder (22.1%) and the pelvis (15.2%), as shown in Figure-2.

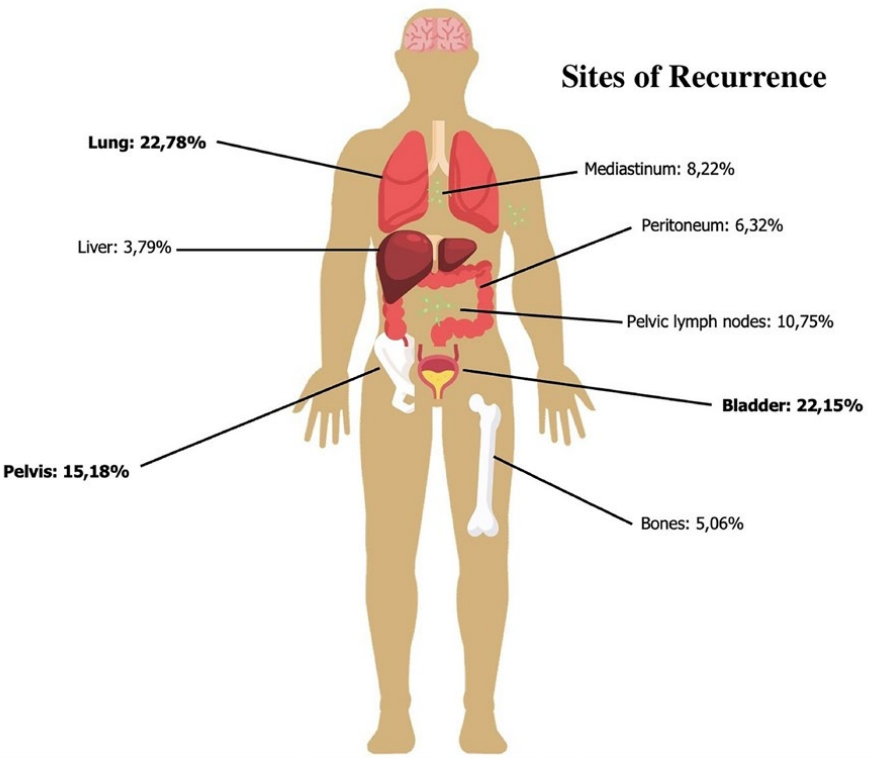
In the studies with oncological outcomes, neoadjuvant therapy was administered to only 8 patients; however, chemotherapy regimens and response data were not available for 3 of these patients. Among the remaining patients receiving neoadjuvant therapy, treatment and outcomes were as follows: 4 cycles of gemcitabine and cisplatin were administered, though response data were unavailable; a 5-fluorouracil and cisplatin regimen achieved a partial response, with the patient remaining disease-free at study conclusion (median follow-up post-surgery was 17 months); and a regimen combining ifosfamide, docetaxel, and cisplatin was associated with disease progression.

A total of 190 patients (9.9%) received adjuvant therapy, with specific chemotherapy regimens reported for 72% of cases, covering 32 unique regimens. Cisplatin was included in 51% of adjuvant regimens, while 5-fluorouracil was used in 26%. Among patients with recurrence or metastatic disease, 93 (4.9%) received systemic treatment, encompassing 24 distinct regimens; cisplatin was administered in 49.5% of these cases, while 5-fluorouracil was included in 46.2%.

Therapeutic responses were documented for 112 patients, 65 patients (58%) who received adjuvant therapy, and 47 patients (42%) who received systemic salvage treatment. In the adjuvant cohort, 63% presented no disease progression, whereas in the metastatic or recurrent group, 14.9% showed a partial or complete response.

In adjuvant therapy, patients treated with a 5-fluorouracil-based regimen showed a 60% rate of no disease progression. Among those receiving cisplatin-based therapy, 65.73% remained disease-free. None of the three patients who received a combination of 5-fluorouracil and cisplatin experienced disease progression.

Figure 2 - Main sites of tumor recurrence in patients with urachal carcinoma following primary treatment.



In salvage treatment, 15.4% of those treated with a cisplatin-based regimen achieved a complete or partial response, while 14.8% of patients on a combined regimen of 5-fluorouracil and cisplatin showed complete or partial response. Only one patient who received a 5-fluorouracil-based regimen had documented oncological outcomes and demonstrated a complete or partial response. In terms of disease stability in the metastatic or recurrent setting, 30.7% of patients treated with a cisplatin-based regimen maintained stable disease, whereas 37% of those on combined 5-fluorouracil and cisplatin regimens achieved disease stability. Supplementary Table-2 lists all systemic treatments used.

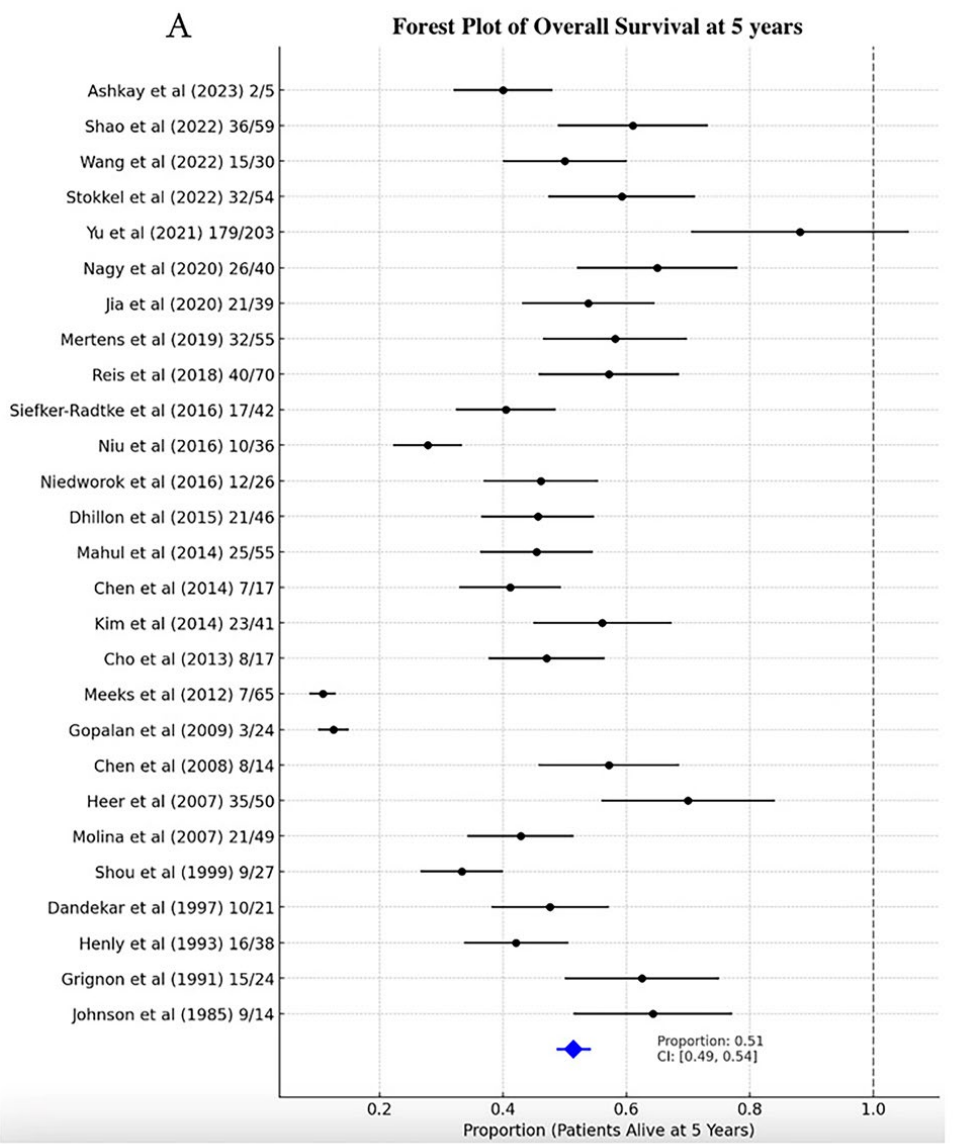
ONCOLOGICAL OUTCOMES

The single-arm meta-analysis indicated a 5-year overall survival rate of 51% (95% CI 0.49–0.54). Tumor recurrence was observed in 35% of cases (95% CI 0.25–0.45), with local recurrence occurring in 28% of cases (95% CI 0.18–0.38). The mean time to recurrence was 27.6 months. Figure 3 presents a forest plot illustrating the oncological outcomes.

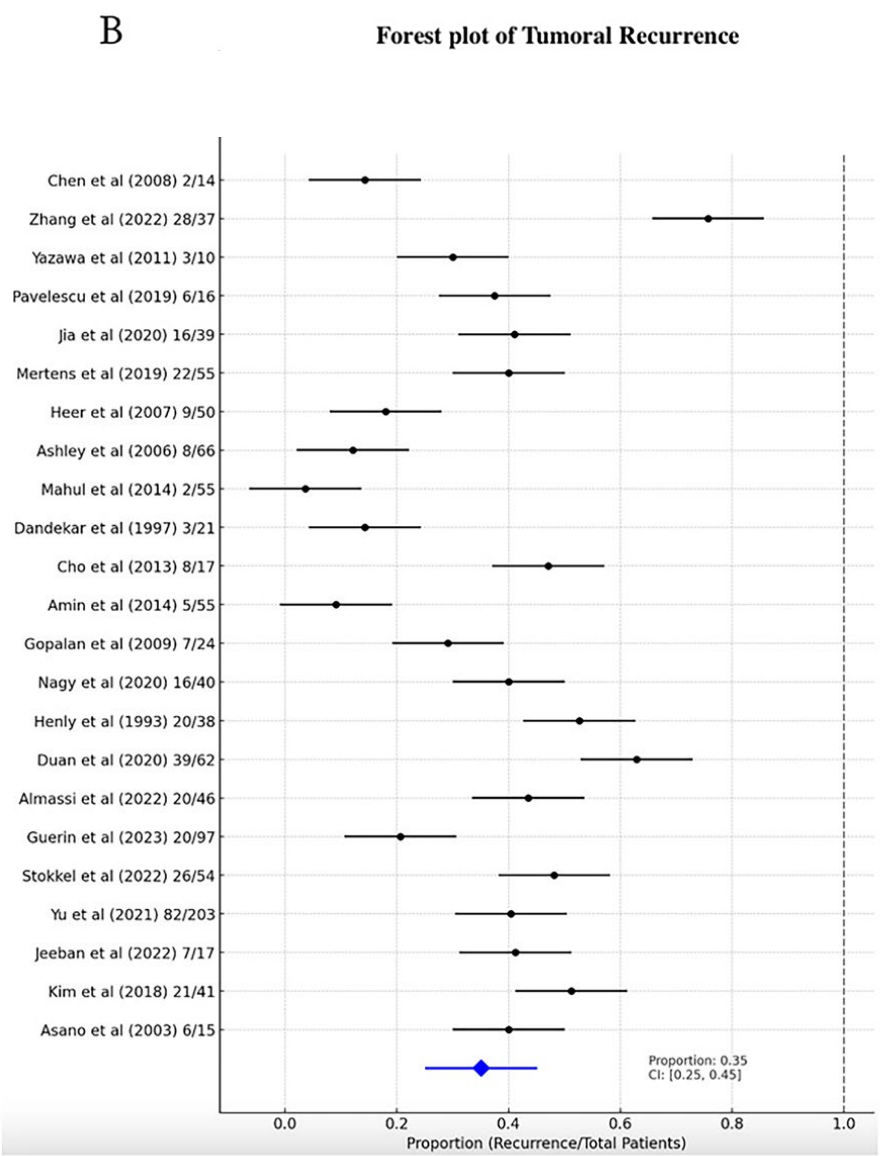
CONCLUSIONS

Urachal carcinoma is a rare malignancy with limited and heterogeneous evidence guiding its management. This meta-analysis, encompassing the largest patient cohort to date, provides a more robust foundation for clinical decision-making in this uncommon disease. Our findings emphasize the oncological benefits of *en-bloc* resection with umbilectomy for affected patients. In the adjuvant setting, regimens containing 5-fluorouracil and cisplatin demonstrated the most efficacy, while cisplatin-based chemotherapy showed favorable responses in metastatic cases. Furthermore, the response rates observed with alternative regimens suggest a potential role for emerging systemic therapies in the treatment of urachal carcinoma.

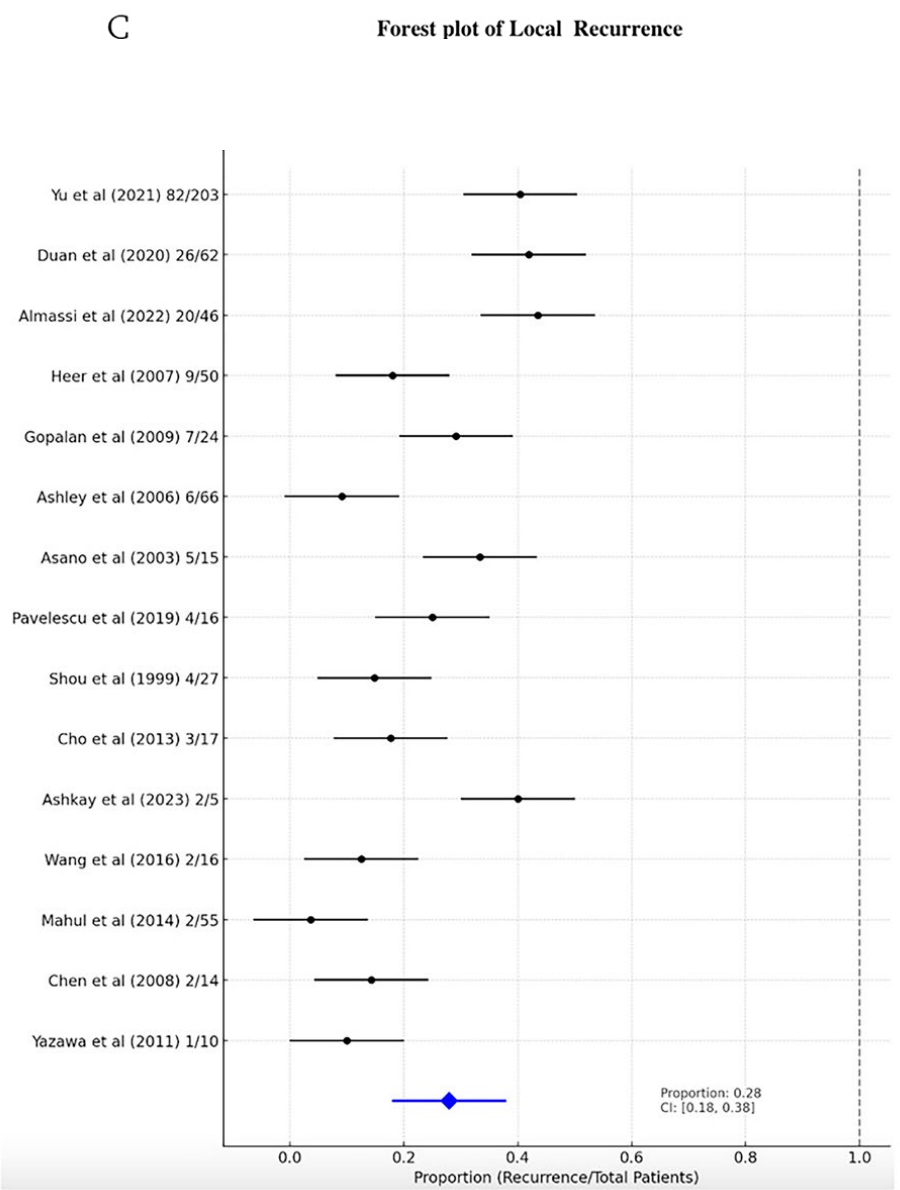
Figure 3 - Forest plot of oncological outcomes.



A - Overall Survival at 5 years;



B - Tumoral recurrence;



C - Local recurrence

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary Table 1 - Studies included in the analysis.

Author	Article Year	Country
Johnson, et al. (8)	1985	USA
Grignon, et al. (9)	1991	USA
Henly, et al. (10)	1993	USA
Dandekar, et al. (11)	1997	India
Shou, et al. (12)	1999	China
Asano, et al. (13)	2003	Japan
Thali-Schwab, et al. (14)	2005	USA
Ashley, et al (15)	2006	USA
Heer, et al (16)	2007	USA
Molina, et al (17)	2007	USA
Chen, et al (18)	2008	China
Gopalan, et al (19)	2009	USA
Paner, et al (20)	2011	USA
Yazawa, et al (21)	2011	Japan
Meeks, et al (22)	2012	USA
Cho, et al (23)	2013	South Korea
Kim, et al (24)	2014	South Korea
Ke, et al (245	2023	China
Jung, et al (26)	2014	South Korea
Chen, et al (27)	2014	China
Amin, et al (28)	2014	USA
Dhillon, et al (29)	2015	USA
Wang, et al (30)	2016	China
Niu, et al (31)	2016	China
Siefker-Radtke, et al (32)	2003	USA

Niedworok, et al (33)	2016	Germany
Xing Bi, et al (34)	2017	China
Hang, et al (35)	2017	China
Reis, et al (36)	2018	Germany
Kim, et al (37)	2018	South Korea
Pavelescu, et al (38)	2019	Romania
Mertens, et al (39)	2019	United Kingdom
Cornejo, et al (40)	2020	USA
Jia, et al (41)	2020	China
Duan, et al (42)	2020	China
Nagy, et al (43)	2020	Hungary
P Das, et al (44)	2022	USA
Yu, et al (45)	2021	South Korea
Almassi, et al (46)	2022	USA
Wang, et al (47)	2022	China
Jeeban, et al (48)	2022	USA
Zhang, et al (49)	2022	China
Shao, et al (50)	2022	China
Stokkel, et al (51)	2022	Netherlands
Stokkel, et al (52)	2023	Netherlands
Varadi, et al (53)	2023	Hungary
Guerin, et al (54)	2023	France
Ashkay, et al (55)	2023	USA
Sang, et al (56)	2023	South Korea
Suartz, et al (57)	2024	Brazil

Supplementary Table 2 - Systematic treatment.

Characteristic	Overall population
Neoadjuvant therapy received; n (%)	8 (0.42)
Type of neoadjuvant treatment; n (%)	
Gemcitabine and Cisplatine	2 (25)
5-fluorouracil and cisplatin-based regimen	2 (25)
Ifosfamide, docetaxel, and cisplatin	1 (12.5)
Not specified	3 (37.5)
Adjuvant therapy received; n (%)	190 (9.99)
Type of adjuvant therapy; n (%)	
Cisplatin and Paclitaxel	5 (2.63)
5-Fluorouracil, doxorubicin, mitomycin	2 (1.05)
Cisplatin-based	19 (10.00)
Paclitaxel	3 (1.58)
Doxorubicin	2 (1.05)
5-Fluorouracil based	3 (1.58)
MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)	4 (2.11)
Taxol and platinum	3 (1.58)
Etoposideo and platinum	1 (0.53)
Gencitabine and cisplatin	12 (6.32)
5-Fluorouracil and cisplatin/carboplatin	20 (10.53)
5-Fluorouracil, cisplatin and gencitabine	7 (3.68)
5-Fluorouracil, cisplatin and doxorrubicine	6 (3.16)
5-Fluorouracil, doxorubicin and etoposide	2 (1.05)
Cisplatin and Nivolumab	2 (1.05)
Bevacizumab and unspecified chemotherapy	2 (1.05)
Gemcitabine, Cisplatin, Afatinib, Tegafur, Gimeracil, Oteracil and Paclitaxel	1 (0.53)
5-fluorouracil or gemcitabine and/or cisplatin.	11 (5.79)
Gemcitabine or Capecitabine combined with Cisplatin or Oxaliplatin	11 (5.79)
Capecitabine combined with Taxol	3 (1.58)
Capecitabine combined with Gemcitabine	2 (1.05)
Taxol combined with Cisplatin or 5-fluorouracil	2 (1.05)
Pembrolizumab	2 (1.05)
Folinic acid, 5-fluorouracil, and oxaliplatin	3 (1.58)
Carboplatin	1 (0.53)
Neratinib	1 (0.53)

Atezolizumab	1 (0.53)
Ipilimumab	1 (0.53)
Nivolumab	1 (0.53)
Capecitabina and oxaliplatin	1 (0.53)
Cisplatin and paclitaxel	1 (0.53)
Capecitabine	1 (0.53)
Paclitaxel, ifosfamide and cisplatin	1 (0.53)
Not specified	53 (27.89)
Systemic salvage treatment received; n (%)	93 (4.89)
Type of Salvage Chemotherapy; n (%)	
5-Fluorouracil and irinotecan	1 (1.08)
5-Fluorouracil or gemcitabine and/or cisplatin.	8 (8.60)
5-Fluorouracil, doxorubicin, and cisplatin	1 (1.08)
5-Fluorouracil, doxorubicin, mitomycin	3 (3.23)
5-Fluorouracil, leucovorin, and oxaliplatin	1 (1.08)
5-Fluorouracil, leucovorin, gemcitabine and cisplatin	6 (6.45)
5-Fluorouracil, mitomycin C, and mitoxantrone	1 (1.08)
5-Fluorouracil, mitomycin, cisplatin and doxorubicin	4 (4.30)
5-Fluorouracil, α-interferon, cisplatin	3 (3.23)
5-Fluouracil and cisplatin	1 (1.08)
5-Fluouracil based	14 (15.05)
Cisplatin ifosfamide and gemcitabine	1 (1.08)
Cisplatin-based	7 (7.53)
Cisplatin, gemcitabine and etoposide	1 (1.08)
Cyclophospamide	3 (3.23)
Docetaxel and cisplatin	1 (1.08)
Doxorubicin	5 (5.38)
Doxorubicin, cisplatin, and mitomycin C	1 (1.08)
Gemcitabine, cisplatin	1 (1.08)
Methotrexate, vinblastine, doxorubicin, cisplatin	5 (5.38)
Mytomycin, cisplatin, cyclophosphamide	1 (1.08)
Paclitaxel	3 (3.23)
Paclitaxel and carboplatin	2 (2.15)
Paclitaxel and cisplatin	2 (2.15)
Paclitaxel, methotrexate and cisplatin	1 (1.08)
Not specified	16 (17.20)

REVIEW ARTICLE

Vol. 51 (3): e20250047, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.0047

Magnetic Resonance Urogram in Pediatric Urology: a Comprehensive Review of Applications and Advances

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ABSTRACT

Magnetic Resonance Urography (MRU) has emerged as a powerful imaging modality in pediatric urology, offering comprehensive anatomical and functional assessment of the urinary tract without exposure to ionizing radiation. This review provides an in-depth analysis of MRU's technical aspects, clinical applications, advantages, and recent advancements. Traditional imaging techniques, such as ultrasound, voiding cystourethrography, and nuclear scintigraphy, have long been utilized for evaluating pediatric urinary tract anomalies; however, these methods have inherent limitations in anatomical resolution and functional assessment. MRU combines high-resolution anatomical imaging with dynamic functional analysis, making it particularly valuable in evaluating conditions such as hydronephrosis, ureteropelvic junction obstruction, and ectopic ureters. Advancements in MRU technology, including the use of 3T MRI for superior spatial resolution, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, have enhanced its diagnostic capabilities. The ability to assess renal transit times and differential renal function allows for precise evaluation of obstructive uropathies and congenital anomalies. Despite requiring sedation in younger children and longer acquisition times, MRU has demonstrated superior accuracy compared to conventional imaging, reducing the need for multiple diagnostic studies. Recent developments in real-time MRI, faster imaging techniques, and AI-based reconstructions have further optimized MRU's efficiency and diagnostic utility. As MRU continues to evolve, its role in pediatric urology is expected to expand, potentially replacing traditional imaging modalities in select cases. This review highlights the growing significance of MRU in pediatric urinary tract evaluation, emphasizing its potential to improve clinical decision-making and patient outcomes.

ARTICLE INFO

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Keywords:
Magnetic Resonance Imaging; Urography; Pediatrics

Submitted for publication:
February 02, 2025

Accepted:
February 15, 2025

Published as Ahead of Print:
February 25, 2025

INTRODUCTION

Magnetic Resonance Urography (MRU) is an advanced imaging technique that combines the principles of magnetic resonance imaging (MRI) with specialized protocols to determine anatomy and evaluate function within the urinary tract. MRU provides highly detailed anatomical and superior functional information about the kidneys, ureters, and bladder without the use of ionizing radiation. MRU is particularly valuable in pediatric patients, where minimizing radiation exposure is crucial. The development of MRU began in the early 2000s, with significant advancements over the past two decades (1-12).

Initially, MRU was primarily used in adult patients, but its application in pediatrics has grown as the technology has improved. The refinement of MRU techniques has allowed for better resolution and faster imaging times, making it more feasible for use in children (13, 14). Imaging the urinary tract in pediatric patients is essential for diagnosing and managing various congenital and acquired conditions. Common indications for imaging include neonatal hydronephrosis, ureteropelvic junction obstruction and megaureter, and congenital anomalies such as duplex kidneys and follow-up of vesicoureteral reflux. Traditional imaging modalities like ultrasound (US), voiding cystourethrography (VCUG), and radionuclide scintigraphy have been used extensively, but each has limitations, particularly in providing comprehensive anatomical and functional information. MRU offers several advantages over traditional imaging techniques. It provides high-resolution images that can delineate complex anatomical structures and assess renal function and urinary tract drainage in a single study (15, 16). Unlike computed tomography (CT) scans and nuclear medicine studies (e.g MAG3 and DMSA scans), MRU does not expose patients to ionizing radiation, making it a safer option for repeated imaging in children. MRU combines the diagnostic capabilities of multiple traditional modalities into a single comprehensive exam. In this article, we describe the basics of how magnetic resonance urography is performed in the pediatric population as well as the common indications and relative performance compared to standard imaging modalities in the context of pediatric hydronephrosis.

TECHNICAL ASPECTS OF MRU

Both 1.5-Tesla (T) and 3T MR scanners may be used in order to perform MRU in pediatric patients. Advantages of 3T MRI include higher signal-to-noise ratio (SNR), which improves the spatial and temporal resolution, critical for detailed anatomical visualization of the urinary tract. This allows for thinner slices and better 3D reconstructions, crucial for evaluating complex anomalies. Higher SNR also improves sensitivity for detecting renal parenchymal and urinary tract abnormalities Furthermore, improved temporal resolution can enhance assessment of renal perfusion and excretion. T2-weighted and other fluid-sensitive sequences benefit also from the higher SNR, which can be advantageous if contrast use is contraindicated. However, artifacts from metal implants, surgical clips, and bowel gas can be worse in a 3T compared to 1.5T, and field signal homogeneity is better at 1.5T, reducing shading artifacts, especially in larger children. Homogeneity of the magnetic field is better at 1.5T, reducing shading artifacts, especially in larger children (17, 18).

A combination of anatomical and functional sequences is used to ensure comprehensive evaluation. Localizer sequences with T2-weighted Half Fourier Single-shot Turbo spin-Echo (HASTE) or SSFSE (Single Shot Fast Spin Echo) provide a reference to guide the placement of imaging planes for the detailed study (19). T2 weighted imaging is a foundation for anatomic imaging, which provides high-contrast images of fluid-filled structures, highlighting the urinary tract. These images allow for visualization of dilated urinary structures (e.g., hydronephrosis), assessment of anatomy in congenital anomalies (e.g., duplex collecting systems, infundibular stenosis), and identification of perirenal fluid collections or cystic lesions. T1 weighted images provided information anatomical structures with a focus on solid organs and tissues, such as the renal parenchyma. Anatomic

imaging also includes diffusion weighted imaging (DWI), which detects renal parenchymal abnormalities, such as acute pyelonephritis, identifies restricted diffusion in tumors or abscesses and helps differentiate between obstructive and non-obstructive hydronephrosis. Sequences targeted at the urinary tract include high resolution 2D and 3D T2-weighted images, which when obtained in a 3D fashion allow multiplanar reformatting and can be used to make a variety of reconstructions to aid in anatomic delineations such as ureteral strictures, ectopic ureteral insertions, and fistulas. (e.g., volume rendered and maximum intensity projection images) (14).

Functional MRU is an advanced imaging modality that analyzes functional parameters to determine whether there is physiologically significant obstruction in a dilated collecting system. It utilizes dynamic contrast-enhanced (DCE) imaging by tracking the passage of gadolinium-based contrast agents through the kidneys and into the collecting system. DCE imaging captures various phases, including the arterial phase (renal artery anatomy), the corticomedullary phase (renal parenchyma), and the excretory phase (contrast transit through the ureters and bladder). This approach provides crucial information for quantifying transit times, time to peak, volumetric and Patlak differential renal functions, estimated glomerular filtration rate, and asymmetry index to determine the severity of obstruction.

Quantitative parameters in functional MRU offer a detailed assessment of renal function and excretion, providing invaluable diagnostic information. One key parameter is renal perfusion, which evaluates blood flow through the kidneys using time-intensity curves derived from dynamic contrast-enhanced imaging. This helps identify perfusion deficits caused by conditions like renal artery stenosis or ischemia. Differential renal function (DRF) is another critical measure, determining the functional contribution of each kidney to overall renal output. It is especially useful in cases involving congenital anomalies, such as duplex kidneys, or in compromised kidneys due to various causes of urinary obstruction.

Transit times are parameters that assess the movement of contrast from the glomeruli to the collecting system, providing insights into urinary flow dynamics. Delays in transit often indicate obstructions or impaired renal function. Excretory dynamics, measured during the post-arterial phase of contrast imaging, help visualize and quantify the excretion of contrast material into the ureters and bladder, distinguishing between obstructive and non-obstructive pathologies. There are three measured transit times. Mean transit time (MTT) is the time required for the gadolinium to transit from renal plasma to the tubular system. Calyceal transit time (CTT) is the time required for the contrast to reach the peripheral calyces. Renal transit time (RTT) is the time it takes for the contrast to reach the proximal ureter below the inferior pole of the kidney.

Quantitative assessments, combined with advanced imaging techniques like diffusion-weighted imaging (DWI), provide a comprehensive understanding of both global and regional renal function. Functional MRU allows precise, radiation-free evaluation of the urinary system, making it a powerful tool for diagnosing a wide range of conditions, from congenital abnormalities to post-surgical complications.

MR urography can be performed on either 1.5T or 3T MRI, and the study is divided into three phases. Before the scan, a patient is encouraged to drink clear liquids until approximately 1 hour prior to the scan. Patients are not allowed to eat any solid food starting six hours prior to imaging. Once the patient arrives at the imaging center, an IV access is established, and normal saline bolus is administered at 20 mL/kg over a period of 30 minutes. After adequate hydration, patient is escorted to the MRI and positioned comfortably on the table. Then, sedation is initialed if the patient is nine years or younger. After sedation, Foley catheter is placed in the bladder and Foley bag positioned on the side of the patient, below the bladder for passive drainage. MR sequences are obtained as summarized in Table-1. It is important to note that IV furosemide is injected into the patient approximately 15 minutes prior to dynamic phase imaging to allow maximum pharmacologic effect on the kidneys. To minimize motion artifact during dynamic imaging, the level of sedation is increased

Table 1 - List of MRI sequences and estimated time for performing MR urography.

MRI Sequences	Est Time (min:sec)
Localizer	0:08
HASTE Sagittal FS	0:16
HASTE Coronal FS	0:15
T2 Axial HR FS Kidneys	5:39
Lasix Given	
T1 FLAIR FS Coronal	4:38
3D T2 Triggered Kidneys/ Ureters	5:00
Increase Sedation	
DWI	2:56
T2 Axial FS Bladder	2:47
Contrast Injection	
3D Dynamic Coronal	10:00
Decrease Sedation	
3D GRE Sagittal	2:50
3D GRE Coronal	2:11
PD Axial FS Kidneys	1:55

several minutes prior to contrast injection. Once the sequences are obtained, data is sent for renal segmentation and analysis at a separate workstation.

Advantages of MRU in pediatric hydronephrosis and comparison to other imaging modalities

Ultrasound is the most widely used imaging modality for evaluating the kidneys and bladder both pre- and postnatally. It offers several advantages, including being non-invasive, free of ionizing radiation, real time imaging, portability, cost effective, and typically performed without sedation. US generally provides sufficient detail to assess renal anatomy and parenchymal changes, such as thinning, altered echogenicity, or cysts, making it the primary tool for identifying and grading hydronephrosis. However, US has limitations in visualizing ureters, particularly when they are non-dilated, and is less effective in imaging the mid-ureter and ureterovesical junction. In cases of significant ureteral dilation anatomical distortion and the limited field of view can make it difficult to fully characterize the urinary tract. Additionally, US does not provide functional information about the kidneys, though future techniques using intravascular contrast agents, such as microbubble contrast, may offer insights into differential perfusion without relying on nuclear medicine or MRI-based contrast agents. Factors like bowel gas, body habitus (e.g., scoliosis, obesity), and patient cooperation can also affect image quality.

Diuretic renal scintigraphy studies still considered the "gold standard" worldwide, offer functional insights into the urinary system depending on the radiopharmaceutical used. Diuretic renal scintigraphy with mercaptoacetyltriglycine (MAG3) evaluates differential renal function and drainage, while dimercaptosuccinic acid (DMSA) scintigraphy assesses renal parenchyma and detects scarring. Diethylenetriaminepentaacetic acid (DTPA) provides information on glomerular filtration-based differential renal function and drainage. Although scintigraphy provides limited anatomical detail, it remains the gold standard for functional assessment. These studies expose patients to ionizing radiation but typically do not require sedation.

CT is occasionally used in pediatric urology, mainly for evaluating renal masses and urinary tract stones. Its limited use is due to the associated ionizing radiation exposure. CT urography, commonly performed in adults, is infrequently used in children because it typically requires multiple image acquisitions (e.g., non-contrast, parenchymal/nephrographic, and ureteral/excretory phases). Techniques like dual-energy CT, which generates virtual non-contrast images, or split-bolus CTU, which combines

nephrographic and excretory phase information in a single acquisition, can reduce the number of scans. While CT can provide a qualitative assessment of renal function across multiple phases, this approach is often impractical in pediatrics due to the associated radiation dose.

MRU stands out as the optimal imaging modality for pediatric hydronephrosis due to its ability to provide comprehensive anatomical and functional information without exposing children to ionizing radiation. Unlike ultrasound, which is highly operator-dependent and limited in functional assessment, MRU offers consistent, high-resolution images that detail both the structure and function of the urinary tract. Compared to VCUG, which is invasive and primarily focused on the bladder and urethra, MRU is non-invasive and provides a complete overview of the entire upper and lower urinary system, including the kidneys and ureters. Additionally, while nuclear scintigraphy has been traditionally used for functional assessment, it lacks the detailed anatomical resolution that MRU provides and exposes patients to radiation. Furthermore, it is the author's opinion that MRU excels in functional assessment by analyzing series of different transit times and differential renal functions compared to nuclear scintigraphy. This makes it the superior choice for evaluating pediatric hydronephrosis, ensuring accurate diagnosis and effective treatment planning.

CLINICAL APPLICATIONS

Pediatric urology often involves complex anatomic variants that traditionally require multiple studies such as ultrasound, VCUG, and scintigraphy, for thorough evaluation. MRU has become increasingly popular for its ability to provide a comprehensive assessment of the urinary tract with corresponding functional data for surgical planning and follow up management (Figures 1 and 2).

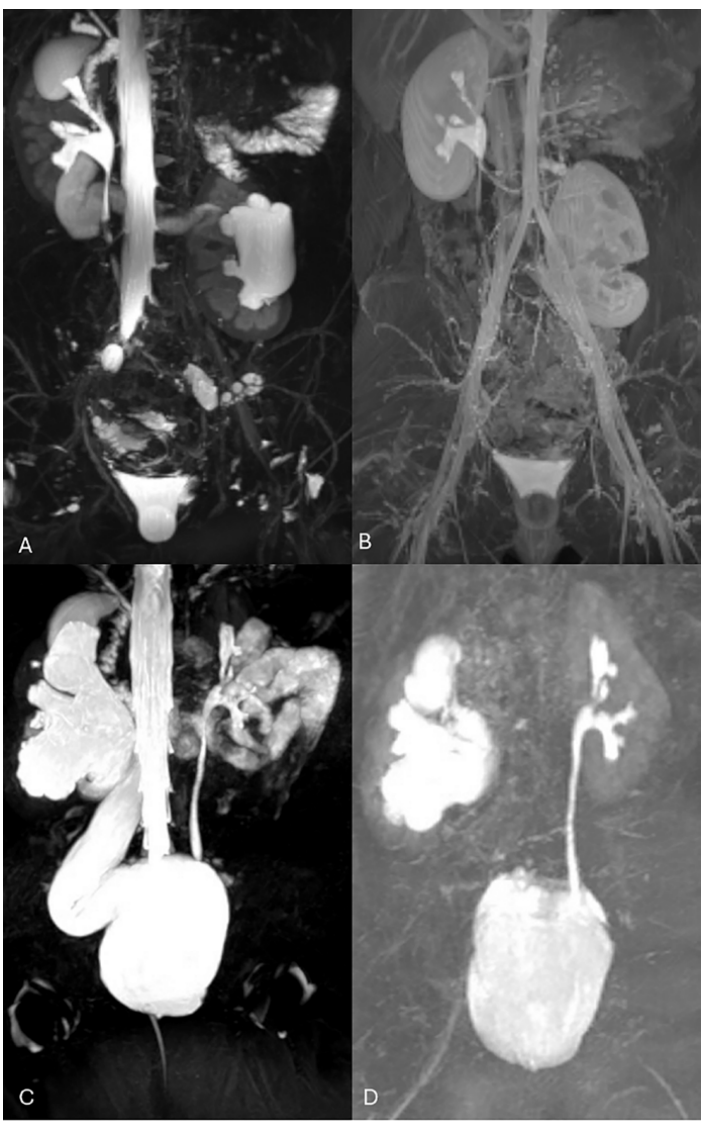
Hydronephrosis

The majority of children with antenatal hydronephrosis have non-obstructive etiologies and pelvicaliectasis decreases over time, without intervention (20). More severe cases of prenatal hydronephrosis have higher chances of urinary tract obstruction such as infundibular stenosis, UPJ obstruction, ureteral stricture, or distal ureter obstruction that may require surgical correction. MRU has proved to be a useful tool to distinguish between non-obstructed patulous renal collecting system from actively obstructed upper urinary tract (21). MRU accurately determines the cause of prenatal hydronephrosis and guides management. It has the potential to replace preoperative multi-modality imaging workup by providing detailed renal pathology information that correlates 100% with surgical findings (22, 23). Severe focal UPJ narrowing, renal parenchymal signal hyperintensity, and hyperintense signal around the kidney or renal collecting system on T2-weighted imaging may be indicative of UPJ obstruction. Post-contrast imaging findings decreased peak signal intensity, prolonged time to peak signal, prolonged contrast transit times, and retention of contrast material in the affected kidney correspond to obstructive pattern (24). MRU is particularly useful for evaluating older children experiencing intermittent flank pain and suspected intermittent hydronephrosis or UPJ obstruction caused by a crossing vessel. These children may have normal ultrasound findings when imaging is performed without fluid stress. While renal scintigraphy can assess kidney function dynamically under fluid stress, MRU offers the added benefit of identifying and visualizing the crossing vessel responsible for the obstruction. Studies have shown that MRU is effective in detecting these vessels in pediatric UPJ obstruction, which can be crucial for planning robot-assisted or laparoscopic surgical interventions (25, 26).

Hydroureter

Ureteric dilatation can be due to a variety of causes in pediatric population, including vesicoureteral reflux, obstructing ureterocele, congenital megaureter, and ectopic insertion. VCUG is the gold standard for diagnosing vesicoureteral reflux, offering excellent visualization of the urethra and reflux grading but involving gonadal exposure to ionizing

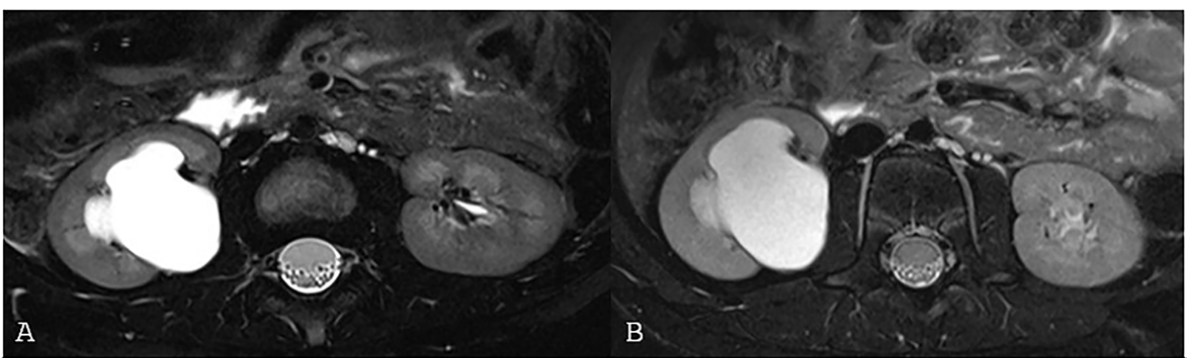
Figure 1 - T1 and T2 sequences provided complimentary information in the evaluation of a ectopic left kidney in a 10-month-old girl (A, B) and of an obstructive right megaureter in a 9-month-old girl (C, D).



A) T2 MIP: left ectopic and malrotated kidney with SFU Grade 3 hydronephrosis, normal right kidney. B) T1 Gd-enhanced MIP: Markedly delayed excretion on the left with asymmetric unit pathologic differential renal function (R 65%/L 35%). C) T2 MIP: Right SFU Grade 4 hydronephrosis and hydroureter, normal right kidney. D) T1 Gd-enhanced MIP: Renal transit time is 2 minutes 9 seconds on the left, which is normal.
Renal transit time is prolonged on the right, which measures greater than 10 minutes

radiation. Introduced in 1992, magnetic resonance voiding cystourethrography (MRVCU) emerged as a potential alternative with the development of near real-time MR fluoroscopy (27). Although technically feasible, it seems unlikely that MRVCU will gain widespread acceptance in pediatric populations due to the limitations including the difficulty of some patients to void in the supine position and incomplete voiding of some infants and young children secondary to sedation (28). MRU also provides value in evaluation for patients with ureteral stricture of ureterovesical junction (UVJ) obstruction by providing high level of anatomic detail necessary for the diagnosis. MRU has been shown to be the most sensitive for

Figure 2 - Axial T2-weighted images through the kidneys show similar dilated right renal collecting system in pre- (A) and post-pyeloplasty (B) kidneys. Functional parameters comparing pre- and post-pyeloplasty show normalization of MTT, CTT, differential renal function (DRF), and unit GFR in the right kidney after pyeloplasty (C).



C	Pre-pyeloplasty	Post-pyeloplasty
MTT (sec)	92.4	50.8
CTT (sec)	211	157
DRF (%)	39	52.2
Patlak GFR	0.21	0.35

detecting ureteral strictures. In one study, children with mid-ureteral strictures underwent a mean of 2.7 imaging studies with less than half (42%) receiving the correct diagnosis prior to MRI, which lead to a definite diagnosis in all cases (29).

MRU is a highly effective tool for detecting ectopic ureters, offering superior anatomic resolution and the ability to visualize the ureter's course and termination in detail (30-33). This is particularly valuable in cases of complex congenital anomalies. MRU provides both anatomical and functional information without exposing patients to ionizing radiation, making it an ideal choice for pediatric evaluations. Using gadolinium-based contrast agents, MRU enhances visualization of the ureters, allowing for clear identification of abnormal trajectories or ectopic insertions. Multiplanar and 3-dimentional reconstruction imaging enables detailed assessment of pelvic and retroperitoneal structures, helping to distinguish ectopic ureters from other abnormalities. Additionally, MRU can identify coexisting anomalies, such as duplex kidney systems and ureteroceles which are often associated with ectopic ureters. These features make MRU an invaluable diagnostic modality, especially when traditional imaging methods provide inconclusive results.

MRU is not without limitations. Protocols are relatively complex, requiring careful dosing and timing of hydration, furosemide, and gadolinium. MRU scans are also longer than its alternatives, which can take up to an hour to complete. Because of this, in young children or patients who cannot remain still, sedation or general anesthesia may be necessary, adding complexity and risk to the procedure. A Foley catheter is required for the study, which may cause discomfort for the patient. Excessive motion will limit or prevent post-processing of data, and achieving adequate hydration is essential for proper functional data. MRU also has decreased spatial resolution compared to CT urography, making it less effective at detecting small structures or abnormalities. Furthermore, MRU is not as reliable in identifying cal-

cifications and urinary stones, which can be critical in diagnosing certain conditions. Post-imaging processing requires separate software, which is technically challenging to operate. Lastly, most cases can be categorized into decompensated or compensated hydronephrosis with anatomic correlation, but there are occasional cases with parameters that do not align with conventional criteria, which suggest disease processes that has not been fully understood to date. Despite these drawbacks, MRU remains a valuable tool due to its ability to provide detailed anatomical images without the use of ionizing radiation.

RECENT ADVANCES

Recent advances in pediatric MRU have significantly improved the diagnosis and management of urinary tract disorders in children. Real-time MRI, while primarily used in orthopedic and cardiac imaging, does have applications in observing the dynamic processes in MRU. Real-time MRI uses advanced imaging sequences like radial FLASH MRI and balanced steady-state free precession (bSSFP). These techniques allow for rapid image capture, often in milliseconds, which is crucial for observing processes in motion. The speed of acquisition minimizes motion artifacts and provides clear images of moving structures, such as the heart or joints, without the need for repeated scans (34). Modern real-time MRI employs iterative reconstruction algorithms that enhance image quality and reduce artifacts. This allows for high-resolution images even with rapid acquisition. Iterative reconstruction algorithms process the acquired data in real time, enhancing image quality by reducing noise and correcting for artifacts, resulting in high-resolution images that are crucial for accurate diagnosis and treatment planning, even when the images are captured quickly (35).

Faster imaging techniques in MRI have significantly enhanced the efficiency and quality of scans (36, 37). Parallel imaging, such as SENSE and GRAPPA, utilize multiple receiver coils to simultaneously capture data from different parts of the body, reducing scan times while improving spatial resolution and signal. Compressed sensing leverages the sparsity of image data to reconstruct images from fewer data points, speeding up acquisition and minimizing motion artifacts. Simultaneous Multi-Slice (SMS) imaging captures multiple slices at once, which is particularly beneficial for functional MRI and diffusion MRI, drastically cutting down scan times. Single-shot acquisition techniques, like echo-planar imaging (EPI), acquire the entire image in one rapid scan, reducing the impact of patient movement. Additionally, AI-based reconstructions enhance image quality by predicting and correcting for artifacts and noise, making MRI more efficient. Advanced pulse sequences, such as fast spin-echo (FSE) and turbo spin-echo (TSE), optimize the timing and order of radiofrequency pulses and gradients, further reducing scan times while maintaining high image quality. These advancements collectively make MRI scans faster, more comfortable for patients, and more effective in diagnosing and monitoring urologic conditions.

CONCLUSIONS

MRU offers one of the most comprehensive assessments of the urinary tract in children, enabling detailed evaluation of the renal parenchyma, collecting systems, ureters, and bladder, while also providing both static and dynamic functional information. This makes MRU a valuable tool for assessing a wide range of pediatric hydronephrosis and congenital urologic abnormalities. Currently, it is generally used as a problem-solving tool when traditional imaging techniques such as US, VCUG, or diuretic renal scintigraphy are not able to provide sufficient information for clinical decision-making. With expanding research and experience MRU will continue to expand its role in evaluating children with genitourinary anomalies.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 51 (3): e20259904, May-June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9904

Management of Adverse Effects in Testosterone Replacement Therapy

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ABSTRACT

Purpose: This narrative review aims to provide the most updated knowledge regarding the treatment of adverse effects secondary to testosterone replacement therapy (TRT), such as gynecomastia, cardiovascular and hematologic risks, prostate health risk, and liver dysfunction risks.

Materials and Methods: An extensive literature review was conducted, incorporating guidelines from the American Urological Association and the Endocrine Society. The studies determined common adverse effects and their most common methods of management.

Results: TRT improves the quality of life, sexual function, and mood in hypogonadal men. Possible adverse effects associated with TRT include increased estrogen levels and gynecomastia, which are usually managed with aromatase inhibitors and tamoxifen. Cardiovascular risks from TRT include hypertension and erythrocytosis, which mandate periodic hematocrit and blood pressure monitoring; therapeutic phlebotomy is indicated if the hematocrit exceeds 52%. No significant concern regarding prostate cancer has been observed in the closely monitored patient. However, TRT should not be administered to individuals with active evidence of untreated prostate cancer, except under rare circumstances such as active surveillance for very low-risk disease. Older oral forms of TRT can affect liver function; therefore, transdermal, newer oral forms and injectables are generally favored in men with a history of liver disease.

Conclusions: Monitoring and management of adverse effects are critical to maximize benefit and minimize the risks of TRT. Ongoing research will further elucidate the safety of TRT while advancing evidence-based practices in managing its associated adverse effects. Effective patient education and counseling are also essential to improve compliance and treatment outcomes.

ARTICLE INFO

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Keywords:
Testosterone; adverse effects [Subheading]; therapy [Subheading]

Submitted for publication:
January 12, 2025

Accepted:
January 20, 2025

Published as Ahead of Print:
January 31, 2025

INTRODUCTION

Hypogonadism, or testosterone deficiency, is a condition that affects approximately 30 million men worldwide, with its prevalence increasing with age (1). Characterized by low serum testosterone levels, associated symptoms of hypogonadism include fatigue, decreased libido, erectile dysfunction, and mood disturbances (2). Signs of testosterone deficiency may also include reduced muscle mass, increased body fat, and diminished bone density. Some underlying illnesses that can exacerbate testosterone deficiency are obesity, metabolic syndrome, and various chronic illnesses (3). Testosterone replacement therapy (TRT) is designed to restore normal testosterone levels, potentially reversing some of these symptoms and improving overall health. In addition to TRT, other treatments aimed at improving testosterone levels are being explored. Varicocele repair, when clinically indicated, has shown potential to increase endogenous testosterone production (4). Additionally, selective estrogen receptor modulators like clomiphene citrate and the use of human chorionic gonadotropin (hCG) have emerged as alternatives, especially for men seeking to preserve fertility while increasing testosterone levels (5, 6). These approaches offer options for tailored management in men with low testosterone, particularly when traditional replacement therapy may not be ideal.

TRT can improve the quality of life, sexual function, and mood in hypogonadal men (7). Administering TRT requires several potential side effects to be considered: the likelihood of increased estrogen levels, gynecomastia, cardiovascular issues, prostate problems, and hematologic changes (8–10). Recent literature contains new information about the safety of TRT and strategies for minimizing adverse effects (11). This narrative review enables an understanding of these factors, allowing for treatment optimization and safety in hypogonadal men receiving TRT. Therefore, complications related to testosterone abuse, as well as changes in male infertility, were not included in this study.

Increased Estrogen Levels and Gynecomastia Management

Gynecomastia has been observed when high levels of estrogen build up in men receiving TRT. Serum estradiol levels above 60 pg/mL may cause gynecomastia(8). Management strategies include the use of aromatase inhibitors such as anastrozole, which effectively reduces estrogen levels when the threshold for serum estradiol is exceeded (7). Dosage adjustment including lower doses of testosterone or even a switch to less aromatizing formulations such as testosterone undecanoate, will minimize estrogenic side effects (2). A wait-and-observe approach may be appropriate in cases of gynecomastia appearing without increased estrogen, as the condition can sometimes resolve spontaneously (9). Symptomatic gynecomastia can be treated with low-dose tamoxifen to alleviate breast tissue enlargement (12). In men with normal estrogen levels who have undergone at least 12 months of observation and experience psychological distress and cosmetic concerns, elective plastic surgery could be considered (12).

Prostate Health

There is some controversy linking TRT with prostate health. Several meta-analyses utilizing contemporary studies have established that carefully monitored TRT has no significant risk for prostate cancer (13). In addition, TRT is contraindicated in patients with a history of untreated prostate cancer or active cancer. Conversely, benign prostatic hyperplasia (BPH) symptoms can be exacerbated with testosterone treatment.

Management strategies include regular monitoring of PSA levels, particularly in older patients or those with any history of prostate issues (3). In most cases, men above 50 years old should be followed up yearly with PSA levels. Younger men with risk factors of prostate cancer should have their PSA checked every 2-4 years (14). Normal PSA levels is usually below 4 ng/mL, though this may be age- dependent; for example, a man between 40-49 can have normal level up to 2.5 ng/mL, while men aged 70 and above may have a higher

acceptable level. Men receiving TRT will have an associated increase of 0.30 ng/mL in PSA levels, with older men experiencing a greater increase of 0.43 ng/mL (15). If PSA levels increase, further investigation is warranted, including a repeat PSA test, a digital rectal exam and possibly imaging studies such as magnetic resonance imaging (MRI) to assess any abnormalities. In cases of TRT in patients who have been treated for prostate cancer, for example, post-radiotherapy or surgery, any rise in PSA level warrants a review of the treatment plan which may include discontinuing TRT and further oncological assessment (14, 16). Counseling regarding possible prostate-related risks associated with the initiation of therapy is imperative (3, 16). The presence of urinary symptoms among patients should be monitored when managing BPH (17, 18). For patients with symptomatic BPH, stopping TRT and definitively treating BPH with surgery may be required if medical management fails.

Cardiovascular and Hematologic Risks

Cardiovascular risks associated with TRT have been well discussed. Some studies indicate that it has been proven to improve lipid profiles as well as endothelial function (19). On the contrary, it is also well known to raise blood pressure and thrombotic risks especially in older men with already pre-existing cardiovascular disease. Erythrocytosis or increased red blood cell mass is one of the common adverse effects of TRT that heighten thrombotic risks. As pointed out by Kohn et al., one of the side effects of TRT is an increase in hematocrit levels and thus this must be carefully monitored (20). Increased hematocrit is associated with a high risk of major adverse cardiovascular events (MACE) particularly if significantly higher from baseline. The hematocrit significantly increases with TRT irrespective of the formulation, with intramuscular testosterone enanthate/cypionate causing the most significant increase of 4.0%. For oral testosterone undecanoate, the increase is roughly 4.3%, but the patch and nasal gel preparations result in much more modest increases. Compared in one of the studies of intranasal versus intramuscular therapies, intramuscular injections significantly increased hematocrit from 42.7% to 46.6%, while there was no significant change with the intranasal gel. Such findings reiterate the variability of hematocrit response with different testosterone formulations and point out the need for monitoring hematologic parameters as a way to prevent cardiovascular risks, most especially in patients with already existing cardiovascular conditions (21, 22).

Management strategies should include referral to a cardiologist and should include regular monitoring of blood pressure and lipid profile in the high-risk group (23). It is also necessary to check the hematocrit regularly, especially in the first year of treatment, every 3-6 months in the beginning and annually thereafter (1).

Ory et al. (24) tried to find the unsafe hematocrit threshold for men receiving TRT and determine whether secondary polycythemia causes an increased risk of cardiovascular complications. They performed a retrospective cohort study from a database of 74 million people including two groups of men with low testosterone who received TRT and subsequently either did or did not develop polycythemia and compared 5,842 men in each group. Polycythemia was defined as a hematocrit above 52%, according to the American Urological Association (AUA) guideline definition. The primary outcome was incidence of MACE and venous thromboembolic events (VTE) in the first year of TRT. The authors found that men on TRT who developed secondary polycythemia had a higher incidence risk of MACE and VET than men who did not develop polycythemia (24). This cutoff can guide our clinical practice, and we can tell patients undergoing TRT that they are at a higher cardiovascular risk if their hematocrit reaches or exceeds 52% during the first year of therapy (25). Therefore, when the hematocrit exceeds these levels, it may be a sign that the patient requires therapeutic phlebotomy to prevent thrombotic complications (11).

Dose adjustment has to be made based on hematocrit; the marked erythrocytosis has to be avoided. El-Khatib et al. (26), indicated that reduction in the dose of testosterone injections coupled with an increase in their frequency of administration should help manage hematocrit and, therefore, reduce the risk of MACE. For instance, splitting a 100 mg dose into two or three smaller doses throughout the week may effectively maintain testosterone levels while minimizing the potential for elevated hematocrit and associated cardiovascular events.

Routine monitoring may also prevent extra cardiovascular risk because of fluid retention (3). Fluid retention may increase blood pressure; hence, patients should be counseled on dietary sodium restriction, monitoring fluid input, and blood pressure monitoring to prevent this complication effectively. It also allows the surveillance of the lipid profile for cardiovascular safety in testosterone-treated patients, since the treatment with testosterone may decrease HDL and probably increase LDL, more conditions that should be closely monitored in order to prevent or minimize the vascular changes resulting from changes in the level of lipids. However, various RCTs and meta-analyses conducted have suggested that routine monitoring of lipid profiles is probably not necessary in all patients. Indeed, a recent study by Calof et al. showed that adverse events from TRT in middle-aged and older men do not support the consistent monitoring of lipids (27). In another systematic review and meta-analysis, Haddad et al. concluded that TT does not result in overall significant changes in cardiovascular risk profiles among this population (28). According to TRAVERSE study, even men with hypogonadism and preexisting or a high risk of cardiovascular disease, TRT was non-inferior to placebo with respect to the incidence of MACE (29). Thus, these findings would suggest that although monitoring may be important, in many instances it may not be required, especially when the total cardiovascular risk is low.

Liver Function

Certain formulations of testosterone, particularly oral routes, carry a risk for hepatic toxicity. Monitoring liver function and regularly testing for liver enzymes is recommended, especially among patients with a history of liver conditions, particularly in men receiving older oral forms of TRT (30). The preferred formulations are transdermal and injectable testosterone due to the lower risk of hepatic toxicity associated with these modes of administration (31). Goldstein et al., 2024 indicate that newer oral formulations, transdermal and injectable testosterone, have a significantly lower risk of hepatic toxicity compared to older oral formulations. The authors indicate that among oral formulations, the newer formulation of oral testosterone undecanoate (Tlando™, Kyzatrex™, and Jatenzo™) are relatively safer regarding liver effects as compared to the older methylated testosterone formulations (Andriol™) (32). The mechanism of absorption plays an important role in this difference. Newer oral preparations, which include testosterone undecanoate, utilize a different route of absorption via the lymphatic system, thereby avoiding major first-pass metabolism of the drug in the liver. Older oral formulations, such as Andriol™, increase liver function toxicity because of first-pass metabolism, exposing the liver to higher concentrations of the drug. Because this pathway minimizes hepatic exposure, liver enzymes are present in low amounts in order to minimize the risk for hepatic toxicity (32). This shift in formulation choice can alleviate the risks associated with liver function, highlighting the importance of selecting an appropriate TRT for each patient.

Acne

Acne is a common consequence of TRT because sebaceous gland activity is increased, which is associated with the androgenic effects of the skin. Topical therapies include the use of retinoids or benzoyl peroxide, that can effectively manage mild to moderate acne. In cases of severe acne, oral antibiotics such as, minocycline, or isotretinoin may be indicated (33). It is also very important that patients are educated on proper skin care to reduce the incidence of acne outbreaks, and referral to the dermatologist should be considered for those with persistent or severe cases.

Sleep Apnea

Obstructive sleep apnea (OSA) issues should be monitored among the patients, particularly when symptoms involve loud snoring or excessive daytime sleepiness (16, 34). OSA must be screened by using the STOP-BANG questionnaire prior to initiating TRT (35). If the screening of the patient comes out positive, then OSA should be appropriately treated. This becomes important because, unless treated, OSA may result in intermittent hypoxia that could lead to increased hematocrit levels as a result of the body adapting to a state of decreased oxygenation. Observation and management of these conditions are important to minimize adverse effects associated with TRT.

Treatment algorithm of complications after TRT is present in Figure 1.

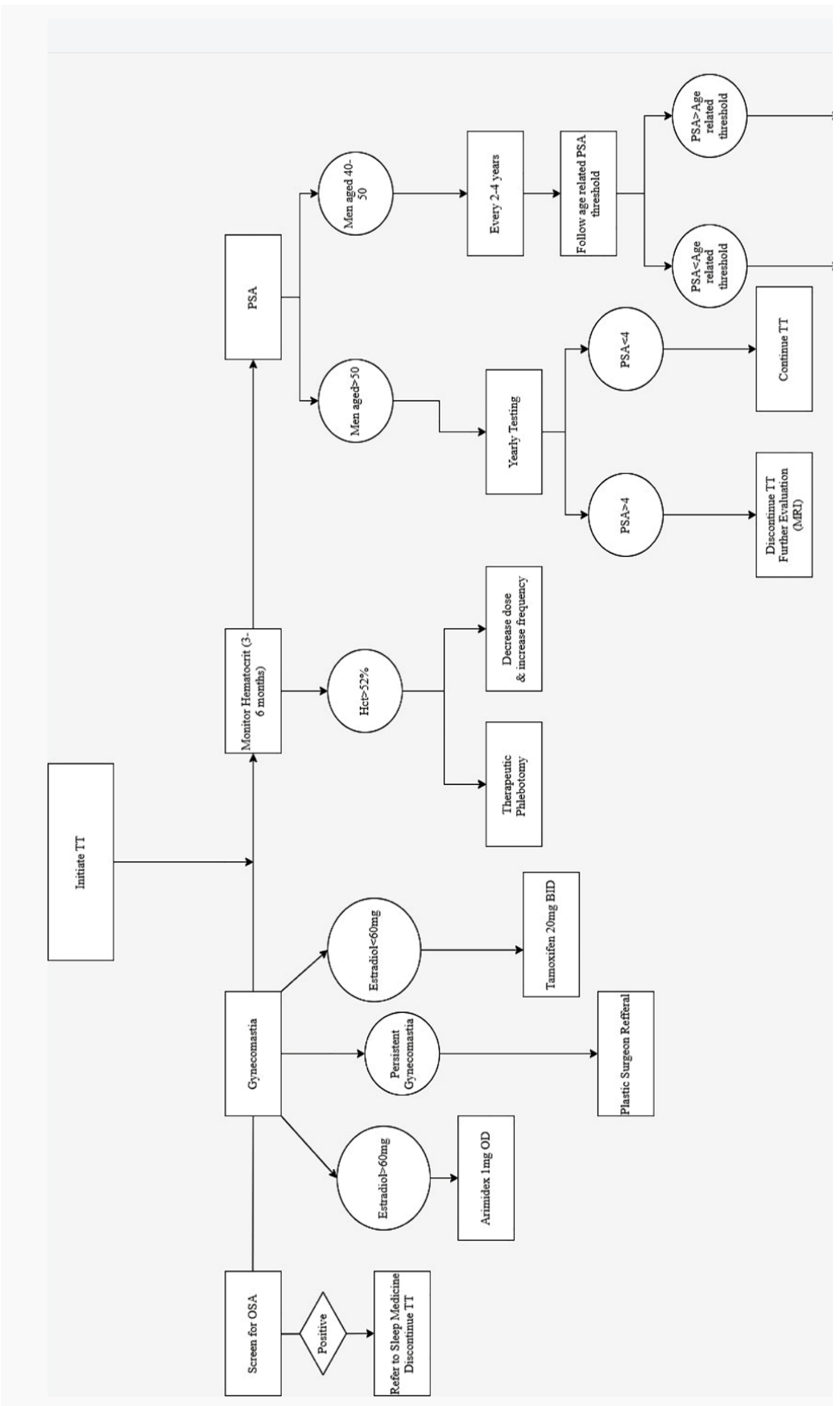

Figure 1 - Treatment algorithm of complications after testosterone replacement therapy.

Patient Education and Informed Consent

Patient education is a vital component of managing adverse effects in TRT. Recent guidelines emphasize the importance of counseling patients on the benefits and risks of TRT (3, 34, 36). Shared decision-making may improve adherence and satisfaction with treatment, allowing patients to make informed choices about their health.

Well-educated patients are more likely to adhere to therapeutic regimens and become more active participants in their care. Effective communication regarding possible adverse effects, monitoring regimens, and lifestyle changes can empower patients and enhance the effectiveness of treatment. Additionally, supporting telemedicine can provide patients with convenient access to healthcare professionals for ongoing education and management. If adverse effects arise, patients should be encouraged to report these issues promptly through telehealth channels, allowing adjustments to their treatment plan.

CONCLUSIONS

TRT is beneficial for patients with testosterone deficiency but monitoring and management of adverse effects are highly relevant to ensure safety and efficacy. Ongoing research will further delineate the safety profile of TRT and evidence-based practices for monitoring and managing adverse effects. With appropriate monitoring protocols, regular follow-ups, and prioritized patient education, healthcare providers can ensure that risks associated with TRT are minimized.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 51 (3): e20259907, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9907

Neurophysiology of Micturition: a Narrative Review on Preventing Mismanagement

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ABSTRACT

Introduction: The insidious interrelation between three key factors underscores the critical need to understand the neural control of the lower urinary tract (LUT): the complexity of its functioning, the epidemiology of conditions that can disrupt it, and the nonspecific presentation of related symptoms. This paper examines the importance of understanding neurophysiology of micturition to prevent mismanagement and reduce unnecessary procedures.
Material and Methods: This review focuses on the neurophysiology of the micturition cycle, the epidemiology of major health conditions that affect it, and the nonspecific nature of lower urinary tract symptoms (LUTS) concerning underlying pathologies. The review was conducted in accordance with the guidelines of the Scale for Assessment of Narrative Review Articles (SANRA). Only articles in English were included, while case reports, editorials, and expert opinion pieces were excluded.
Results: The ability of the LUT to store and release urine requires precise coordination and is mediated by a complex network involving the brain, spinal cord, peripheral ganglia, and nerves. Epidemiological data reveal a growing global burden of diseases that impact LUT functioning (LUTF). Moreover, the nonspecific nature of LUTS often leads to diagnostic challenges, and inappropriate treatment strategies.
Conclusion: The interplay between the complexity of LUTF, the widespread prevalence of conditions that can disrupt it, and the nonspecific nature of related symptoms frequently complicate urological decision-making. Overlooking associated neurological factors can result in suboptimal outcomes, diminished quality of life, and serious adverse consequences. A systematic approach is crucial to minimizing the risk of misdiagnosis and mismanagement, especially when considering invasive interventions.

ARTICLE INFO

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Keywords:
Urinary Bladder; Neurophysiology; Lower Urinary Tract Symptoms

Submitted for publication: January 20, 2025

Accepted after revision: February 15, 2025

Published as Ahead of Print: February 22, 2025

INTRODUCTION

The insidious interrelation between three key factors underscores the critical need to understand the neural control of the LUT. These factors include the intricate nature of LUTF, the myriad ways in which multiple epidemiologically significant health conditions can disrupt it, and the nonspecific presentation of LUTS, which do not always correspond to the underlying dysfunction. This understanding can serve as a powerful tool for safeguarding patients from iatrogenic harm and protecting physicians from the consequences of inappropriate management.

Comprehending the neurophysiology of micturition is inherently challenging, as patients' complaints and long-term complications often fail to correlate directly (1). As Turner-Warwick aptly observed, highlighting the complex and sometimes misleading nature of bladder dysfunction, one must not trust the bladder as a witness (2). This complexity emphasizes the importance of proper bladder management in neurologic patients. For instance, in individuals with spinal cord injury (SCI), advances in understanding LUTF have led to significant improvements in care, reducing mortality rates, and diminishing the historical predominance of urinary complications as primary causes of death during early rehabilitation and follow-up (3–5).

The objective of this paper is to evaluate the importance of understanding the neurophysiology of the micturition cycle, with a focus on its role in preventing mismanagement and reducing unnecessary procedures in cases involving neurological diseases.

MATERIAL AND METHODS

This narrative review focuses on the neurophysiology of the micturition cycle, the epidemiology of key health conditions that affect it, and the specificity of LUTS in relation to underlying pathologies.

The study was conducted in accordance with the SANRA guidelines (6). Relevant literature was retrieved from the PubMed database using Medical Subject Heading (MeSH) terms, with no restrictions on the year of publication.

For the neurophysiology of micturition, we used the search terms "Neurophysiology," "Urination," "Urinary Bladder, Neurogenic," and "Lower Urinary Tract Symptoms."

To gather epidemiological data on "Stroke," "Dementia," "Diabetes Mellitus," "Spinal Cord Injuries," "Intervertebral Disc Disease," "Intervertebral Disc Displacement," "Spinal Stenosis" we used the respective terms combined with "Global Disease Burden," "Epidemiology" and "worldwide" (not a MeSH term).

To assess the specificity of LUTS, the search included terms such as "Urinary Bladder, Underactive," "Urinary Bladder Neck Obstruction," "Urinary Bladder, Overactive," and the terms "Lower Urinary Tract Symptoms," and "overlap" (not a MeSH term).

Only articles written in English were included, while case reports, editorials, and expert opinion pieces were excluded. Only studies deemed significantly relevant to the review's objectives were selected. In addition to the studies retrieved through the systematic search, we also included other literature regarded as fundamental references in this field.

RESULTS

NEURAL CONTROL

Lower Urinary Tract Functions

The LUT exhibits unique behavior that is highly dependent on central nervous system (CNS), setting it apart from other visceral systems—such as the gastrointestinal and cardiovascular systems—which can maintain basic function even in the absence of extrinsic neural input (7). LUT also has a switch-like or phasic pattern of activity unlike the tonic patterns characteristic of autonomic pathways regulating cardiovascular organs. Furthermore, micturition is also under voluntary control and depends on learned behavior whereas many other visceral functions are regulated involuntarily (8).

The ability of the LUT to store and release urine depends heavily on CNS pathways, requiring precise coordination between the bladder body, bladder neck, urethra, and urinary sphincter. This coordination is mediated by a complex network involving the brain, spinal cord, peripheral ganglia,

and nerves. In addition to the nervous system, bladder musculature, urethra, and pelvic floor, structures such as the urothelium, suburothelial and intradetrusorial interstitial cells, and bladder stroma also play significant roles in the micturition cycle (9). These modulators, however, fall outside the scope of this article.

During the micturition cycle, LUT manages urine in two distinct phases: filling and emptying (8). Understanding LUTF is facilitated by correlating its dynamic processes with parameters assessed during urodynamic studies (UDS):

Filling Phase - The bladder must accommodate adequate urine volumes without significant increases in pressure, transmit appropriate sensations (neither diminished nor exaggerated), and there must be no involuntary contractions or urinary leakage.

Emptying Phase - The bladder must generate contractions of sufficient strength and duration. Simultaneously, the urinary sphincter must relax, without anatomical obstruction or significant postvoid residual urine (10).

The Voiding Reflex - An essential component of LUTF is the spinobulbospinal voiding reflex, also known as the bladder-to-bladder reflex (11) or simply the voiding reflex (Figure-1A). This reflex serves as a central switch between the two micturition cycle phases (12, 13).

During filling, bladder stretch receptors detect increases in bladder volume and transmit sensory signals via the pelvic and hypogastric nerves to the spinal cord. These signals are then relayed to the periaqueductal gray (PAG) in the brainstem.

Once PAG activity reaches a critical threshold—that can be called micturition threshold (7)—it excites the pontine micturition center (PMC), also referred to as the M-region or Barrington's nucleus (14, 15). The PMC is believed to send descending signals to the sacral spinal cord, which, through spinal circuitry, induces urethral sphincter relaxation and, some seconds later (8), bladder contraction (13). This transition, from a completely off mode (storage) to a maximum on mode (voiding), is intrinsic to the very switchlike activity pattern of the pons (16).

In the absence of higher brain control, PAG activation alone can autonomously excite the PMC and trigger the reflex (7, 8, 13). However, under normal circumstances, higher brain regions exert significant control over this process. These regulations will be later described in the Working Model.

Filling Phase and Storage Control

Sensory signals from the bladder body are conveyed to the spinal cord via the pelvic and hypogastric nerves (17), while sensory input from the bladder neck and the urethra is transmitted through the pudendal and hypogastric nerves. The afferent components of these nerves include myelinated (Aδ) and unmyelinated (C) fibers (8).

Afferent Nerve Activity - The Aδ-fibers respond to passive distension and active contraction (17) providing critical information about bladder filling. Conversely, C-fibers, which are considered 'silent' under physiological conditions, are primarily activated by noxious stimuli such as chemical irritation (18) or cooling (19).

Sympathetic Regulation - During bladder filling, relaxation of the detrusor muscle is mediated by sympathetic innervation. Norepinephrine activates β3-adrenergic receptors in the bladder wall, promoting relaxation, and α1-adrenergic receptors in the bladder neck and proximal urethra, inducing smooth muscle contraction to enhance closure (20, 21). Sympathetic reflex activity during the filling phase can be triggered by vesical afferent signals in the pelvic nerves and helps the bladder accommodate larger volumes. This can be called the vesicosympathetic reflex, which is inhibited upon reaching the micturition threshold (22).

External Urethral Sphincter Guarding Reflex - The pudendal nerve maintains tonic contraction of the external urethral sphincter (EUS), contributing to continence. This tonic activity increases with bladder filling and is mediated, in part, by the guarding reflex, a spinal reflex pathway activated by low-level bladder afferent input, reinforcing EUS contraction (7).

Additionally, contraction of the EUS induces afferent signaling via the pudendal nerve, which, in

turn, activates inhibitory interneurons within the spinal cord. These interneurons suppress reflex bladder activity (23) by inhibiting preganglionic neurons and interneurons in the micturition reflex pathway (24). The bladder-to-EUS-to-bladder reflex, along with the vesicosympathetic reflex (7), functions as a negative feedback mechanism to promote urinary continence.

Pontine Regulation - During the storage phase, the PMC is typically inactive. However, in another region in the pons, the pontine continence center or pontine urine storage center (PUSC), also called the L-region (8), is active. PUSC, first described neuroanatomically and later by its response to electrical stimulation, not only excites the EUS but also inhibits reflex bladder activity, increasing bladder capacity and the inhibiting the bladder excitatory effect of PMC stimulation (11), probably mediated by stimulation of the urethral sphincter mechanism (25).

Transition to Voiding - As bladder volume increases, afferent signals from stretch receptors intensify, informing the brainstem and cortex about bladder fullness. Micturition in the heathy adult occurs only when afferent signals inform enough urine in the bladder, the mechanical requirement, but other criteria must meet, such as safety and social appropriateness (26).

The Working Model

Advances in understanding the neural control of micturition, coupled with functional brain imaging studies, have led to the development of a working model based on a framework of circuits that organize brain activity (Figure-1B) (26). While many animal studies have contributed to these advances, a key distinction must be made between micturition in animals and humans: the intention to void. Unlike humans, the intention to void in animals cannot be precisely evaluated, and their micturition models may, in fact, reflect urgency incontinence rather than voluntary control. It is important to note that the working model is a speculative (7) simplification, and its circuits may not function independently.

The working model assumes that three circuits are responsible for the higher control of micturition and ensuring that in a normal adult, micturition occurs only when consciously desired, emotionally safe, and socially appropriate (7).

Circuit one, especially the medial prefrontal cortex (mPFC), assesses social appropriateness. mPFC can either delay or advance voiding by modulating the excitation along the pathway from the mPFC to PAG (26).

Circuit two comprises the anterior insula, the dorsal anterior cingulate cortex (dACC), and the supplementary motor area. The insula (previously assigned to circuit 1) is considered the seat of interoception - the perception of sensations from inside the body (13, 27) and registers the degree of bladder filling, while dACC can create the associated emotion—desire to void or urgency (26). Activation of the supplementary motor area, usually coactivated with dACC, is associated with contraction of the pelvic floor and striated sphincter muscles.

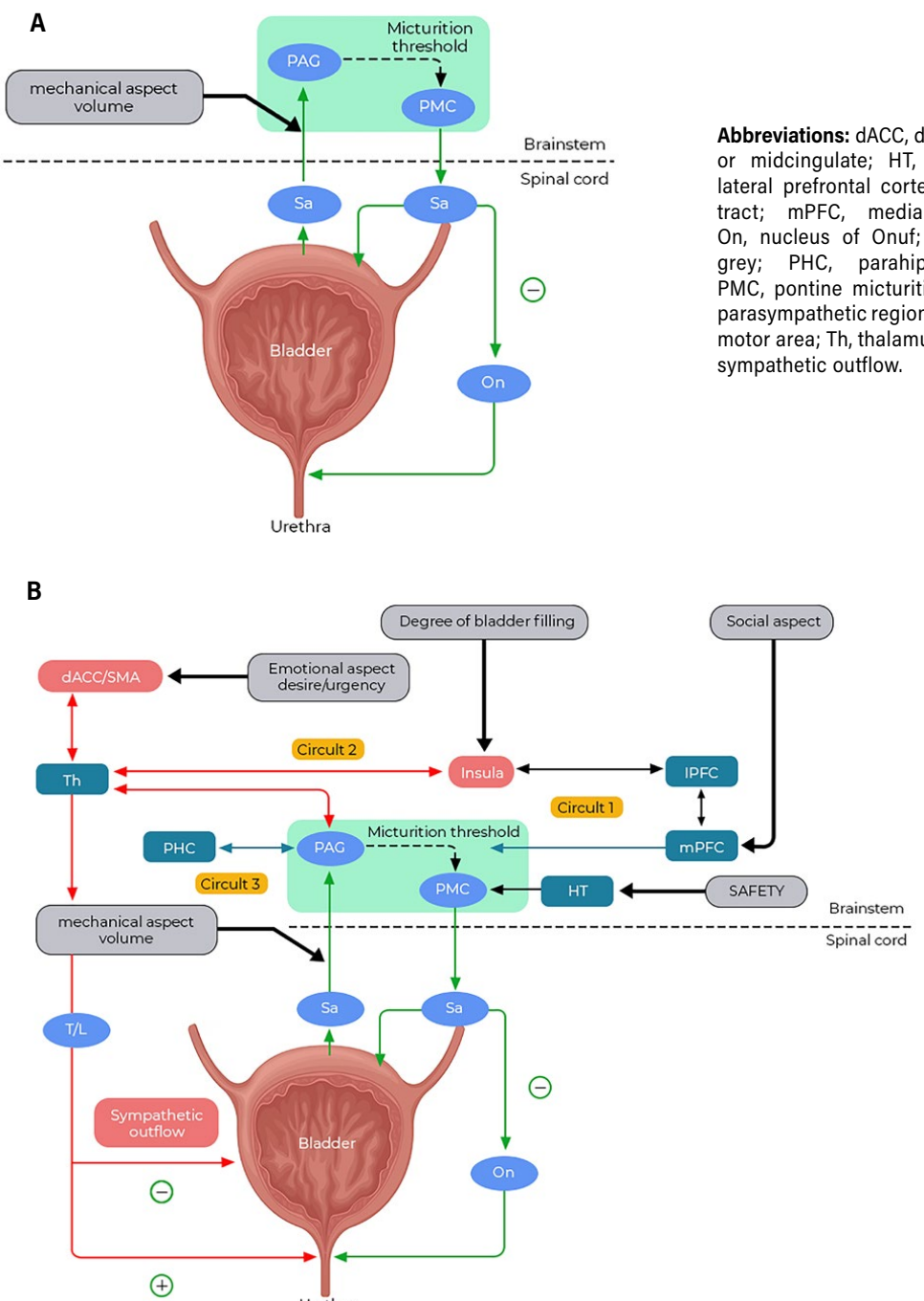
Circuit three encompasses the parahippocampal complex, which may serve as the route through which the PAG monitors bladder behavior and exchanges bladder-related signals with the rest of the brain. This circuit also includes the PAG itself and likely the hypothalamus, which plays a role in ensuring safety for voiding—such as protection from predators—an adaptive mechanism developed through evolution (7, 26).

The PAG activity is modulated by incoming sensory information and communicates with these higher cortical areas. These regions allow conscious decision-making and social appropriateness for voiding. If voiding is deemed acceptable, the PAG activates the PMC.

The PAG plays a pivotal role in voiding, in addition to maintaining homeostasis by regulating systems such as cardiovascular and bowel function, pain, and emotion. Acting as a central hub, the PAG distributes incoming spinal afferent signals to various forebrain regions, generating sensations or motor outputs to prevent incontinence.

In this context, the PAG and the PMC are often considered to function together as the "switch" of the micturition cycle. However, this switch re-

Figure 1 – Comparison of the relative simplicity of the voiding reflex pathways and the complexity of higher brain circuit control of the LUT. A) Schematic representation of the voiding reflex, in which the PAG alone can activate the PMC and trigger micturition. B) Higher brain circuits involved in LUT control, with a summary of their respective functions. In circuits one and three, deactivation of the mPFC and parahippocampal regions tends to suppress voiding at the PAG. The hypothalamus, which may be part of circuit three, sends a 'safe' or 'unsafe' signal to the pontine micturition center. In circuit two, activation of the insula and dACC/SMA generates a strong desire to void or urgency, along with sympathetic motor output to the LUT.



Abbreviations: dACC, dorsal anterior cingulate or midcingulate; HT, hypothalamus; lPFC, lateral prefrontal cortex; LUT, lower urinary tract; mPFC, medial prefrontal cortex; On, nucleus of Onuf; PAG, periaqueductal grey; PHC, parahippocampal complex; PMC, pontine micturition center; Sa, sacral parasympathetic region; SMA, supplementary motor area; Th, thalamus; T/L, thoracolumbar sympathetic outflow.

quires modulation, which is thought to be primarily exerted by the forebrain—particularly the medial prefrontal cortex (mPFC). In humans, the mPFC is the site where conscious and voluntary control over voiding is exercised (13), making it the likely seat of executive control (26).

Voiding Phase

Once afference signaling has reached micturition threshold in PAG and forebrain modulation favors voiding so that the switch can be done, PMC is then activated, and urine can be eliminated.

Voiding involves parasympathetic activation, trough the pelvic nerve which stimulates detrusor muscle contraction, sympathetic Inhibition, trough the hypogastric nerve that reduces bladder outlet resistance, and somatic relaxation, through the pudendal nerve that reduces external urethral sphincter tone. The synchronized contraction of the detrusor and relaxation of the outlet ensures efficient voiding. Interruptions in this coordination can result in incomplete emptying or incontinence.

Parasympathetic excitation to the bladder is done via acetylcholine (Ach) release, acting on postjunctional muscarinic receptors. In the human bladder, the messenger RNA for all five muscarinic receptor subtypes have been demonstrated (28), with a predominance of M2 and M3 receptors. M3 receptors are believed to be the most important for detrusor contraction (29). When activated, M3 receptors triggers intracellular Ca2+ release; whereas M2 receptors inhibits adenylate cyclase, that contributes to bladder contractions by suppressing adrenergic inhibitory mechanisms which are mediated by β adrenergic receptors and stimulation of adenylate cyclase (30).

Parasympathetic signals can also induce a non-cholinergic detrusor contraction mediated by the released of ATP. ATP excites the detrusor acting on P2X purinergic receptors (30). This route is not important in a healthy adult, but can be involved in some pathological conditions like bladder outlet obstruction, overactive bladder, and interstitial cystitis/bladder pain syndrome (31).

In urethra smooth muscle there is parasympathetic nitric oxide induced relaxation (32) and cessation of adrenergic sympathetic and somatic excitatory inputs to the urethra.

External Urethral Sphincter - During the storage phase, increased tonic activity of the EUS is maintained through the spinal guarding reflex and stimulation from the PUSC. However, during micturition, bladder afferent signaling—which contributes to EUS stimulation—is suppressed, resulting in the cessation of the guarding reflex. Additionally, stimulation of the PMC and activation of bulbospinal pathways inhibit EUS motor neurons, leading to sphincter relaxation (33).

Modulation on spinal and supraspinal level

In addition to the complex modulatory systems at the autonomic ganglia level, numerous neurotransmitters play key roles in modulating the micturition reflex at both the spinal and supraspinal levels. Many of these neurotransmitters can exert excitatory or inhibitory effects, depending primarily on the receptors they activate. It is important to note that most research on neurotransmitters at these levels has been conducted in animal models.

Glutamate - Glutamate is considered the principal excitatory neurotransmitter in the micturition reflex pathway, influencing both excitatory and inhibitory regulation of micturition in the central nervous system (13). Other transmitter systems, such as noradrenergic, dopaminergic, and GABAergic, modulate glutamatergic transmission (34).

On the descending pathway from the PMC, glutamate activates N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionotropic receptors, exerting excitatory effects (35). Conversely, activation of metabotropic receptors produces inhibitory effects (36). This inhibitory stimulus on the descending limb of the micturition reflex is also believed to involve the pathway to the EUS (37).

Notably, serotonin and noradrenaline terminals in Onuf's nucleus release glutamate, which induces contraction of the urethral rhabdosphincter. Duloxetine, a norepinephrine and serotonin reup-

take inhibitor, enhances urethral rhabdosphincter activity and increases urethral pressures, making it a potential treatment option for stress urinary incontinence (SUI) (38).

At the supraspinal level, glutamate predominantly exerts excitatory effects and is considered essential for voiding function (39).

Noradrenaline - The noradrenergic system modulates the micturition reflex by acting as an excitatory input in the efferent limb and an inhibitory input in the afferent limb. The lumbar sympathetic outflow is regulated by α1-excitatory and α2-inhibitory mechanisms (7).

Evidence suggests that α2-adrenoceptor-mediated inhibition and α1-adrenoceptor-mediated tonic facilitation also influence sphincter function, with α2-adrenoceptor-mediated inhibition being the dominant adrenergic modulator of the pudendal nerve reflex (40).

Serotonin – Serotonin (5-HT) pathways modulate both the afferent and efferent limbs of the micturition reflex.

Activation of serotonergic neurons on 5-HT receptors in the spinal cord inhibits reflex bladder contractions and sacral efferent pathway firing to the bladder in animal models (41). Descending serotonergic pathways tonically depress the afferent limb of the micturition reflex through 5-HT2 and/or 5-HT3 receptors, enhancing urine storage by facilitating sphincter reflexes in cats and rats (7).

The role of 5-HT1 receptors varies across species, with 5-HT1A receptor agonists increasing bladder capacity in cats (42) but facilitating bladder activity in rats (43).

GABA and Glycine - GABA and glycine act as inhibitory neurotransmitters at both spinal and supraspinal levels, increasing bladder capacity, raising the volume threshold for initiating micturition, and reducing voiding pressures in animal studies (7). A GABAergic inhibitory mechanism in the PAG is known to tonically regulate the bladder volume set-point for initiating micturition (44).

Acetylcholine - Muscarinic acetylcholine receptors inhibit the micturition reflex in the spinal cord, whereas in the brain, they can exert both inhibitory and facilitatory effects (45).

Nicotinic receptor activation has inhibitory effects on the micturition reflex in the brain but excitatory effects in the spinal cord, enhancing the reflex in rats (46).

Dopamine – At the suprapontine level, dopamine plays dual roles: acting on D1-like receptors, it inhibits reflex bladder contractions in cats; acting on D2-like receptors, it facilitates micturition in rats, cats, and monkeys (7).

Opioids - Opioid peptides inhibit reflex pathways at both spinal and supraspinal levels, increasing bladder capacity and providing modulatory effects on the micturition reflex (7).

EPIDEMIOLOGY OF CONDITIONS AFFECTING LUT FUNCTION

The importance of understanding how LUT functions is underscored by epidemiological data showing the growing global impact of diseases that interfere with it. These trends are primarily driven by population aging and growth, but also increases in age-standardized prevalence rates.

Below, we present some of the most common conditions that impact LUTF, categorized as suprapontine, infrapontine-suprasacral, and sacral or more distal conditions.

Stroke - According to the Global Burden of Disease (GBD) 2021 study, the age-standardized prevalence of stroke in 2021 was 1,099.31 per 100,000 persons (47). The GBD 2019 study reported an 85% increase in the absolute number of stroke cases from 1990 to 2019, despite a 6% decline in age-standardized prevalence rates during this period (48). This disparity reflects demographic shifts, as population growth and aging contribute to the rising overall burden (48, 49).

Dementia - GBD 2019 data revealed significant increases in the global burden of Alzheimer's disease and other dementias between 1990 and 2019, with incidence and prevalence rising by 147.95% and 160.84%, respectively. The age-standardized rates of incidence, prevalence, death, and disability-adjusted

life-years have also increased. Women consistently exhibited higher rates, although the rate of increase was more pronounced in men (50).

In high-income countries, the crude prevalence of dementia increased by 119% between 1990 and 2017, despite a 5% decline in global age-standardized incidence rates during the same period. This pattern again suggests that while the risk per individual may be decreasing, the absolute number of cases is rising due to population growth and aging (51). For instance, in Norway, the age-standardized incidence of dementia decreased by 5.4% from 1990 to 2019, while the absolute number of cases rose by 35% (52).

Spinal cord injury - The global prevalence of SCI was estimated at 20.6 million individuals in 2019, representing an 85% increase since 1990 (53, 54). However, age-standardized prevalence increased modestly by 5.8% during the same period (53)

The trend is corroborated by other studies, that demonstrate broad regional variations in prevalence rates and a general increase over recent decades (55, 56). These changes are attributed to demographic factors such as population growth and aging, which contribute to a higher number of individuals living with SCI (56, 57).

Despite the rise in absolute numbers, the age-standardized incidence rate of SCI has remained stable, indicating that the prevalence increase reflects demographic changes rather than higher rates of new cases (54, 58). The burden of SCI remains higher in males and older adults, with falls and road injuries being the leading causes (53, 57).

Diabetes - The worldwide prevalence of diabetes has risen significantly in recent decades. According to the 2021 GBD study, approximately 529 million people were living with diabetes globally in 2021, with an age-standardized prevalence of 6.1%. Projections suggest this number will exceed 1.31 billion by 2050 (Figure-2), with prevalence rates surpassing 10% in regions such as North Africa, the Middle East, and Latin America (59).

Another pooled analysis of 1108 population-representative studies estimated that in 2022, around 828 million adults had diabetes, revealing a substantial increase from 1990 (60). The age-standardized prevalence of diabetes has risen in many countries, particularly in low- and middle-income regions such as South and Southeast Asia, Middle East, and Latin America (60). This trend is largely driven by increases in type 2 diabetes, which is closely associated with rising obesity rates and other lifestyle factors (59, 60).

Diabetes is strongly associated with voiding dysfunction, particularly in patients with polyneuropathy. Early studies reported that 75-100% of patients with documented peripheral neuropathy had underactive bladder (61). A subsequent study using urodynamic evaluations found detrusor underactivity (defined as a Bladder Contractility Index < 100) in 78,8% of diabetic male patients presenting with LUTS (62).

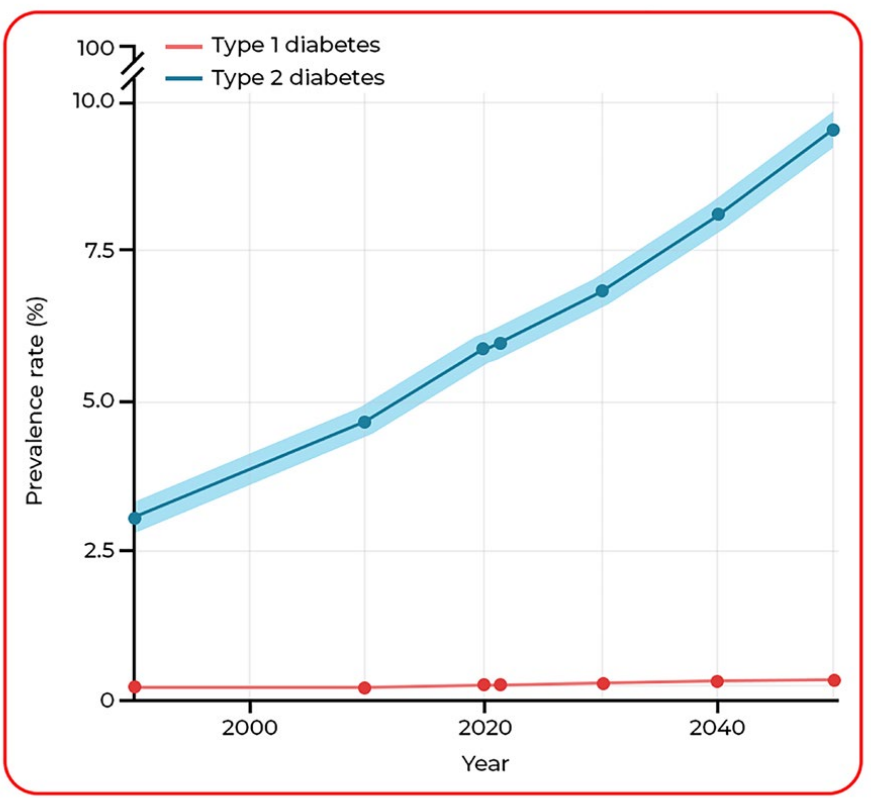
Lumbar Spine Conditions - The prevalence of lumbar spine degenerative disease, lumbar disc herniation, and lumbar canal stenosis varies globally and is influenced by factors such as age, gender, and diagnostic criteria.

A Medicare-based study reported overall prevalence of diagnosed spinal degenerative disease of approximately 27.3%, with numbers increasing with age. The study highlights that degenerative findings are common, and the prevalence is likely underestimated due to undiagnosed asymptomatic cases (63).

A study based on magnetic resonance imaging findings reported a prevalence of lumbar disc herniation of 55.1% among individuals with low back pain, with or without lower limb symptoms. The prevalence was higher in those with accompanying lower limb symptoms (82.1%) compared to those with only low back pain (51.6%). The numbers tend to initially increase with age and then decrease in older age groups, with the L4/L5 and L5/S1 segments being most affected (64)

The prevalence of lumbar spinal stenosis in the general population is estimated to be approximately 11% based on clinical diagnoses, with higher rates observed in older adults. It increases with age and affects approximately 103 million people worldwide. Prevalence rates based on radiological diagnoses vary, ranging from 11% in asymptomatic populations to 38% in the general population (65, 66).

Figure 2 - Global age-standardized prevalence of type 1 and type 2 diabetes from 1990 to 2050, including projections. The shaded area represents the 95% uncertainty intervals. The worldwide rise in diabetes prevalence is particularly striking. Between 1990 and 2021, the global age-standardized prevalence of diabetes increased by 90.5%, from 3.2% to 6.1%. Projections indicate a further 59.7% increase between 2021 and 2050, reaching 9.8%, with an estimated 1.31 billion people living with diabetes by 2050. This growth is primarily driven by type 2 diabetes, which is expected to rise by 61.2%, from 5.9% in 2021 to 9.5% in 2050.



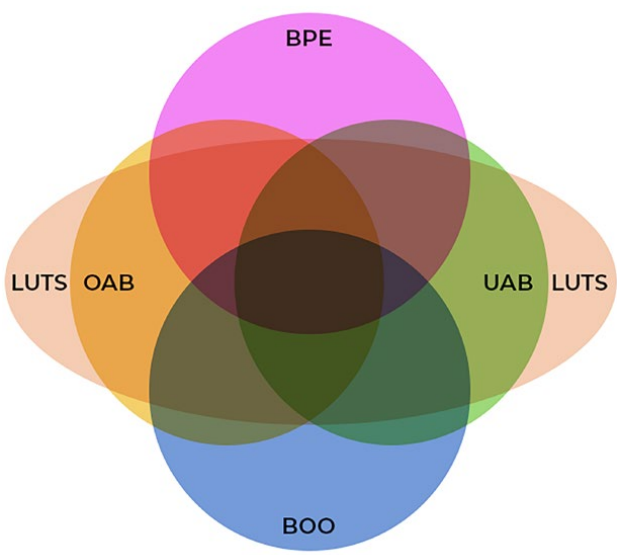
Overall, there is a trend of increasing prevalence of these conditions, largely driven by an aging population and improved diagnostic capabilities. However, the estimates should be interpreted with caution due to potential biases in the studies and variations in diagnostic criteria.

DISCREPANCY BETWEEN SYMPTOMS AND DYSFUNCTION

It is well established that LUTS do not always correlate with the underlying dysfunction, often leading to misdiagnosis and inappropriate management. The discrepancy between symptoms and urodynamic findings has been extensively documented across a variety of conditions affecting LUTF in both male and female patients, spanning different age groups. This dissociation is observed in clinical syndromes such as bladder outlet obstruction (BOO), overactive bladder (OAB), and underactive bladder (UAB) (67–76). Moreover, these dysfunctions often coexist or are associated with other entities, such as pelvic organ prolapse, further complicating accurate diagnosis (Figure-3).

The diagnostic challenge is particularly pronounced in cases of UAB, where patients typically

Figure 3 - Schematic representation of the overlap between LUTS in the male population. Abbreviations: BPE, benign prostate enlargement; BOO, bladder outlet obstruction; OAB, overactive bladder; UAB, underactive bladder; LUTS, lower urinary tract symptoms.



present with a combination of both storage and voiding symptoms (77–79).

Nevertheless, the role of LUTF investigation in SUI has been a subject of ongoing debate. A landmark randomized clinical trial (RCT) concluded that "preoperative office evaluation alone is non-inferior to evaluation with UDS in terms of outcomes at one year" and deemed UDS "not justified" in this context (80). Two smaller RCTs reached similar conclusions (81, 82), prompting revisions to influential guidelines (83, 84). Notably, among lower urinary tract conditions, SUI exhibits the highest concordance between clinical complaints and urodynamic findings surpassing conditions such as OAB/urgency urinary incontinence/ detrusor overactivity, voiding dysfunction, and positive post-void residuals (74).

It is essential to recognize, however, that only 22.3% to 39.5% of women presenting with SUI meet the VALUE trial criteria for "uncomplicated" SUI prior to surgery (85, 86). Voiding dysfunction is identified via urodynamic evaluation in approximately 25.6% of patients (86) with higher prevalence in the "complicated" group (32,4%) compared to the "uncomplicated" group (14,7%) (85). Furthermore, urodynamic findings result in the cancellation or modification of planned interventions in nearly 20% of cases (87).

Although not typically classified as neurogenic conditions, loss of bladder capacity and compliance due to radiation or tuberculosis is often overlooked and must be considered in this discussion. These conditions, which, result from direct structural changes in bladder wall, produce symptoms and urodynamic patterns and that overlap with neurogenic bladder dysfunction.

These findings unequivocally demonstrate the complexity of LUT dysfunctions and the potential discrepancies between clinical symptoms and urodynamic findings. Accurate diagnosis is crucial not only to avoid unnecessary surgeries but also to optimize treatment outcomes.

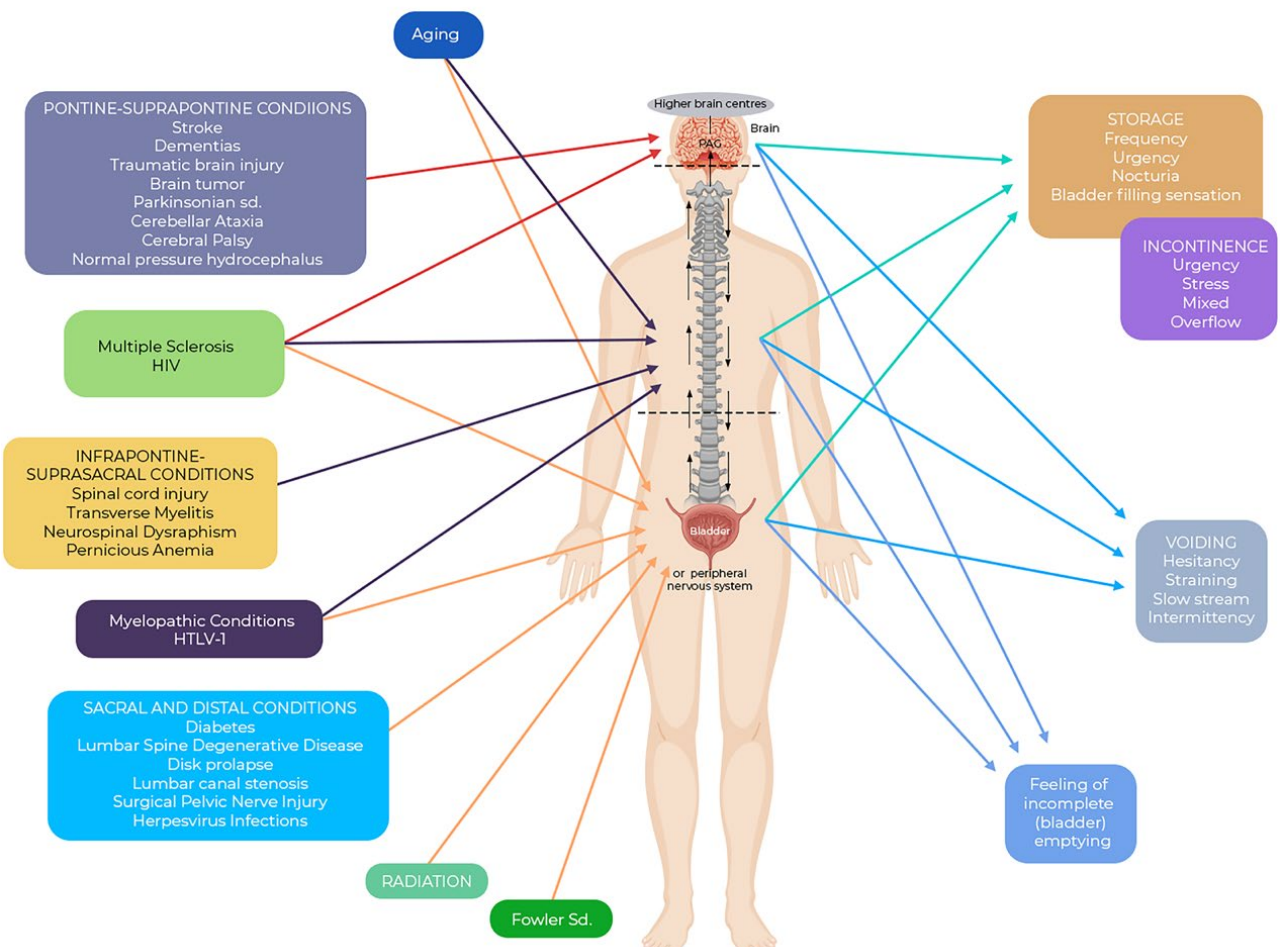
AVOIDING MISMANAGING

Managing a patient presenting with LUTS who may have a non-urological condition affecting LUTF requires a nuanced understanding of underlying pathophysiological mechanisms, particularly when the condition has not yet been clearly diagnosed (Figure-4).

Patients with undiagnosed or overlooked neurological conditions often do not report key medical histories—such as prior spinal surgery or neurodegenerative diseases—due to a lack of awareness of their potential connection to urinary dysfunction. Furthermore, physicians managing the primary condition may not fully understand its implications for the lower urinary tract. In some cases, the underlying condition affecting LUTF remains undiagnosed, further complicating patient management.

Gender-based diagnostic biases can also impede accurate evaluation. While atypical presen-

Figure 4 - The interplay between three factors: medical conditions affecting LUTF (left), the complexity of neural control of micturition (center), and the non-specificity of LUTS (right), can pose significant diagnostic challenges, increasing the risk of misdiagnosis and inappropriate management. While certain scenarios present with typical clinical patterns (e.g., BOO due to prostatic enlargement often causing voiding symptoms), exceptions exist. For instance, urinary incontinence may result from UAB rather than OAB or stress incontinence, underscoring the need for comprehensive evaluation.



Abbreviations: LUTF, lower urinary tract function; LUTS, lower urinary tract symptoms; BOO, bladder outlet obstruction; OAB, overactive bladder; UAB, underactive bladder.

tations in women, such as BOO, may result in further investigation more readily, symptoms in males are frequently attributed to prostatic pathology, potentially leading to unnecessary interventions. For instance, performing transurethral resection of the prostate in a patient with a non-contractile bladder is unlikely to improve quality of life. Similarly, treating overflow incontinence caused by a low-sensitivity bladder with a mid-urethral sling in a female patient may exacerbate symptoms rather than resolve them.

Certain conditions, such as hydronephrosis resulting from voiding dysfunction or low-capacity, low-compliance bladders, secondary to radiation or tuberculosis, require careful evaluation. Upper tract dilation may also occur in the case of an underactive bladder, such as following extensive pelvic surgery.

Mismanagement in these scenarios can have severe consequences. For example, in a patient with an underactive bladder following extensive pelvic surgery, placing a nephrostomy tube may be detrimental and a simple urethral catheter could suffice.

CONCLUSION

Caring for patients with neurological conditions affecting LUTF presents significant challenges for urologists. The interplay between three key factors - the complexity of LUTF, the widespread prevalence of conditions that can disrupt it, and the nonspecific nature of related symptoms - frequently complicates clinical decision-making, particularly in complex or atypical cases. Overlooking associated neurological factors can lead to suboptimal outcomes, diminished quality of life, and, in severe cases, serious adverse consequences.

While this discussion has highlighted several prevalent conditions, numerous other disorders impacting LUTF also warrant attention and should not be overlooked. Therefore, it is essential for urologists to consistently consider differential diagnoses beyond more common conditions such as benign prostatic hyperplasia or SUI. Adopting a comprehensive, systematic, and patient-centered approach can significantly reduce the risk of misdiagnosis and mismanagement, especially when invasive interventions are being considered.

ABREVIATIONS

Ach = acetylcholine
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BOO = bladder outlet obstruction
dACC = dorsal anterior cingulate cortex
EUS = external urethral sphincter
GBD = Global Burden of Disease
LUT = lower urinary tract
LUTF = lower urinary tract functioning
LUTS = lower urinary tract symptoms
mPFC = medial prefrontal cortex
NMDA = N-methyl-D-aspartate
OAB = overactive bladder
PAG = periaqueductal gray
PMC = pontine micturition center
PUSC = pontine urine storage center
RCT = randomized clinical trial
RNA = ribonucleic acid
SANRA = Scale for Assessment of Narrative Review Articles
SCI = spinal cord injury
CNS = central nervous system
SUI = stress urinary incontinence
UAB = underactive bladder
UDS = urodynamic studies

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 51 (3): e20240509, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0509

Predictive Value of Multiparametric Magnetic Resonance Imaging (T2-weighted Imaging and Apparent Diffusion Coefficient) for Pathological Grading of Prostate Cancer: a Meta-Analysis

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ABSTRACT

Objective: This meta-analysis aimed to evaluate the predictive value of multiparametric magnetic resonance imaging (mpMRI), specifically T2-weighted imaging (T2WI) and apparent diffusion coefficient (ADC) maps, in the pathological grading of prostate cancer.

Methods: A comprehensive literature search was conducted across multiple databases, including PubMed, the China National Knowledge Infrastructure dataset, Web of Science, Springer Link and Cochrane Library. Studies evaluating the use of mpMRI for prostate cancer grading were included. The quality of the included studies was assessed using the risk of bias tool. Meta-analyses were performed to calculate pooled areas under the curve (AUC) and prostate cancer detection rates.

Results: Seven studies met the inclusion criteria, comprising 843 patients in the experimental group and 962 in the control group. The meta-analysis revealed a significant improvement in diagnostic performance with mpMRI, with a pooled mean difference in AUC of 0.10 (95% confidence interval [CI]: 0.04–0.16, p = 0.002) favouring the mpMRI group. The odds ratio for prostate cancer detection was 2.60 (95% CI: 1.57–4.29, p = 0.0002), indicating a higher detection rate with mpMRI compared with standard techniques. Substantial heterogeneity was observed among the studies (I^2 = 73% for AUC and 66% for detection rate).

Conclusion: This meta-analysis demonstrates that mpMRI, particularly T2WI and ADC imaging, has a significant predictive value in the pathological grading of prostate cancer. The technique shows improved diagnostic accuracy and higher cancer detection rates compared with conventional methods. However, the substantial heterogeneity among studies suggests that standardisation of mpMRI protocols and interpretation criteria is needed.

ARTICLE INFO

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Keywords:
Prostatic Neoplasms; Multiparametric Magnetic Resonance Imaging; Meta-Analysis [Publication Type]

Submitted for publication: January 07, 2025

Accepted after revision: February 10, 2025

Published as Ahead of Print: February 10, 2025

INTRODUCTION

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, with significant implications for public health (1). The accurate diagnosis and grading of prostate cancer are crucial for determining appropriate treatment strategies and predicting patient outcomes. Traditionally, prostate-specific antigen (PSA) testing and systematic transrectal ultrasound (TRUS)-guided biopsies have been the standard approach for prostate cancer detection and grading. However, these methods have limitations, including overdiagnosis of clinically insignificant cancers and undersampling of significant tumours (2).

In recent years, multiparametric magnetic resonance imaging (mpMRI) has emerged as a promising tool in the diagnostic armamentarium for prostate cancer. Multiparametric magnetic resonance imaging (MRI) combines anatomical T1-weighted and T2-weighted imaging (T2WI) with functional techniques, such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging (3). Among these, T2WI provides excellent soft-tissue contrast and anatomical detail, while apparent diffusion coefficient (ADC) maps derived from DWI offer insights into tissue cellularity and tumour aggressiveness (4).

The potential of mpMRI to improve prostate cancer detection and characterisation has led to its increasing adoption in clinical practice. The Prostate Imaging Reporting and Data System (PI-RADS) has been developed to standardise the acquisition, interpretation and reporting of prostate mpMRI (5). However, the precise role of mpMRI in predicting the pathological grade of prostate cancer remains a subject of ongoing research and debate.

Several studies have investigated the correlation between mpMRI parameters, particularly T2WI and ADC values, and prostate cancer Gleason scores (6, 7). These studies suggest that mpMRI can provide valuable information for distinguishing between low- and high-grade prostate cancers. However, the results have been heterogeneous, and the overall predictive value of mpMRI for pathological grading remains unclear.

Multiparametric MRI, specifically T2WI and ADC maps, has significant predictive value in the pathological grading of prostate cancer, offering improved diagnostic accuracy and higher cancer detection rates compared with conventional diagnostic methods. This meta-analysis aims to evaluate comprehensively the predictive value of mpMRI, specifically focusing on T2WI and ADC imaging, in the pathological grading of prostate cancer. By synthesising data from multiple studies, we seek to provide a more robust assessment of the diagnostic performance of mpMRI and its potential role in clinical decision-making for prostate cancer management.

METHODS

Search strategy and study selection

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, the China National Knowledge Infrastructure (CNKI), Web of Science, Springer Link and Cochrane Library. The search strategy employed a combination of Medical Subject Headings terms and key words related to magnetic resonance imaging and prostate cancer. The specific search terms included variations of 'Magnetic Resonance Imaging', 'NMR Imaging', 'Zeugmatography', 'fMRI', 'Functional Magnetic Resonance Imaging', 'MRI Scans', 'Spin Echo Imaging' and 'Magnetic Resonance Image' for the imaging modality. These were combined with terms related to prostate cancer, including 'Neoplasms, Prostatic', 'Prostate Cancer' and 'Cancer of Prostate'. This study has been registered at inplasy.com, registration number is INPLASY202520044.

The initial database search identified a total of 214 records: 16 from PubMed, 107 from CNKI, 17 from Web of Science, 8 from Springer Link and 66 from Cochrane Library. After removing duplicates, 107 unique records remained for screening.

Inclusion and exclusion criteria

This systematic review employed specific inclusion and exclusion criteria to ensure the relevance and quality of the included studies. Eligible studies

evaluated the use of mpMRI (including T2WI and ADC) for prostate cancer detection or grading, included a comparison group, reported outcomes in terms of areas under the curve (AUC), sensitivity, specificity or prostate cancer detection rates, involved human subjects and were published in English or Chinese. Studies were excluded if they were case reports, reviews or conference abstracts, focused solely on other imaging modalities or MRI sequences, lacked a clear comparison group or provided insufficient data for quantitative analysis.

Study selection process

The study selection process followed a systematic approach. Initially, 89 records were excluded based on title screening. The remaining 18 records underwent abstract review, resulting in the exclusion of 10 more studies. A full-text assessment was performed on 8 articles, of which 1 was excluded due to non-synthesisable results. Ultimately, 7 studies were included in the qualitative and quantitative synthesis.

Data extraction

Data extraction was performed by two independent reviewers using a standardised form. The extracted information encompassed key details, such as author names and publication year, MRI parameters used, sample sizes for both intervention and control groups, age range of participants, outcome measures and study design. This comprehensive data extraction process allowed for a thorough analysis of the included studies and facilitated the synthesis of results across different research efforts in the field of multiparametric MRI for prostate cancer detection and grading.

Quality assessment

The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. This tool evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Each domain was categorised as low risk, unclear risk or high risk of bias.

Statistical analysis

Meta-analyses were performed using Review Manager 5.3 software. For continuous outcomes (AUC), the mean difference with 95% confidence interval (CI) was calculated. For dichotomous outcomes (prostate cancer detection rates), odds ratios (ORs) with 95% CI were computed.

The inverse variance method with random-effects models was used to account for potential heterogeneity among studies. Heterogeneity was assessed using the I^2 statistic, with I^2 values of 25%, 50% and 75% considered as low, moderate and high heterogeneity, respectively. Forest plots were generated to represent the results of the meta-analyses visually. Funnel plots were created to assess potential publication bias. All statistical tests were two-sided, with a p-value of <0.05 considered statistically significant.

RESULTS

Study characteristics

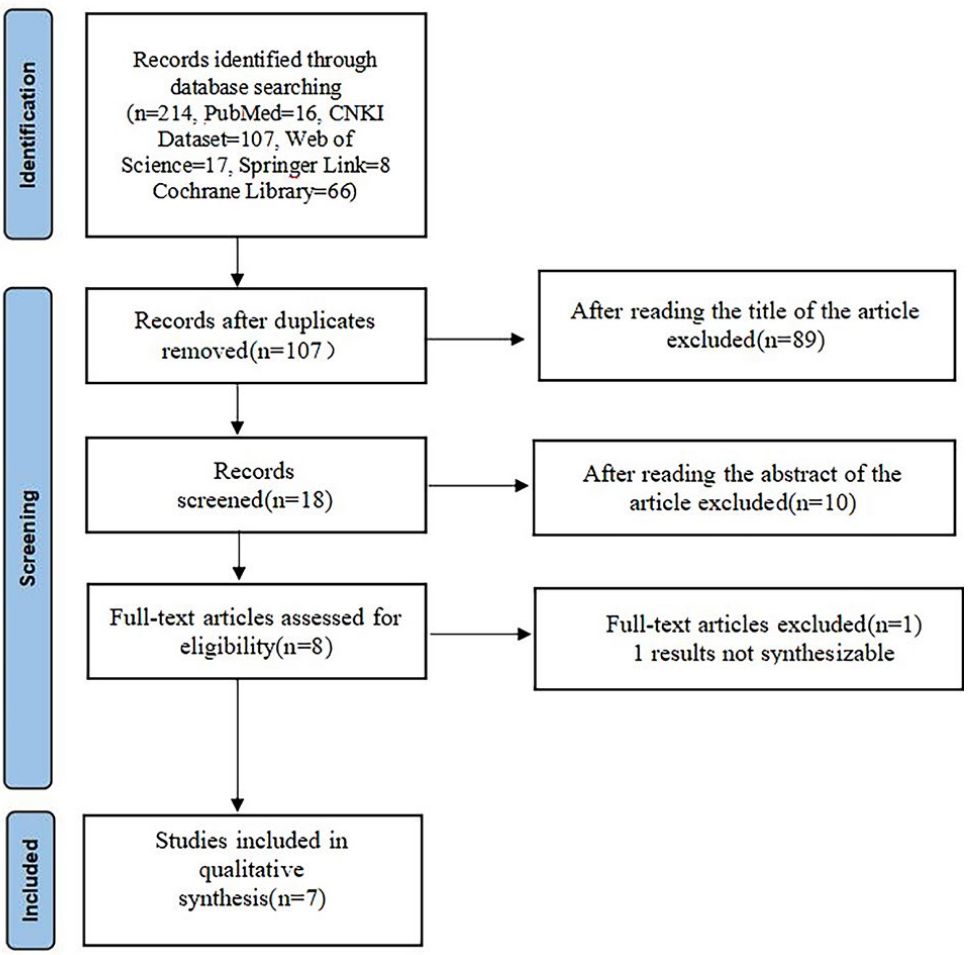
The systematic review process resulted in the inclusion of seven studies (8-14) for qualitative and quantitative synthesis. These studies, published between 2007 and 2024, collectively involved 843 patients in the experimental group (mpMRI) and 962 patients in the control group (Figure-1).

The basic characteristics of the included studies are summarised in Table-1. The included studies utilised various MRI parameters, with all studies incorporating T2WI and ADC maps. Some studies also included additional parameters, such as DCE imaging and DWI. The age range of participants across studies was 26–91 years, with most studies focusing on men in their 60s and 70s.

Quality assessment

The risk of bias assessment for the included studies, as presented in Figure-2, reveals a moderate to high overall quality, though with some areas of

Figure 1 - The flow chart of literature screening.



concern. Random sequence generation was generally well-handled, with approximately 60% of studies judged to have a low risk of bias, while the remaining 40% had an unclear risk. Allocation concealment was less clearly reported, with only 30% of studies demonstrating a low risk of bias and 70% having an unclear risk. Blinding of participants and personnel was adequately addressed in 75% of studies, showing a low risk of bias, while 25% were unclear. The blinding of outcome assessment was evenly split, with half of the studies having a low risk and half having an unclear risk. Notably, all studies (100%) were assessed as having a low risk of bias regarding incomplete outcome data, indicating strong reporting in this domain. Selective reporting was a concern in 60% of studies with an unclear risk, while 40% demonstrated a low risk. Last, other potential sources of bias were largely unclear, with 70% of studies having an unclear risk and only 30% judged to have a low risk. These findings highlight areas where future research could improve methodological clarity and reporting, particularly in allocation concealment, selective reporting and addressing other potential sources of bias.

Diagnostic accuracy

The meta-analysis of the AUC included five studies with a total of 484 patients in the experimental group and 409 in the control group. The forest plot (Figure-3A) demonstrates a significant improvement in diagnostic performance with mpMRI. The pooled

Table 1 - The summarized basic characteristics of included studies.

Author (year)	MRI	Number	Invention condition	Age	Outcome index	Research type	Reference
		invention/ control					
Zhang, et al. 2024	T2WI, DWI, ADC	106/105	MRI	-	AUC	Controlled trial	(8)
Salami, et al. 2017	T2WI, DWI, ADC	202/110	Mp-MRI	59-72	AUC	Controlled trial	(9)
Morgan, et al. 2007	T2WI, DWI	27/27	DW-MRI	-	Sensitivity and specificity for tumor identification, AUC	Controlled trial	(10)
Wu, et al. 2019	K_{trans} K_{ep}, ADC	17/22	Mp-MRI	60-79	AUC	Controlled trial	(11)
Kasivisvanathan, et al. 2018	T2WI	252/248	MRI	-	Sensitivity and specificity for tumor	Controlled trial	(12)
Wang, et al. 2015	DWI, MPS	132/345	Mp-MRI	26-91	PI-RADS score, AUC, accuracy	Controlled trial	(13)
Porpiglia, et al. 2017	ADC, DWI	107/105	Mp-MRI	-	AUC, accuracy	Controlled trial	(14)

MP-MRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and DataSystem; AUC = areas under the curve; ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; T2WI = T2-weighted imaging; MPS = Multiphasic Screening

mean difference in AUC was 0.10 (95% CI: 0.04–0.16) favouring the mpMRI group. This result was statistically significant (Z = 3.16, p = 0.002). However, substantial heterogeneity was observed among the studies (I^2 = 73%), indicating considerable variability in the reported AUC values across different studies.

Prostate cancer detection rate

Four studies reported on the rate of prostate cancer detection, involving a total of 588 patients in the experimental group and 490 in the control group. The forest plot (Figure-3B) shows that mpMRI significantly improved the detection rate of prostate cancer. The pooled OR was 2.60 (95% CI: 1.57–4.29) in favour of mpMRI. This result was highly statistically significant (Z = 3.73, p = 0.0002).

Similar to the AUC analysis, substantial heterogeneity was observed among these studies (I^2 = 66%), suggesting variability in the detection rates across different study populations and settings.

Publication bias

Funnel plots for both the AUC (Figure-4A) and prostate cancer detection rate (Figure-4B) analyses were generated to assess potential publication bias. Although the limited number of included studies makes it challenging to draw definitive conclusions about publication bias, the funnel plots do not show clear evidence of asymmetry, suggesting that significant publication bias is unlikely.

Figure 2 - Risk of bias graph. A: Review authors' judgements about each risk of bias item presented as percentages across all included studies. B: Review authors' judgements about each risk of bias item for each included study.

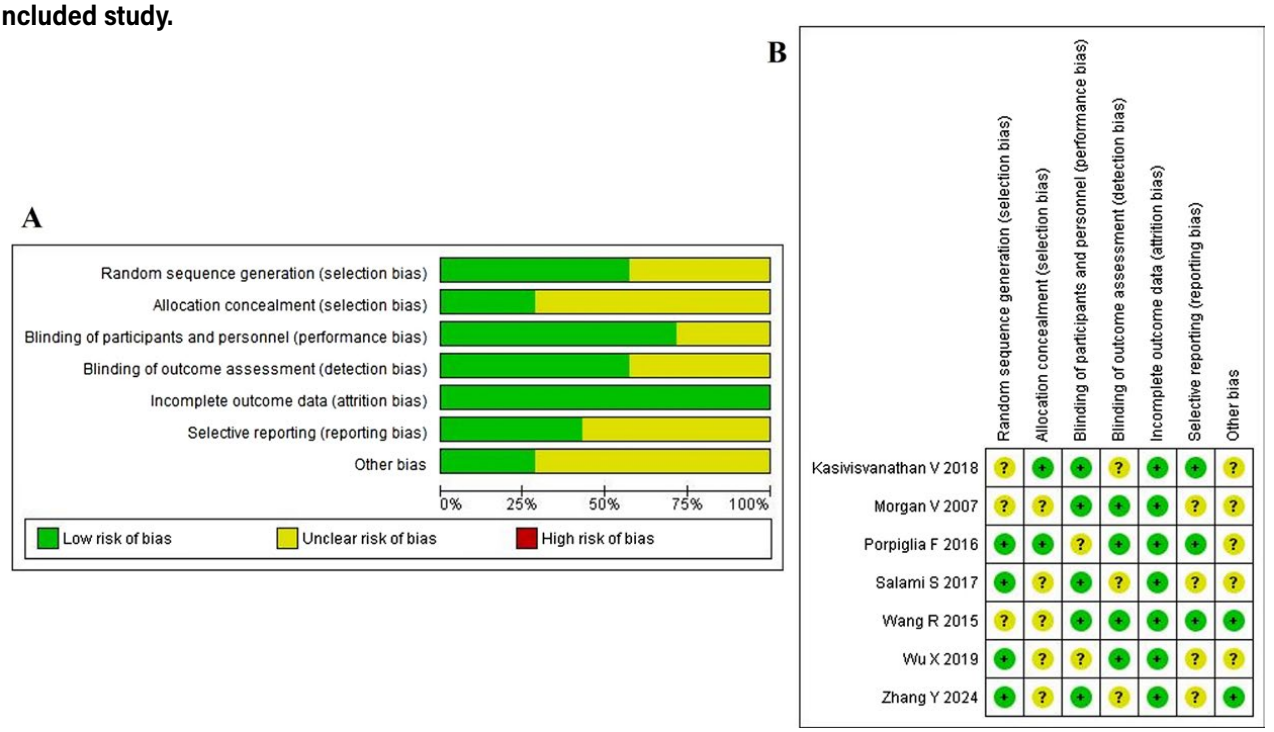


Figure 3 - Diagnostic accuracy and prostate cancer detection rate. A) Forest map of area under the curve (AUC). B) Forest map of the rate of prostate cancer detection.

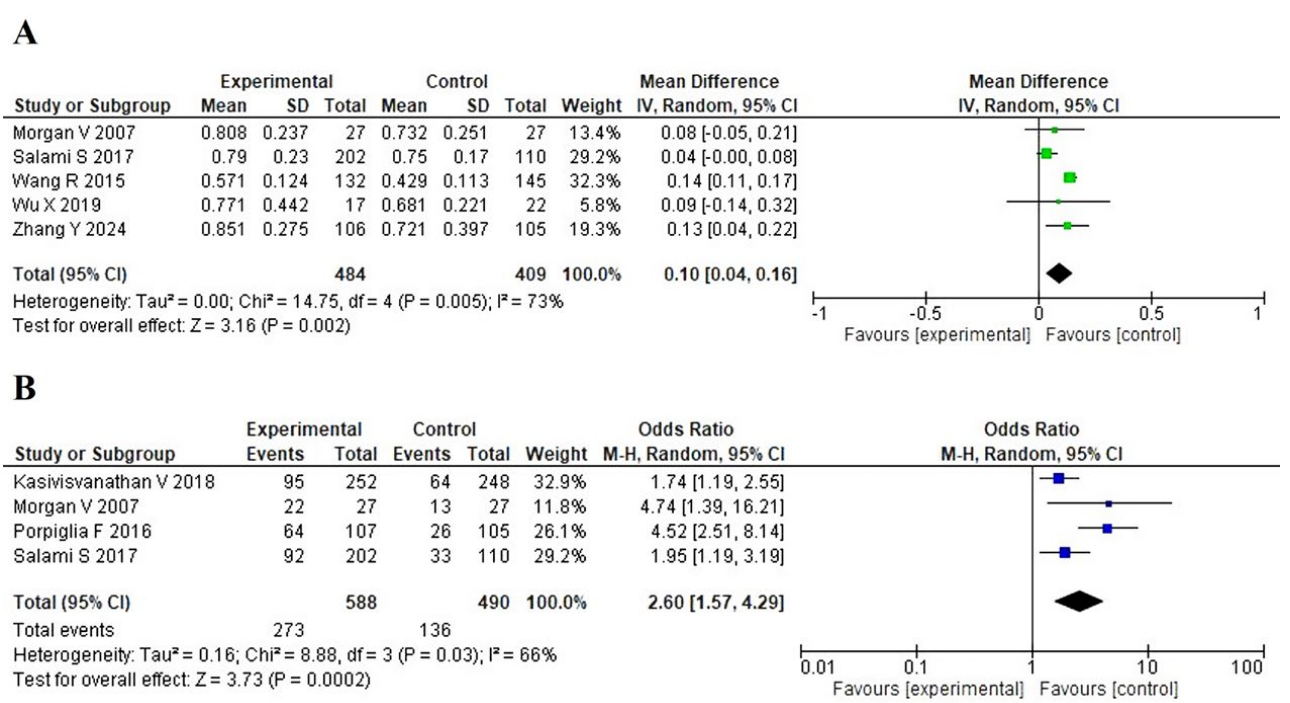
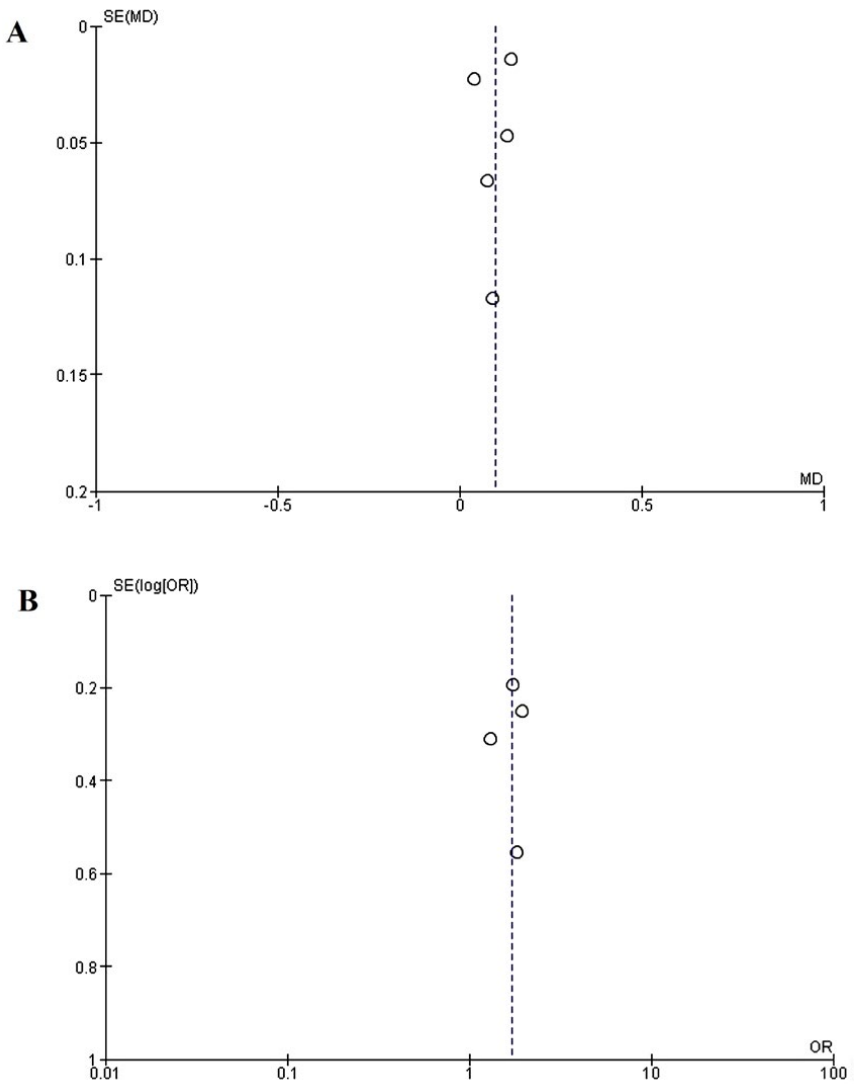


Figure 4 - Publication Bias. A) Funnel map of area under the curve (AUC). B) Funnel map of the rate of prostate cancer detection.



DISCUSSION

This meta-analysis provides a comprehensive evaluation of the predictive value of mpMRI, specifically focusing on T2WI and ADC maps, in the pathological grading of prostate cancer. The results demonstrate significant improvements in both diagnostic accuracy and prostate cancer detection rates when using mpMRI compared with conventional diagnostic methods.

For the diagnostic accuracy, the pooled analysis of AUC values revealed a mean difference of 0.10 (95% CI: 0.04–0.16) favouring mpMRI. This finding suggests that mpMRI offers superior diagnostic performance in distinguishing different grades of prostate cancer. The improved accuracy can be attributed to the combination of anatomical information from T2WI and functional data from ADC maps, which together provide a more comprehensive assessment of prostate tissue characteristics (15).

The enhanced diagnostic accuracy of mpMRI has important clinical implications. It may allow for more precise targeting of biopsies, potentially re-

ducing the number of unnecessary procedures and improving the detection of clinically significant cancers. Furthermore, accurate grading is crucial for treatment planning, as it influences decisions regarding active surveillance, focal therapy or radical treatment options (16).

Our meta-analysis demonstrated that mpMRI significantly improved the detection rate of prostate cancer, with a pooled OR of 2.60 (95% CI: 1.57–4.29). This finding aligns with previous studies suggesting that mpMRI can detect prostate cancers that may be missed by conventional systematic biopsies (17). The improved detection rate is especially important for identifying clinically significant cancers while potentially reducing overdiagnosis of indolent tumours.

The higher detection rate with mpMRI may be explained by its ability to visualise suspicious areas within the prostate that can be targeted for biopsy. This targeted approach contrasts with the systematic sampling used in conventional TRUS-guided biopsies, which may miss cancers in areas not routinely sampled (18).

Despite the promising results, it is important to note the substantial heterogeneity observed among the included studies (I^2 = 73% for AUC and 66% for detection rate). This heterogeneity may be attributed to several factors. Variability in MRI protocols is a key consideration; while all studies included T2WI and ADC, some incorporated additional sequences, such as DCE imaging, which may influence diagnostic performance (19). Differences in study populations also contribute to this heterogeneity, as the age ranges and risk profiles of participants varied across studies, potentially affecting the prevalence and characteristics of detected cancers (20). Furthermore, variations in reference standards, particularly in the methods used for pathological confirmation and grading, may have differed between studies, introducing potential bias (21).

The level of interpreter experience is another crucial factor. The expertise in reading prostate mpMRI can significantly impact diagnostic accuracy and may have varied across studies (22). This variability in reader experience could contribute substantially to the observed differences in results. Last, it is important to consider technological advancements over time. The included studies span nearly two decades, during which MRI technology and interpretation techniques have evolved considerably (23). This temporal factor adds another layer of complexity to the heterogeneity observed in the meta-analysis. These sources of heterogeneity highlight the need for standardisation in mpMRI acquisition, interpretation and reporting. Initiatives such as PI-RADS aim to address this issue, but further refinement and widespread adoption are necessary to improve consistency across different clinical settings (24). Morote et al. reported (25) that the Barcelona MRI predictive model has been successfully validated when mpMRI was reported with PI-RADS v2.1 and prostate biopsies were conducted via the transrectal and transperineal route. Lv et al. found (26) that the mean PSA density combined with PI-RADS showed utility in guiding optimisation of the prostate biopsy mode. Higher PSAD and PI-RADS values were associated with greater confidence in implementing mono-targeted biopsy and safely omitting systematic biopsy, thus effectively balancing the benefits and risks. In addition, some relevant reports have investigated the accuracy and key role of mpMRI in predicting different prostate cancers (27, 28).

The limited number of studies meeting our inclusion criteria precluded subgroup analyses that may have shed light on the impact of specific factors on diagnostic performance. Additionally, the lack of individual patient data restricted our ability to assess the influence of patient characteristics on mpMRI performance. However, the findings of this meta-analysis support the integration of mpMRI into the diagnostic workflow for prostate cancer. The improved diagnostic accuracy and detection rates suggest that mpMRI could play a crucial role in reducing unnecessary biopsies, improving the detection of clinically significant cancers and guiding treatment decisions (12).

Future research should focus on large-scale prospective studies with standardised protocols to further elucidate the role of mpMRI in prostate can-

cer management. However, several challenges need to be addressed to optimise the clinical utility of mpMRI in prostate cancer management. Standardisation remains a crucial issue, with ongoing efforts required to harmonise mpMRI protocols, interpretation criteria and reporting systems to reduce variability in clinical practice (29). Additionally, exploring the integration of mpMRI with novel biomarkers may further enhance its predictive value in prostate cancer grading and risk stratification (30).

CONCLUSIONS

This study provides the first comprehensive assessment of the predictive value of T2WI and ADC in mpMRI for the pathological grading of prostate cancer through a systematic literature review and meta-analysis. The findings of this meta-analysis support the integration of mpMRI into the diagnostic workflow for prostate cancer. Its improved accuracy could lead to more precise targeting of biopsies, potentially reducing unnecessary procedures and improving the detection of clinically significant cancers. Although mpMRI shows great promise in improving the diagnosis and grading of prostate cancer, its optimal implementation requires addressing challenges related to standardisation, training and cost-effectiveness.

ACKNOWLEDGEMENTS

Subo Zhang and Jinxin Wan contributed similarly as first author.

FUNDING

Health Science and Technology Project of the Lianyungang Health Commission (202325). Scientific Research Project of the Lianyungang Anti-Cancer Association (MS202312)

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 51 (3): e20240500, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0500

External Validation and Comparison of Current Scoring Systems in Encrusted Ureteral Stent Management: a Multicenter Study

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ABSTRACT

Purpose: To compare the external validation of four existing scoring systems for encrusted ureteral stents (EUS) and their relationship with stent indwelling time, stone-free rates, multiple surgery sessions, multimodal procedures, and prolonged operation times exceeding 120 minutes in total.

Materials and Methods: The data of 208 patients who underwent surgery for EUS reviewed. All EUSs were evaluated with 4 scoring systems: ESB (encrusted stone burden), FECal (forgotten, encrusted, calcified), KUB (kidney, ureter and bladder), V-GUES (visual grading for ureteral stone burden).

Results: As the duration of stent indwelling time prolonged, a significant increase is observed in the scores of ESB, FECal, KUB and V-GUES systems (p<0.001). In multivariate logistic regression analysis, V-GUES score (p=0.025) and stent indwelling time (p=0.014) in stone-free rate, FECal grade (p<0.001) in multimodal procedure requirement, FECal (p=0.002) and V-GUES (p=0.032) scores in multiple surgery sessions, and stent indwelling time (p=0.019) and KUB score (p<0.001) in prolonged operation time were found to be predictors. When the area under receiver operating characterictic (ROC) curves (AUC) of the nomograms were examined, V-GUES score (AUC=0.685) in stone-free rate, FECal grade (AUC=0.780) in multimodal procedure requirement, FECal grade (AUC=0.845) in multiple surgery sessions, and KUB score (AUC=0.860) in prolonged operation time were found to be superior.

Conclusions: The management of EUSs is often challenging for urologists. Although the current scoring systems for EUS differ somewhat, it is important to use scoring systems to guide the management of these patients.

ARTICLE INFO

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Keywords:
Stents; Factor Analysis, Statistical; Urolithiasis

Submitted for publication:
August 31, 2024

Accepted after revision:
December 13, 2024

Published as Ahead of Print:
January 22, 2025

INTRODUCTION

Ureteral stents are widely used in urological practice to relieve upper urinary tract obstruction (1). Although ureteral stents are generally well tolerated by patients, they can cause pain, dysuria, bleeding, and lower urinary tract symptoms as a result of being a foreign body (2).

One of the complications that may occur due to a prolonged stent indwelling time is encrustation. Encrusted ureteral stent (EUS) is defined as a stent that cand not be removed using conventional cystoscopic methods and that requires additional intervention. EUS occurs in up to 13% of the cases (3). EUS can also cause renal failure and sepsis (4). Usually, ureteral stents are removed by cystoscopy without any problems. However, if there is encrustation additional procedures cand be required. Encrustation is the most challenging complication associated with ureteral stents, and requires a variety of complex procedures to manage (5).

Various scoring systems have been developed to enable accurate planning for EUS removal and ensure a stone-free status. The four scoring systems currently available are encrusted stone burden (ESB), forgotten, encrusted, calcified (FECal), kidney, ureter, and bladder (KUB), and visual grading for ureteral stone burden (V-GUES) (5-8) (supplementary appendix).

This study aimed to compare the external validation of four existing scoring systems for EUS and their relationship with stent indwelling time, stone-free rates, multiple surgery sessions, multimodal procedures, and prolonged operation times exceeding 120 minutes in total.

MATERIALS AND METHODS

This clinical trial was approved by the Institutional Review Board (IRB No. 2022/04-15). The data of patients who underwent surgery for EUS between 2013 and 2023 in three tertiary care referral centers in three different regions of our country were retrospectively reviewed. Regardless of stent duration, patients whose stents were not encrusted or could easily be removed cystoscopically in a single attempt were excluded from the study. As a result of this review, data from 208 patients who met the inclusion criteria were evaluated.

The following data were collected: patient demographics (age, gender, diabetes mellitus (DM), Charlson comobidity index (CCI)), stent characteristics (symptom, indication of stent insertion, stent indweeling time, stone side, encrustation site, preoperative extracorporeal shock wave lithotripsy (ESWL), KUB score, FECal grade, V-GUES score, ESB , operative data (operation time, number of procedures, number of surgery sessions). The following outcomes were evaluated: stone-free rate, complications according to the Clavien–Dindo classification (9), hospitalization. Four available scoring systems for EUS were compared in relation to stent indwelling time, stone-free rates, multiple surgery sessions, multimodal procedures, and prolonged operation times exceeding 120 minutes in total.

Non-contrast computed tomography (NCCT) was performed in all patients after whose ureteral stents could not be removed cystoscopically in a single attempt to evaluate the surgery to be performed. The surgical method was decided according to the intraoperative EUS status. There are differences in brands and features of instruments and surgical equipment. Due to the large number of patients in the centers and the experience in complicated surgeries, ureterorenoscopy (URS), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL), ESWL could be applied without interruption in these centers. Multiple surgery sessions were defined as surgical interventions requiring more than one anesthesia, and multimodal procedures were defined as surgical interventions performed using more than one method. In patients who underwent multiple surgical sessions, the total operation time and hospital stay were reported. Patients were followed-up with NCCT one month after surgery. Success rate was defined as removal of the stent and stones <4 mm in NCCT performed one month after the procedure.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences version 22 for Windows (SPSS Inc., IBM, NY, USA). Pearson Chi-Square

or Fisher's exact tests and the two-proportion Z test with adjusted p-values (Bonferroni method) were used for the comparison of independent categorical variables. The one-sample Kolmogorov-Smirnov test was applied to determine whether the data showed a normal distribution for the variables with quantitative values. One-way analysis of variance (ANOVA) was used for the variables of quantitative data that had a normal distribution after Tukey's post-hoc correction, and the Kruskal-Wallis test was used for the other variables. For comparison between the two groups, the t-test was used for the variables of quantitative data that had a normal distribution, and the Mann-Whitney test was performed for the other variables. Mean ± standard deviation was found in the data with normal distribution and median (minimum-maximum) values were recorded in the data without normal distribution. A receiver operating characteristic (ROC) curve was generated by plotting the sensitivity as a function of (1-specificity) to investigate the predictive values of the grading systems. Binary logistic regression analysis was performed to determine the independent risk factors for predicting the stone-free rate, multimodal procedure requirement, multiple surgery sessions requirements, and prolonged operation time. Multivariate analysis was performed using the significant parameters in the univariate analysis. Data were examined using 95% confidence intervals (CI). The likelihood of a type I error was considered α=0.05 for all tests.

RESULTS

Considering the exclusion criteria, 208 patients who required surgical intervention due to EUS were included in the study. The demographic data and operative data of the patients are presented in Table-1 and Table-2. The mean age of the patients was 47.9 years. The indication for stent insertion was due to urinary system stone disease in 79.3%. The mean stent indwelling time was found to be 16.7 months. 46.2% of the encrustations occurred only in the bladder part of the ureteral stent. When the scoring systems were examined, the mean ESB, FECal, KUB and V-GUES scores were found to be 250 mm2, 2.2, 6.2 and 2, respectively. Although 47.1% of the patients underwent multimodal procedures and 16.8% underwent multiple surgical sessions, a stone-free status was achieved in 83.2% of the patients after all the interventions. Patients who were not stone-free were either lost to follow-up or had records that could not be accessed. Complications occurred at a rate of 17.8%, mostly Grade 1. Grade 4 complications developed in 2 patients: 1 patient with sepsis and 1 patient with septic shock. The mean hospital stay was 3.6 days.

The data obtained when grouped according to the stent indwelling time are shown in Table-3. When the relationship between stent indwelling time and operation times exceeding 90 minutes, 120 minutes and 180 minutes were investigated, no statistical difference was observed for operation times shorter than 120 minutes. Therefore, we evaluated prolonged surgery times exceeding 120 minutes in our study. At the same time, as the duration of the stent indwelling time was prolonged, a significant increase was observed in the ESB, FECal, KUB, and V-GUES systems ($p<0.001$).

The multivariate logistic regression analysis of the factors predicting the postoperative stone-free rate is shown in Table-4. Accordingly, while a low V-GUES score ($p=0.025$) and short stent indwelling time ($p=0.014$) were associated with a high stone-free rate in the multivariate analysis, ESB, FECal grade and KUB score were not found to be predictive factors for the stone-free rate. In the ROC curve created using nomograms to predict the postoperative stone-free rate, the area under the curve (AUC) values were 0.610, 0.657, 0.677, and 0.685 for ESB, FECal, KUB and V-GUES, respectively (Figure-1).

The results of the multivariate logistic regression analysis of the factors predicting the requirement for multimodal procedures are shown in Table-5. Accordingly, only an increase in the FECal grade was found to be a predictive factor for an increase in the number of multimodal procedures ($p<0.001$). In the multivariate analysis, ESB, KUB score, V-GUES score, and stent indwelling time were not associated with

Table 1- Demographic data of the patients.

Variables	
Number of patients	208
Mean age (years), mean ± SD	47.9 ± 15.0
Gender, n (%)	
Female	72 (34.6)
Male	136 (65.4)
Diabetes Mellitus, n (%)	36 (17.3)
CCI, median (min-max)	1 (0-7)
Symptomatic patients, n (%)	137 (65.9)
Indication of stent insertion, n (%)	
URS	79 (38)
RIRS-PCNL-ESWL	86 (41.3)
Pyelolithotomy-Pyeloplasty-UNC	37 (17.8)
Ureteral obstruction-Hydronephrosis-Acute renal failure	6 (2.9)
Stent indwelling time (months), (mean ± SD)	16.7 ± 18.5
≤ 6 mo, n (%)	74 (35.6)
6-12 mo, n (%)	38 (18.3)
13-24 mo, n (%)	50 (24)
>24 mo, n (%)	46 (22.1)
Stone side, n (%)	
Right	109 (52.4)
Left	90 (43.3)
Bilateral	9 (4.3)
Encrustation site, n (%)	
Kidney	23 (11.1)
Ureter	17 (8.2)
Bladder	96 (46.2)
Kidney+Ureter	7 (3.4)
Kidney+Bladder	23 (11.1)
Ureter+Bladder	20 (9.6)
Whole length	22 (10.6)

SD = standard deviation; CCI = charlson comorbidity index; URS = ureterorenoscopy; RIRS = retrograde intrarenal surgery; PCNL = percutaneous nephrolithotomy; ESWL = extracorporeal shock wave lithotripsy; UNC = ureteroneocystostomy; mo = month; n = number

Table 2 - Operative data of the patients.

Variables	
Number of patients	208
Preoperative ESWL, n (%)	35 (16.8)
KUB score, (mean ± SD)	6.2 ± 2.9
FECal grade, (mean ± SD)	2.2 ±1.5
Grade 1, n (%)	104 (50)
Grade 2, n (%)	26 (12.5)
Grade 3, n (%)	23 (11.1)
Grade 4, n (%)	34 (16.3)
Grade 5, n (%)	21 (10.1)
V-GUES score, (mean ± SD)	2.0 ± 1.1
Type A, n (%)	96 (46.2)
Type B, n (%)	37 (17.8)
Type C, n (%)	47 (22.6)
Type D, n (%)	28 (13.5)
Encrusted stone burden (mm2), mean ± SD	250.0 ± 491.4
Operation time (min), mean ± SD	74.0 ± 52.8
Operation time >90 min, n (%)	52 (25)
Operation time >120 min, n (%)	29 (13.9)
Operation time >180 min, n (%)	11 (5.3)
Number of procedures, mean ± SD	1.8 ± 1.1
Multimodal procedures, n (%)	98 (47.1)
Number of surgery sessions, mean ± SD	1.2 ± 0.5
Multiple surgery sessions, n (%)	35 (16.8)
Stone-free rate, n (%)	173 (83.2)
Complication, n (%)	37 (17.8)
Clavien-Dindo classification, n (%)	
Grade 1	24 (11.5)
Grade 2	8 (3.8)
Grade 3A	3 (1.4)
Grade 3B	0
Grade 4A	1 (0.5)
Grade 4B	1 (0.5)
Grade 5	0
Hospitalization (day), mean ± SD	3.6 ± 4.7

SD = standard deviation; ESWL = extracorporeal shock wave lithotripsy; mo = month; n = number

Table 3 - Relationship between stent indwelling time and scoring systems.

	≤ 6 mo (n=74)	7-12 mo (n=38)	13-24 mo (n=50)	>24 mo (n=46)	P value
Age, mean ± SD	47.6 ± 13.9	47.6 ± 15.1	50 ± 16.5	46.3 ± 15.0	0.666[A]
Gender					0.670
Female	23 (31.1)	14 (36.8)	16 (32)	19 (41.3)	
Male	51 (68.9)	24 (63.2)	34 (68)	27 (58.7)	
Diabetes Mellitus, n (%)	13 (17.6)	3 (7.9)	13 (26)	7 (15.2)	0.162
Symptomatic patients, n (%)	48 (64.9)	24 (63.2)	33 (66)	32 (69.6)	0.932
Stone side, n (%)					0.125
Right	38 (51.4)	25 (65.8)	22 (44)	24 (52.2)	
Left	30 (40.5)	13 (34.2)	25 (50)	22 (47.8)	
Bilateral	6 (8.1)	0	3 (6)	0	
Preoperative ESWL, n (%)	6 (8.1)	4 (10.5)	13 (26)	12 (26.1)	**0.012[Z]**
KUB score, mean ± SD	4.9 ± 2.0	5.5 ± 2.2	6.7 ± 2.7	8.4 ± 3.3	**<0.001[A]**
KUB score ≥ 9	3 (4.1)	3 (7.9)	11 (22)	20 (43.5)	**<0.001[Z]**
FECal score					
Grade 1, n (%)	54 (73)	23 (60.5)	21 (42)	6 (13)	**<0.001[K]**
Grade 2, n (%)	2 (2.7)	5 (13.2)	4 (8)	15 (32.6)	
Grade 3, n (%)	11 (14.9)	2 (5.3)	3 (6)	7 (15.2)	
Grade 4, n (%)	5 (6.8)	7 (18.4)	15 (30)	7 (15.2)	
Grade 5, n (%)	2 (2.7)	1 (2.6)	7 (14)	11 (23.9)	
FECal score ≥ Grade 3	18 (24.3)	10 (26.3)	25 (50)	25 (54.3)	**0.001[Z]**
V-GUES Score					**<0.001[K]**
Type A, n (%)	45 (60.8)	22 (57.9)	18 (36)	11 (23.9)	
Type B, n (%)	19 (25.7)	5 (13.2)	7 (14)	6 (13)	
Type C, n (%)	6 (8.1)	10 (26.3)	17 (34)	14 (30.4)	
Type D, n (%)	4 (5.4)	1 (2.6)	8 (16)	15 (32.6)	
V-GUES Score ≥ C	10 (13.5)	11 (28.9)	25 (50)	29 (63)	**<0.001[Z]**
Encrusted stone burden (mm^2), mean ± SD	89.6±116.9	310.5±603.6	214.6±528.2	496.6±613.4	**<0.001[K]**
Encrusted stone burden >250 mm^2, n (%)	6 (8.1)	9 (23.7)	11 (22)	29 (63)	**<0.001[Z]**
Operation time >90 min, n (%)	26 (35.1)	6 (15.8)	9 (18)	11 (23.9)	**0.069 [Z]**
Operation time >120 min, n (%)	1 (1.4)	3 (7.9)	7 (14)	18 (39.1)	**<0.001[Z]**
Operation time >180 min, n (%)	0a	1 (2.6)	3 (6)	7 (15.2)	**0.003[Z]**

A = One-Way ANOVA; Z = Z Test; K = Kruskal-Wallis test; ESWL = extracorporeal shock wave lithotripsy; SD = standard deviation; mo = month; n = number

Table 4 - Multivariate logistic regression analysis of predicting factors for stone-free rate following surgery.

	Binary Logistic Regression (n=208)					
	Univariate Model			Multivariate Model		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.006	0.982-1.031	0.621			
Gender (Ref: female)	1.759	0.842-3.678	0.133			
DM	1.310	0.471-3.645	0.605			
Indications of stent insertion (Ref: URS)	0.855	0.550-1.328	0.485			
Preoperative ESWL	0.511	0.215-1.214	0.128			
Encrusted Stone Burden	0.999	0.999-1.000	0.063			
KUB score	0.830	0.743-0.928	0.001			
FECaL score	0.698	0.548-0.888	0.003			
V-GUES score	0.553	0.397-0.770	<0.001	0.661	0.461-0.949	0.025
Stent indwelling time	0.968	0.950-0.985	<0.001	0.976	0.958-0.995	0.014

OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; URS = ureterorenoscopy; ESWL = extracorporeal shock wave lithotripsy

Figure 1 - ROC curves of the nomograms for prediction of stone-free rate following surgery.

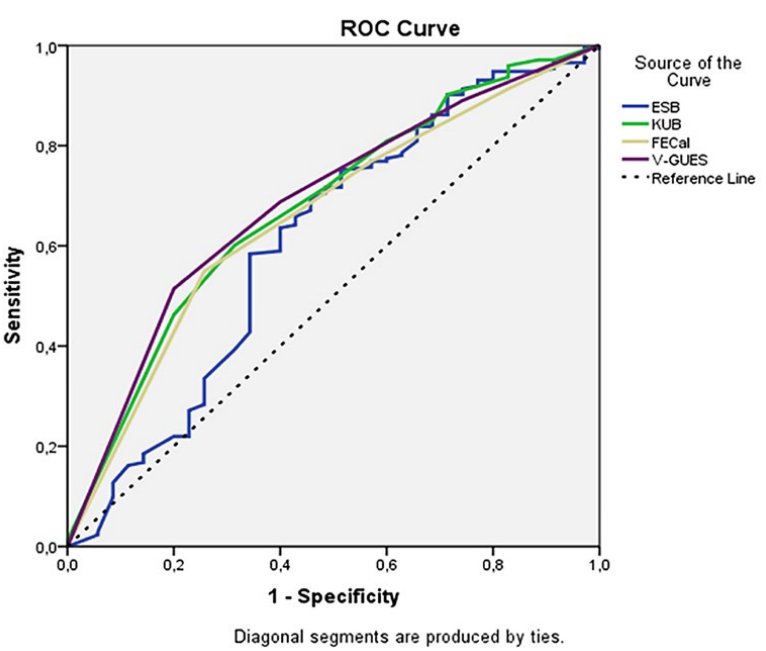


Table 5 - Multivariate logistic regression analysis of predicting factors for multimodal procedure requirement.

	Binary Logistic Regression (n=208)					
	Univariate Model			Multivariate Model		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.989	0.971-1.007	0.230			
Gender (Ref: female)	0.769	0.434-1.364	0.369			
CCI	0.899	0.755-1.069	0.229			
Indications of stent insertion (Ref: URS)	0.892	0.636-1.251	0.507			
Preoperative ESWL	1.870	0.892-3.919	0.097			
Encrusted Stone Burden	1.001	1.000-1.002	**0.006**			
KUB score	1.525	1.307-1.778	**<0.001**			
FECal score	2.587	1.983-3.373	**<0.001**	2.587	1.983-3.373	**<0.001**
V-GUES score	1.952	1.485-2.566	**<0.001**			
Stent indwelling time	1.020	1.003-1.037	**0.024**			

OR = odds ratio; CI = confidence interval; CCI = charlson comorbidity index; URS = ureterorenoscopy; ESWL = extracorporeal shock wave lithotripsy

the requirement for multimodal procedures. The AUC values in the ROC curve created using the nomograms for the prediction of multimodal procedure requirements were 0.659, 0.780, 0.746, and 0.689 for ESB, FECal, KUB, and V-GUES, respectively (Figure-2).

Multivariate logistic regression analysis of the factors predicting multiple surgery session requirements is shown in Table-6. Accordingly, it was found that an increase in FECal (p=0.002) and V-GUES (p=0.032) scores predicted an increase in the number of multiple surgical sessions. In the multivariate analysis, an increase in ESB, KUB score, and stent indwelling time did not predict the requirement for multiple surgical sessions. The AUC values in the ROC curve created using nomograms for the multiple surgery session requirements were 0.650, 0.845, 0.807, and 0.835 for ESB, FECal, KUB, and V-GUES, respectively (Figure-3).

Multivariate logistic regression analysis of the factors predicting the total duration of all surgical procedures ≥ 120 minutes is shown in Table-7. Accordingly, it was found that an increase in KUB score (p<0.001) and stent indwelling time (p=0.019) predicted prolonged operation time; however EBS, FECal grade, and V-GUES score were not predictive factors for operation time >120 minutes. The AUC values in the ROC curve created using the nomograms were 0.703, 0.804, 0.860, and 0.802 for ESB, FECal, KUB, and V-GUES, respectively, for operation times >120 minutes (Figure-4).

In our study, preoperative ESWL was not found to be significant predictive factors for stone-

Figure 2 - ROC curves of the nomograms for prediction of multimodal procedure requirement.

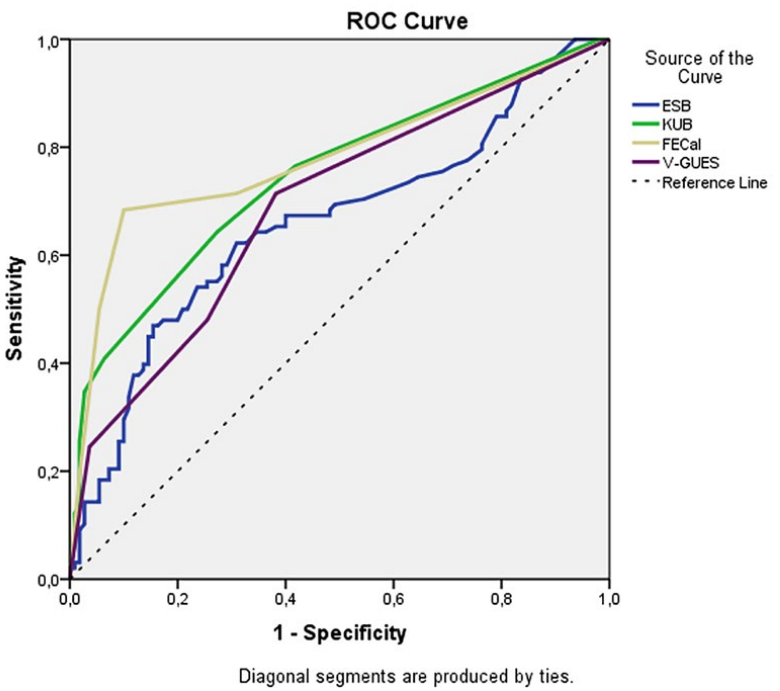


Table 6 - Multivariate logistic regression analysis of predicting factors for multiple surgery sessions requirement.

Binary Logistic Regression (n=208)						
	Univariate Model			Multivariate Model		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.993	0.969-1.018	0.586			
Gender (Ref: female)	1.655	0.730-3.752	0.228			
CCI	0.854	0.665-1.097	0.217			
Indications of stent insertion (Ref: URS)	0.852	0.536-1.355	0.499			
Preoperative ESWL	0.846	0.485-1.812	0.317			
Encrusted Stone Burden	1.001	1.000-1.001	**0.041**			
KUB score	1.453	1.275-1.655	**<0.001**			
FECal score	2.729	1.971-3.780	**<0.001**	1.951	1.267-3.004	**0.002**
V-GUES score	3.565	2.313-5.492	**<0.001**	1.896	1.058-3.397	**0.032**
Stent indwelling time	1.015	0.998-1.032	0.075			

OR = odds ratio; CI = confidence interval; CCI = charlson comorbidity index; URS = ureterorenoscopy; ESWL = extracorporeal shock wave lithotripsy

Figure 3 - ROC curves of the nomograms for prediction of multiple surgery session requirement.

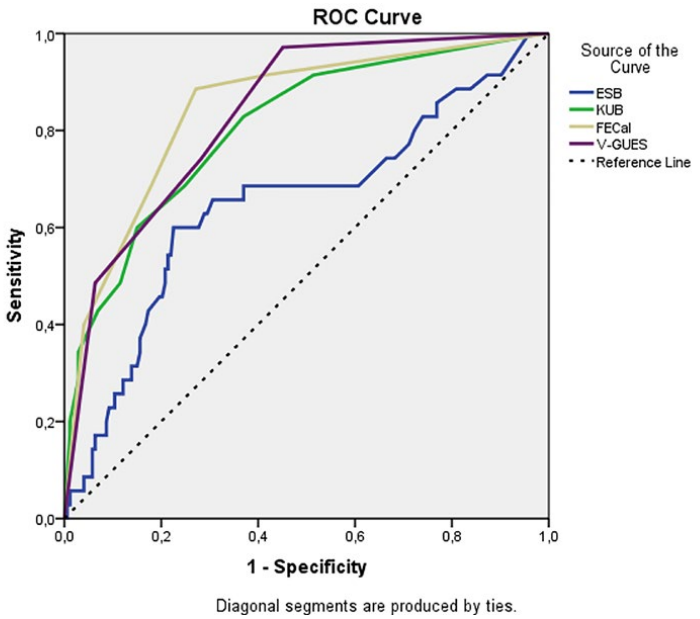
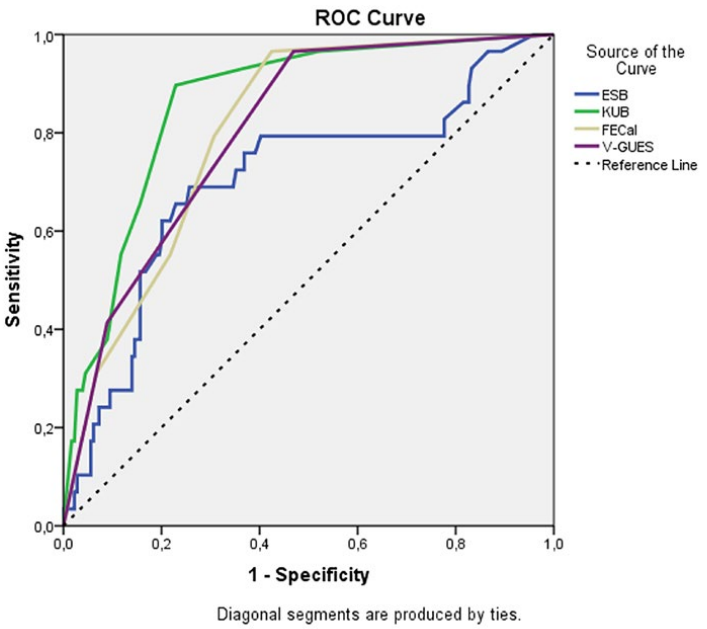


Table 7 - Multivariate logistic regression analysis of predicting factors for operation time >120 minutes.

	Binary Logistic Regression (n=208)					
	Univariate Model			Multivariate Model		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.988	0.963-1.015	0.381			
Gender (Ref: female)	1.207	0.519-2.808	0.662			
CCI	0.953	0.739-1.228	0.709			
Indications of stent insertion (Ref: URS)	0.630	0.366-1.083	0.095			
Preoperative SWL	2.145	0.862-5.335	0.101			
Encrusted Stone Burden	1.001	1.000-1.001	**0.009**			
KUB score	1.470	1.284-1.683	**<0.001**	1.381	1.197-1.595	**<0.001**
FECaL score	2.102	1.560-2.831	**<0.001**			
V-GUES score	2.884	1.893-4.394	**<0.001**			
Stent indwelling time	1.048	1.025-1.070	**<0.001**	1.027	1.005-1.050	0.019

OR = odds ratio; CI = confidence interval; CCI = charlson comorbidity index; URS = ureterorenoscopy; ESWL = extracorporeal shock wave lithotripsy

Figure 4 - ROC curves of the nomograms for prediction of prolonged operation time (>120 min.).



free rates, multiple surgical sessions, multimodal procedures, and prolonged surgery times exceeding 120 minutes in multivariate analysis.

DISCUSSION

Preoperative imaging is crucial to determine the treatment modality for EUS. Plain radiographs are insufficient to precisely determine the location and extent of calcification (10).Given the challenging nature of EUS management and the frequency of high-grade complications, NCCT is currently the preferred imaging method for evaluating the stone burden, degree of encrustation, and surrounding organs (11, 12). Preoperative and postoperative imaging of all patients in our study were performed using NCCT.

Surgery for patients with EUS carries high risk. There are many factors that put these patients at risk for postoperative complications, such as multiple comorbidities, large stone burden, and the presence of a potentially infected stent. Therefore, preoperative optimization is invaluable (13).

In a review conducted by Massella et al. on 1067 patients, it was found that more than half of the studies did not use any scoring system, making it difficult to draw a roadmap to guide the type and number of interventions required for stone-free status (1). After determining the degree of encrustation on EUS imaging, various grading systems are used to counsel patients and anticipate surgical difficulties that may arise during stent removal.

An ESB is a system that is calculated based on the encrustation volume. It is useful in determining the severity of encrustation, but it does consider the location of encrustation (5). FECal grade is an easy-to-apply scoring system. Although the treatment of encrustation at both ends of the stent was different, encrustation at the proximal or distal end did not affect the grade in this scoring. It was also developed in a study conducted on only 9 patients. However, it offers a treatment algorithm based on the grade (7). The KUB score evaluated encrustations involving the proximal and distal loops of the stent, separately. This is important in terms of the surgical method to be applied. However, this approach is complex and difficult to implement (14). The V-GUES score is the most up-to-date scoring system developed to help surgeons determine both the probability of EUS removal and the stone-free status. This is a visual scor-

ing method based on NCCT and does not require calculations (8).

Although stent material, bacterial colonization, and patient-specific factors affect stent encrustation, the main risk factor for encrustation is stent indwelling time (15). Studies have shown that prolonged stent indwelling time is associated with a higher encrusted stone burden ($p<0.001$) (11, 16). The literature has mostly examined the relationship between stent indwelling time and the KUB and FECal scores. In all studies investigating the relationship between the total KUB score and stent indwelling time, prolongation of the stent indwelling time resulted in an increase in the KUB score (7, 14, 16, 17). In almost all studies that evaluated the FECal system, a positive relationship was found between increasing scores and stent indwelling time (6, 14, 17, 18). Only Lopes et al. found no association between stent indwelling time and FECal grade ($p=011$) (19). They attributed this result to their small sample size. Cicione et al. also stated that prolongation of stent indwelling time was associated with increased scores in the four existing scoring systems (20). Similarly, in our study, prolonged stent indwelling time caused an increase in all the scoring systems.

Achieving a stone-free status is one of the primary goals of EUS treatments. In the study by Lopes et al. no statistically significant relationship was found between the FECal grade and stone-free status ($p=0.081$) (19). Although one study reported that a total KUB score ≥ 9 was associated with a decreased stone-free rate ,another study found that a total KUB score ≥ 9 was not associated with stone-free rates (7, 16). In a study comparing FECal and KUB scores by Guner et al. both scoring systems were found to be significant predictors of stone-free status in multivariate regression analysis ($p<0.001$) (17). Manzo et al. reported that the V-GUES score was associated with both stent removal and stone-free rates (8). In our study, the predictive factors for stone-free status in the multivariate analysis were V-GUES score ($p=0.025$) and stent indwelling time ($p=0.014$).

Multimodal procedures may be required to remove EUS and ensure stone-free status. There are conflicting results in the literature regarding multimodal procedures and scoring systems. In a study by Polat et al. an increase in ESB was found to be associated with multimodal intervention ($p=0.012$), while in another study, this relationship was not found (11, 18), Studies often report that a total KUB ≥ 9 is not associated with multimodal procedures, but an increase in FECal score correlates with the need for multimodal procedures (7,16,18). Guner et al. emphasized that the multimodal procedure was associated with the KUB score, but not with the FECal score (17). In a study by Saadi et al. FECal ≥ grade 3 was found to be a predictor of multimodal procedures. In this study, it was stated that both the KUB and FECal scores were useful for EUS removal, but the FECal score was advantageous in predicting the multimodal procedure (14). In our study, FECal was the only scoring system that predicted the requirement for multimodal procedures in multivariate logistic regression analysis ($p<0.001$).

In some series, it has been reported that stone-free status in patients with EUS can be achieved in a single surgical session; however, it has been shown that 1-3 surgical sessions are required in most cases (16). In a study by Weedin et al. stent indwelling time and ESB were not found to be significant in the multivariate analysis of factors predicting multiple surgery sessions (21). In contrast, Polat et al. found that an increase in ESB was associated with multiple surgical sessions ($p=0.004$) (11). Studies have reported that a total KUB score ≥ 9 is associated with multiple surgery sessions, and conversely, a total KUB score ≥ 9 is not associated with multiple surgery sessions (7, 16). In a study comparing FECal and KUB scores, total KUB ≥ 9 and FECal ≥ Grade 3 were found to be predictors of multiple surgery sessions in the multivariate regression analysis (14). In a study evaluating the V-GUES score, it was stated that multiple surgical sessions may be required as the score increases (8). In our study, the scoring systems that predicted the requirement for multiple surgery sessions in the multivariate logistic regression analysis were FECal ($p=0.002$) and V-GUES ($p=0.032$).

Prolonged operation time is a known risk factor for postoperative sepsis in stone surgery; therefore, attention should be paid to the operation time in surgeries performed for EUS (22). The scoring systems investigated in the literature for their relationship with prolonged operation time are KUB and FECal. When the FECal score was

evaluated, both FECal≥ Grade 3 and high FECal grade were associated with prolonged operation time (14, 18, 19). Similarly, a total KUB score ≥ 9 and an increasing KUB score were also found to be associated with prolonged operation time (7, 14, 16). In our study, the KUB score ($p<0.001$) and stent indwelling time ($p=0.019$) were found to be significant in the multivariate analysis of the factors predicting the operation time exceeding 120 minutes.

The most important limitations of our study are that it was retrospective, the surgeries were performed by different surgeons with different endourological experiences, the stents were graded by different clinicians in different clinics, and the surgical equipment used was differed. The choice of surgery applied to encrusted stents was primarily based on urolithiasis guidelines, but while there are surgical recommendations according to stones in the guidelines, there is no clear recommendation for encrusted stents. In this respect, the decision-making process is left to the endourologist's preference. Other limitations of our study include the lack of data on the stent material and coating, and chemical analysis of the stones.

CONCLUSIONS

EUSs are rare cases. Their management is a difficult procedure that requires experience and various equipment. In our study, among the scoring systems developed for EUS, V-GUES was found to be superior in predicting postoperative stone-free rate, FECal in predicting the need for multimodal procedures and multiple surgical sessions, and KUB in predicting prolonged surgical times exceeding 120 minutes. It may be useful to use all 4 KUB,FECal and V-GUES scoring systems to prepare both ourselves and the patient for the results of surgery in terms of different parameters with an individualized approach.

ABBREVIATIONS

EUS = Encrusted ureteral stents
ESB = Encrusted stone burden
FECa l= Forgotten, encrusted, calcified
KUB = Kidney, ureter, bladder
V-GUES = Visual grading for ureteral stone burden
CCI = Charlson comorbidity index
DM = Diabetes mellitus
ROC = Receiver operating characteristic
AUC = Area under curves
IRB = Institutional review board
NCCT = Noncontrast computed tomography

Compliance with Ethical Standards

Informed consent was obtained from patients.

Ethics Statement

The study protocol was approved by Institutional Review Board (IRB No. 2022/04-15). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 51 (3): e20240556, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0556

Radical Cystectomy with Elective Indication to Cutaneous Ureterostomy: Single-Center Comparative Analysis Between Open and Robotic Surgery in Frail Patients

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ABSTRACT

Objectives: Radical cystectomy (RC) is a surgical procedure associated with high rates of morbidity. The aim of the study is to provide a comparison between robotic (RARC) and open RC (ORC) in patients elected to cutaneous ureterostomy (CUS).

Materials and Methods: This is a retrospective single-center cohort study performed at a high-volume institution. The study involved 64 patients undergoing RC with CUS, 42 ORC and 22 RARC. The indication for RC was based on EAU guidelines and the choice of CUS was planned due to advanced oncological stage or patient's frailty. Patient allocation to the robotic or open approach for RC was casual, determined by surgeon preference and/or the availability of a robotic operating room. The Adverse events were systematically graded utilizing the Clavien–Dindo classification system.

Results: Complications of Clavien Dindo ≥ 2 occurred in 27 out of 42 (64.2%) ORC and 3/22 (13.6%) RARC ($p < 0.001$); complications of Clavien Dindo ≥ 3 occurred in 10/42 (23.8%) ORC and only 1/22 (4.5%) RARC, respectively ($p = 0.08$). Multivariable analysis revealed that robotic surgery was the only variable inversely associated with Clavien Dindo ≤ 2 complications.

Conclusions: In conclusion, RARC appears to be associated with lower morbidity and reduced incidence of complications, elements that make it particularly suitable for frail patients with an elective indication for CUS.

ARTICLE INFO

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Keywords:
Ureterostomy; Cystectomy; Robotic Surgical Procedures

Submitted for publication: October 05, 2024

Accepted after revision: December 15, 2024

Published as Ahead of Print: January 22, 2025

INTRODUCTION

Radical cystectomy (RC) is a surgical procedure associated with high rates of morbidity and non-negligeable mortality (1). The use of the robotic approach was firstly introduced by Menon et al. in 2003 (2). Thereafter, robotic-assisted radical cystectomy (RARC) has surged worldwide after several randomized controlled trials (RCTs), that stated its non-inferiority to the open approach in terms of oncological results (3-6). For example, the multi-institutional RAZOR trial confirmed similar 2-year progression-free survival rate, 3-year recurrence-free, progression-free survival, and overall survival between RARC and open RC (ORC) (5). As far as post-operative results are concerned, a reduction in morbidity is expected with the robotic approach. Systematic reviews, retrospective, prospective and RCTs reported shorter lengths of hospital stays (LOS) and reduced transfusion need after RARC, if compared to ORC (7–12). Ileal conduit and neobladder have been both applied in robotic surgery, either within an extracorporeal and intracorporeal approach (13). Nevertheless, for some patients, cutaneous ureterostomy (CUS) may be preferred because they result to be faster and simpler than other diversion types: the lack of bowel use may reduce operative time, intensive care unit (ICU) requirement, and incidence of perioperative complications, especially those related to intestinal manipulation (14). CUS are often applied in case of locally advanced disease: in those patients, a salvage cystectomy could be performed to debulk the disease and relieve symptoms such as bleeding (14, 15). While previous evidence focused on the comparison between robotic and open surgery with the reconfiguration of a urinary intestinal diversion, to now the evaluation of robotic and open RC with CUS has never been addressed. The aim of the paper is to provide a single center comparison between RARC and ORC in patients selectively elected to CUS.

MATERIALS AND METHODS

This is a retrospective single-center study on a prospectively maintained dataset of patients treated with ORC or RARC and CUS from January 2022 to September 2023 at ASST Santi Paolo and Carlo, Milan, Italy. This study was conducted and reported in accordance with the STROBE guidelines for observational research (16). Patient allocation to the robotic or open approach for radical cystectomy was casual, determined by surgeon preference and/or the availability of a robotic operating room. The study involved patients elected to RC with upfront selection of CUS as urinary diversion.

The choice of CUS was pre-operatively planned and deemed necessary due to the following condition/s:

- Advanced clinical oncological stage defined from pre-operative CT scan or MRI.
- Patient's frailty as graded by the ASA score and/or Charlson Comorbidity Index (CCI) and/or anesthesiologic indication to short operative time.

Inclusion criteria were age ≥ 18 years and a diagnostic TURBt for BCa with a T stage (cT) 2-3 or recurrent BCG failure high-grade cancer with indication to RC according to the EAU Guidelines (17). All patients were informed about the diversion type and signed informed consent to the procedure. Exclusion criteria were the simultaneous resection of other organs (including nephroureterectomy) and missing follow up data. RARCs were carried out with either Da Vinci or Hugo RAS system. All surgeries were performed by experienced operators (B.R., F.T., P.D.O. and A.R.) with extensive experience in the approach they chose.

Pre-operative evaluation

Intestinal preparation was preoperatively omitted. The implementation of an Enhanced Recovery After Surgery (ERAS) protocol was undertaken, whether deemed feasible (18). Notwithstanding, prompt mobilization within the 24-hour postoperative window and initiation of enteral nutrition were encouraged. Concurrently, prophylactic administration of low molecular weight heparin was kept for a duration of four weeks in accordance with established clinical guidelines. Postoperative management included the removal of the abdominal drain on 1-2 PO days; ureteral catheters were left and changed every 2-3 months thereafter. Adverse events were systematically graded utilizing the Clavien-Dindo classification system (18). Routine post-discharge

follow-ups were conducted on a weekly basis, extending up to 30 days post-discharge.

Surgical technique for RARCs

The patient is positioned in a standardized 21° Trendelenburg inclination. The docking is performed according to the robotic system as previously described (19, 20). Then, bilateral identification and isolation of the ureters are executed, and extended superiorly from the iliac vessels until their respective insertions into the bladder. Subsequent ligation and transection of the ureters are performed using a median-sized Hem-o-lok clip. In male subjects, the dissection is initiated at the level of the seminal vesicles (SV), creating a surgical plane between Denonvillier's fascia and the posterior aspect of the prostate (or alternatively, between the bladder and vagina in females). Bilateral isolation of the bladder is then accomplished, followed by the systematic transection of vesical pedicles after their secure clipping. The use of the fourth robotic arm facilitates optimal access to posterior plate and lateral pedicles, particularly in scenarios characterized by considerable tumoral burdens. After this step, an inverse U peritonectomy is meticulously executed between the two internal inguinal rings, following ligation of the umbilical arteries to facilitate access to the Retzius space. The anterior dissection of the bladder is carried out up to the Santorini complex. The urethra is carefully isolated and subsequently incised, following the placement of a Hem-o-lok clip to avoid urinary spillage. Frozen sections from the distal ureters and urethra are obtained. Afterwards, bilateral extended pelvic nodal dissection (LND) is performed; the dissection runs in proximity to the aortic bifurcation, presacral nodes, those adjacent to the common iliac vessels bordering the lateral margins of the genitofemoral nerves, nodes caudal to the circumflex iliac vein and the lacunar ligament, in addition to the Cloquet's node. A solitary case required a super-extended LND, consequent to the presence of macroscopically pathological nodes extending cranially to the level of the inferior mesenteric artery. The periureteral sheath is carefully preserved to maintain blood supply; ureters are mobilized only as much as required and each ureter is anastomosed on separate sides of the abdomen.

Surgical technique for open cystectomy

Of the total cohort, 35 out of 42 patients (83%) underwent extraperitoneal radical cystectomy (RC). Pelvic lymph node dissection was performed in accordance with the previously described template. In certain cases, CUS was performed on the right side, with the left ureter transposed through the left colon mesentery to facilitate additional length.

Variables and data collection

The included variables are depicted as follows:

- Pre-operative variables: baseline demographics (age, BMI), performance status assessed using the CCI and the ASA score.
- Post-operative variables: pathological stage (pT), transfusion rate, complications as graded by Clavien-Dindo, number of Clavien-Dindo ≥ 2 complications, and 30-day readmission rate.

Data were collected in a prospectively maintained Excel database; variables were entered from two Authors (E.P. and T.C.) who were not - or only marginally - involved in surgeries.

Primary endpoint

The primary endpoint is to compare the rate of complication Clavien-Dindo ≥ 2 between ORC and RARC with CUS. The absolute number of complications per-patient is a secondary endpoint, as well as the complication rate (stratified as Clavien-Dindo ≥ 3).

Statistical Analysis

Continuous variables were presented as median and interquartile range, whereas categorical variables were reported in terms of absolute and relative frequencies. To analyze differences in the distribution of continuous variables between open and robotic radical cystectomy groups, the Wilcoxon non-parametric rank-sum test was utilized. Fisher's exact test was employed to assess differences in proportions among the two study groups for categorical variables. To identify the factors associated with complications of Clavien-Dindo ≥ 2, a multivariable logistic model was estimated. For

each factor, odds ratio (OR), 95% confidence interval (CI), and Wald test p-value were computed. Statistical analysis was also conducted after excluding pT4 cases, to eliminate instances potentially involving surgery-related complications due to complex or life-threatening dissections. All statistical analyses were performed using Stata version 16 (StataCorp. 2019. College Station, TX). A significant level of 5% was chosen for the analysis.

RESULTS

Overall, 64 patients underwent RC with CUS, 42 (66%) with an open and 22 (34%) with a robotic approach. Among the latter, 2 cases underwent surgery with the Hugo RAS system. Overall, 49 (76%) males and 15 (24%) females were included. A descriptive analysis of the cohort stratified into robotic and open surgery is reported in Table-1. Baseline characteristics were similar between groups, except CCI score, which was significantly higher in the robotic group. Complications of Clavien-Dindo ≥ 2 occurred in 64.2% (27/42) of the open group and 13.6% (3/22) of the robotic group, respectively (p < 0.001); complications of Clavien-Dindo ≥ 3 occurred in 23.8% (10/42) and 4.5% (1/22) of the open and robotic group, respectively (p = 0.08). Open surgery was significantly associated with a higher number of complications. When excluding pT4 cases, complications ≥ Clavien-Dindo 2 occurred in 63.6% (21/33) and 10% (2/20) within open and robotic group, respectively (p < 0.001); complications Clavien-Dindo ≥ 3 occurred in 21.2% (7/33) and 5% (1/20) within open and robotic group, respectively (p = 0.2). Table-2 summarizes post-operative variables stratified by surgical procedure. Multivariable analysis revealed that robotic surgery was the only variable inversely associated with Clavien Dindo ≥ 2 complications (Table-3).

DISCUSSION

In the current series, the robotic approach to radical cystectomy with CUS provided advantages over open surgery in terms of transfusion and post-operative complication rate. The benefit particularly applies for complications Clavien-Dindo ≥ 2; furthermore, the number of such complications in the same patient is lower after RARC. Our outcomes are consistent with those of previous series and RCTs comparing robotic and open RC. While it is generally difficult and uncommon to con-

Table 1 - Descriptive analysis of pre-operative variables stratified by surgical approach.

Variable	Open cystectomy (n=42)	Robotic cystectomy (n=22)	p
Age, years, median (IQR)	80 (67 – 85)	78 (69 – 85)	0.5
BMI Kg/m^2, median (IQR)	25 (22 – 27)	25.5 (24 – 28)	0.4
CCI, median (IQR)	7 (5 – 8)	8 (7 – 9)	0.04
ASA score (n, %)			0.3
2	11 (26.8)	10 (45.4)	
3	20 (48.8)	8 (36.4)	
4	10 (24.4)	4 (18.2)	
CCI (n, %)			0.06
3 – 6	20 (47.6)	3 (15.8)	
7 – 8	13 (31)	10 (52.6)	
> 9	9 (21.4)	6 (31.6)	

p = p-value from the Wilcoxon rank-sum test.

Table 2 - Post-operative outcomes stratified by surgical approach. The data are shown as absolute frequencies with relative frequencies (in parentheses).

Variable (n, %)	Open cystectomy (n=42)	Robotic cystectomy (n=22)	p
pT			0.12
pT1	12 (28.6)	9 (40.9)	
pT2	4 (9.5)	6 (27.3)	
pT3	17 (40.5)	5 (22.7)	
pT4	9 (21.4)	2 (9.1)	
Transfusion rate	19 (45.2)	1 (4.6)	0.001
Clavien complications (n, %)			<0.001
0 – 1	15 (35.7)	19 (86.4)	
2 – 5	27 (64.3)	3 (13.6)	
			0.08
0 – 2	32 (76.2)	21 (95.5)	
3 – 5	10 (23.8)	1 (4.5)	
No. of complications (n, %)			0.005
0	11 (26.2)	9 (42.8)	
1	13 (30.9)	11 (52. 4)	
≥2	18 (42.9)	1 (4.8)	
30-day re-admission	7 (17.5)	4 (18.2)	1

Table 3 - Multivariable analysis of factors associated with Clavien-Dindo grade ≥ 2 complica-tions.

	OR (95%CI)	p
Open cystectomy	**Reference**	
Robotic cystectomy	0.1 (0.02 – 0.5)	0.007
Age	0.99 (0.9 – 1.1)	0.80
CCI 3 – 6	**Reference**	
CCI 7 – 8	0.54 (0.7 – 3.8)	0.54
CCI ≥ 9	0.75 (0.08 – 6.9)	0.80
ASA 2	**Reference**	
ASA 3	7 (1.0 – 47.3)	0.03
ASA 4	10.6 (1.0 – 91.1)	0.99

OR = odds ratio; p= p-value from the Wald test for assessing the significance of the OR

duct well-designed RCTs in surgery, research on radical cystectomy stands out. This field boasts a wealth of 8 RCTs, enabling precise comparisons between open and robotic RC. Khetrapal et al. (21) performed a systematic review and meta-analysis of perioperative, oncological, and quality of life outcomes from RCTs. By analyzing 8 trials accounting for 1024 participants, authors found that patients who underwent open cystectomy had higher rate of thromboembolic events (odds ratio [OR] 1.84, 95% CI 1.02–3.31, p = 0.04), incremented blood loss (MD 322 mL, 95% CI 193–450, p < 0.001) and transfusion rate (OR 2.35, 95% CI 1.65–3.36, p < 0.001). An extracorporeal realization of the diversion may mitigate a possible advantage on peri-operative morbidity that would have been expected for robotic RC. When addressing trials with only inclusion of intracorporeal diversions, the benefit in reduced venous thromboembolism and wound infection becomes even more evident; the lower use of ICU admission and a superior early recovery profile are advantages as well (22, 23). Provided that these benefits apply for complex reconstruction such as neobladder or ileal conduit, the use of robotic surgery for radical cystectomy is therefore expected to maintain its advantages also in candidates to a simple CUS. To our knowledge, this is the first study comparing robotic and open surgery in the setting of CUS as an elective indication. To now, robotic surgery for RC has been evaluated in frail patients with regards to age: two clinical studies addressed robotic surgery in octogenarian. Tanabe et al. (24) performed a retrospective cohort study on 74 patients, concluding that the incidence of perioperative complications of RARC in patients aged more than 80 years was not different from those in non-elderly individuals. Similar outcomes are reported by Chen et al. (25): authors compared 478 RARC cases in octogenarian with 2257 in a younger group. Complication rate, blood transfusion rate, and in-hospital mortality were similar to those in non-elderly. In the study, the authors also addressed the comparison between robotic surgery and other surgical approaches to RC and found that the RARC group had the lowest complication rate, and the shortest length of hospital stay. In our series, the use of robotic surgery in patients with a high CCI score (all patients were > 3) provided diminished blood loss, Clavien-Dindo ≥ 2 complications and a lower number of absolute complications Clavien-Dindo ≥ 2. We arbitrarily decided to address the number of complications as a separate variable, beyond their grade: unsurprisingly, 42.8% patients who underwent ORC experienced more than 2 complications, whereas a single patient (4.5%) of the robotic group had multiple adverse events. Furthermore, we addressed complication rate also after the exclusion of pT4 cases, those particularly prone to surgical complications due to the complexity of the surgical dissection. After excluding bulky bladder cancer, the rate of Clavien-Dindo ≥ 2 complications remains much lower in the robotic group compared to open surgery, confirming the less invasive fashion of robotics, which led to lower side effects.

Studying is not devoid of limitations. First, the single center fashion and the restricted sample size are main limits. Second, the absence of patient randomization. As aforementioned, the allocation of patients to the open or to the robotic arm was casual and driven by the surgeon's choice or local planning. Despite recognizing this limitation, it is worth noting that the ASA scores were similar between groups, and the CCI was even higher in the robotic cases. Third, there is a lack of consistent data related to length of stay (LOS). In our context of a public healthcare system, factors other than surgical complexity or complications, such as the time required to acquire self-stoma care skills and to organize outpatient services, often prolong LOS. Therefore, LOS data, influenced by these factors, could not be considered a reliable outcome measure. As a strength, it is noteworthy that this study is the first to explore the role of robotics in patients with an elective indication for CUS. Surgeons tend to select for robotic surgery only those patients who are suitable for complex surgery and/or have minor comorbidities. This series opens a new perspective, where the benefits of robotic surgery become increasingly apparent as patient frailty increases. The robotic cohort's low incidence of medical side effects (fewer thromboembolic events, less blood loss, lower wound infection rates) likely contributed to this finding. It is also important to note that the Trendelenburg position can be limited to 18° in RARC with CUS, thus broadening eligibility even for patients who cannot undergo a steep Trendelenburg position. From a technical perspective, RARC is marginally more complex

than robotic assisted radical prostatectomy (RARP) and the operative times for RARC are like those for RARP. Thus, for surgeons experienced in RARP, the learning curve for the cystectomy component is minimal. This study has certain limitations, including a small sample size and the absence of long-term follow-up data.

CONCLUSIONS

The current series confirms that robotic radical cystectomy is associated with lower morbidity, with reduced incidence of Clavien-Dindo ≥ 2 complications, and a lower number of adverse events. Therefore, robotic surgery appears to be particularly suitable for frail patients with an elective indication for cutaneous ureterostomy, where the benefits of a minimally invasive approach are more pronounced and could lead to a faster post-operative recovery.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 51 (3): e20240615, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0615

Multicenter Retrospective Registry Study on BCG Use in Non-Muscle Invasive Bladder Cancer in Latin America: BLATAM (Bladder Cancer in Latin America) Group

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ABSTRACT

Objectives: This study, conducted by the Bladder Cancer in Latin America (BLATAM) group, aims to analyze epidemiological and therapeutic data on non-muscle invasive bladder cancer (NMIBC) in Latin American patients. It seeks to identify factors contributing to suboptimal responses to Bacillus Calmette-Guérin (BCG) therapy and assess areas for improvement in regional treatment practices.

Materials and Methods: A multicenter retrospective study was carried out in collaboration with reference Urology Departments across Latin America. Data were collected using an electronic Case Report Form (CRF) from 2011 to 2021, capturing demographics, clinical presentation, treatment details, and follow-up of NMIBC patients treated with BCG. Statistical analyses included Kaplan-Meier survival analysis for relapse-free survival (RFS).

Results: Data from 292 patients across five countries were analyzed, with a mean age of 70.3 years and a male prevalence of 74%. Smoking history was reported in 70.6% of patients. The mean time to the first BCG dose was 2.4 months post-TURBT, with 26.7% of patients exceeding the recommended 60-day window for induction initiation. While 84% of patients completed BCG induction, only 45.9% followed the recommended Lamm maintenance schedule. Delays in starting maintenance cycles were observed, with a median delay of

ARTICLE INFO

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Keywords:
Urinary Bladder Neoplasms; Non-Muscle Invasive Bladder Neoplasms; BCG Vaccine

Submitted for publication: November 05, 2024

Accepted after revision: December 15, 2024

Published as Ahead of Print: January 23, 2025

over 36 days for the first cycle and 65 days for the second cycle. RFS at 1 year and 5 years for high-risk patients was 87.3% and 53.3%, respectively.

Conclusions: This study highlights critical deviations from recommended NMIBC management protocols in Latin America, including delayed BCG initiation and inconsistencies in maintenance therapy. These findings emphasize the need for standardized treatment protocols and improved adherence to international guidelines, which could enhance NMIBC patient outcomes in the region. Collaborative efforts are essential to develop region-specific strategies, improve data collection, and ultimately provide better care for bladder cancer patients in Latin America.

INTRODUCTION

Bladder cancer ranks among the most prevalent malignancies worldwide, with a notably increasing incidence in recent years (1-3). The disease's multifaceted clinical presentation and diverse therapeutic approaches pose significant challenges for healthcare systems and clinicians globally.

Within the spectrum of bladder cancer, non-muscle invasive bladder cancer (NMIBC) predominates as the most common subtype. Characterized by its non-invasive nature, NMIBC presents substantial management dilemmas, especially regarding its high recurrence rate and the progression to muscle-invasive disease (4).

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy has emerged as a cornerstone in the management of high-risk and intermediate-risk NMIBC, demonstrating remarkable efficacy in reducing recurrence and progression rates. However, a substantial proportion of patients fail to achieve a satisfactory response to BCG (5, 6), underscoring the need for tailored therapeutic approaches and predictive biomarkers.

In Latin America, the challenges posed by NMIBC (non-muscle-invasive bladder cancer) and BCG therapy are exacerbated by unique regional factors, such as disparities in healthcare access, genetic heterogeneity, and socioeconomic determinants (7-9). Despite these challenges, the marked paucity of complementary data hinders the analysis of regional differences associated with treatment efficacy.

Therefore, our hypothesis was that regional differences in Latin America, including disparities in healthcare access and genetic and socioeconomic particularities, are associated with a lower response to BCG therapy in patients with NMIBC.

This study, facilitated by the creation of the first collaborative group of Latin American urologists dedicated to bladder cancer (BLATAM), aims to collect relevant epidemiological and therapeutic data on the disease, as well as to identify factors that may contribute to a suboptimal response to BCG therapy in Latin American patients.

The information obtained from this study promises to reveal local therapeutic weaknesses, which could contribute to the implementation of regional health policies to improve outcomes for NMIBC patients in Latin America.

MATERIALS AND METHODS

A multicenter retrospective cohort study was conducted by inviting members of reference Urology Departments from the Latin American Confederation of Urology (CAU) and members of the BLATAM group (Bladder Cancer in Latin America) to participate. Participating centers were asked to complete an electronic Case Report Form (CRF) provided by the CAU during the 12 months of 2021, which contained clinical, pathological, treatment, and follow-up data for patients with NMIBC treated with BCG in the 10 years prior to the study initiation in 2021. Patients with inconsistencies in treatment data were excluded. The protocol was reviewed

by the CAU Ethics Office, protocol number 002/2020, no objections were found, and given that anonymous retrospective data would be entered, approval from local Ethics Committees was not required.

Through the electronic CRF, demographic data such as Country and Treatment Center, age, gender, smoking history, as well as information on the original bladder tumor (histological type, grade, previous treatments, number and size of tumors, and performance of re- transurethral resection of bladder tumor [TURBT]) were collected. Follow-up data included time to BCG induction, frequency and intervals of administration, type of BCG regimen, number of doses received, and occurrence of recurrence or progression.

To measure time to the start of induction (six weekly instillations for six weeks), the interval from TURBT to the first dose of BCG was considered, and in cases of re-TURBT, the time from re-TURBT to the start of the first dose of BCG was taken. For time to recurrence or progression, the interval from the first dose of BCG to the diagnosis of the event or the last visit was considered. Recurrence was defined as the appearance of a new tumor diagnosed during follow-up by cystoscopy, while progression referred to the appearance of invasive tumor or distant disease.

For all cases, the frequency of BCG administration was requested. In addition, the frequency of oncological evaluations and the methods employed (cystoscopy, image, cytology, and others) were recorded.

The optimal time for maintenance regimens was considered to be according to the Lamm schedule: three weekly instillations for three weeks at 3, 6, 12, 18, 24, 30, and 36 months from the start of the first induction BCG ± 15 days. For example, the first maintenance cycle should be at 3 months or 90 days from the first induction BCG instillation, with a window for receiving this maintenance from day 75 to 105 (90 days ± 15 days).

Statistical Analysis

Convenience sampling was used given the characteristics of the study. Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to the distribution. Categorical variables are summarized as absolute value and percentage (%). Kaplan-Meier survival analysis was used to estimate 1- and 5-year survival, along with a 95% confidence interval (95% CI). The software used was SPSS 22.0™ (IBM Corp, New York, USA).

RESULTS

Of a total of 454 cases entered into the electronic Case Report Form (CRF), 292 were eligible for inclusion in the study. The percentages of included patients by country were as follows: Argentina (56.4%), Mexico (15.5%), Chile (14.4%), Peru (9.9%), and Brazil (3.8%). Four centers from Argentina (Instituto Alexander Fleming, Hospital Italiano de Buenos Aires, Hospital Alemán de Buenos Aires, and Centro Bengió), 2 from Mexico (Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" and Hospital Central Militar), 2 from Brazil (Instituto Armando Viera de Carvalho and Hospital Regional Paraiba), 1 from Chile (Fundación Arturo López Pérez), and 1 from Peru (Clínica Oncosalud AUNA) participated.

The age range of included population was 20 to 98 years (mean 70.3, SD 11.2), with 216 patients (74%) being male and 76 (26%) females. Regarding medical history, 206 cases (70.6%) were current or former smokers, and 10 (3.3%) had exposure to toxins such as anilines or similar substances. Regarding the clinical presentation of bladder cancer, hematuria was the most common, with 219 cases (75%) (Table-1).

In 201 cases (68.8%), the diagnosis was primary (non-recurrent) cancer. The most common form of presentation at the time of initial TURBT was lesions smaller than 3 cm in 65.1% of cases.

The vast majority of patients had histopathological diagnosis of urothelial carcinoma (98.2%), with a minimal number of reports describing histological variants (urothelial with glandular differentiation and micropapilar). Post-initial TURBT staging revealed 28.8% of patients with pTa disease, 58.6% with pT1, a small proportion with CIS of 2.4%, and the combination of pT1/CIS in 5.5%. A total of 73.6% of patients presented with high-grade disease, with

Table 1 - Descriptive anlaysis: Diagnosis, TNM, Histology, tumor size, Transurethral resection of bladder tumor (TURBT) quality and BCG treatment characteristics.

Diagnosis (%)	Total (n 292)
Haematuria	219 (75)
Incidental	35 (12)
Urinary tract infection	2 (0.7)
Others	36 (12.7)
Histology (%)	
Urotelial	287 (98.2)
Urotelial, glandular differentiation	3 (1)
Micropapilar	2 (0.8)
High grade (%)	215 (73.6)
T Stage (%)	
pTa	84 (28.8)
pT1	171 (58.6)
CIS	7 (2.4)
pT1+CIS	16 (5.5)
Others	14 (10.3)
Tumor Size	
Multiple tumors (%)	102 (34.9)
Largest tumor < 3 cm (%)	190 (65.1)
High risk (%)	193 (66.1)
TURBT quality (%)	
Muscle in TURBT	232 (79.5)
Re TURBT	167 (57.2)
BCG Schedule	
Started Induction	268 (91.8)
Finished Induction	245 (84)
No Maintenance	59 (20.2)
LAMM Maintenance	134 (45.9)
No LAMM Maintenance	99(33.9)
BCG doses	
0-1 doses	120 (41)
2-9 doses	126 (43.1)
>10 doses	46 (15.8)
BCG Intolerance	26 (8.9)

66.1% classified as high-risk according to the 2020 EAU guidelines. The percentage of patients who underwent re-TURBT was 57.2%, as shown in Table-1.

Regarding the quality of the initial TURBT, detrusor muscle was reported in the specimen of 232 patients (79.4%). A re-TURBT was performed in 167 patients, corresponding to 57.2%.

Among patients indicated for intravesical BCG treatment, 268 (91.8%) started induction with a weekly instillation for 6 weeks, only 245 patients (84%) completed it; therefore, only 7.8% of patients did not complete the full regimen of six instillations.

Of the total number of patients, only 45.9% received BCG according to LAMM Maintenance schedule, 33.9% followed a different maintenance regimen, and 20.2% did not receive any maintenance treatment.

The median time to initiation of induction was 1 month (IQR 0-2) (mean time 2.4 months), with 78 cases (26.7%) where the initiation of induction exceeded 60 days. The first maintenance cycle was initiated in 154 patients. The median time to the first maintenance cycle was 126 days (IQR 100-161). Notably, 89.4% of patients began the first maintenance cycle outside the 90-day ± 15-day window, with an average delay of more than 36 days. Among the 118 patients with a reported second maintenance regimen, the median time to initiation was 245 days (IQR 203-294), where 93.2% started outside the 180-day ± 15-day window, with an average delay of 65 days. During the follow up, the median number of doses administered post induction was 3 (IQR 0-9) with only 74 patients (25.3%) receiving 9 or more doses. A total of 29 patients (8.9%) experienced BCG intolerance resulting in treatment interruption (Table-1).

The mean follow-up time was 22.5 months (IQR 12-50), with significant patient loss during this period, as 28.8% of patients did not reach the one-year follow-up. During this time, 69 recurrences (23.6%) were documented. Of the patients who were followed for at least one year, 65% did not receive 9 post-induction doses of BCG.

Among the 222 high-risk patients assessed, the 1-year relapse-free survival (RFS) rate was 87.3% (95% CI 82.8-91.8), the 2-year RFS rate was nearly

80% and the 5-year RFS was 53.3% (95% CI 42.4-64.6) (Figure-1).

Reported treatment for recurrence cases included: additional BCG regimens in 22 cases (31.9%), mitomycin in 5 cases (7.2%), and gemcitabine, or inclusion in clinical trials in 4 cases (5.8%). Cystectomy was performed in nine cases (13%), while treatment was not reported in 28 cases.

Regarding follow up cystoscopies, 85% of patients (248) underwent the first cystoscopy at 3 months, with a decreasing number at 6 months (175 patients, 60%), 9 months (147 patients, 50%), and only 100 (34%) at 12 months.

Urine cytology was taken as follows: 140 PAPs at 3 months (56.5%), 112 (38%) at 6 months, 81 (28%) at 6 months, and 71 (24%) at 12 months.

DISCUSSION

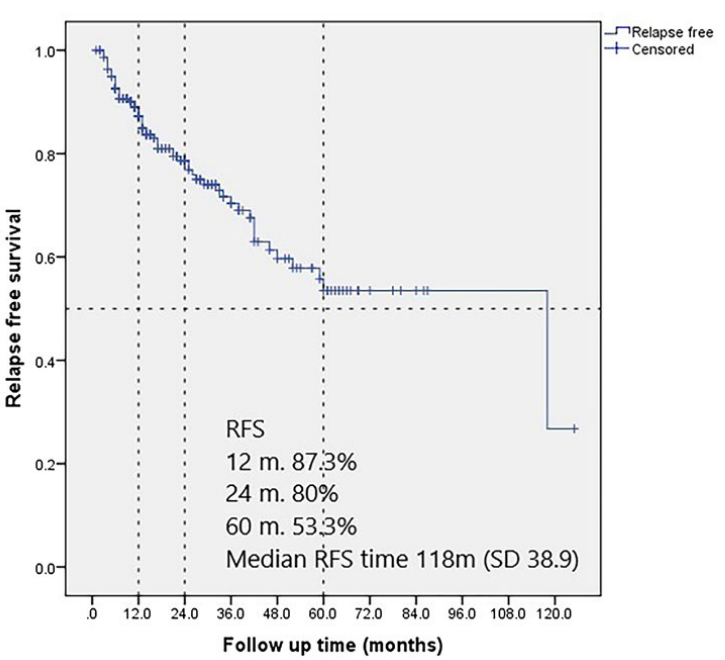
Bladder cancer has distinct characteristics that differentiate it from other types of cancer, primarily due to the difficulty in predicting its behavior. Not only does it have a high recurrence rate, but in some cases, it can potentially progress to more advanced stages. Bladder Carcinoma In Situ (CIS), unlike other locations, can behave aggressively, with a high probability of progressing to the deeper layers of the bladder wall if not treated adequately (10).

Our study provides valuable information on the clinical presentation, epidemiological aspects of non-muscle-invasive bladder cancer (NMIBC) in Latin American patients, and how these patients are treated in this region. While our findings, for the most part, agree with established global trends regarding the prevalence of initial diagnostic symptoms and the widespread use of Bacillus Calmette-Guérin (BCG) therapy, our analysis reveals inconsistencies related to the quality of treatments.

Our data of age and gender are consistent with the global trend of a higher incidence in men. However, it is interesting to note that, globally, incidence rates increase more sharply between the ages of 50 and 54, especially in men (11).

The use of tobacco is the most frequent risk factor and is associated with approximately 50% of bladder cancer cases (11, 12), in our registry, a higher

Figure 1 - Kaplan Meier curve. Relapse free survival (RFS) and medial survival time in high-risk patients.



percentage of 70.6% was found to be related to smoking.

Our findings agree with those reported by Ramírez et al. (13), who found that gross hematuria was the most common presenting symptom in 75% of our bladder cancer patients, a figure similar to the 78.3% described in their study. This high prevalence of gross hematuria at diagnosis reinforces the importance of this clinical manifestation as a warning sign. Additionally, our data corroborate the association between gross hematuria and more advanced pathological stages, underscoring the need for early detection to improve prognosis.

Regarding reported histological variants, our detection rate was 1.8%, significantly lower than the average of 25% described in literature. The results obtained underscore the crucial importance of having specialized pathologists in multidisciplinary teams (14) to optimize diagnosis and, ultimately, patient outcomes. Similarly, our detection rate of carcinoma in situ (CIS) was 7.9%, lower than the reported (10%) (14, 15). These findings highlight the potential of advanced imaging technologies such as blue light cystoscopy, although its high cost limits its implementation in Latin America.

The quality of the first transurethral resection of the bladder (TURB) is fundamental to the management of bladder cancer. The presence of detrusor muscle in the specimen, which in our series was 80%, is a key indicator of an adequate resection and has been associated with better oncological outcomes, including recurrence time and cancer-specific survival (16, 17). However, the percentage of patients who required a re-TURB in our cohort (57%) suggests that there is still room for improvement. Recent studies, such as the NIMBUS trial (18), have demonstrated that a higher rate of re-TURB, close to 90%, can improve oncological outcomes. These findings highlight the importance of following current guidelines and considering re-TURB more aggressively, especially in cases of incomplete resections or pT1 lesions.

Our analysis revealed significant deviations from established treatment guidelines for NMIBC, particularly regarding the initiation of intravesical BCG therapy. In our study, the mean initiation of the first induction dose of BCG was 2.4 months post-TURBT, considerably later than recommended in pivotal studies such as SWOG 8507 (6) and EORTC 30962 (6,19), where initiation was recommended 15 days post-TURBT. This delay in treatment initiation could compromise the efficacy of BCG and oncological outcomes. It is essential to align our clinical practices with international recommendations to optimize the management of these patients.

Maintenance schedules with BCG have been shown to be essential in preventing bladder cancer recurrence. However, our results indicate that a significant percentage of patients did not receive the recommended number of BCG instillations according to established regimens, such as the Lamm protocol. 84.3% of our patients received less than 9 maintenance doses in the first year, and furthermore, significant delays in the initiation of maintenance cycles were observed. These deviations from clinical guidelines could compromise treatment efficacy and increase the risk of recurrence.

Despite protocols recommending 15 BCG instillations during the first year, as demonstrated in NIMBUS trial, our findings indicate suboptimal adherence to treatment. This lack of compliance with established guidelines raises concerns about the efficacy of intravesical therapy and could increase the risk of recurrence and disease progression. Delays in the initiation of treatment and deviations in dosing regimens may compromise the immune response induced by BCG and consequently affect oncological outcomes.

In our study, we detected a considerable patient lost to follow up. Despite this characteristic, the RFS results were not so distant from those reported. However, it is not intended to emphasize that by performing an incorrect scheme or follow-up, the same results are obtained as when performing the scheme correctly. Our study is biased due to all the factors described above, but mainly because of the limited recording of recurrences, the significant loss of follow-up, and the large amount of missing data we encountered. This RFS should not be considered as an indicator that good results can be achieved by doing things incorrectly. Instead, it should serve as a

reminder to improve our treatments and report data more accurately.

A significant limitation of our study relies on the inability to accurately quantify the proportion of non-responders to BCG, reflecting the lack of standardized follow-up protocols in the region. This observation highlights the need for more robust monitoring systems to evaluate treatment response. In parallel, recent years have witnessed an evolution in the management guidelines for non-muscle-invasive bladder cancer, with a greater emphasis on the continuity of BCG treatment even in the face of low-grade recurrences. This new perspective, supported by growing evidence, seeks to optimize outcomes for patients. Additionally, the incorporation of office-based electrocoagulation has expanded therapeutic options for the management of low-grade lesions, improving patient accessibility and quality of life (20).

Treatment protocols for bladder cancer have been significantly impacted by two several factors. The COVID-19 pandemic, disrupting in healthcare and compromising treatment adherence and highlighting the need to develop more flexible and adaptable care systems. Secondly, the recurrent global shortage of the drug (19, 21), this scarcity can be attributed to various factors, including increased demand, production constraints, and regulatory hurdles (20, 22). The lack of access to BCG is heterogeneous across the region, being more evident in some countries, such as Brazil (8).

The adoption of electronic health records (EHRs) in Latin American healthcare institutions lacks a homogeneous planning. While it has improved operational and registration efficiency, it has introduced new challenges for research. Data fragmentation, lack of compatibility between systems, and the loss of historical information during the transition have limited the ability to perform comprehensive retrospective analyses. These inherent limitations of EHRs have affected the robustness of our findings, demonstrating the need to develop standards for transitions and the analysis of clinical data in the region.

The heterogeneity in the management of NMIBC in Latin America and the challenges identified in our study underscore the need to strengthen research in this area. Through collaborative research, we can develop more effective treatment protocols, identify predictive biomarkers of response, and evaluate the impact of interventions on patients' quality of life. It is essential to invest in research to improve outcomes for NMIBC patients in our region.

Therapeutic options have traditionally been limited, primarily relying on intravesical Bacillus Calmette-Guérin (BCG) and mitomycin C (MMC). Currently, treatment options remain constrained, with the only approved systemic therapy being intravenous pembrolizumab and the sole approved intravesical therapy being nadofaragene firadenovec, both indicated for BCG-unresponsive carcinoma in situ (CIS) in the United States. However, research in this field is highly active, with numerous promising alternative therapies under development that have the potential for regulatory approval in the near future. For intermediate-risk NMIBC, a preference exists for ablative approaches over adjuvant therapies. In contrast, for high-risk NMIBC, clinical trials predominantly focus on investigating alternatives to BCG, such as substituting BCG entirely or minimizing patient exposure by employing induction-only courses, often in conjunction with novel therapeutic agents.

CONCLUSIONS

In conclusion, the need to consolidate collaborative registries in Latin America is imperative. By joining efforts and collecting data more efficiently, we can obtain a more accurate and up-to-date view of the clinical reality in our region. This will not only enrich our caseload and pathological diagnoses but also evaluate the efficacy of implemented therapeutic alternatives. It is essential to promote the creation of new prospective studies with a larger number of patients and long-term follow-up to strengthen the scientific evidence and improve care for our patients.

ACKNOWLEDGEMENT

We are grateful to Ferring S.A. for their generous sponsorship of this study. Their support made it possible to conduct this multicenter registry, provid-

ing valuable insights into the management of non-muscle invasive bladder cancer in Latin America.

COMPLIANCE WITH ETHICAL STANDARDS

Ethics approval and consent to participate

We obtained the ethics approval

Consent for publication

We obtained written consent for publication from the patients

Availability of data and material

The information was obtained from patient's medical records

FUNDING

We obtained funding sources from Ferring SA.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 51 (3): e20259905, May-June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9905

Novel Role Of DSNB in Staging of Primary Urethral Cancer: New Standard?

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ABSTRACT

We describe the novel use of dynamic sentinel node biopsy (DSNB) in five patients with primary urethral squamous cell carcinoma (U-SCC) and no evidence of inguinal node disease across two centers in North America and Europe between 03/2021 and 06/2024. Each of these referral centers sees over 75 cases of penile cancer per year and approximately 10 cases of U-SCC per year. Patients underwent DSNB concomitant to surgical resection of the primary tumor (n=3), or in a deferred manner (n=2), six weeks after primary surgery. In the five DSNBs performed, clinically occult nodal metastasis was discovered in one patient. In this patient DSNB was performed after local recurrence and repeat imaging confirming cN0 status. Only one minor complication with DSNB was observed. Awaiting further investigations in larger series, this study highlights the feasibility of DSNB in primary U-SCC with clinically node negative disease.

ARTICLE INFO

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Keywords:
Urethral Neoplasms; Sentinel Lymph Node Biopsy

Submitted for publication:
January 12, 2025

Accepted:
January 15, 2025

Published as Ahead of Print:
January 31, 2025

INTRODUCTION

Case series

Urethral squamous cell carcinoma (U-SCC) is a rare disease (1). Despite similarities in histology and lymphatic drainage with penile squamous cell carcinoma (PSCC), the clinical recommendations in management of inguinal lymph nodes are different and less defined. Current EAU and NCCN guidelines do not support diagnostic sentinel lymph node surgical excision or prophylactic superficial inguinal lymph node dissection (ILND) for primary urethral carcinoma in the setting of patients that are cN0, regardless of primary stage (2, 3). Werntz et al., studied the node positive rates in 86 cN0 patients with U-SCC undergoing prophylactic inguinal lymph node dissection (ILND), demonstrating only a 9% lymph node positive rate in pT1-T4, cN0 tumors, although rate of pN+ was not risk stratified by primary T stage (4).

However, it is well-established that nodal metastasis is one of the strongest predictors of recurrence and survival in primary urethral carcinoma (5-7). By the time patients have clinically evident nodes, treatment strategies are often multidisciplinary, with limited curative potential. In this context, the value of early identification of patients at risk of harboring early nodal metastasis cannot be overstated. Herein, we share a case series utilizing a previously unreported dynamic sentinel node biopsy (DSNB) technique in patients with clinically node negative primary U-SCC.

We identified five patients with cN0 U-SCC (all were confirmed to be primary urethral tumors by genitourinary pathologists). Tumoral characteristics and DSNB protocol are shown in Table-1. 99mTc-nanocolloid was injected subcutaneously, immediately proximal to tumor. A dynamic recording was started immediately following tracer injection with the detector positioned anteriorly at the level of the pelvis. This procedure was repeated until a SN was visible (uni- or bilaterally) up to a maximum of 60 minutes. Finally, a SPECT/CT of the pelvis was performed to detect and localize the SNs. Late imaging (static planar and/or SPECT/CT) was acquired, with or without additional tracer injection, if no SN was visible after the initial imaging phase. Initial radiotracer dosing was not standardized. Intraoperatively, subcutaneous isosulfan blue dye was injected in 3 cases and free indocyanine green (ICG) was used in 2 cases. The number and location of sentinel nodes were described as first echelon if within Dressler's Triangles (primary echelon), above the inguinal ligament (secondary echelon) and pelvic nodes (tertiary echelon). SNs were pursued using a gamma probe (Neoprobe, Johnson & Johnson Medical) and fluorescence camera (FIS-00, Photodynamic eye, Hamamatsu Photonics) in cases utilizing ICG. All harvested nodes were embedded in sections of 2mm thickness and screened with H&E staining. If the SN seemed negative for carcinoma during initial screening, deeper sections of 500 microns were made and stained for prekeratin (AE1/AE3). Follow up consisted of physical examination and inguinal imaging every 3 months during the first 2 years after DSNB.

One patient was found to have a DSNB positive for disease 7 months after initial diagnosis and 1 month after local recurrence. His initial treatment was a partial penectomy and distal urethrectomy revealing a pT3a, Grade 2, primary urethral carcinoma with negative surgical margins. At the time of LR, repeat contrasted MRI revealed no regional lymphadenopathy (cN0). LR was treated with total penectomy and urethrectomy. DSNB patient revealed 1/7 nodes positive with a unifocal 6mm with extranodal extension (Figure-1). He underwent a bilateral superficial and deep inguinal lymphadenectomy with all 8 nodes negative. He remains clinically disease free since DSNB without receipt of adjuvant therapy.

DISCUSSION

Urethral squamous cell carcinoma (U-SCC) appears to be a separate entity from PSCC despite similarities in histology, location and lymphatic drainage. Unlike PSCC, where prophylactic ILND for cN0 disease has shown survival benefit, early ILND has no current role in cN0 U-SCC (8). There are very few studied examining inguinal nodal management of male U-SCC. The largest study examining nodal management of primary U-SCC in men found that ILND was only associated with an improvement in overall survival in cN+ patients (4). This study did not differentiate pN+ rates in cN0 patients based on primary T stage and grade, which questions

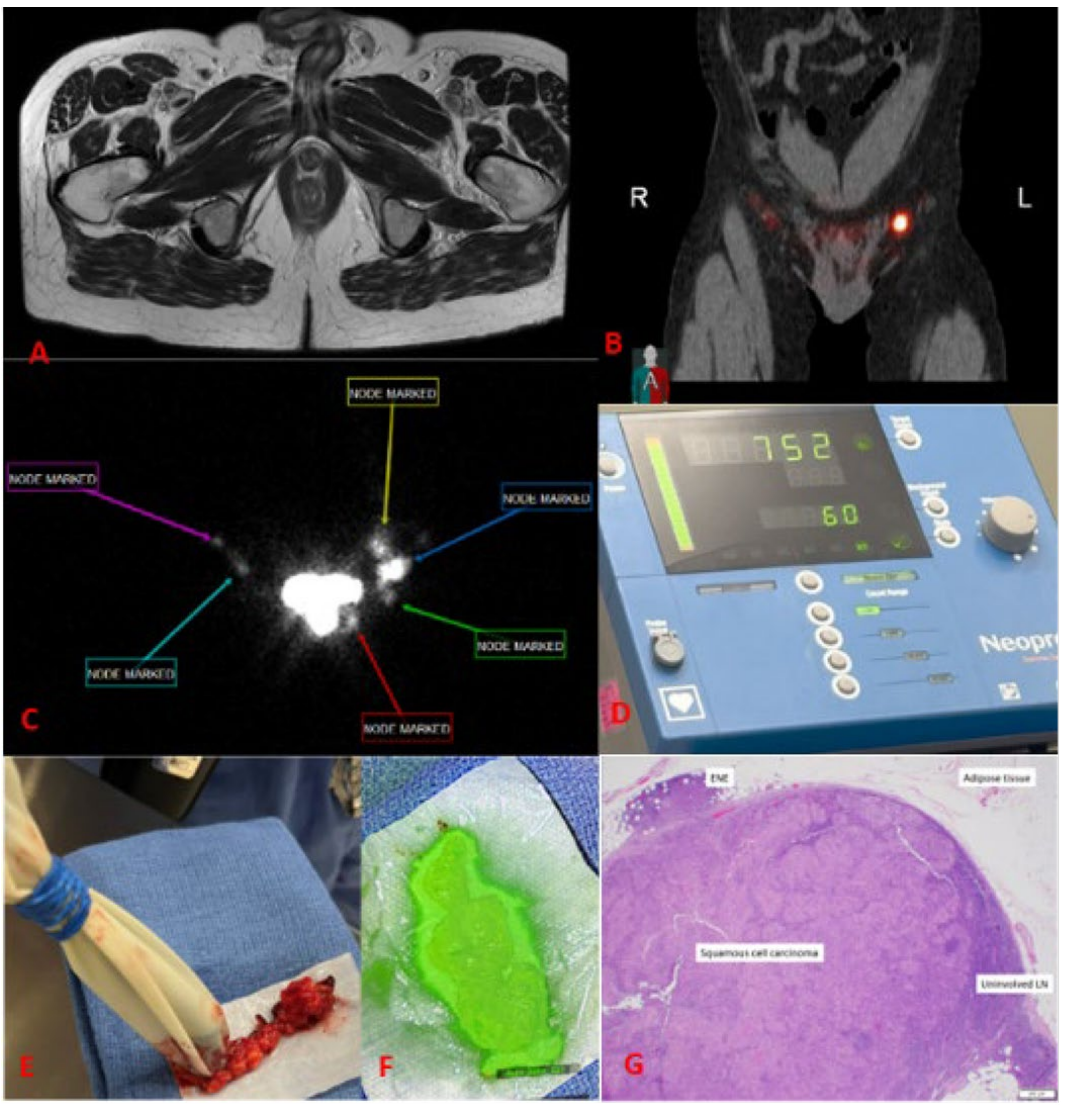
Table 1 - Outcomes for patients undergoing DSNB for cN0 primary urethral carcinoma. Pt = Patient.

	P1	P2	P3	P4	P5
Age at Diagnosis (yrs)	71	57	67	85	67
History of urethral stricture	No	No	Yes	No	No
History of CIC	No	No	Yes	No	No
Smoking status	Former	Never	Current	Never	Never
Primary tumor location	Distal urethra	Bulbar urethra	Bulbar urethra	Bulbar urethra	Distal urethra
Primary tumor investigation	Cysto	Cysto+MRI	Cysto+MRI	Cysto	Cysto
HPV status	Positive	Negative	Negative	Negative	Positive
Primary surgery	PP+DU	TP+TU	TP+TU	PP+DU	PP+DU
pT stage	2	3	3	2	3
Histology	NA	NA	NA	NA	Warty-Basaloid
Grade	3	2	2	3	2
Margin status	Invasive	Negative	Negative	Negative	Negative
Inguinal node investigation	US+PET/CT	US+PET/CT	US+ CT	CT	MRI
DSNB radiotracer	99mTc-COL	99mTc-COL	99mTc-COL	99mTc-COL	99mTc-COL
Dosage (MBq)	80	120	60	16.9	16
Injection site	Adjacent	Adjacent	Adjacent	Adjacent	Adjacent
Adjunct dye	Isosulfan blue dye	Isosulfan blue dye	Isosulfan blue dye	Free ICG	Free ICG
Primary Imaging of SN	NM SPECT/CT	NM SPECT/CT	NM SPECT/CT	NM SPECT/CT	NM SPECT/CT
# of SN on imaging (R)	3	1	1	1	4
# of SN on imaging (L)	0	1	1	1	2
Location of SN (R)	1º, 2º	1º	1º	1º	1º
Location of SN (L)	Non-visible	1º	1º	1º	1º, 2º
# nodes harvested (R)	3	1	1	1	6
# nodes harvested (L)	0	2	1	1	1
DSNB pN stage	0	0	0	0	III
Complication	None	None	None	None	Lymphocele

CIC = Clean intermittent catheterization. MRI = Magnetic resonance imaging. US = Ultra-sonography. CT = Computed tomography PET = Positron emission tomography. 99mTc-nanoCOL = Technetium nanocolloid nuclear isomer.

NM SPECT = Nuclear Medicine single-photon emission computed tomography. PP = Partial Penectomy. TP = total penectomy. DU = Distal urethrectomy TU = Total penectomy.

Figure 1: DSNB protocol for primary urethral squamous cell carcinoma.



whether a certain subset of cN0 patients with primary urethral cancer may benefit from invasive regional node sampling.

The prognosis of node positive, pure squamous cell urethral carcinoma remains unknown and studies assessing the impact of histology on outcomes in primary urethral carcinoma are limited. Studies including patients with urothelial, squamous cell and adenocarcinoma histology report overall survival outcomes of primary urethral carcinoma of all histologic types at 5 and 10 years at 46% and 29%, respectively, and report that the presence of nodal spread independently predicts an increased likelihood of death [HR 2.07 (1.17-3.67) p=0.013] (5). A study of 46 males with predominantly squamous cell carcinoma of the urethra by Dalbagni et al. identified squamous cell and epidermoid histology as a predictor of worse overall and cancer specific survival (p=0.0001) and reported 5 years overall and disease specific survival rates at 42% and 50% respectively (6). In this study we demonstrate that DSNB can identify patients with early nodal spread and provide an opportunity for early curative therapy.

We highlight the similarities and differences of DSNB technique between the two institutions. The

choice of radiotracer and imaging nodality to detect sentinel nodes was identical. Interestingly, the European technique incorporates the use of inguinal ultrasound to further select patients for DSNB. Only patients without suspect lymph node on ultrasound or patients with questionable nodes on ultrasound but negative fine needle aspiration cytology (FNAC) are selected for DSNB. This additional measure is interesting and studies from the Netherlands Cancer Institute have been shown this to potentially enhance the sensitivity of DSNB (9). At our institution, provided patients had no suspicious inguinal nodes on axial imaging obtained within 6 weeks of the procedure, we prefer to use free unbound indocyanine green injection peri-urethrally and evaluate nodes intraoperatively using real time infrared photography. Only nodes that are intraoperatively radioactive and ICG positive are resected. In contrast, our colleagues in Europe use methylene blue, allowing visualization of blue dye within lymphatic channels and sentinel nodes. Collaborative efforts to standardize techniques will be beneficial in providing a uniform guideline for successful DSNB.

We hypothesize that DSNB alone may potentially cure a subset of patients with micro-metastatic disease, while discovering and selecting patients with more aggressive disease for early curative measures. Penile cancer and urethral cancer are thought to exhibit predictable stepwise lymphatic metastasis from inguinal to pelvic and para-aortic nodes. Distant metastasis is atypical without concurrent LN spread (10, 11) Radical LN surgery remains the cornerstone of management for early nodal disease (cN1–2) but is associated with significant morbidity and the benefit of adjuvant treatments is uncertain. Nodal surgery alone is often not curative in cases of extensive LN involvement. Therefore, multimodal treatment approaches with (neo)adjuvant chemotherapy and/or radiotherapy (RT) are often considered (12-14). In current guidelines, neoadjuvant chemotherapy is recommended in patients presenting bulky inguinal disease, pelvic metastases on imaging. In the group of patients without radiological signs of pelvic LN involvement with two or more tumor-positive ipsilateral inguinal LN metastasis or the presence of extranodal extension (ENE), surgical treatment of the pelvis (so-called prophylactic pelvic treatment) is recommended.

Clearly, the paradigm of clinical care for primary urethral cancer continues to evolve and we suspect the application of DSNB may represent a further refinement in clinical care. We encourage prospective validation of our work as an international collaborative effort, possibly through organizations like the Global Society of Rare Genitourinary Tumors. We hope that the novel use of this technique is further investigated as a diagnostic and treatment standard in those with locally advanced (pT2-4) urethral cancer in the setting of cN0. DSNB, with its relatively low complication rates, may represent an accommodating middle ground between the need for diligent surveillance with physical exam and imaging in an effort to avoid occult nodal metastatic progression versus potentially morbid ILND surgery which patients and physicians alike are hesitant to propose without a clear benefit it can offer.

COMPLIANCE WITH ETHICAL STANDARDS

Ethics

This study was conducted following the Declaration of Helsinki.

Data Availability

Data is available upon request from the corresponding author.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 51 (3): e20259906, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9906

Qualitative and quantitative characterization of the Rhesus monkey (*Macaca mulatta*) penis

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ABSTRACT

Background: Knowledge of the anatomy of laboratory animals is important for experimental research. Erectile dysfunction has been studied using the penises of different laboratory animals such as rats, mice, rabbits, dogs, etc. However, these animals have penises with different characteristics to the human penis. If these differences are not taken into account, the conclusions may be questionable. The Rhesus monkey (*Macaca mulatta*), due to its similarities to humans, could be a good model.

Objective: To characterize and quantify the components of the penis of the Rhesus monkey (*Macaca mulatta*), qualifying it as a model for experimental studies.

Methods: Ten adult Rhesus monkey penises were fixed in 10% buffered formalin and processed for paraffin embedding. Histological sections 5-μm thick were made and stained using histochemical techniques. We assessed the thickness of the tunica albuginea, and in the erectile tissue, the following parameters were analyzed: in the corpus cavernosum (CC): total area, area densities of collagen fibers, muscle fibers and elastic system fibers; in the corpus spongiosum (CS): area densities of collagen fibers, muscle fibers and elastic system fibers. Histomorphometric analyses were carried out on photomicrographs by using ImageJ software.

Results: The penis of the Rhesus monkey (*Macaca mulatta*) has a single CC. The tunica albuginea was thicker in the dorsal region (1.11 ± 0.03 mm) than in the ventral region (0.87 ± 0.01 mm). The quantitative analysis of the CC showed the following values: total area (20.33 ± 5.67 mm^2), collagen fibers (24.00 ± 4.00%), muscle fibers (31.52 ± 9.93%) and elastic system fibers (8.46 ± 3.20%). The quantitative analysis of the CS showed the following values: collagen fibers (52.50 ± 11.76%), muscle fibers (10.50 ± 6.36%) and elastic system fibers (15.07 ± 4.78%).

Conclusion: The predominance of muscle tissue over connective tissue in the corpus cavernosum, similar to what is observed in humans, qualifies the Rhesus monkey penis as a good experimental model for erectile dysfunction.

ARTICLE INFO

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Keywords:
Penis; Macaca mulatta; Models, Theoretical; anatomy and histology [Subheading]

Submitted for publication: January 12, 2025

Accepted after revision: February 14, 2025

Published as Ahead of Print: February 25, 2025

INTRODUCTION

Different studies classify the penis into two types according to different species: fibroelastic, in which the penis increases in length and changes little in diameter; and muscle-cavernous, in which the penis increases in both length and diameter (1, 2).

The human penis is muscle-cavernous and composed of the glans, two corpora cavernosa (CC) and the corpus spongiosum (CS). The CCs are completely surrounded by the tunica albuginea, which is composed of collagen fibers and fibers from the elastic system. The elastic fibers usually form an irregular network on which the collagen fibers rest. The CCs contain smooth muscle fibers and fibrous connective tissue that form the wall of the sinusoids. The CS surrounds the urethra and, similar to the CC, is composed of smooth muscle and connective tissue fibers. Smooth muscle is an essential component of the sinusoids in the CC, CS and glans penis (3-5).

Rats and mice are widely used as experimental models for studies on the urogenital system (6-8). However, the rat penis is of the fibroelastic type, as well as has a bone component and a predominance of connective tissue in the CC (1, 5, 9).

Among non-human primates, the Rhesus monkey (*Macaca mulatta*) is the species most used in scientific research. This is due to the similarities between the Rhesus monkey and the human being (10). The penis of the Rhesus monkey is of the muscle-cavernous type (10).

There are several works in the literature on the structure of the Rhesus monkey's organs: lower urinary tract (11), kidneys (12-14), prostate (15), vas deferens (16), immune (17) and lymphatic systems (18), bone tissue (19) and metabolic disorders (20).

A detailed description of the Rhesus monkey penis, as well as a characterization of the different structures that compose it, has not yet been done. A study along these lines, showing very similar parameters to the human penis, could justify the use of the Rhesus monkey penis as an experimental model.

This study aims to determine, using qualitative and quantitative methods, the morphological and histological characteristics of the penis of the Rhesus monkey (*Macaca mulatta*), qualifying it as a model for experimental studies in humans.

MATERIAL AND METHODS

The study protocol was approved by the Animal Ethics Committee (CEUA Protocol No. 014/2015) of the Institute of Biological and Health Sciences of the Federal Rural University of Rio de Janeiro (UFRRJ).

Ten penises from adult Rhesus monkeys were collected, fixed in 4% buffered formalin and processed for paraffin embedding. Histological sections 5-μm thick were obtained from each sample and stained using the following histochemical techniques: hematoxylin and eosin to evaluate tissue integrity; Picrosirius red without polarized light to analyze the density of collagen fiber areas in the CC and CS; Picrosirius red with polarized light for qualitative analysis of collagen fibers in the tunica albuginea; Masson's trichrome for the thickness of the tunica albuginea, analysis of the area of the CC and the area density of the muscle fibers in the CC and CS; and Weigert's resorcin-fuchsin with previous oxidation for analysis of the area density of the fibers of the elastic system in the CC, CS and qualitative analysis in the tunica albuginea.

All histomorphometric analyses were carried out using ImageJ® software, version 1.50i, loaded with its own plug-in (http://www.imagej.nih.gov/ij).

Histomorphometric analyses of the thickness of the tunica albuginea and the area of the CC of the penis, including the tunica albuginea, were carried out using X12 magnification photomicrographs taken with a stereomicroscope (SteREO Discovery.V8, Zeiss, Göttingen, Germany) coupled to a digital camera (Axiocam 506 color, Carl Zeiss, Göttingen, Germany).

The "straight line" tool was used to analyze the thickness of the tunica albuginea of the CC (expressed in mm), in which three random linear measurements were taken in the dorsal and ventral regions, and the average of the measurements was taken to obtain the thickness of the tunica albugin-

ea in each region. The "freehand" tool was used to analyze the area of the CC (expressed in mm^2), in which three measurements were taken in each field, and these were averaged to obtain the area of the CC. For both analyses, five sections of each sample were analyzed, and one field of each section was observed, for a total of five fields in each sample.

Histomorphometric analyses of the area densities of collagen fibers, muscle fibers and elastic system fibers (expressed as percentages) in the CC and CS were carried out using photomicrographs at X600 magnification, obtained by using a microscope (Olympus BX51, Tokyo, Japan) equipped with a digital camera (Olympus DP71, Tokyo, Japan). The area density of these parameters was estimated using the quantification evaluation method, by superimposing a 100-point test grid (multipurpose test system) on the magnified images on the video monitor screen (21). For all these analyses, five sections of each sample were analyzed and five random fields of each section were observed, for a total of 25 fields in each sample.

RESULTS

In the qualitative analysis, we observed a single CC (Figure-1), surrounded by a thick tunica albuginea, composed mainly by type-I collagen, due to the presence of thick collagen fibers with red birefringence and less numerous elastic system fibers (Figure-2). The tunica albuginea was thicker in the dorsal region (+21.62%) than in the ventral region (Table-1). The analysis of the density of smooth muscle, collagen and elastic fibers areas, the Corpus Cavernosum showed a predominance of smooth muscle fibers (49%) over collagen (38%) and elastic system fibers (13%). On the other hand, the Corpus Spongiosum showed a predominance of collagen (67%), over elastic system fibers (19%) and smooth muscle fibers (14%). The quantitative analyses of

Figure 1 - Photomicrograph of the Rhesus monkey penis. Tunica albuginea (yellow arrow), corpus cavernosum (red arrow), corpus spongiosum (black arrow), urethra (asterisk). Masson's Trichrome, X12.

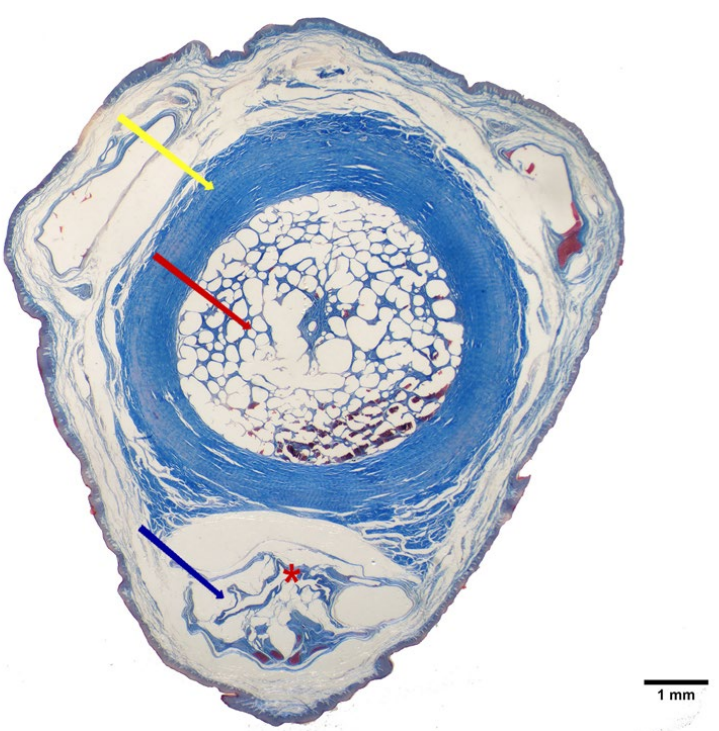


Figure 2 - Photomicrographs of the tunica albuginea of the Rhesus monkey penis. A) Thick collagen fibers (yellow arrow), type-I collagen, picrosirius red with polarization, X600. B) Elastic system fibers are less numerous (black arrow). Weigert's resorcin-fuchsin, X600.

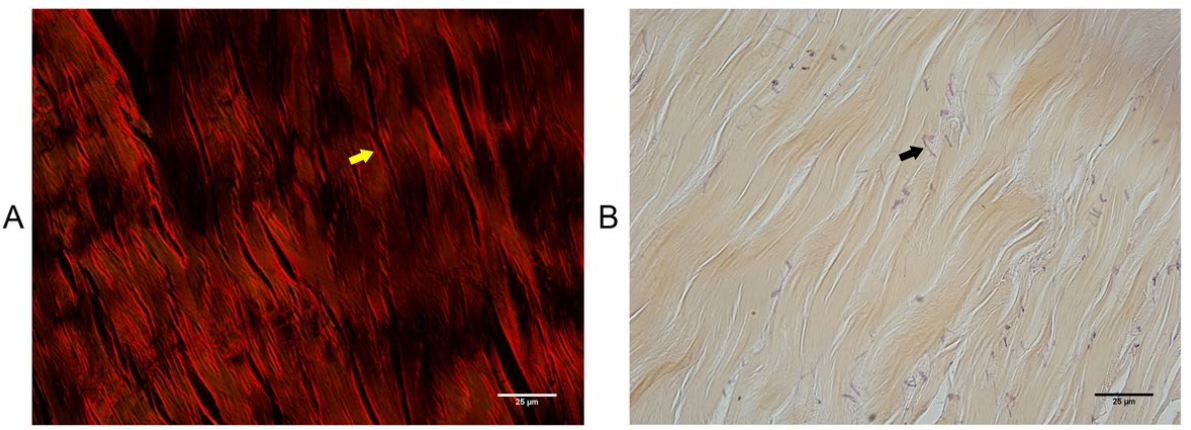


Table 1 - Data on the parameters analyzed in the corpus cavernosum and corpus spongiosum of the penis of the Rhesus monkey (Macaca mulatta)

Data	Values (mean ± standard deviation)	
	Corpus cavernosum parameters	Corpus spongiosum parameters
Thickness of the dorsal tunica albuginea (mm)	1.11 ± 0.03	-
Thickness of the ventral tunica albuginea (mm)	0.87 ± 0.01	-
Total area (mm^2)	20.33 ± 5.67	-
Sv [collagen fibers] (%)	24.00 ± 4.00	52.50 ± 11.76
Sv [muscle fibers] (%)	31.52 ± 9.93	10.50 ± 6.36
Sv [elastic system fibers] (%)	8.46 ± 3.20	15.07 ± 4.78

Sv = surface densities

the components of the CC and CS are shown in Table-1. Figure-3 shows the different components of CC and CS.

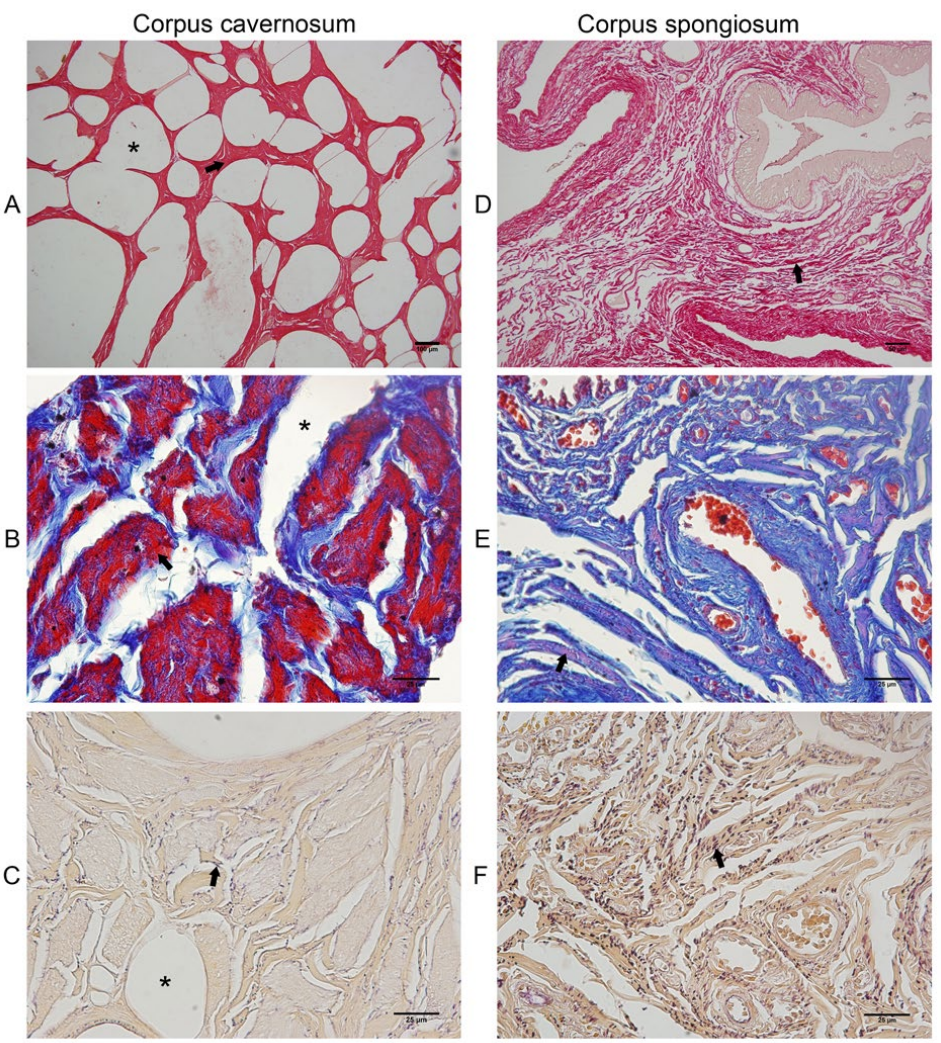
DISCUSSION

Knowledge of the anatomy of laboratory animals is essential for experimental research, allowing the animal to be adapted to the study being carried out. Erectile dysfunction, for example, has been studied using the penises of different species (22), including rats and mice (23, 24), rabbits (25) and monkeys (26).

Although these species have several characteristics similar to those of the human penis, there are differences in the penile anatomy of these animals compared to the human penis (1, 5, 9).

The rat's CC is predominantly composed of connective tissue (1, 5, 9). In contrast, the male penis is predominantly muscular. This could make it difficult to make a comparison using these animals

Figure 3 - Photomicrographs of the corpus cavernosum and corpus spongiosum of the Rhesus monkey penis. A) Corpus cavernosum, sinusoids (*), collagen fibers (arrow), picrosirius red, X100. B) Smooth muscle fibers (arrow), sinusoids (*), Masson's trichrome, X600. C) Elastic system fibers (arrow), sinusoids (*), Weigert's resorcin-fuchsin, X600. D) Corpus spongiosum, collagen fibers (arrow), picrosirius red, X200. E) Smooth muscle fibers (arrow), Masson's trichrome, X600. F) Elastic system fibers (arrow), Weigert's resorcin-fuchsin, X600.



as a model. As in rats, the penises of dogs and cats also have a bony component in their cranial part, which is considered to be an ossified part of the CC and is part of the erectile components (27, 28).

The human penis has two paired corpora cavernosa (4), as is the case with other species such as rats, dogs and rabbits, in which the penis has two distinct corpora cavernosa, partially separated by the median septum (27). The penis of the Rhesus monkey was not clearly divided into two corpora cavernosa. De Siqueira et al. (29) also observed a single non-septated CC in the marmoset. Despite being unique, the components of the Rhesus monkeys CC are very similar to those of humans, such as the predominant presence of smooth muscle fibers in relation to the fibrous component. This characteristic allows for a more reliable comparison. The proportion of smooth muscle fibers in the CC of the human penis is approximately 40% (30). Simi-

larly, the CC of the Rhesus monkey penis had 49% more muscle fibers than the other components analyzed.

The tunica albuginea of the CC in humans is a structure composed of inner circular and outer longitudinal layers which have bundles of thick collagen fibers resting on a network of irregularly arranged elastic fibers (3, 31, 32). In the CC of the penis of the Rhesus monkey, we observed a thick tunica albuginea enveloping the entire CC, which showed thick collagen fibers birefringent in red when observed under polarized light, which may characterize type-I collagen fibers. The analysis of the tunica albuginea in adult men showed that the dorsal region was thicker than the ventral region, making the ventral region a more vulnerable area, as in humans (33). Even from the human fetal period, the tunica albuginea already shows a morphological difference in relation to the dorsal and ventral regions. Gallo et al. (34) studied human fetuses between 13- and 36-weeks post-conception and reported that the thickness of the tunica albuginea was greater in the dorsal than ventral region. In our study, the tunica albuginea of the Rhesus monkey penis also showed this characteristic of being thicker dorsally than ventrally (+21.62%).

It is known that the elastic system fibers form an interconnected network in order to keep the collagen fiber bundles together (32). The density of elastic system fibers in the CS of the Rhesus monkey penis was higher than in the CC (+ 43.86%). These characteristics are very similar to those described in the human penis, where there is also a predominance of elastic fibers in the CS (31).

All the similarities between the different structures when comparing the penis of the Rhesus monkey and humans, fully justify the use of this animal as a good experimental model for the study of the human penis.

CONCLUSIONS

The predominance of smooth muscle fibers over connective tissue in the corpus cavernosum, similar to what is observed in humans, qualifies the penis of the Rhesus monkey as a good experimental model.

FUNDING

This study was supported by grants from the National Council for Scientific and Technological Development (CNPq - Brazil) and the Rio de Janeiro Foundation for Research Support (FAPERJ - Brazil)

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

NEUROUROLOGY

Vol. 51 (3): e20249908, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9908

Editorial Comment: Does Surgical Treatment for Benign Prostate Enlargement (BPE)-Related Bladder Outlet Obstruction (BOO) Benefit Patients with Central Nervous System Diseases? A Systematic Review

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J Clin Med. 2024 Sep 30;13(19):5846.

DOI: 10.3390/jcm13195846 | ACCESS: 39407906

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COMMENT

The risk of bladder outlet obstruction (BOO) related to benign prostate enlargement (BPE) increases with age and concerns all men, even those with central nervous system (CNS) diseases, who can also experience lower urinary tract symptoms (LUTS) secondary to the neurogenic lower urinary tract dysfunction (NLUTD) itself (1). Although prostatic surgery is well known to improve outcomes in BPE-related BOO, its efficacy and safety in patients with CNS diseases generates controversy (2, 3). Charalampous et al. conducted a PRISMA systematic review to evaluate postoperative outcomes after surgery for BPE-Related BOO in men with CNS diseases and NLUTD. The review included 13 studies and involved 1,144 patients stratified in four groups: spinal cord injury, Parkinson's disease, post-cerebrovascular accident, and

multiple system atrophy. Transurethral resection of the prostate (TURP) was the most frequently performed de-obstruction procedure, followed by prostatic artery embolism and open prostatectomy. The primary outcomes pointed to a substantial improvement in symptoms, with a success rate of 81.4% in spinal cord injury, 27.1% in Parkinson's disease, and 66.7% in post-cerebrovascular accident populations. Continence status was assessed in six studies, pointing out a high risk of postoperative urinary incontinence, particularly in patients with multiple system atrophy, 60% of whom developed de novo incontinence symptoms. Perioperative complications, such as urinary infections, were more prevalent in spinal cord injury patients, and higher perioperative mortality rates were observed in post-cerebrovascular accident patients. These results emphasize the possible benefits of prostatic surgery in properly selected neuro-urological patients while highlighting the importance of careful preoperative assessments to discriminate BPE-related BOO from other etiologies. However, this review only included retrospective studies with a high risk of bias, as well as significant heterogeneity in patient characteristics, diagnosis of BOO, surgery technique, and reported outcomes. Furthermore, most of the studies had a limited number of subjects. Therefore, well-designed prospective studies with standardized inclusion criteria, surgical techniques, and longer follow-up are still needed to determine the real advantage of this intervention in distinct neuro-urological groups.

ABBREVIATIONS

BPE = Benign Prostate Enlargement
BOO = Bladder Outlet Obstruction
CNS = Central nervous system

CONFLICT OF INTEREST

None declared.

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Submitted for publication:
January 01, 2025

Accepted:
January 10, 2025

Published as Ahead of Print:
February 15, 2025

UPDATE IN UROLOGY

NEUROUROLOGY

Vol. 51 (3): e20249909, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2025.9909

Editorial Comment: Epidemiology of Spinal Cord Injury in Adults in Sweden, 2016-2020: A Retrospective Registry-Based Study

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Neuroepidemiology. 2024 Aug 13:1-9 Online ahead of print.

DOI: 10.1159/000540818 | ACCESS: 39137737

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COMMENT

This is a retrospective registry-based study over 4 years at the National Quality Register for Rehabilitation Medicine in Sweden, which included 26 units around the country and evaluated the epidemiological characteristics of the Swedish spinal cord injury (SCI) population from January 2016 to December 2020. The data analyzed were gender, age, etiology, level of injury, neurogenic bowel, bladder dysfunction, complications during rehabilitation and the need for positive airway pressure or ventilator. Mean age was 56 years (male = 66%). Tetraplegia was more common among traumatic SCI (TSCI) than non-traumatic SCI (NTSCI). The incidence was 11.9–14.8 per million for TSCI and 8.9–11.8 per million for NTSCI. At discharge, 8% of patients needed a breathing aid. Of those who were ventilator-dependent at discharge, 75% had a TSCI. Disturbed bowel and bladder functioning were noted in 58% of patients at discharge. The median time spent at the unit was 40 days, but it was approximately 2 weeks longer for those with a TSCI.

SCI is a major cause of long-term disability, with a higher prevalence among males (1,2). The main complications among these patients were pyelonephritis (14.5% of TSCI cases and 4.5% of NTSCI cases) and pressure ulcers (10.2% of TSCI cases and 3.3% of NTSCI cases). Sweden has a lower incidence of SCI and its complications in comparison to Western Europe and globally (3), maybe due to increased awareness initiatives. With falls being the primary cause of TSCI and a high age at beginning, the Swedish SCI population has a pattern resembling that of other Scandinavian countries.

CONFLICT OF INTEREST

None declared.

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Submitted for publication:
January 01, 2025

Accepted:
January 10, 2025

Published as Ahead of Print:
February 15, 2025

VIDEO SECTION

Vol. 51 (3): e20240653, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0653

Pulsed Tm-yag laser (Thulio®): a new weapon in endourologists' hand in the conservative management of imperative cases of Upper Tract Urothelial Carcinoma (UTUC)

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ABSTRACT

Introduction: Urothelial carcinomas (UC) represent the sixth most common tumor by incidence, involving the lower or upper urinary tracts (UTUC) (1). High-risk patients should be treated by nephroureterectomy with complete bladder cuff excision (2), conservative approach is reserved for low-risk UTUCs and/or imperative cases (3).

Materials and Methods: We present a 70-year-old male patient, smoker, with history of urothelial carcinoma. He underwent distal ureterectomy with ileal replacement in April 2019. Since then, he has developed several UTUC recurrences bilaterally and in the bladder, which have been treated conservatively. In August 2023, CT- scan showed multiple recurrences in the left kidney and ureter. Hence, on November 2023, we performed cystoscopy, monopolar resection of bladder tumor and bilateral flexible ureteroscopy (fURS) with pulsed thulium:YAG (p-Tm:YAG) ablation of the tumors.

We performed a no-touch technique fURS with Video Uretero-Renoscope FLEX-XC1 by Storz. After this, we placed an ureteral access sheath and then a biopsy by using a tipless basket.

The laser fiber used was 272 µm and the laser settings were 0.8 J – 10 Hz – Long pulse Ablation (10 W).

Results: The pathological results showed UTUC bilaterally and high-grade UC in the bladder. Then, he underwent intravenous therapy with enfortumab - vedotin and the follow-ups, in February 2024 and June 2024, showed no evidence of recurrences at the multiple biopsies.

Conclusion: The p-Tm:YAG laser can be considered a valid alternative option for the conservative treatment of UTUCs. With that said, stringent follow-up remains a mainstay in the conservative treatment of imperative cases of UTUC.

CONFLICT OF INTEREST

None declared.

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Submitted for publication:
November 29, 2024

Accepted:
December 29, 2024

Published as Ahead of Print:
January 22, 2025

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Available at: http://www.intbrazjurol.com.br/video-section/20240690_Scalia_et_al

VIDEO SECTION

Vol. 51 (3): e20240663, May - June, 2025
doi: 10.1590/S1677-5538.IBJU.2024.0663

Advancing Surgical Management of Penile Cancer: Single Port Bilateral Inguinal Lymph Node Dissection

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ABSTRACT

Introduction: Penile cancer is a rare but aggressive malignancy, with inguinal lymph node involvement representing a key prognostic indicator (1, 2). NCCN guidelines recommend prophylactic inguinal lymph node dissection (ILND) for intermediate-to-high-risk patients (pT1b, ≥T2) with non-palpable nodes, aiming for early staging and improved outcomes (3).

The SP-approach employs a single incision and advanced robotic instrumentation to enhance maneuverability, reduce morbidity, and optimize recovery.

Widely used in kidney and prostate surgery (4, 5), this is, to our knowledge, its first application for ILND in Europe.

Material and Methods: This video shows a novel robotic-assisted bilateral, superficial and deep ILND using the DaVinci SP™ system.

In this patient, a preoperative 3D reconstruction allowed detailed visualization of lymph nodes and surrounding structures, enabling precise dissection and an improved intraoperative orientation using Tilepro feature.

Results: Compared to open techniques, robotic ILND offers similar lymph node yields with superior cosmetic outcomes and reduced postoperative pain (6). These benefits are amplified with the SP system, which excels in the constrained inguinal region by minimizing instrument interference and enhancing efficiency (7). Fewer incisions minimized risks such as wound infections and skin necrosis (8).

Limitations of the SP-technique might include extended operative times, especially during the learning phase, and the absence of long-term oncological data. Additionally, complex cases requiring concurrent pelvic lymphadenectomy may necessitate repositioning the robotic system, increasing procedure time.

Conclusions: SP robotic-assisted ILND can represent a significant advancement in the surgical management of penile cancer, combining oncological safety with reduced surgical morbidity. Future studies are needed to validate these findings, compare surgical outcomes, and assess long-term efficacy.

ACKNOWLEDGEMENTS

We thank Alessandra Trocino, librarian at the Istituto Nazionale Tumori di Napoli, IRCCS "G. Pascale", Italy, for her bibliographic assistance.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY

Data relating to this research can be found at:
https://zenodo.org/records/14499695

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Submitted for publication:
November 29, 2024

Accepted:
December 15, 2024

Published as Ahead of Print:
January 22, 2025

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Available at: http://www.intbrazjurol.com.br/video-section/20240663_Spena_et_al

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- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

- Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

- Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

- Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

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Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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