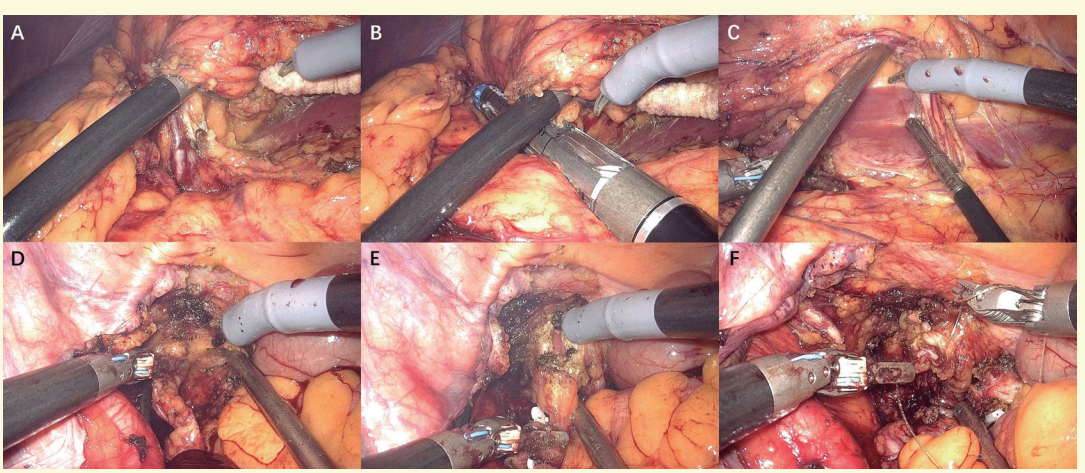
ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY and
OFFICIAL JOURNAL OF THE AMERICAN CONFEDERATION OF UROLOGY
VOLUME 50, NUMBER 6, NOVEMBER - DECEMBER, 2024

SOCIEDADE BRASILEIRA DE UROLOGIA

Confederación Americana de Urología



Surgical procedures of RARNU. (Page 732)

(A) The renal hilum was identified and dissected. (B) The renal artery and the renal vein were transected using Endo-GIA. (C) The kidney and the proximal ureter were dissected. (D) The ureter was dissected carefully caudally until the ureterovesical junction. (E) BCE was performed with endoscissors. (F) The bladder was closed with a two-layer running manner using a barbed suture.

50 YEARS INTERNATIONAL BRAZ J UROL

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

Full Text Online Access Available
www.intbrazjurol.com.br

INTERNATIONAL
BRAZ J UROL
OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

Eletronic Version: Full text with fully searchable articles on-line:

https://www.intbrazjurol.com.br

Correspondence and Editorial Address:

Rua Real Grandeza, 108 - conj. 101 - 22281-034 — Rio de Janeiro — RJ — Brazil
Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

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.

ONLINE manuscript submission: **www.intbrazjurol.com.br**

DISCLAIMER

CONTENTS

Volume 50 | number 6 | November . December, 2024 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

REVIEW ARTICLE

ORIGINAL ARTICLE

EDITORIAL
IN THE ISSUE

Vol. 50 (6): 667-669, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.06.01

Telesurgery and of the International Brazilian Journal of Urology in 2024

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil; [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

The November-December number of Int Braz J Urol is the 31nd under my supervision. In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Bladder Cancer, Kidney Cancer, Basic Research, Peyronie Disease, Endourology and Telesurgery. The papers came from many different countries such as Brazil, Italy, USA, Egypt and China, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Amorim and collegues from Brazil, presented in page 670 (1) a nice systematic review about the retrograde intrarenal surgery with or without ureteral access sheath and concluded that ureteral access sheath (UAS) leads to a lower rate of post-operative fever and infection. However, UAS did not significantly reduce or increase the SFR or the rate of ureteral injuries during RIRS for patients with urolithiasis. The use of UAS should be considered to decrease the risk of infectious complications, particularly in those who may be at higher risk for such complications

Dr. Yang and collegues from China, performed in page 683 (2) a interesting systematic review about the robot-assisted radical cystectomy (RARC), laparoscopic radical cystectomy (LRC), and open radical cystectomy (ORC) in bladder cancer and concluded that LRC and RARC could be considered as a feasible and safe alternative to ORC for bladder cancer. Notably, compared with LRC, RARC may benefit from significantly lower transfusion rates, fewer complications and lower positive surgical margin rates. These data thus showed that RARC might improve the management of patients with muscle invasive or high-risk non-muscle invasive bladder cancer.

Dr. Mesquita and collegues from Brazil and USA performed in page 703 (3) a narrative review about the evidence of restorative therapies in the treatment of peyronie disease and concluded that restorative therapies has emerged as an innovative treatment option for PD and the results from current studies appear to be promising and demonstrated good safety profile. Unfortunately, due to scarce evidence, PRP and SCT are still considered experimental by American Urological Association (AUA) and European Association of Urology (EAU) guidelines. ESWT is recommended, by the same guidelines, for pain control only. More high-quality studies with long-term follow-up outcomes are needed to evaluate efficacy and reproducibility of those therapies.

Dr. Pellanda and collegues from Brazil, performed in page 714 (4) a interesting study about the endoscopic combined intrarenal surgery: best practices and future perspectives. Endourology is a very important topic with lot publications in Int Braz J Urol (5-8). In this study the authors concluded that Endoscopic Combined Intrarenal Surgery (ECIRS) demonstrates significant advantages in the management of large kidney stones. Future research should focus on well-designed randomized control trials to provide robust evidence of its efficacy, safety, and cost-effectiveness, potentially establishing ECIRS as the first option treatment for complex kidney stones.

Dr. Zhang and collegues from China, performed in page 727 (9) a nice study about Robotic-assisted radical nephroureterectomy using the KangDuo Surgical Robot-01 System versus the da Vinci System: a multicenter prospective randomized controlled trial and concluded that the KangDuo (KD)- Surgical Robot-01 (KD-SR-01) system is safe and effective for robot-assisted radical nephroureterectomy (RARNU) compared to the DV Si or Xi system. Further randomized controlled studies with larger sample sizes and longer durations are required. This paper is the cover of the present edition.

Dr. Kolanukuduru and collegues from Egypt performed in pag 737 (10) a very interesting study about the safety and efficacy of vacuum- assisted percutaneous nephrolithotomy (VmPCL) for the treatment of renal stone disease: an analysis of stone free status (SFR) and postoperative infections complications and concluded that vmPCNL is safe and efficacious, with an SFR of 74% at three months. The incidence of postoperative fever and SIRS/Sepsis is 5.5% and 2.9% respec- tively. Further randomized studies with large sample sizes are required to ascertain the rates of these complications in comparison to conventional approaches.

Dr. Moschovas and collegues from USA, permormed in page 754 (11) a very imporatant study about Telesurgery robotic-assisted radical prostatectomy using the Edge medical – a hot topic in urology. The authors concluded that as technological progress introduced novel robotic platforms and high-speed networks, the concept of Telesurgery became a tangible reality while 5G technology solved latency and transmission concerns. However, with these advancements, ethical consider- ations and regulatory frameworks should underline the importance of transparency and patient safety with responsible innovation in the field.

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

CONFLICT OF INTEREST

None declared.

REFERENCES

1. de Amorim LGCR, Campos MEC, Dumont LS, Peñafiel JAR, de Abreu ES, Marchini GS, et al. Retrograde intrarenal surgery with or without ureteral access sheath: a systematic re-view and meta-analysis of randomized controlled trials. Int Braz J Urol. 2024;50:670-82. doi: 10.1590/S1677-5538.IBJU.2023.0452.
2. Yang Z, Dou X, Zhou W, Liu Q. Robot-assisted, laparoscopic and open radical cystectomy for bladder cancer: A sys-tematic review and network meta-analysis. Int Braz J Urol. 2024;50:683-702. doi: 10.1590/S1677-5538.IBJU.2024.0191.
3. Mesquita FC, Barros R, Lima TFN, Velasquez D, Favorito LA, Pozzi E, Dornbush J, Miller D, Petrella F, Ramasamy R. Evidence of restorative therapies in the treatment of Peyronie disease: A narrative review. Int Braz J Urol. 2024;50;703-13. doi: 10.1590/S1677-5538.IBJU.2024.9920.
4. Pellanda AB, Torricelli FCM, Denstedt J, Danilovic A, Danilovic A, Marchini GS, et al. Endoscopic Combined Intrarenal Surgery: best practices and future perspectives. Int Braz J Urol. 2024;50:714-26. doi: 10.1590/S1677-5538.IBJU.2024.9921.
5. Xie F, Deng S, Fei K, Xu H, Zhang H. Nomogram to predict the risk of adverse outcomes in patients with residual stones following percutaneous nephrolithotomy. Int Braz J Urol. 2023;49:599-607. doi: 10.1590/S1677-5538.IBJU.2023.0111.
6. Danilovic A, Talizin TB, Torricelli FCM, Marchini GS, Batagello C, Vicentini FC, et al. One week pre-operative oral antibiotics for percutaneous nephrolithotomy reduce risk of infection: a systematic review and meta-analysis. Int Braz J Urol. 2023;49:184-93. doi: 10.1590/S1677-5538.IBJU.2022.0544.
7. Sahan M, Yarimoglu S, Polat S, Nart B, Koras O, Bozkurt IH, et al. A novel nomogram and a simple scoring system for urinary leakage after percutaneous nephrolithotomy. Int Braz J Urol. 2022;48:817-27. doi: 10.1590/S1677-5538.IBJU.2022.0091.
8. Qin P, Zhang D, Huang T, Fang L, Cheng Y. Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis. Int Braz J Urol. 2022;48:637-48. doi: 10.1590/S1677-5538.IBJU.2021.0347.
9. Zhang Z, Li Z, Xu W, Wang X, Zhu S, Dong J, et al. Robot-assisted radical nephroureterectomy using the KangDuo Surgical Robot-01 Sys-tem versus the da Vinci System: a multicenter prospective randomized controlled trial. Int Braz J Urol. 2024;50:727-36. doi: 10.1590/S1677-5538.IBJU.2024.0230.
10. Kolanukuduru KP, Zaytoun O, Tillu N, Mandel A, Dovey Z, Buscarini M. Safety and efficacy of vacuum-assisted mini-percutaneous nephrolithotomy for the treatment of renal stone disease: an analysis of stone free status and postoperative infectious complications. Int Braz J Urol. 2024;50:737-45. doi: 10.1590/S1677-5538.IBJU.2024.0308.
11. Moschovas MC, Rogers T, Xu W, Perera R, Zhang X, Patel V. First impressions of Telesurgery robotic-assisted radical prostatectomy using the Edge medical robotic platform.Int Braz J Urol. 2024;50:754-63. doi: 10.1590/S1677-5538.IBJU.2024.0458.

Luciano A. Favorito, MD, PhD
Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

Int Braz J Urol. 2024; 50: 667-9

REVIEW ARTICLE

Vol. 50 (6): 670-682, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0452

Retrograde intrarenal surgery with or without ureteral access sheath: a systematic review and meta-analysis of randomized controlled trials

Lucas Guimarães Campos Roriz de Amorim [1], Marcelo Esteves Chaves Campos [1], Lígia Sant'Ana Dumont [2], José Augusto Rojas Peñafiel [3], Eliabe Silva de Abreu [4], Giovanni Scala Marchini [5], Manoj Monga [6], Eduardo Mazzucchi [5]

[1] Departamento de Urologia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil; [2] Departamento de Medicina, Universidade Evangélica de Goiás, Anápolis, GO, Brasil; [3] Department of Medicine, SEK International University, Quito, Ecuador; [4] Department of Medicine, Mayo Clinic-Rochester, Rochester, MN, USA; [5] Departamento de Urologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brasil; [6] Department of Urology, UC San Diego Health, La Jolla, CA, USA

ABSTRACT

Introduction: The ureteral access sheath (UAS) is a medical device that enables repeated entrance into the ureter and collecting system during retrograde intrarenal surgery (RIRS). Its impact on stone-free rates, ureteral injuries, operative time, and postoperative complications remains controversial. Therefore, we performed a systematic review and meta-analysis comparing RIRS with versus without UAS for urolithiasis management.

Purpose: To compare outcomes from retrograde intrarenal surgery (RIRS) for stone extraction with or without ureteral access sheath (UAS); evaluating stone-free rate (SFR), ureteral injuries, operative time, and postoperative complications.

Materials and Methods: We systematically searched PubMed, Embase, and Cochrane Library in June 2024 for randomized controlled trials (RCTs) evaluating the efficacy and safety outcomes of UAS use in RIRS for urolithiasis treatment. Articles published between 2014 and 2024 were included. Pooled risk ratios (RRs) and mean differences (MDs) were calculated for binary and continuous outcomes, respectively.

Results: Five RCTs comprising 466 procedures were included. Of these, 246 (52.7%) utilized UAS. The follow-up ranged from 1 week to 1 month. UAS reduced the incidence of postoperative fever (RR 0.49; 95% confidence interval [CI] 0.29–0.84; p=0.009), and postoperative infection (RR 0.50; 95% CI 0.30–0.83; p=0.008). There were no significant differences between groups in terms of SFR (RR 1.05; 95% CI 0.99–1.11; p=0.10), ureteral injuries (RR 1.29; 95% CI 0.95–1.75; p=0.11), operative time (MD 3.56 minutes; 95% CI -4.15 to 11.27 minutes; p=0.36), or length of stay (MD 0.32 days; 95% CI -0.42 to 1.07 days; p=0.40).

Conclusion: UAS leads to a lower rate of post-operative fever and infection. However, UAS did not significantly reduce or increase the SFR or the rate of ureteral injuries during RIRS for patients with urolithiasis. The use of UAS should be considered to decrease the risk of infectious complications, particularly in those who may be at higher risk for such complications.

ARTICLE INFO

Lucas Amorim
https://orcid.org/0009-0008-2054-1978

Keywords:
Urolithiasis; Meta-Analysis as Topic; Surgical Procedures, Operative

Int Braz J Urol. 2024; 50: 670-82

Submitted for publication:
July 31, 2024

Accepted after revision:
August 12, 2024

Published as Ahead of Print:
August 20, 2024

INTRODUCTION

The ureteral access sheath (UAS) is a medical device used to guide and facilitate the passage of the scope and improve visualization during retrograde intrarenal surgery (RIRS) for kidney stone management. The UAS facilitates multiple entries into the ureter and collecting system, reduces intrarenal pressure, and preserves the scope during stone extraction. UAS may additionally preserve the ureteral mucosa since it prevents direct contact between the scope and the mucosal lining (1). However, transient ureteral ischemia and the risk of ureteral injuries potentially increases the risk of postoperative ureteral stricture and obstruction (2), which contributes to the remarkable controversy regarding the routine utilization of UAS during RIRS.

Several primary studies and systematic reviews have addressed the efficacy and safety of RIRS with versus without UAS (1, 3–5). However, they included observational data, which may have introduced bias and confounding factors and led to less generalizable findings. Due to the scarcity of high-level evidence, most recommendations in international guidelines are based on a non-randomized prospective cohort (6). Considering this limitation and the recent release of key randomized controlled trials (RCTs), we aimed to conduct an updated systematic review and meta-analysis restricted to RCTs comparing the outcomes of patients undergoing RIRS with versus without UAS to provide more reliable and updated evidence, thereby enhancing internal validity, reducing the risk of bias and reinforcing the importance of this study in guiding urologic practice.

MATERIAL AND METHODS

Our study was conducted and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines (7, 8). The study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under protocol CRD42023429216.

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: RCTs; published between 2014 and 2024; comparing the RIRS approach with versus without UAS to manage kidney or proximal ureteral calculi; and reporting any of the outcomes of interest. We excluded studies lacking a control group; evaluating mid or lower ureteral calculi; unpublished full-text articles (conference abstracts); and preliminary results from published RCTs.

Search strategy

We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials in June 2024 for studies that met our inclusion criteria. Articles published between 2014 and 2024 were included. The following medical subject heading terms were included for a Medline search and adapted for other databases as needed: ("ureteral access" OR "ureteric access" OR ureteroscopy OR ureteroscopic OR "retrograde intrarenal" OR "retrograde intra renal" OR "retrograde intra-renal" OR ureterorenoscopy) AND (RCT OR random OR randomization OR randomly OR randomized). There were neither language nor patient population size restrictions for the search.

All identified articles were systematically assessed using the above-cited prespecified criteria. Two authors independently performed screening and selection of studies (L.A. and L.D.). Disagreements were resolved through consensus among the authors.

Data extraction and missing data

Two authors (L.A. and L.D.) independently extracted data from the selected studies utilizing a standardized data extraction sheet. The authors resolved disagreements through consensus. We requested relevant missing or potentially inconsistent information from the selected studies by email to the authors.

Endpoints and definitions

The intraoperative endpoints of interest were operative time, and ureteral injuries. The postoperative endpoints of interest were stone-free rates (SFR), length of stay (LOS), postoperative fever, and postoperative infection.

Among the studies, the SFR outcome was defined as having residual fragments measuring < 3 or 4 millimeters. The follow-up time at which residual fragments were evaluated (at 3, 7, 14, or 30 days), as well as the imaging method used for assessment (radiography, ultrasonography, or computed tomography scan), varied among studies, as detailed in Table-1.

The diagnosis of postoperative symptomatic urinary tract infection was defined based on patient-reported symptoms, physical examination, postoperative fever (>38°C), postoperative urosepsis, bedside dipstick urinalysis, or urine culture.

In each study, urologists closely observed the final endoscopic passage exiting the ureter to evaluate postoperative ureteral injuries. The lesions were graded based on the Post-Ureteroscopic Lesion Scale (PULS) grading system (9). This scale categorizes lesions into six groups. Grade 0 indicates no lesions or insignificant abrasions, while grade 1 represents superficial mucosal lesions, significant mucosal edema, or hematoma. Grade 2 signifies submucosal lesions without contrast media extravasation. Grade 3 denotes perforation with less than 50% (partial) transection and contrast media extravasation. Grade 4 corresponds to perforation with more than 50% but less than 100% (partial) transection. Grade 5 indicates complete transection. Lesion grading remains independent of their location or extent. The severity of the most significant lesion determines the overall PULS grading in cases involving multiple lesions.

Quality assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (RoB 2) for quality assessment of RCTs (10). Three authors independently conducted the risk of bias evaluation (L.A., L.D., and J.P.). The authors resolved disagreements through consensus. Small study effects (publication bias) were assessed through funnel plot analysis for the outcome of SFR (main outcome) and evaluation for a symmetrical distribution of trials with similar weights. We also performed a leave-one-out sensitivity analysis to assess whether the results largely relied on a single study.

Statistical analyses

Treatment effects for binary endpoints were computed using pooled risk ratios (RRs) with 95% confidence intervals (CIs), whereas continuous endpoints were computed using mean differences (MDs) with 95% CIs. The Mantel–Haenszel statistical effect model was utilized for all binary endpoints, while the inverse-variance method was applied for continuous endpoints using the DerSimonian Laird random-effects model. Heterogeneity was assessed through I^2 statistics, and prediction intervals. Review Manager version 5.4.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analyses, and the Comprehensive Meta-Analysis Prediction Intervals Program was utilized for the calculation of the prediction intervals.

RESULTS

Study selection and baseline characteristics

As detailed in Figure-1, our initial search yielded 3,206 results. After the removal of duplicate records and ineligible studies, 21 remained and were fully reviewed based on prespecified criteria. Of these, a total of five RCTs, published between 2021 and 2024, were included. These trials encompassed 466 procedures, of which 246 (52.7%) were performed with UAS (11–15).

Individual study characteristics are reported in Table-1. Most patients were male (59.6%). The mean age ranged from 38.9 to 51.4 years, with a mean follow-up duration ranging from 1 week to 1 month. Four studies limited their inclusion criteria to renal stones, while one study also included 3 patients (4.6%) with upper ureteral stones (11).

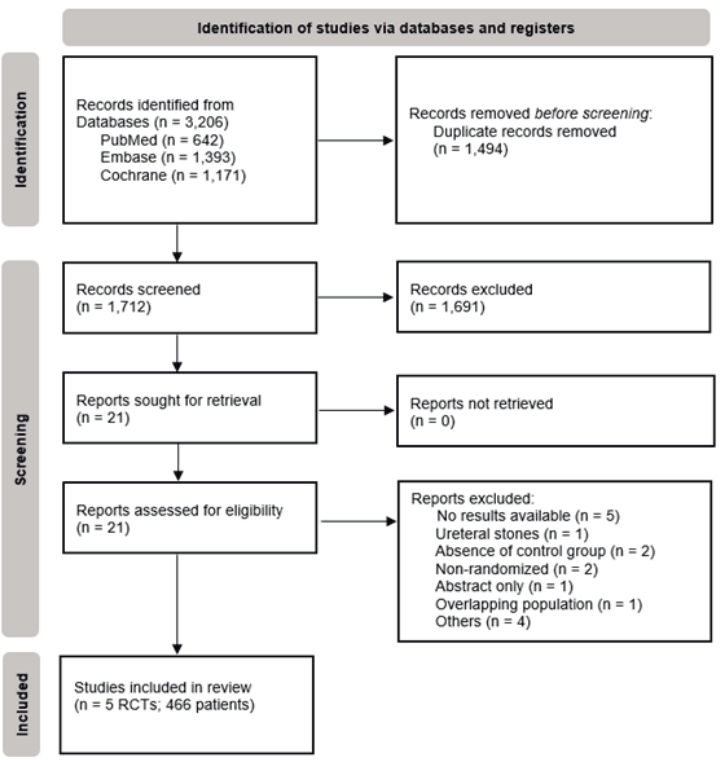
RIRS was performed using flexible scopes across all patients. In two studies, an 8-Fr rigid or semi-rigid ureteroscopy preceded UAS placement (13, 15).

Table 1 - Individual characteristics of studies and their SFR assessments.

Study	Procedures (n)	Age (years)*	Male (%)	BMI (kg/m^2)*	Stone burden (mm or mm^2)*	Stone location (%)	Follow-up	SFR definition	SFR imaging method	SFR time assessment (POD)
Abdelfatah Zaza et al., 2023 (11)	33/31	43.8/42.7	64/58	29/28.7	16.8/16.5 mm	Upper pole: 33.3/32.3 Mid pole: 30.3/25.8 Lower pole: 21.2/25.8 Renal pelvis: 12.1/9.7 Upper ureter: 3.0/6.5	1 week	CIRF <4 mm	NC-CT KUB	7
Bozzini et al. 2024 (12)	92/89	51.4/48.3	44/47	NA	15.8/14.1 mm	NA	2-4 weeks	CIRF <3 mm	CT KUB	3
Ecer et al. 2022 (13)	40/20	47.1/50.5	72/65	28.6/29.8	13.6/14.9 mm	Upper pole: 7.5/10 Mid pole: 22.5/15 Lower pole: 22.5/25 Renal pelvis: 17.5/25 Multiple: 30/25	2 weeks	CIRF <3 mm	US and/or NC-radiography (previously diagnosed with abdominopelvic CT)	14
Singh et al. 2023 (14)	41/40	38.9/39.1	78/57	26.7/26.7	14.7/15.33 mm	Lower pole: 39/37.5	1 month	CIRF <3 mm	NC-CT KUB	30
Turan et al. 2024 (15)	40/40	48.8/48.5	75/72.5	25/25.3	139/141 mm^2	Upper pole: 10/12.5 Mid pole: 25/30 Lower pole: 30/25 Renal pelvis: 35/32.5	1 month	CIRF <4 mm	NC-CT KUB	30

Values refer to groups with/without ureteral access sheath; * mean or median; BMI = body mass index; CIRF = Clinically insignificant residual fragments; CT = computed tomography; KUB = kidneys, ureters and bladder; NA = not available; NC = non-contrast; POD = postoperative days; SFR = stone-free rate; US = ultrasound.

Figure 1 - PRISMA flow diagram of study screening and selection.



RCTs, randomized controlled trials.

Notably, one of these studies presented two patient cohorts using UAS: the standard UAS (STUAS) group and dual-lumen UAS (DLUAS) group (13). The DLUAS is a vacuum-assisted sheath, a single lumen sheath with an oblique side designed for connection to a vacuum system for active drainage. However, it is noteworthy that in this study, the DLUAS was not connected to a suction apparatus and functioned similarly to a standard UAS (16). Therefore, we aggregated data from both cohorts into our 'with UAS' group for statistical analysis using Review Manager 5.4.1.

Additionally, in one study, all patients underwent preoperative stenting with double-J at least 10 days before the procedure and received postoperative Tamsulosin 0.4 mg once daily until removal of the postoperative stent, which occurred 2 weeks after the procedure (and 2 weeks before assessing SFR) (14). The procedural characteristics of the included studies are detailed in Table-2.

Pooled analysis of all studies

The use of UAS during RIRS significantly reduced the incidence of postoperative fever (12.8% vs. 28.4%; RR 0.49; 95% CI 0.29–0.84; p=0.009; I^2=0%; Figure-2A), and postoperative infection (8.9% vs. 17.9%; RR 0.50; 95% CI 0.30–0.83; p=0.008; I^2=0%; Figure 2B). There was no difference between groups in terms of SFR (89.0% vs. 85.4%; RR 1.05; 95% CI 0.99–1.11; p=0.10; I^2=0%; Figure-3A), and ureteral injuries (32.0% vs. 24.4%; RR 1.29; 95% CI 0.95–1.75; p=0.11; I^2=0%; Figure-3B).

There were no significant differences between groups in operative time (MD 3.56 minutes; 95% CI -4.15 to 11.27 minutes; p = 0.36; I^2 = 80%; Figure-4A) or LOS (MD 0.32 days; 95% CI -0.42 to 1.07 days; p = 0.40; I^2 = 64%; Figure-4B).

Table 2 - Procedural characteristics of the included studies.

Study	Abdelfatah Zaza et al. 2023 (11)	Bozzini et al. 2021 (12)	Ecer et al. 2022 (13)	Singh et al. 2023 (14)	Turan et al. 2024 (15)
UAS Size, (Fr)	NA	10-12	11-13	9.5-11.5	9.5-11.5
Prior URS before UAS placement	NA	No previous URS	Cystoscopy followed by 8-Fr rigid URS	NA	8-Fr semi-rigid URS
Preoperative ureteral dilatation type	NA	No preoperative dilatation	No preoperative dilatation	Preoperative stenting with DJ at least 10 days prior procedure	NA
Postoperative stent, n (%)	NA	92(100)/89(100)	39(97.5)/19(95)	41(100)/40(100)	40(100)/40(100)
Postoperative stent type	NA	6 Ch DJ, removed in 14-28 days	DJ, removed in 14 days if possible	4.8-Fr DJ, removed in 14 days; or per urethral catheter	DJ
Fragmentation device	NA	272μm Ho:YAG	200μm Ho:YAG 10 Hz/2.5 J	365μm Ho:YAG 10 Hz/1 J	Ho:YAG
Basketing or Grasping	NA	Kobot Filter basket to retrieve some fragments	NA	Basket or tri-prong flexible forceps to relocate inferior calyx stones	NA
Irrigation	NA	Gravity irrigation supplemented with on-demand Traxer Flow® dual port flushing	Gravity irrigation (kept at 60cm height)	Path finder saline irrigation (kept at 40cm height)	Gravity irrigation (kept at 100 cm height)

Values refer to groups with/without UAS; DJ = double-J ureteral stent; Ho:YAG = Holmium Yttrium Aluminium Garnet fibre laser; NA = not available; UAS = ureteral access sheath; URS = ureteroscopy

Quality assessment

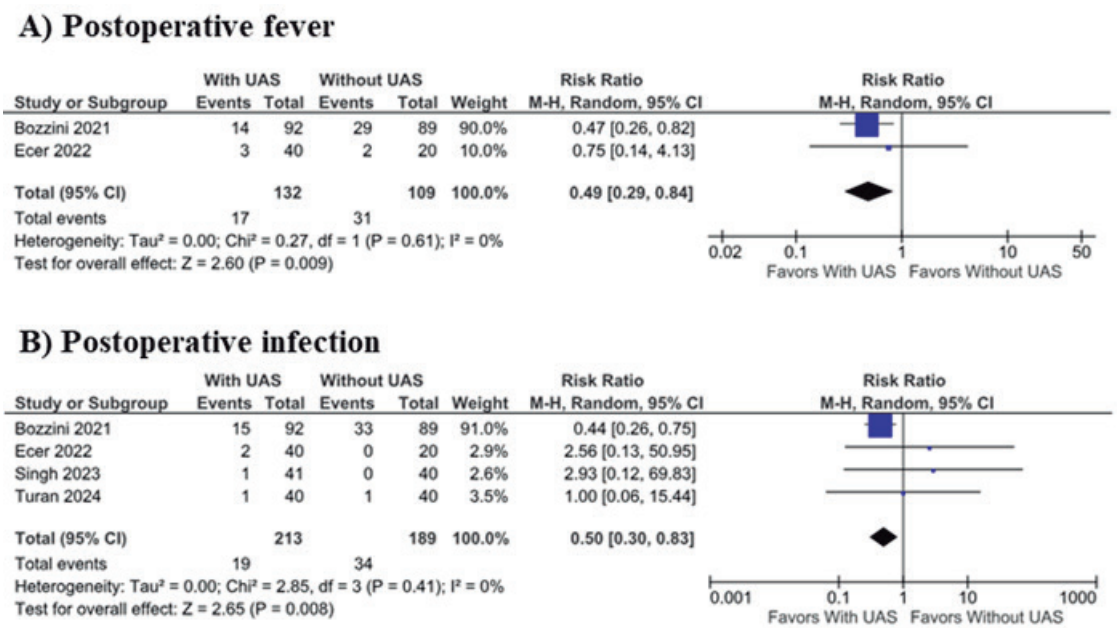
Individual RCT appraisals, performed as per the Cochrane Collaboration's RoB2 tool, are reported in Figure-5. One study was deemed to be of some concern for not using computed tomography (CT) scans to evaluate SFR, while another study was rated as having concerns due to a significant difference in male prevalence between groups (13, 14).

A funnel plot analysis for the outcome of SFR revealed no evidence of small study effects (publication bias), as reported in Figure-6. Studies exhibited a symmetrical distribution according to weight and converged toward the pooled effect as weight increased. Egger's regression test could not be performed due to the limited number of included studies (n < 10).

Sensitivity analyses

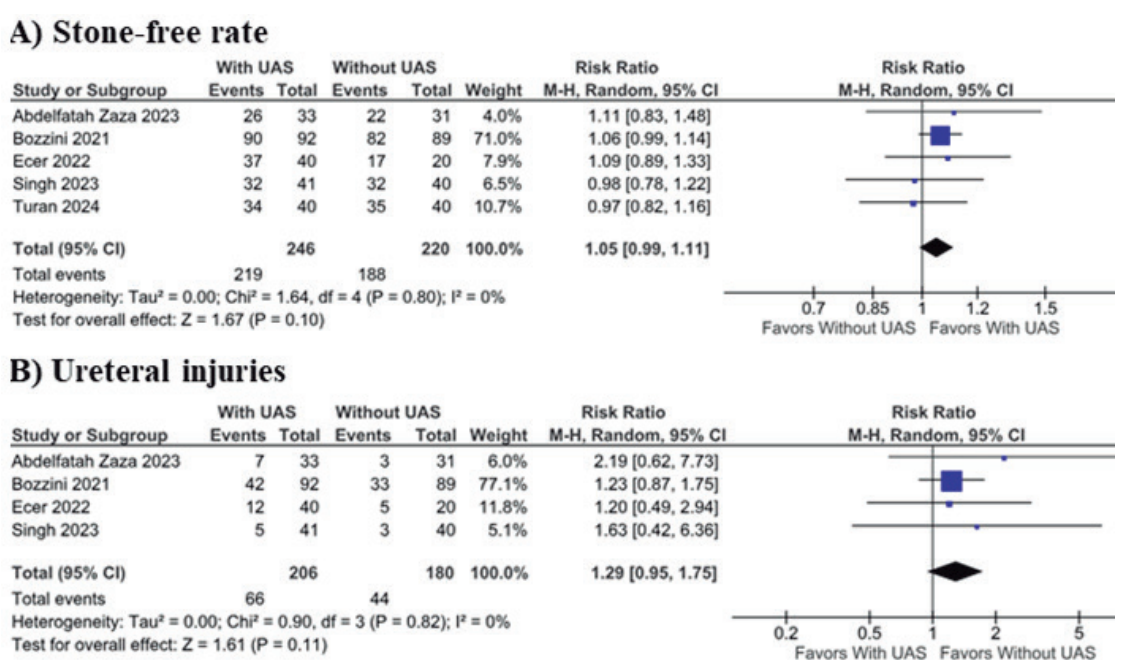
Overall, sensitivity analyses using the leave-one-out approach revealed consistent results compared with the pooled analysis of all studies when individual studies were sequentially excluded from the analysis for the outcomes of SFR, ureteral injuries, and operative time. This approach could not be employed in postoperative fever and LOS due to the limited number of studies included in these outcomes analyses.

Figure 2 - Incidence of (A) postoperative fever and (B) postoperative infection in UAS x Without UAS groups.



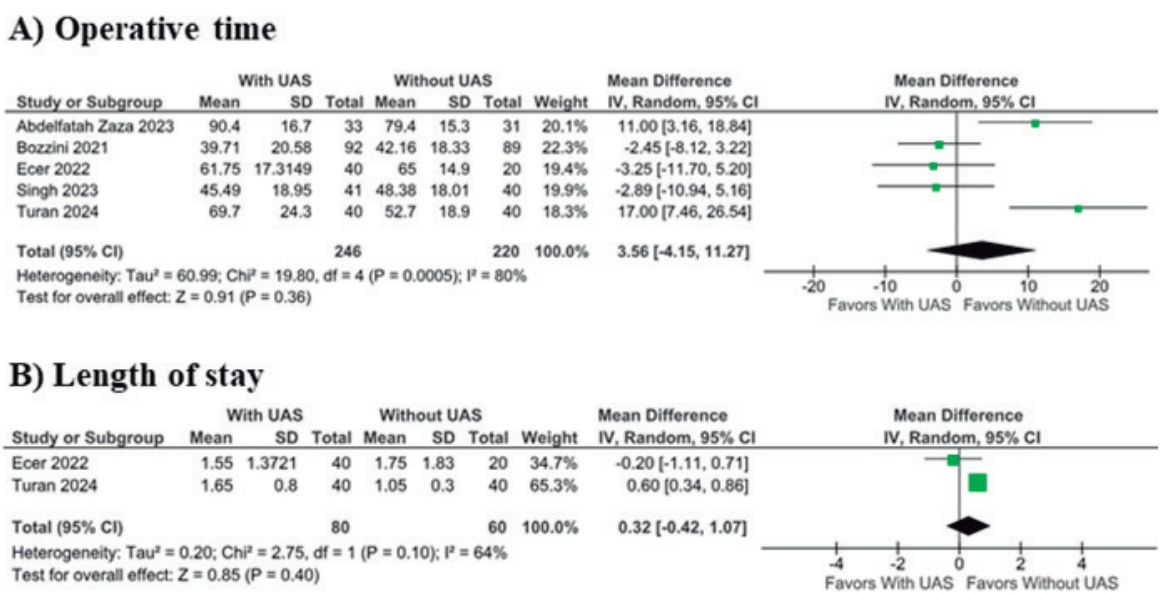
The incidence of (A) postoperative fever (p = 0.009) and (B) postoperative infection (p = 0.008) were significantly reduced in the group with UAS compared to the group without UAS.
CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; UAS, ureteral access sheath

Figure 3 - The (A) SFR and the rate of (B) ureteral injuries in UAS x Without UAS groups.



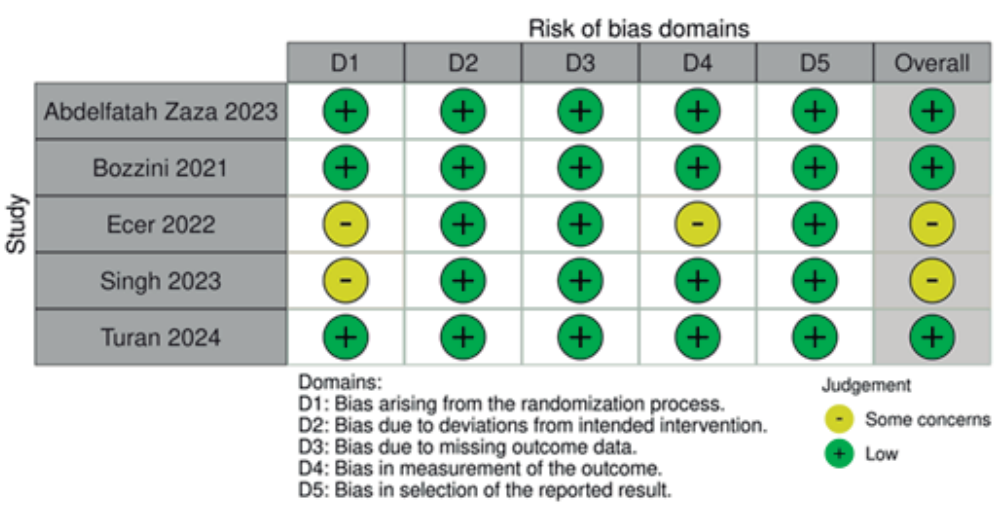
The (A) SFR and the rate of (B) ureteral injuries were not significantly different between groups.
CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; SFR, stone free rate; UAS, ureteral access sheath.

Figure 4 - The (A) operative time and (B) LOS in UAS x Without UAS groups.



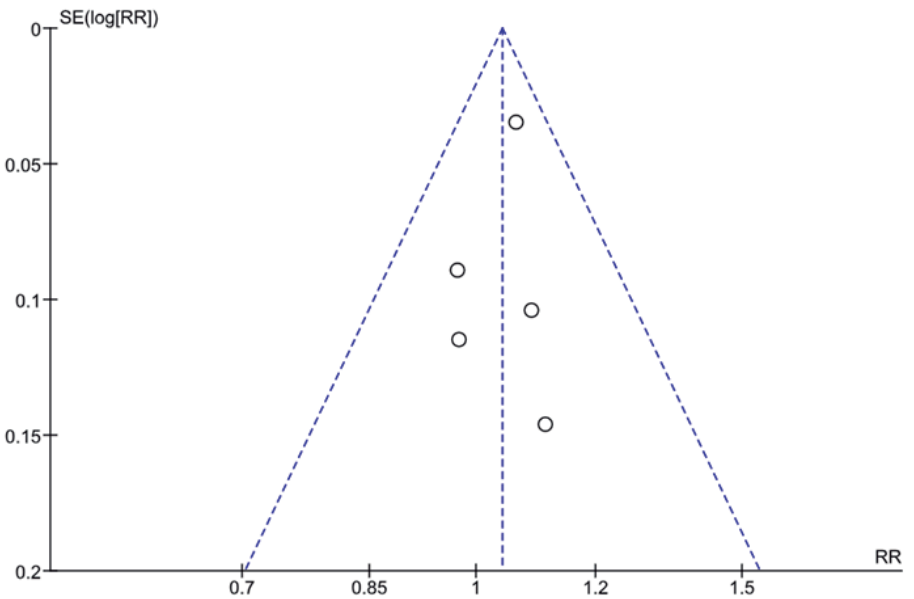
The (A) operative time and (B) LOS were not significantly different between groups.
CI, confidence interval; df, degrees of freedom; IV, inverse-variance; SD, standard deviation; UAS, ureteral access sheath.

Figure 5 - Risk of bias assessment using RoB 2 tool.



Ecer`s study was deemed to be of some concern for not using computed tomography (CT) scans to evaluate SFR, while Singh`s was rated as having concerns due to a significant difference in male prevalence between groups. Overall, no major concerns were observed regarding the quality of the studies individually.

Figure 6 - Funnel plot for the SFR outcome.



A funnel plot analysis for the outcome of SFR revealed no evidence of small study effects (publication bias). Studies exhibited a symmetrical distribution according to weight and converged toward the pooled effect as weight increased. RR = risk ratio; SE = standard error; SFR = stone free rate

Although exhibiting null heterogeneity in the pooled analysis, the postoperative infection leave-one-out sensitivity analysis revealed that its results were driven mostly by one study, probably due to its elevated weight (12). When excluding this study, no significant difference was found between groups.

The binary endpoints exhibited null heterogeneity. In contrast, the outcomes of operative time, and LOS had elevated heterogeneity, with I^2 values of 80% and 64%, respectively. In the assessment of operative time, considering that the true MDs within the universe of comparable populations follow a normal distribution, we can estimate a 95% prediction interval for MDs to range from -24.36 to 31.55 minutes, as illustrated in Figure-7. Due to the limited number of included studies (n < 10), further meta-regression analyses were not feasible.

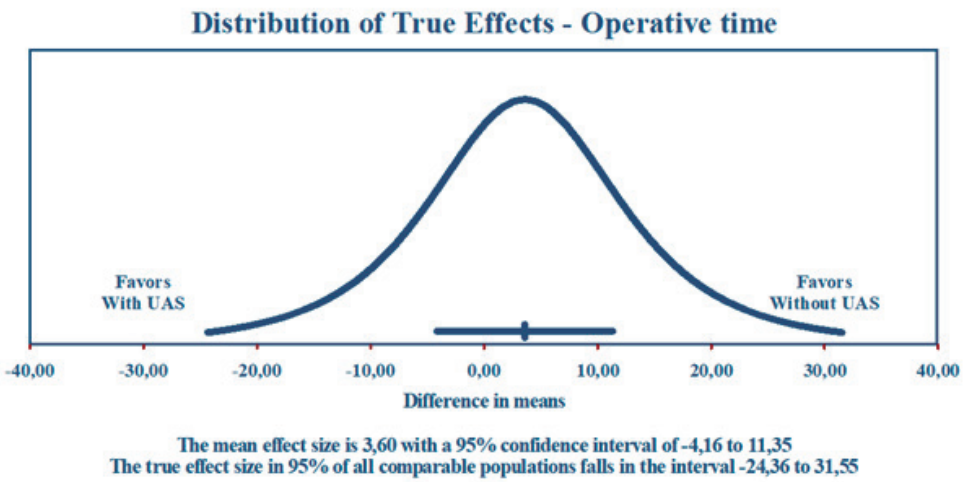
DISCUSSION

In this meta-analysis of five RCTs and 466 patients comparing RIRS with versus without UAS for the treatment of urolithiasis, our main findings were as follows: the use of UAS was associated with a significant reduction in the postoperative incidence of fever and infection; there was no significant difference between groups in the incidence of ureteral injuries; and the SFR was comparable between RIRS with and without UAS.

A previous meta-analysis evaluating the role of UAS in urolithiasis found no significant differences in SFR, operative time, hospitalization time, or intraoperative complications, while it significantly increased the risks of postoperative complications (5). However, this study relied heavily on observational data, making it susceptible to the influence of confounding factors. To address this limitation and provide more reliable and updated evidence, we restricted inclusion to recently released RCTs (11–15).

By doing so, our study confirmed prior results of comparable outcomes between groups, especially SFR, operative time, LOS, and intraoperative complications, but increased confidence and generalizability given the above-cited methodological improve-

Figure 7 - Prediction interval for the operative time outcome.



UAS = ureteral access sheath

ments. More importantly, our meta-analysis found a significantly lower incidence of postoperative fever and infection in the UAS arm, which has not been demonstrated previously.

UAS is associated with enhanced fluid drainage during RIRS, leading to reduced intrapelvic pressure compared with RIRS without UAS (17, 18). This mechanism potentially explains the observed decrease in postoperative fever and infection rates noted in the group with UAS. Our findings align with a large retrospective study conducted by Traxer et al., which included 2239 patients (67% in the UAS group) and reported significantly lower rates of postoperative fever and infection in the UAS arm, 28,6% and 18,6%, respectively (19).

As the device aids in the visualization of the superior urinary tract and drainage of stone fragments, a greater SFR would theoretically be expected when UAS is used in RIRS. Interestingly, our meta-analysis revealed no significant difference between the groups with and without UAS in this outcome. In fact, a few factors may have a greater impact on SFR than using UAS during RIRS, especially the surgeon's experience, preoperative medical expulsive therapy with an α-blocker one week prior to the procedure, and ureteral stenting placement before the ureteroscopy (20–23).

Besides, new technologies are significantly enhancing kidney stone management across all stages. The use of artificial intelligence can improve detection, reducing the diagnostic time and accelerating decision-making (24). New laser instruments, including high-powered Holmium, which was used as the fragmentation device in all the RCTs included, enhance precision and efficacy in stone elimination (25). However, in cases such as lower pole stones with acute infundibulopelvic angles, hard stones (CT value > 1000), or stones encased in abscess-like material, basketing might still be preferred (26). Additionally, combined approaches have been proposed for stones larger than 2 cm, such as ultrasound-guided endoscopic combined intrarenal surgery (23), which may offer a solution beyond the "either/or" dilemma between percutaneous nephrolithotomy and endoscopic procedures (27).

Ureteral injuries remain the main shortcoming of the literature when using UAS in RIRS. Although the device enables multiple straightforward passages of ureteroscopic instruments through a single insertion, it may cause ureteral mucosal injuries directly (4, 28).

Nonetheless, RIRS itself is associated with ureteral trauma, irrespective of UAS (9). Of note, some independent factors may increase the risks of ureteral damage, such as male gender, higher stone burden, difficulty in placing sheaths, longer insertion time, repeated attempts to position the scope, and use of rigid instruments (29, 30). In this sense, our meta-analysis showed no significant differences between groups in the incidences of ureteral injuries, indicating that UAS may improve visualization during ureteroscopic procedures without increasing or decreasing this intrinsic procedural risk.

While the studies included in our analysis did not specifically evaluate the occurrence of ureteral strictures following UAS placement due to the short follow-up period, a prospective study conducted by Stern et al. revealed that the incidence of strictures associated with high-grade ureteral injuries secondary to UAS placement is comparable to that observed in cases without UAS, not resulting in clinically significant outcomes in the long-term (31).

Our study has limitations. First, there were differences among the included RCTs in terms of follow-up time and imaging method used to measure the SFR. Second, our meta-analysis included a limited number of patients and RCTs, due to the scarcity of available randomized research. This potentially diminishes the statistical power to detect significant differences, while impacting the reliability of estimates for between-study variance in the random-effects, summary effects, confidence intervals, and heterogeneity assessments (32). Finally, we observed elevated between-study heterogeneity in operative time and LOS. Nevertheless, the results were consistent after the leave-one-out sensitivity analysis.

CONCLUSION

In this meta-analysis of 466 patients from RCTs, we compared RIRS for urolithiasis with versus without UAS. Our findings revealed no significant differences between groups in terms of ureteral injury and SFR, albeit the incidence of postoperative fever and infection were substantially reduced in the group with UAS. Hence, UAS should be considered especially in those patients where infectious complications are a significant concern.

ABBREVIATIONS

CI = Confidence interval
LOS = Length of stay
MD = Mean difference
PULS = Post-ureteroscopic lesion scale
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT = Randomized controlled trial(s)
RIRS = Retrograde intrarenal surgery
RoB 2 = Risk of bias 2
RR = Risk ratio
SFR = Stone-free rate(s)
UAS = Ureteral access sheath

CONFLICT OF INTEREST

None declared.

REFERENCES

1. De Coninck V, Keller EX, Rodríguez-Monsalve M, Audouin M, Doizi S, Traxer O. Systematic review of ureteral access sheaths: facts and myths. BJU Int. 2018;122:959-69. doi: 10.1111/bju.14389.
2. Cooper JL, François N, Sourial MW, Miyagi H, Rose JR, Shields J, et al. The Impact of Ureteral Access Sheath Use on the Development of Abnormal Postoperative Upper Tract Imaging after Ureteroscopy. J Urol. 2020;204:976-81. doi: 10.1097/JU.0000000000001147.
3. Breda A, Territo A, López-Martínez JM. Benefits and risks of ureteral access sheaths for retrograde renal access. Curr Opin Urol. 2016;26:70-5. doi: 10.1097/MOU.0000000000000233.
4. Traxer O, Thomas A. Prospective evaluation and classification of ureteral wall injuries resulting from insertion of a ureteral access sheath during retrograde intrarenal surgery. J Urol. 2013;189:580-4. doi: 10.1016/j.juro.2012.08.197.

5. Huang J, Zhao Z, AlSmadi JK, Liang X, Zhong F, Zeng T, et al. Use of the ureteral access sheath during ureteroscopy: A systematic review and meta-analysis. PLoS One. 2018;13:e0193600. doi: 10.1371/journal.pone.0193600.
6. Lima A, Reeves T, Geraghty R, Pietropaolo A, Whitehurst L, Somani BK. Impact of ureteral access sheath on renal stone treatment: prospective comparative non-randomised outcomes over a 7-year period. World J Urol. 2020;38:1329-33. doi: 10.1007/s00345-019-02878-5.
7. Higgins JPT, Cochrane Collaboration, editors. Cochrane handbook for systematic reviews of interventions. Second edition (Cochrane book series). Hoboken, NJ. Wiley-Blackwell. 2019; vol. 694 p.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
9. Schoenthaler M, Wilhelm K, Kuehhas FE, Farin E, Bach C, Buchholz N, et al. Postureteroscopic lesion scale: a new management modified organ injury scale--evaluation in 435 ureteroscopic patients. J Endourol. 2012;26:1425-30. doi: 10.1089/end.2012.0227.
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898.
11. Abdelfatah Zaza MM, Farouk Salim A, El-Mageed Salem TA, Mohammed Ezzat A, Hassan Ali M. Impact of ureteric access sheath use during flexible ureteroscopy: A comparative study on efficacy and safety. Actas Urol Esp (Engl Ed). 2024;48:204-209. English, Spanish. doi: 10.1016/j.acuroe.2023.10.005.
12. Bozzini G, Bevilacqua L, Besana U, Calori A, Pastore A, Romero Otero J, et al. Ureteral access sheath-related injuries vs. post-operative infections. Is sheath insertion always needed? A prospective randomized study to understand the lights and shadows of this practice. Actas Urol Esp (Engl Ed). 2021:S0210-4806(21)00125-X. English, Spanish. doi: 10.1016/j.acuro.2020.11.010. Epub ahead of print.
13. Ecer G, Sönmez MG, Aydın A, Topçu C, Alalam HNI, Güven S, et al. Comparison of retrograde intrarenal stone surgery with and without a ureteral access sheath using kidney injury molecule-1 (KIM-1) levels: a prospective randomized study. Urolithiasis. 2022;50:625-33. doi: 10.1007/s00240-022-01345-y.
14. Singh S, Parmar K, Devana SK, Singh SK. Effect of ureteric access sheath on outcomes of retrograde intrarenal surgery for renal stone disease: a randomized controlled trial. World J Urol. 2023;41:1401-6. doi: 10.1007/s00345-023-04369-0.
15. Turan A, Hirik E, Erdoğan A, Altun A, Mertoğlu C, Şam E, et al. Evaluation of the effect of 9.5/11.5-fr ureteral access sheath use on acute kidney injury with the myo-inositol oxygenase biomarker in patients undergoing retrograde intrarenal surgery: a prospective, randomized, and controlled study. Minim Invasive Ther Allied Technol. 2024:1-7. doi: 10.1080/13645706.2024.2340730. Epub ahead of print.
16. Wang D. Re: Comparison of retrograde intrarenal stone surgery with and without a ureteral access sheath using kidney injury molecule-1 (KIM-1) levels: A prospective randomized study by Gökhan Ecer, Mehmet Giray Sönmez, Arif Aydın, Cemile Topçu, Haider Nihad Izaddin Alalam, Selçuk Güven, and Mehmet Balasar. Urolithiasis. 2023;51(1):44. doi: 10.1007/s00240-023-01420-y. Erratum in: Urolithiasis. 2023 Sep 21;51(1):115. doi: 10.1007/s00240-023-01489-5.
17. Patel RM, Jefferson FA, Owyong M, Hofmann M, Ayad ML, Osann K, et al. Characterization of intracalyceal pressure during ureteroscopy. World J Urol. 2021;39:883-9. doi: 10.1007/s00345-020-03259-z.
18. Berardinelli F, De Francesco P, Marchioni M, Cera N, Proietti S, Hennessey D, et al. Infective complications after retrograde intrarenal surgery: a new standardized classification system. Int Urol Nephrol. 2016;48:1757-62. doi: 10.1007/s11255-016-1373-1.
19. Traxer O, Wendt-Nordahl G, Sodha H, Rassweiler J, Meretyk S, Tefekli A, et al. Differences in renal stone treatment and outcomes for patients treated either with or without the support of a ureteral access sheath: The Clinical Research Office of the Endourological Society Ureteroscopy Global Study. World J Urol. 2015;33:2137-44. doi: 10.1007/s00345-015-1582-8.
20. Cheng C, Ma Y, Wen J, Xiang L, Jin X. The Effect of Preoperative Tamsulosin on Ureteral Navigation, Operation, and Safety: A Systematic Review and Meta-Analysis. Urol Int. 2023;107:557-63. doi: 10.1159/000528889.
21. Chen H, Pan Y, Xiao M, Yang J, Wei Y. The Outcomes of Pre-Stenting on Renal and Ureteral Stones: A Meta-Analysis. Urol Int. 2022;106:495-503. doi: 10.1159/000519473.

22. Skolarikos A, Jung H, Neisius A, Petřík A, Somani B, Tailly T, et al. EAU-Guidelines-on-Urolithiasis-2024. 2024 [cited 2024 Jun 30]. European Association of Urology (EAU) Guidelines on Urolithiasis. Edn. Presented at the EAU Annual Congress Paris 2024. [Internet]. Available at. <https://uroweb.org/guidelines>
23. Vicentini FC, El Hayek KKR, Szwarc M, Perrella R, Kuriki P, Cohen D, et al. Ultrasound guided endoscopic combined Intrarenal surgery - 10 steps for the success. Int Braz J Urol. 2022;48:874-5. doi: 10.1590/S1677-5538.IBJU.2022.0029.
24. Caglayan A, Horsanali MO, Kocadurdu K, Ismailoglu E, Guneyli S. Deep learning model-assisted detection of kidney stones on computed tomography. Int Braz J Urol. 2022;48:830-9. doi: 10.1590/S1677-5538.IBJU.2022.0132.
25. Santa Cruz JAC, Danilovic A, Vicentini FC, Brito AH, Batagello CA, Marchini GS, et al. Ureteral access sheath. Does it improve the results of flexible ureteroscopy? A narrative review. Int Braz J Urol. 2024;50:346-58. doi: 10.1590/S1677-5538.IBJU.2024.9907.
26. Liao N, Tan S, Yang S, Zhai G, Li C, Li T, et al. A study comparing dusting to basketing for renal stones ≤ 2 cm during flexible ureteroscopy. Int Braz J Urol. 2023;49:194-201. doi: 10.1590/S1677-5538.IBJU.2022.0382.
27. Azal W Neto, de Salles LC, di Domenico B, Miyaoka R, Reis LO. Will the advances in retrograde intrarenal surgery extinguish percutaneous nephrolithotomy for stones larger than 2 cm? Int Braz J Urol. 2023;49:143-9. doi: 10.1590/S1677-5538.IBJU.2022.0533.
28. Guzelburc V, Guven S, Boz MY, Erkurt B, Soytas M, Altay B, Albayrak S. Intraoperative Evaluation of Ureteral Access Sheath-Related Injuries Using Post-Ureteroscopic Lesion Scale. J Laparoendosc Adv Surg Tech A. 2016;26:23-6. doi: 10.1089/lap.2015.0294.
29. Loftus CJ, Ganesan V, Traxer O, Schold JD, Noble M, Sivalingam S, et al. Ureteral Wall Injury with Ureteral Access Sheaths: A Randomized Prospective Trial. J Endourol. 2020;34:932-6. doi: 10.1089/end.2018.0603.
30. Harmon WJ, Sershon PD, Blute ML, Patterson DE, Segura JW. Ureteroscopy: current practice and long-term complications. J Urol. 1997;157:28-32. doi: 10.1016/s0022-5347(01)65272-8.
31. Stern KL, Loftus CJ, Doizi S, Traxer O, Monga M. A Prospective Study Analyzing the Association Between High-grade Ureteral Access Sheath Injuries and the Formation of Ureteral Strictures. Urology. 2019;128:38-41. doi: 10.1016/j.urology.2019.02.032.
32. Borenstein M, Hedges LV, Higgins J, Rothstein HR. Introduction to meta-analysis. Second edition. Hoboken, NJ. Wiley; 2021; p. 500.

Correspondence address:
Lucas Guimarães Campos Roriz de Amorim, MD
Departamento de Urologia,
Universidade Federal de Minas Gerais,
Belo Horizonte, MG, Brasil
E-mail: lucasgcrda@ufmg.br

REVIEW ARTICLE

Vol. 50 (6): 683-702, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0191

Robot-assisted, laparoscopic and open radical cystectomy for bladder cancer: A systematic review and network meta-analysis

Zhanpo Yang [1], Xinmeng Dou [1], Wenhui Zhou [1], Qian Liu [1]

[1] *Department of Urology, Tianjin First Central Hospital, Tianjin, China*

ABSTRACT

Objectives: To evaluate the safety and effectiveness of robot-assisted radical cystectomy (RARC), laparoscopic radical cystectomy (LRC), and open radical cystectomy (ORC) in bladder cancer.

Methods: A literature search for network meta-analysis was conducted using international databases up to February 29, 2024. Outcomes of interest included baseline characteristics, perioperative outcomes and oncological outcomes.

Results: Forty articles were finally selected for inclusion in the network meta-analysis. Both LRC and RARC were associated with longer operative time, smaller amount of estimated blood loss, lower transfusion rate, shorter time to regular diet, fewer incidences of complications, and fewer positive surgical margin compared to ORC. LRC had a shorter time to flatus than ORC, while no difference between RARC and ORC was observed. Considering lymph node yield, there were no differences among LRC, RARC and ORC. In addition, there were statistically significant lower transfusion rates (OR=-0.15, 95% CI=-0.47 to 0.17), fewer overall complication rates (OR=-0.39, 95% CI=-0.79 to 0.00), fewer minor complication rates (OR=-0.23, 95% CI=-0.48 to 0.02), fewer major complication rates (OR=-0.23, 95% CI=-0.68 to 0.21), fewer positive surgical margin rates (OR=0.22, 95% CI=-0.27 to 0.68) in RARC group compared with LRC group.

Conclusion: LRC and RARC could be considered as a feasible and safe alternative to ORC for bladder cancer. Notably, compared with LRC, RARC may benefit from significantly lower transfusion rates, fewer complications and lower positive surgical margin rates. These data thus showed that RARC might improve the management of patients with muscle invasive or high-risk non-muscle invasive bladder cancer.

ARTICLE INFO

Wenhui Zhou
https://orcid.org/0009-0007-5560-357X

Keywords:
Urinary Bladder Neoplasms; Robotic Surgical Procedures; Laparoscopy

Int Braz J Urol. 2024; 50: 683-702

Submitted for publication:
April 04, 2024

Accepted after revision:
July 15, 2024

Published as Ahead of Print:
August 20, 2024

INTRODUCTION

Bladder cancer is the 10th most common malignancy in the World, accounting for approximately 573,000 new cases and 213,000 deaths in 2020 (1). The incidence and mortality rate of bladder cancer in men is about 4 times that of women. According to the classification of invasion depth, bladder cancer can be divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (2). Approximately 75% of new cases are diagnosed as NMIBC, and 25% present as MIBC. Unfortunately, approximately 40% of NMIBC patients eventually progress to MIBC (3).

Currently, open radical cystectomy (ORC) is still the standard surgical treatment for patients with MIBC or high-risk of NMIBC (4), which can effectively achieve local control of the tumor and long-term disease-free survival (5, 6). However, ORC is associated with a high postoperative morbidity, such as urinary tract infection, urinary leak, renal failure, ileus and thromboembolic complications. Previous research data show that the incidence of postoperative complications after ORC is as high as 40% to 60%, even if the surgeon knows enough about pelvic anatomy and the surgical technique is continuously improved (7).

Recently, with the development of minimally invasive technology, laparoscopic radical cystectomy (LRC) and robotic assisted radical cystectomy (RARC) have become new methods of treating bladder cancer and are gradually being promoted (8, 9). Compared to LRC, RARC has technological superiorities of better visibility, improved degrees of freedom, and lower learning curves, which helps to overcome the technical difficulties of LRC, including operator fatigue, tremor, and internal suturing. Nevertheless, the cost of RARC is much higher than that LRC, which remains a common alternative to ORC in many medical centers (10).

There is limited evidence comparing RARC, LRC and ORC for bladder cancer. Dong et al. (11) compared long-term oncologic outcomes of three surgical methods but didn't include perioperative outcomes. Kowalewski et al. (12) identified ten randomized controlled trials that compared RARC, LRC and ORC, the results showed that no differences in overall survival and recurrence-free survival between RARC and ORC, with moderate certainty of evidence. These studies had small sample sizes and low levels of probative medical evidence. Therefore, we aimed to undertake a contemporary up-to-date systematic review and network meta-analysis to compare RARC, LRC and ORC for bladder cancer. The primary outcomes of this review were total operative time, estimated blood loss (EBL), intraoperative blood transfusion rate; length of hospital stays (LOS), days to regular diet, time to flatus and complications. The secondary outcomes were positive surgical margin (PSM) and lymph node yield.

MATERIALS AND METHODS

This systematic review and meta-analysis protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42024547617).

Evidence acquisition

The systematic review and network meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (13). Ethical approval was unnecessary in this study, because it was a meta-analysis of existing articles, and no individual patient data were handled.

Literature search

A systematic search was performed in electronic databases, including PubMed, Embase, Ovid, Cochrane library and Clinical Trials.gov. The search terms were as follows: "bladder cancer", "cystectomy", "robot", "robotic", "laparoscopic", "RARC", "LRC", "ORC" and their synonyms or similar words. The searches were conducted without date restriction, from database inception to February 29, 2024, and limited to English-language articles in human adults. In addition, reference lists of all included articles and relevant reviews were searched manually to prevent missing articles. The literature search was done independently by two investigators and was resolved by discussing with the third investigator when the search results were inconsistent.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients with bladder cancer; (2) comparing at least two of three different approaches (open, laparoscopic or robot-assisted radical cystectomy); (3) the study provided analyzable data of interest: total operative time, estimated blood loss (EBL), intraoperative blood transfusion rate, length of hospital stays (LOS), days to regular diet, time to flatus, complication rate, positive surgical margin (PSM) and lymph node yield; (4) whole text was accessible.

Conference abstracts, review articles, editorials, comments, and letters to the editor were excluded.

Study selection and Data extraction

The detailed data were as follows: (1) first author's name and publication time; (2) study design; (3) treatment and sample size; (4) patient characteristics (gender ratio and age distribution); (5) perioperative outcomes: total operative time, estimated blood loss (EBL), intraoperative blood transfusion rate; length of hospital stays (LOS), days to regular diet, time to flatus and 90-day postoperative complication (stratified by Clavien-Dindo classification (14) into all, minor [grade 1–2] and major [grade 3–5] complications); (6) oncological outcomes: positive surgical margin (PSM), lymph node yield.

Risk of bias assessment

Two investigators independently assessed the methodological quality of articles using the Cochrane Risk of Bias Assessment Tool (15). These studies were classified into three degrees: low risk of bias, middle-risk of bias, or high risk of bias. The writers came to an agreement on certain points where they disagreed.

Statistical analysis

Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were utilized for continuous variables. All median and IQR values were transformed to means and SDs through the methodology described by Hozo et al. (16).

Statistical analyses were performed using Review Manager (Version 5.4, Cochrane Collaboration, Oxford, UK) and Stata software (version 14.0, Stata Corporation LLC). Binary variable data are combined with relative risk (RR) or relative odds ratio (OR) statistical measures, and the 95% confidence interval (95% CI) is calculated. Continuous variables are represented by standardized mean difference (SMD) or mean difference (MD), and the 95% CI is calculated. We generated league tables and rankograms based on surface under the cumulative ranking (SUCRA) values.

RESULTS

Literature search results

Totally of 730 relevant articles were retrieved according to the customized search strategy, 284 repeatedly published and cross-published were removed. Furthermore, 382 articles were excluded by evaluating the title and abstract. After the remaining 64 articles were searched for full text, reading, and quality assessment, twenty-four studies were excluded for the following: irrelevant data (n=15); incomplete data (n=9). Finally, 40 (3, 8, 17-53) articles were eventually included in this network meta-analysis (Figure-1), including ten RCTs, seventeen prospective articles, and twelve retrospective studies, and one case control study.

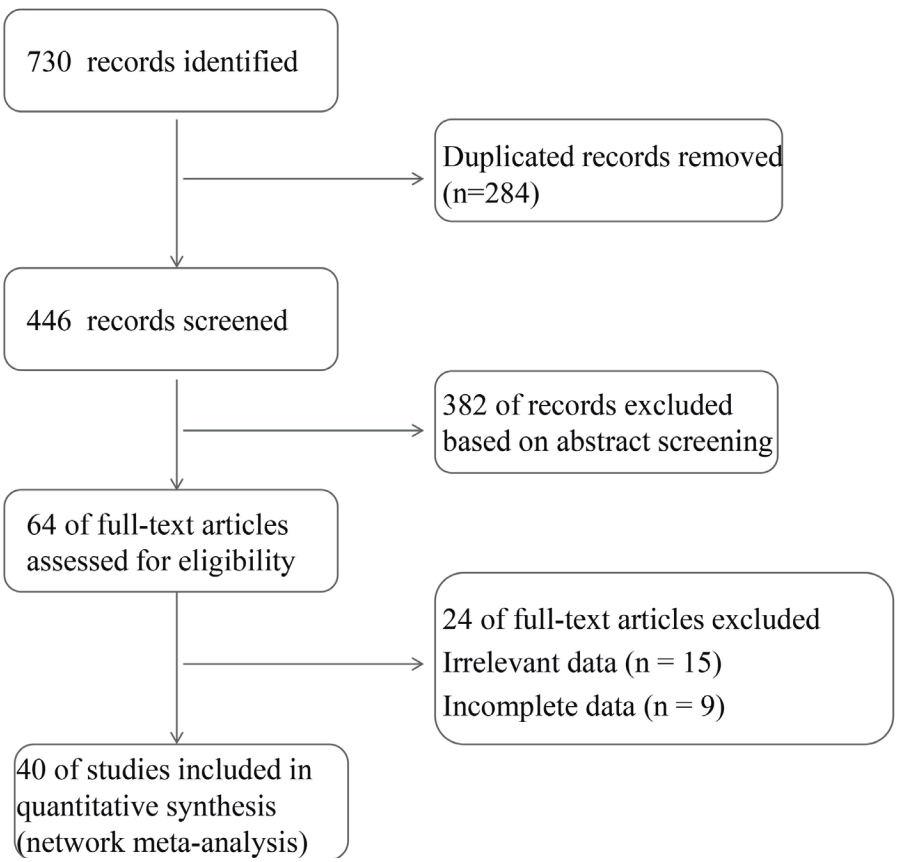
Characteristics and risk of bias of the included studies

The basic information of the included studies is presented in Table-1. The oldest study was published in 2006 and the most updated in 2024. A total of 7156 cases were analyzed, with 2625 (37.1%) in RARC group, 924 (12.9%) in the LRC arm and 3580 (50%) in ORC arm. Median age ranged between 60 and 70 years old.

The risk of bias according to the Cochrane Collaboration's tool ranged from intermediate to low.

The protocols and methods of all included studies were reviewed according to the Cochrane Collaboration's tool, and generally considered to have an overall low risk of bias with adequate randomization (Figure-2). Due to the physical component of

Figure 1 - The flow diagram about the study retrieval process.



surgery, blinding was not attempted in most studies. Thus, most studies were deemed at high risk of performance bias.

Perioperative outcomes

Total operative time

Both LRC (SMD=0.81, 95% CI=0.44 to 1.17) and RARC (SMD=1.15, 95% CI=0.84 to 1.45) had significantly longer operative time compared to ORC. No statistically difference between LRC and RARC (SMD=0.34, 95% CI=-0.02 to 0.7) (Figure-3A). Concerning SUCRA results, ORC ranked first in operative time, followed by LRC, RARC (Figure-3B), this means that RARC has the longest surgical time, followed by LRC, and ORC.

Estimated blood loss and transfusion rate

Compared to ORC, the amount of blood loss during LRC (SMD=-1.21, 95% CI=-1.61 to -0.82) and RARC (SMD=-1.06, 95% CI=-1.37 to -0.75) was reduced at a statistically significant level. No statistically significant difference in blood loss between LRC and RARC (SMD=0.15, 95% CI=-0.24 to 0.54) was observed (Figure-3C). Concerning SUCRA results, LRC ranked first in estimated blood loss, followed by RARC, ORC (Figure-3D), this means that LRC has the least bleeding volume, followed by RARC, ORC.

Both LRC (OR=-1.18, 95% CI=-1.54 to -0.82) and RARC (OR=-1.33, 95% CI=-1.67 to -1.00) had statistically fewer transfusion rates compared to ORC. Besides, RARC had statistically fewer transfusion rates than LRC (OR=-0.15, 95% CI=-0.47 to 0.17) (Figures-4A and B).

Length of hospital stays (LOS)

LRC (SMD=-0.48, 95% CI=-0.77 to -0.18) and RARC (SMD=-0.43, 95% CI=-0.66 to -0.19) had a shorter hospital day than ORC. No statistically significant difference in hospital stays between LRC and RARC

Table 1 - Main characteristics of the studies included in network meta-analysis.

Included studies	Studies design	Treatment 1	Treatment 2	Treatment 3	Sample size	Age, years	Sex(male/female)
Abraham et al. 2007 (17)	Prospective study	RARC	LRC	/	14/20	76.5/77.6	/
Arora et al. 2020 (18)	Retrospective study	RARC	LRC	/	188/112	68/67	168:20/92:20
Bai et al. 2021 (19)	Retrospective study	RARC	LRC	/	136/82	62.6/61	101:35/65:17
Bochner et al. 2015 (20)	RCT	RARC	/	ORC	60/58	66/65	51:9/42:16
Borghesi et al. 2018 (21)	Prospective study	RARC	/	ORC	17/33	72/72	/
Catto et al. 2022 (22)	RCT	RARC	/	ORC	161/156	69.3/68.7	128:33/122:34
Chen et al. 2017 (61)	RCT	/	LRC	ORC	29/28	78/77	20:9/19:9
Chow et al. 2018 (23)	Prospective study	RARC	/	ORC	26/13	70/75	21:5/10:3
Dixon et al. 2023 (24)	RCT	RARC	/	ORC	157/148	/	/
Galich et al. 2006 (25)	Retrospective study	RARC	/	ORC	13/24	70/70.5	10:3/18:6
Gan et al. 2013 (26)	Prospective study	RARC	LRC	ORC	20/20/19	/	/
Gastecka et al. 2018 (62)	Retrospective study	RARC	LRC	/	52/37	67/66	40:12/33:4
Guillotreau et al. 2009 (63)	Prospective study	/	LRC	ORC	38/30	67.9/64.9	36:2/25:5
Kader et al. 2013 (28)	Retrospective study	RARC	/	ORC	103/100	67/66	74:29/73:27
Khan et al. 2012 (29)	Prospective study	RARC	LRC	ORC	48/58/52	66.5/69.8/65	41:7/54:4/40:12
Khan et al. 2016 (30)	RCT	RARC	LRC	ORC	20/19/20	68.6/68.6/66.6	17:3/15:5/18:2
Kim et al. 2016 (31)	Retrospective study	RARC	LRC	ORC	58/22/150	61.5/65/68	54:4/20:2/123:27
Lin et al. 2014 (32)	RCT	/	LRC	ORC	35/35	63.2/63.6	32:3/32:3
Lisinski et al. 2022 (33)	Prospective study	/	LRC	ORC	77/82	66/65	62:15/62:20
Maibom et al. 2022 (34)	RCT	RARC	/	ORC	25/25	70/67	20:5/18:7
Mastroianni et al. 2022 (35)	RCT	RARC	/	ORC	58/58	64/66	44:14/40:18

Matsumoto et al. 2019 (36)	Retrospective study	RARC	LRC	ORC	10 10 16	67.3/67/69.2	8:2/8:2/11:5
Messer et al. 2014 (37)	Prospective study	RARC	/	ORC	20/20	69.5/64.5	18:2/16:4
Ng et al. 2010 (38)	Prospective study	RARC	/	ORC	83/104	70.9/67.2	65:18/73:31
Nix et al. 2010 (39)	RCT	RARC	/	ORC	21/20	67.4/69.2	14:7/17:3
Panwar et al. 2018 (40)	Prospective study	RARC	LRC	ORC	24/5/54	57/54/58	/
Parekh et al. 2018 (42)	RCT	RARC	/	ORC	150/152	70/67	126:24/128:24
Porpiglia et al. 2007 (43)	Prospective study	/	LRC	ORC	20/22	63.5/71	19:1/20:2
Porreca et al. 2022 (8)	Prospective study	RARC	LRC	ORC	368/46/1009	67/76/72	314:54/39:7/ 803:206
Ram et al. 2018 (44)	Prospective study	RARC	/	ORC	125/45	61.76/60.07	109:16/40:5
Rhee et al. 2006 (45)	Prospective study	RARC	/	ORC	7/23	60/67	6:1/14:9
Sharma et al. 2017 (46)	Prospective study	RARC	/	ORC	65/407	70.9/70.2	63:2/298:109
Styn et al. 2012 (64)	Retrospective study	RARC	/	ORC	50/100	66.6/65.6	□
Su et al. 2019 (47)	Retrospective study	RARC	LRC	/	189/126	62/62.6	160:29/64:62
Tan et al. 2018 (48)	Prospective study	RARC	/	ORC	45/50	65.0/62.8	32:13/36:14
Teishima et al. 2014 (49)	Prospective study	RARC	LRC	/	6/5	68.7/67.3	/
Wang et al. 2008 (51)	Case control study	RARC	/	ORC	33/21	70/66	29:4/13:8
Yang et al. 2024 (52)	Retrospective study	RARC	/	ORC	128/461	71/70	102:26/351:110
Zhang et al. 2020 (53)	Retrospective study	RARC	LRC	/	172/126	68.1/66.2	147:25/103:23
Zhou et al. 2023 (3)	Retrospective study	/	LRC	ORC	45/45	65.5/65.3	21:24/22:23

Figure 2 - Risk of bias assessment.

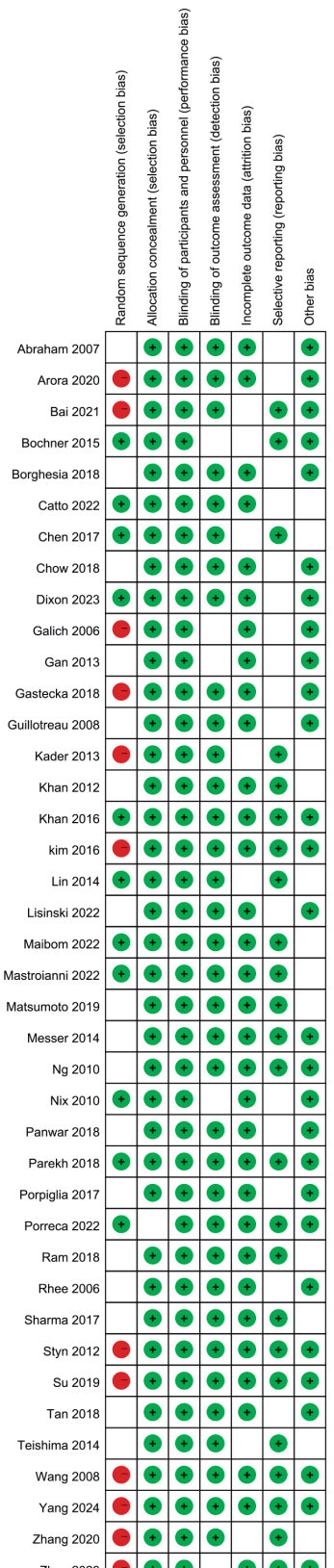


Figure 3 - Forest plots and surface under the cumulative ranking (SUCRA) plots summarizing the meta-analyses between LRC, RARC and ORC for: (A) (B) Operative time; (C)(D) Estimated blood loss; (E)(F) Transfusion rate.

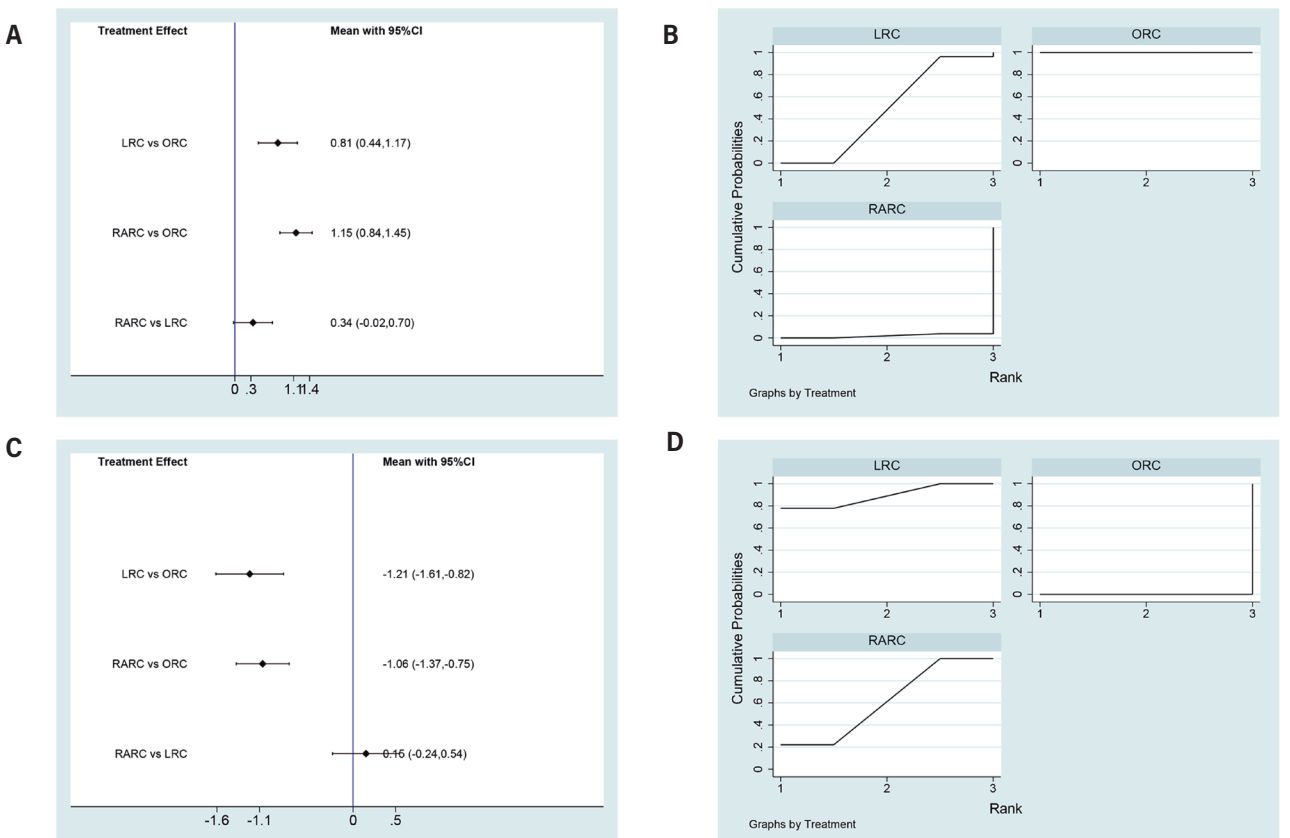
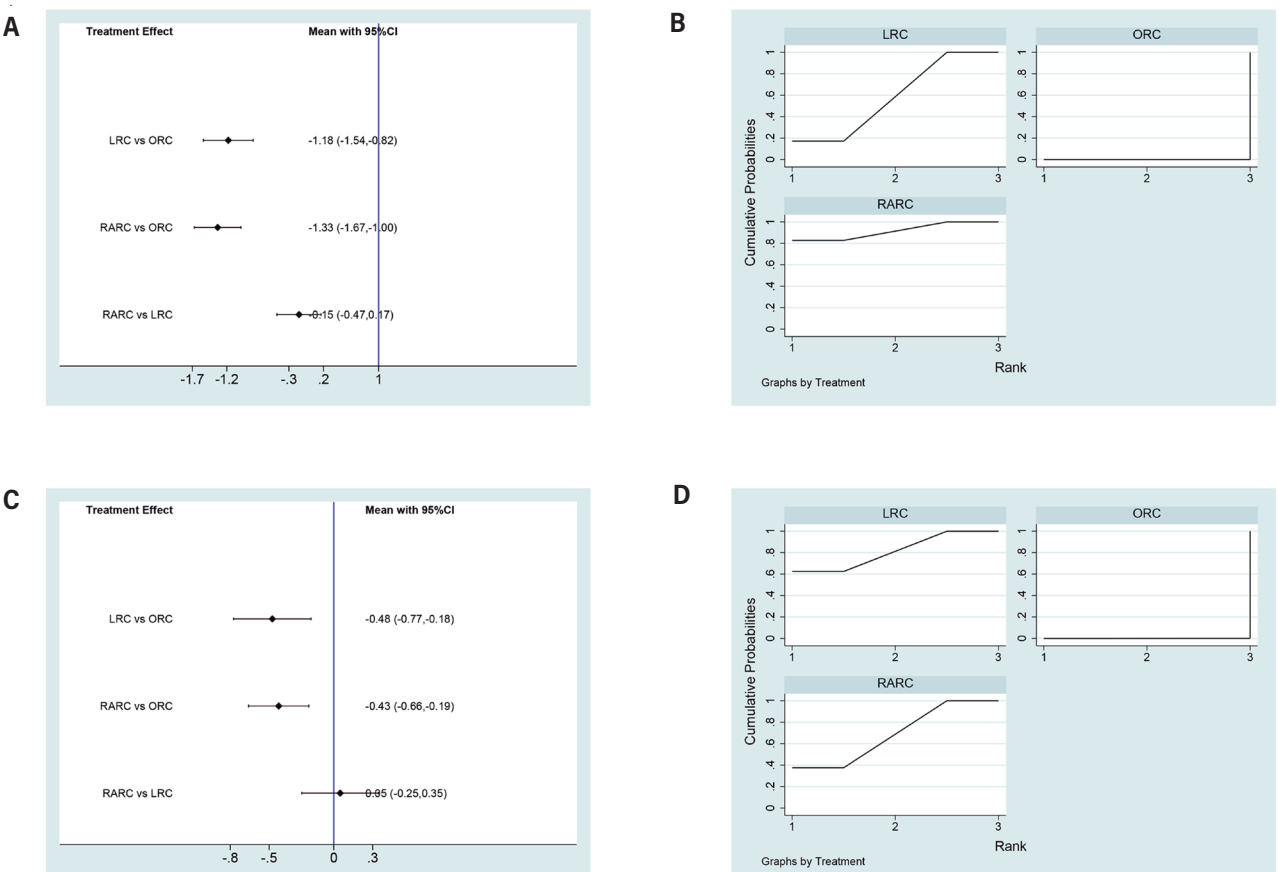


Figure 4 - Forest plots and surface under the cumulative ranking (SUCRA) plots summarizing the meta-analyses between LRC, RARC and ORC for: (A) (B) transfusion rate; (C)(D) length of hospital stays (LOS).



(SMD=0.05, 95% CI=-0.245 to 0.35) was observed (Figure-4C). Concerning SUCRA results, LRC ranked first in operative time, followed by RARC, LRC (Figure-4D), this means that LRC has the shortest length of stay, followed by RARC, ORC.

Days to regular diet

LRC (SMD=-0.66, 95% CI=-0.99 to -0.34) and RARC (SMD=-0.66, 95% CI=-1.01 to -0.3) had a significant shorter time to regular diet than ORC. No statistically significant difference in time to regular diet between LRC and RARC was observed (SMD=0.01, 95% CI=-0.36 to 0.37) (Figure-5A). Concerning SUCRA results, ORC ranked first in operative time, followed by LR, RARC (Figure-5B), this means that RARC has the shortest time to restore normal diet, followed by LRC, ORC.

Time to flatus

LRC (SMD=-73, 95% CI=-1.44 to -0.32) had a shorter time to flatus than ORC. No statistically significant difference in time to flatus between RARC and ORC was observed (SMD=-0.04, 95% CI=-0.3 to 0.23) (Figure-5C). Concerning SUCRA results, LRC ranked first in operative time, followed by RARC, ORC (Figure-5D), this means that LRC has the shortest time to flatus, followed by LRC, ORC.

Complication rates

Both LRC (OR=-0.03, 95% CI=-0.49 to 0.44) and RARC (OR=-0.42, 95% CI=-0.74 to -0.11) had statistically fewer incidences of overall complications within 90 days compared to ORC. Besides, RARC had statistically fewer overall complication rates than LRC (OR=-0.39, 95% CI=-0.79 to 0.00) (Figure-6A). Similarly, LRC and RARC had statistically lower minor complication rates (LRC: OR=0.03, 95% CI=-0.26 to 0.33 and RARC: OR=-0.2, 95% CI=-0.39 to -0.01) and major complication rates (LRC: OR=0.06, 95% CI=-0.254 to 0.43 and RARC: OR=-0.29, 95% CI=-0.61 to 0.03) compared to ORC. Besides, RARC had statistically lower minor complication rates (OR=-0.23, 95% CI=-0.48 to 0.02) and major complication rates (OR=-0.23, 95% CI=-0.68 to 0.21) than LRC (Figures-6B and C). Concerning SUCRA results, RARC ranked first in complication rates, followed by LRC, ORC (Figure-6D), this means that RARC has the fewest complications, followed by LRC, ORC.

Oncological outcomes

Lymph node yield

No differences in lymph node yield were found for LRC versus ORC (SMD=-0.01, 95% CI=-0.29 to 0.28), RARC versus ORC (SMD=0.04, 95% CI=-0.18 to 0.26), and RARC versus LRC (SMD=0.05, 95% CI=-0.27 to 0.36) (Figure-7A). Concerning SUCRA results, RARC ranked first in lymph node yield, followed by LRC, ORC (Figure-7B), this means that RARC has the highest lymph node yield, followed by LRC, ORC.

Positive surgical margin

Both LRC (OR=-0.25, 95% CI=-0.72 to 0.22) and RARC (OR=-0.05, 95% CI=-0.38 to -0.29) had statistically fewer positive surgical margin rates compared to ORC. Besides, RARC had statistically fewer positive surgical margin rates than LRC (OR=0.22, 95% CI=-0.27 to 0.68) (Figures-7C and D), which can reduce the risk of positive margins.

Publication bias

The publication bias is important for interpreting the conclusions. As shown in Figure-8, the funnel plots had good symmetry, indicating that there had no selectivity and publication bias.

DISCUSSION

ORC is the "gold standard" for the treatment of MIBC and high-risk NMIBC. However, the surgical procedure is more complicated, time-consuming, and more bleeding (32). With the rapid development of minimally invasive surgical techniques, laparoscopic techniques have been widely used in various urological surgeries, LRC and RARC becoming more and more applied. Parra et al. (54) reported the first LRC in 1992, Menon (55) completed the first RARC in 2003. Compared to LRC, RARC has technological superiorities of better visibility, improved degrees of freedom, and lower learning curves. Despite higher cost and steeper learning curves, minimally invasive surgeries like RARC are being used in

Figure 5 - Forest plots and surface under the cumulative ranking (SUCRA) plots summarizing the meta-analyses between LRC, RARC and ORC for: (A) (B) days to regular diet; (C)(D) time to flatus.

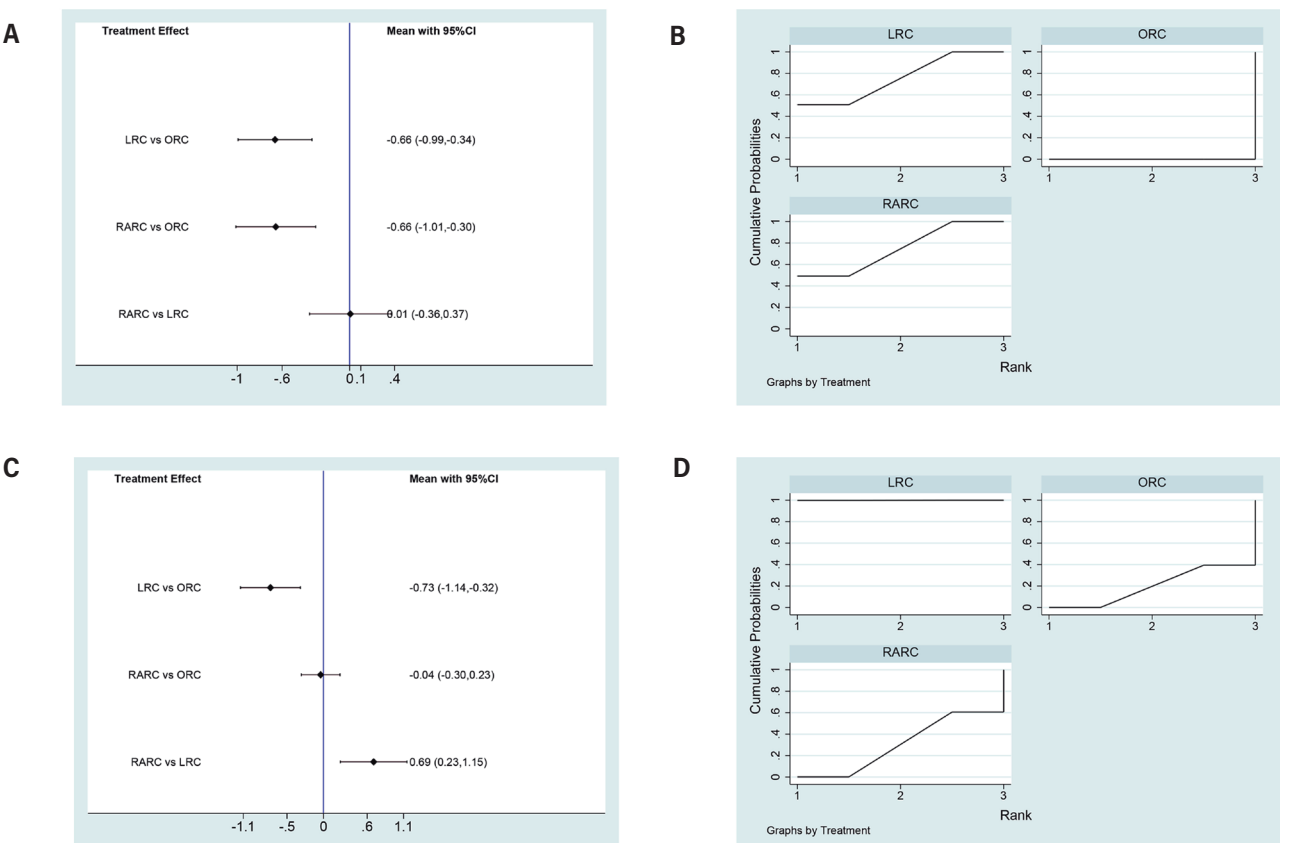


Figure 6 - Forest plots summarizing the meta-analyses between LRC, RARC and ORC for: (A) overall complication rates; (B) minor complication rates; (C) major complication rates. (D) surface under the cumulative ranking (SUCRA) plots.

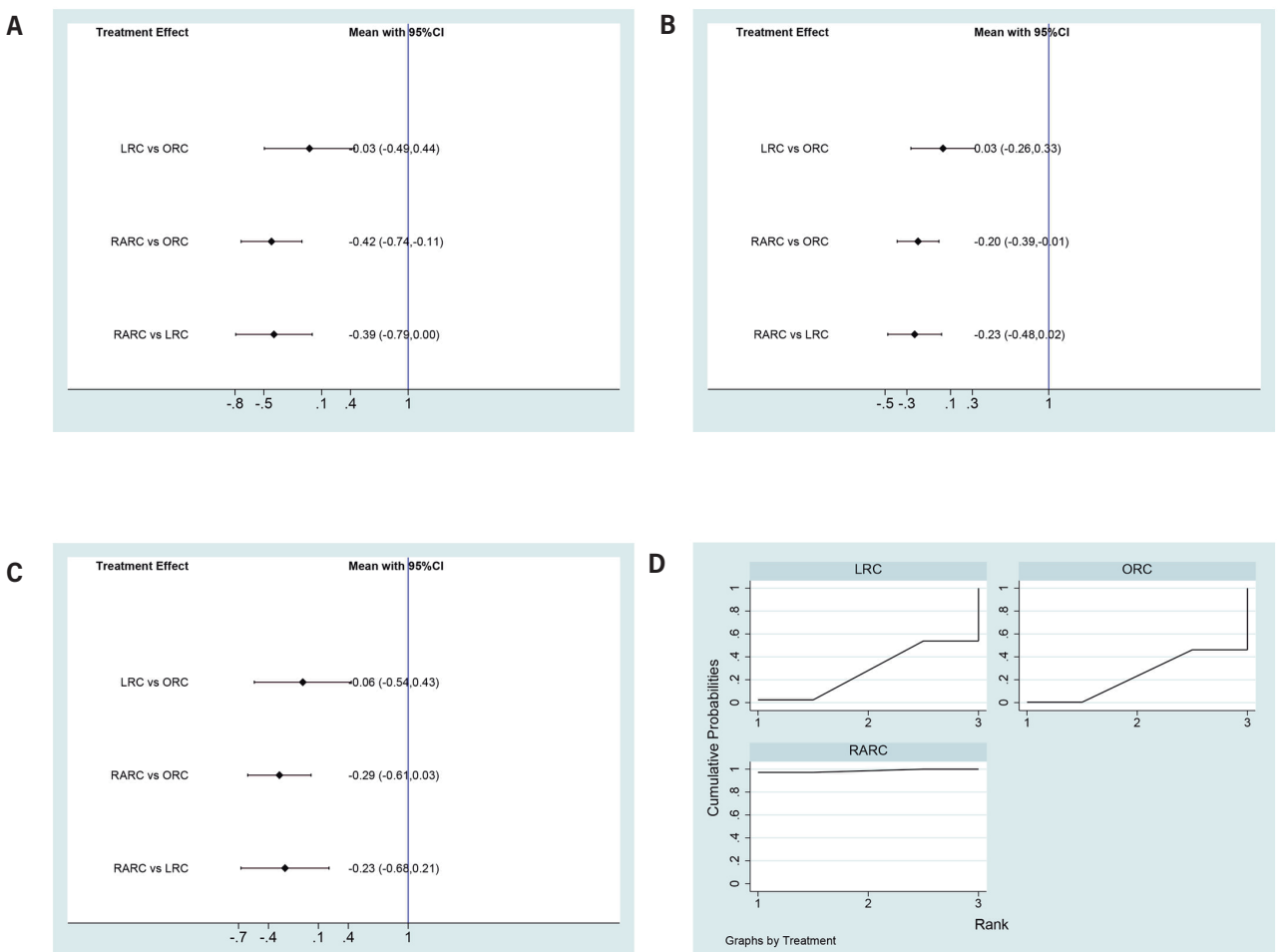


Figure 7 - Forest plots and surface under the cumulative ranking (SUCRA) plots summarizing the meta-analyses between LRC, RARC and ORC for: (A) (B) lymph node yield; (C)(D) positive surgical margin rates.

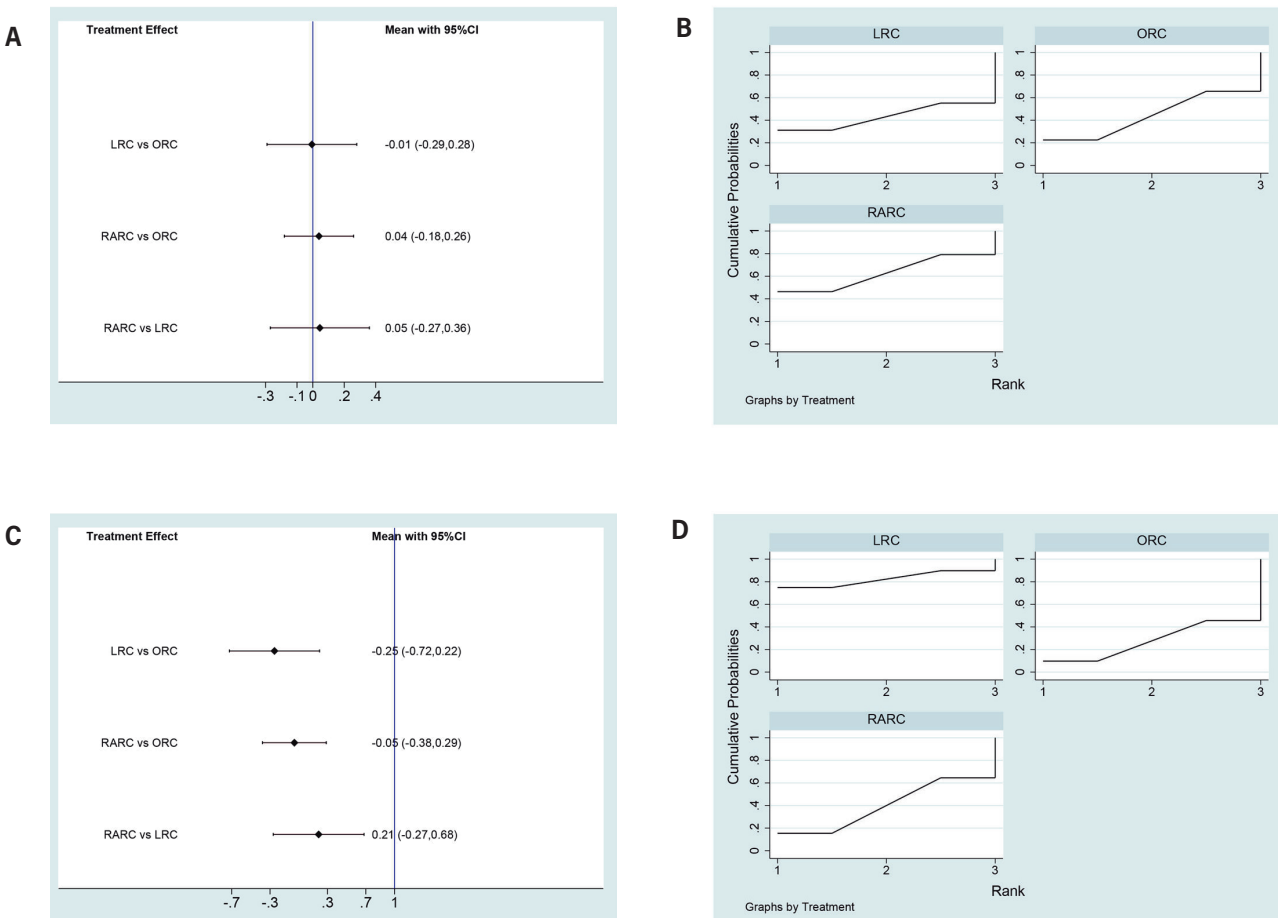
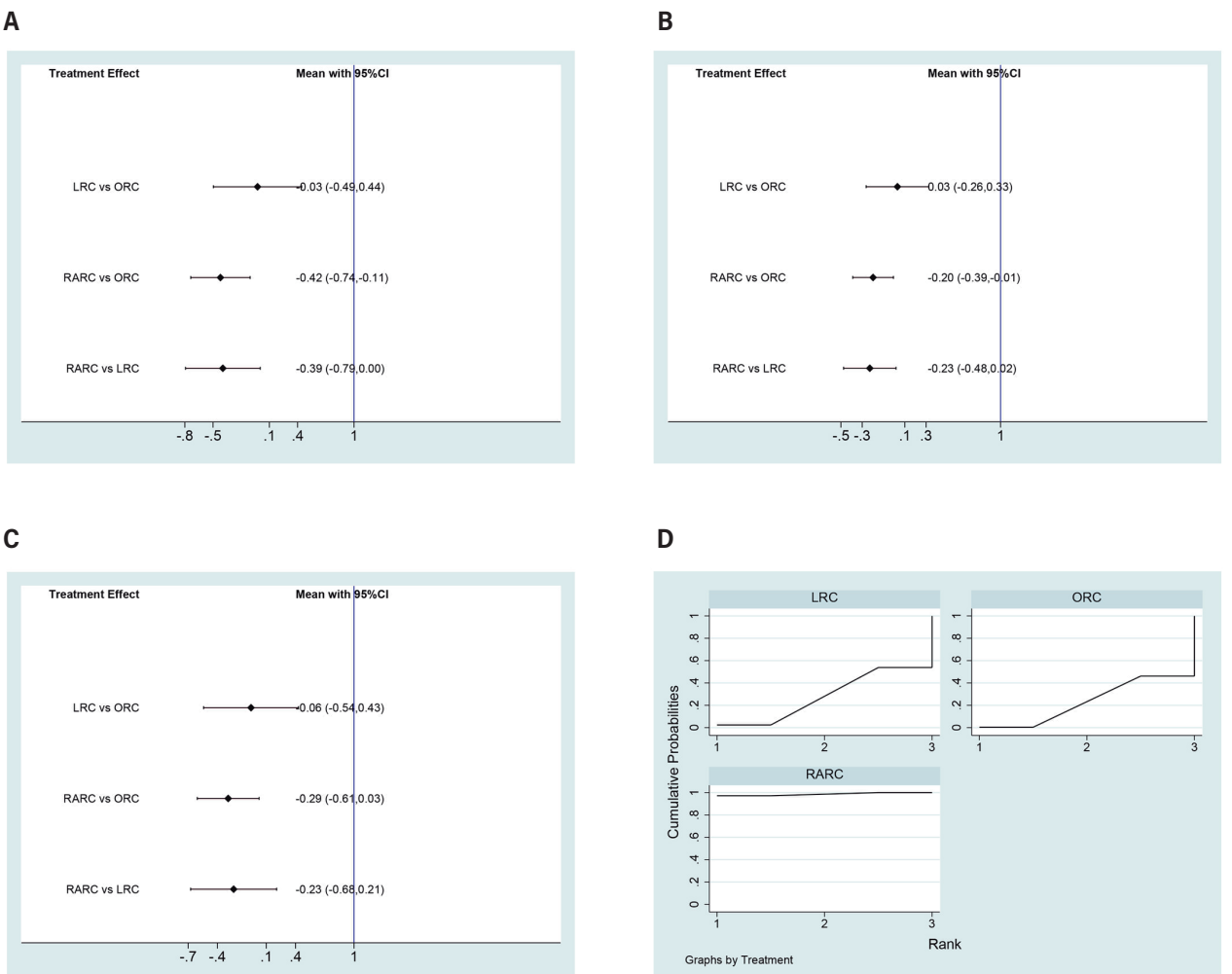


Figure 8 - Funnel plot for network meta-analysis of all the outcomes. (A) operative time. (B) overall complication rates.



many medicine fields (10, 56). According to reports, the proportion of RARC in the United States increased from 0.6% in 2004 to 12.8% in 2010 (57).

In this study, we present an up-to-date network meta-analysis to compare the perioperative and pathological outcomes of RARC, LRC and ORC in bladder cancer. Forty studies were included in our meta-analysis, and the main findings of the present research are as follows: Both LRC and RARC had a longer operative time compared to ORC, no statistically significant difference LRC and RARC. Based on the SUCRA, RARC has the longest surgical time. The amount of blood loss during LRC and RARC was reduced at a statistically significant level compared to ORC, no statistically significant difference LRC and RARC. Based on the SUCRA, LRC has the least bleeding volume. In addition, both LRC and RARC had statistically fewer transfusion rates compared to ORC, RARC had statistically fewer transfusion rates than LRC. No statistically significant difference in hospital stays between LRC and RARC was observed. Based on the SUCRA, LRC has the shortest length of stay. LRC and RARC had significantly shorter time to regular diet than ORC. No statistically significant difference in time to regular diet between LRC and RARC. Based on the SUCRA, RARC has the shortest time to restore normal diet. LRC had significantly shorter time to flatus than ORC. Based on the SUCRA, LRC has the shortest time to flatus. Both LRC and RARC had statistically fewer incidences of overall complications, minor complications, and major complications within 90 days compared to ORC. Besides, RARC had statistically fewer overall complication rates, minor and major complication rates than LRC. LRC, RARC and ORC were comparable in terms of lymph node yield. Both LRC and RARC had statistically fewer positive surgical margin rates compared to ORC. Besides, RARC had statistically fewer positive surgical margin rates than LRC.

The operation time of LRC and RARC is longer than that of ORC because of the complexity of the operation, the high requirements for equipment, and the obvious learning curve. There was no significant difference in surgical time between RARC and LRC. It should be noted that there is no unified standard for surgical time statistics in major medical centers, and robotic surgical systems often require processes such as docking and undocking of operating arms, which may prolong surgical time (49). The actual surgical operation time of RARC may be shorter, but further statistics are needed to determine. In addition, in the early stages of introducing robotic surgery, surgeons and assistants may have a certain learning curve due to lack of experience.

The LRC and RARC surgical incisions are small, which avoids the damage to the skin, muscles and blood vessels caused by the large incisions of ORC surgery, and the intestinal exposure time is short, resulting in less bleeding loss, lower blood transfusion proportion, shorter time to restore normal diet, exhaust time, and hospital stay (58). RARC requires less intraoperative transfusion than LRC, and the amount of intraoperative transfusion required is often determined by intraoperative blood loss and the patient's vital signs.

Both LRC and RARC had statistically fewer incidences of complications than ORC. In addition, the incidence of complications in RARC is the lowest, possibly due to the robot system having a high-definition three-dimensional perspective compared to laparoscopy, allowing surgical operators to distinguish the structure of blood vessels and tissues more clearly and accurately. The seven freely movable robotic arms of the robot can reduce hand tremors while achieving surgical angles that cannot be achieved by laparoscopy. In the narrow space of the pelvic cavity, more precise operations can be performed, reducing errors (42, 59).

Lymph node yield and positive surgical margin status have previously been shown to serve as surrogates for oncologic outcomes. In our network meta-analysis, no significant difference between lymph node yields for LRC, RARC and ORC was observed. Although SUCRA result showed that RARC has the highest lymph node yield, the finding was not significant. The scope of pelvic lymph node dissection under the laparoscope was the same as the open. Due to the magnifying effect of the laparoscope and the clearer field of vision, it can see the lymphatic vessels, swollen lymph nodes, Iliac vessels, obturator nerves, and other important structures to benefit from the complete removal of lymphoid tissues while avoiding neurovascular damage (11). A possible reason for this apparent discrepancy could be

the different sampling methods of lymph node collection between the operations. For the robotic groups, at the completion of lymphadenectomy for each side, nodes are submitted as right and left pelvic lymph nodes, whereas in the open group lymph nodes are handed off as discrete anatomical packets (41). The potential risk factors for positive surgical margins are as follows: 1) characteristics of advanced cancer, such as lymphatic vessel invasion, extravesical diseases, and mixed histology; 2) depending on the surgeon's factors, including surgical type, technique, and experience; 3) sample processing. Weihong Xu (60) conducted the first meta-analysis to investigate the effect of surgical margin status on the prognosis of bladder cancer, the findings demonstrate that positive surgical margins were associated with poor outcomes in terms of recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) in bladder cancer patients treated with radical cystectomy.

The present study includes some limitations. Firstly, language conditions were set, and data from studies in other languages could not be included. Secondly, the lack of data on some of the study indicators may have an impact on the overall study results.

CONCLUSIONS

LRC and RARC could be considered as a feasible and safe alternative to ORC for bladder cancer. Notably, compared with LRC, RARC may benefit from significantly lower transfusion rates, fewer complications and lower positive surgical margin rates. These data thus showed that RARC might improve the management of patients with muscle invasive or high-risk non-muscle invasive bladder cancer.

FUNDING

This study was supported by Tianjin Key Medical Discipline(Specialty) Construction Project (TJYXZDXK-073C).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49. doi: 10.3322/caac.21660.
2. Weinstock C, Agrawal S, Chang E. Optimizing Clinical Trial Design for Patients with Non-muscle-invasive Bladder Cancer. Eur Urol. 2022;82:47-8. doi: 10.1016/j.eururo.2022.02.014.
3. Zhou Y, Yang H, Liang Z. Efficiency and Safety of Laparoscopic Radical Cystectomy for Muscle-Invasive Bladder Cancer, and Postoperative Recurrence. Arch Esp Urol. 2023;76:196-202. doi: 10.56434/j.arch.esp.urol.20237603.23.
4. Sobhani S, Ghoreifi A, Douglawi A, Ahmadi H, Miranda G, Cai J, et al. Perioperative mortality for radical cystectomy in the modern Era: experience from a tertiary referral center. Int Braz J Urol. 2023;49:351-8. doi: 10.1590/S1677-5538.IBJU.2022.0405.
5. Alfred Witjes J, Max Bruins H, Carrión A, Cathomas R, Compérat E, Efstathiou JA, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2023 Guidelines. Eur Urol. 2024;85:17-31. doi: 10.1016/j.eururo.2023.08.016.
6. Dinney CP. Therapy of invasive bladder cancer. Urology. 2006;67(3 Suppl 1):56-9; discussion 60-1.
7. Maibom SL, Joensen UN, Poulsen AM, Kehlet H, Brasso K, Røder MA. Short-term morbidity and mortality following radical cystectomy: a systematic review. BMJ Open. 2021;11:e043266. doi: 10.1136/bmjopen-2020-043266.
8. Porreca A, Di Gianfrancesco L, Artibani W, Busetto GM, Carrieri G, Antonelli A, et al. Robotic-assisted, laparoscopic, and open radical cystectomy: surgical data of 1400 patients from The Italian Radical Cystectomy Registry on intraoperative outcomes. Cent European J Urol. 2022;75:135-44. doi: 10.5173/ceju.2022.0284.
9. Gaya JM, Uleri A, Sanz I, Basile G, Verri P, Hernandez P, et al. Robot-assisted radical cystectomy and ileal conduit with HugoTM RAS system: feasibility, setting and perioperative outcomes. Int Braz J Urol. 2023;49:787-8. doi: 10.1590/S1677-5538.IBJU.2023.0349.

10. Li P, Meng C, Peng L, Gan L, Xie Y, Liu Y, et al. Perioperative comparison between robot-assisted and laparoscopic radical cystectomy: An update meta-analysis. Asian J Surg. 2023;46:3464-79. doi: 10.1016/j.asjsur.2023.04.030.
11. Dong L, Xiaoli F, Ya L, Dan W, Jingwen H, Xun L, et al. Bayesian network analysis of long-term oncologic outcomes of open, laparoscopic, and robot-assisted radical cystectomy for bladder cancer. Medicine (Baltimore). 2022;101:e30291. doi: 10.1097/MD.0000000000030291.
12. Kowalewski KF, Wieland VLS, Kriegmair MC, Uysal D, Sicker T, Stolzenburg JU, et al. Robotic-assisted Versus Laparoscopic Versus Open Radical Cystectomy-A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. Eur Urol Focus. 2023;9:480-90. doi: 10.1016/j.euf.2022.12.001.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
14. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-96. doi: 10.1097/SLA.0b013e3181b13ca2.
15. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142. doi: 10.1002/14651858.ED000142.
16. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. doi: 10.1186/1471-2288-5-13.
17. Abraham JB, Young JL, Box GN, Lee HJ, Deane LA, Ornstein DK. Comparative analysis of laparoscopic and robot-assisted radical cystectomy with ileal conduit urinary diversion. J Endourol. 2007;21:1473-80. doi: 10.1089/end.2007.0095.
18. Arora A, Pugliesi F, Zugail AS, Moschini M, Pazeto C, Macek P, et al. Comparing Perioperative Complications Between Laparoscopic and Robotic Radical Cystectomy for Bladder Cancer. J Endourol. 2020;34:1033-40. doi: 10.1089/end.2020.0112.
19. Bai Y, Wang S, Zheng W, Li E, Quan J, Wei F, et al. Clinical outcome of laparoscopic versus robot-assisted radical cystectomy for patients with bladder cancer: a retrospective study. BMC Surg. 2021;21:388. doi: 10.1186/s12893-021-01382-1.
20. Bochner BH, Dalbagni G, Sjoberg DD, Silberstein J, Keren Paz GE, Donat SM, et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. Eur Urol. 2015;67:1042-50. doi: 10.1016/j.eururo.2014.11.043.
21. Borghesi M, Schiavina R, Antonelli A, Buizza C, Celia A, Parma P, et al. Peri-Operative Outcomes after Open and Robot-Assisted Radical Cystectomy by Using an Advanced Bipolar Seal and Cut Technology (Caiman®): A Prospective, Comparative, and Multi-Institutional Study. Curr Urol. 2019;12:64-9. doi: 10.1159/000489421.
22. Catto JWF, Khetrapal P, Ricciardi F, Ambler G, Williams NR, Al-Hammouri T, et al. Effect of Robot-Assisted Radical Cystectomy With Intracorporeal Urinary Diversion vs Open Radical Cystectomy on 90-Day Morbidity and Mortality Among Patients With Bladder Cancer: A Randomized Clinical Trial. JAMA. 2022;327:2092-103. doi: 10.1001/jama.2022.7393.
23. Chow K, Zargar H, Corcoran NM, Costello AJ, Peters JS, Dundee P. Robotic-assisted radical cystectomy with intracorporeal urinary diversion versus open: early Australian experience. ANZ J Surg. 2018;88:1028-32. doi: 10.1111/ans.14361.
24. Dixon S, Hill H, Flight L, Khetrapal P, Ambler G, Williams NR, et al. Cost-Effectiveness of Robot-Assisted Radical Cystectomy vs Open Radical Cystectomy for Patients With Bladder Cancer. JAMA Netw Open. 2023;6:e2317255. doi: 10.1001/jamanetworkopen.2023.17255.
25. Galich A, Sterrett S, Nazemi T, Pohlman G, Smith L, Balaji KC. Comparative analysis of early perioperative outcomes following radical cystectomy by either the robotic or open method. JSLS. 2006;10:145-50.
26. Gan C, Ismail F, Cheung G, Patel A, Watkins J, O' Brien T, et al. 1624 A pilot prospective single-centre 3-arm randomised controlled trial of open, robotic and laparoscopic (coral) radical cystectomy for bladder cancer. J Urol. [Internet]. 2013 Apr 1 [cited 2024 Aug 9];189(4S):e667–8. Available from: https://doi.org/10.1016/j.juro.2013.02.3174.
27. Haudebert C, Hascoet J, Freton L, Khene ZE, Dosin G, Voiry C, et al. Cystectomy and ileal conduit for neurogenic bladder: Comparison of the open, laparoscopic and robotic approaches. Neurourol Urodyn. 2022;41:601-8. doi: 10.1002/nau.24855.

28. Kader AK, Richards KA, Krane LS, Pettus JA, Smith JJ, Hemal AK. Robot-assisted laparoscopic vs open radical cystectomy: comparison of complications and perioperative oncological outcomes in 200 patients. BJU Int. 2013;112:E290-4. doi: 10.1111/bju.12167.
29. Khan MS, Challacombe B, Elhage O, Rimington P, Coker B, Murphy D, et al. A dual-centre, cohort comparison of open, laparoscopic and robotic-assisted radical cystectomy. Int J Clin Pract. 2012;66:656-62. doi: 10.1111/j.1742-1241.2011.02888.x.
30. Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). Eur Urol. 2016;69:613-21. doi: 10.1016/j.eururo.2015.07.038.
31. Kim TH, Sung HH, Jeon HG, Seo SI, Jeon SS, Lee HM, et al. Oncological Outcomes in Patients Treated with Radical Cystectomy for Bladder Cancer: Comparison Between Open, Laparoscopic, and Robot-Assisted Approaches. J Endourol. 2016;30:783-91. doi: 10.1089/end.2015.0652.
32. Lin T, Fan X, Zhang C, Xu K, Liu H, Zhang J, et al. A prospective randomised controlled trial of laparoscopic vs open radical cystectomy for bladder cancer: perioperative and oncologic outcomes with 5-year follow-upT Lin et al. Br J Cancer. 2014;110:842-9. doi: 10.1038/bjc.2013.777.
33. Lisiński J, Kienitz J, Tousty P, Kaczmarek K, Lemiński A, Słojewski M. Comparison of Laparoscopic and Open Radical Cystectomy for Muscle-Invasive Bladder Cancer. Int J Environ Res Public Health. 2022;19:15995. doi: 10.3390/ijerph192315995.
34. Maibom SL, Røder MA, Aasvang EK, Rohrsted M, Thind PO, Bagi P, et al. Open vs robot-assisted radical cystectomy (BORARC): a double-blinded, randomised feasibility study. BJU Int. 2022;130:102-13. doi: 10.1111/bju.15619.
35. Mastroianni R, Ferriero M, Tuderti G, Anceschi U, Bove AM, Brassetti A, et al. Open Radical Cystectomy versus Robot-Assisted Radical Cystectomy with Intracorporeal Urinary Diversion: Early Outcomes of a Single-Center Randomized Controlled Trial. J Urol. 2022;207:982-92. doi: 10.1097/JU.0000000000002422.
36. Matsumoto K, Tabata KI, Hirayama T, Shimura S, Nishi M, Ishii D, et al. Robot-assisted laparoscopic radical cystectomy is a safe and effective procedure for patients with bladder cancer compared to laparoscopic and open surgery: Perioperative outcomes of a single-center experience. Asian J Surg. 2019;42:189-96. doi: 10.1016/j.asjsur.2017.11.002.
37. Messer JC, Punnen S, Fitzgerald J, Svatek R, Parekh DJ. Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs open radical cystectomy. BJU Int. 2014;114:896-902. doi: 10.1111/bju.12818.
38. Ng CK, Kauffman EC, Lee MM, Otto BJ, Portnoff A, Ehrlich JR, et al. A comparison of postoperative complications in open versus robotic cystectomy. Eur Urol. 2010;57:274-81. doi: 10.1016/j.eururo.2009.06.001.
39. Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. Eur Urol. 2010;57:196-201. doi: 10.1016/j.eururo.2009.10.024.
40. Panwar P, Mavuduru RS, Mete UK, Kumar S, Bora GS, Devana SK, et al. Perioperative outcomes of minimally invasive versus open radical cystectomy: A single-center experience. Indian J Urol. 2018;34:115-21. doi: 10.4103/iju.IJU_166_17.
41. Parekh DJ, Messer J, Fitzgerald J, Ercole B, Svatek R. Perioperative outcomes and oncologic efficacy from a pilot prospective randomized clinical trial of open versus robotic assisted radical cystectomy. J Urol. 2013;189:474-9. doi: 10.1016/j.juro.2012.09.077.
42. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018;391:2525-36. doi: 10.1016/S0140-6736(18)30996-6.
43. Porpiglia F, Renard J, Billia M, Scoffone C, Cracco C, Terrone C, et al. Open versus laparoscopy-assisted radical cystectomy: results of a prospective study. J Endourol. 2007;21:325-9. doi: 10.1089/end.2006.0224.
44. Ram D, Rajappa SK, Rawal S, Singh A, Singh PB, Dewan AK. Is robot-assisted radical cystectomy superior to standard open radical cystectomy? An Indian perspective. J Minim Access Surg. 2018;14:298-303. doi: 10.4103/jmas.JMAS_150_17.

45. Rhee JJ, Lebeau S, Smolkin M, Theodorescu D. Radical cystectomy with ileal conduit diversion: early prospective evaluation of the impact of robotic assistance. BJU Int. 2006;98:1059-63. doi: 10.1111/j.1464-410X.2006.06372.x.
46. Sharma P, Zargar-Shoshtari K, Poch MA, Pow-Sang JM, Sexton WJ, Spiess PE, et al. Surgical control and margin status after robotic and open cystectomy in high-risk cases: Caution or equivalence? World J Urol. 2017;35:657-63. doi: 10.1007/s00345-016-1915-2.
47. Su S, Gu L, Ma X, Li H, Wang B, Shi T, et al. Comparison of Laparoscopic and Robot-assisted Radical Cystectomy for Bladder Cancer: Perioperative and Oncologic Outcomes. Clin Genitourin Cancer. 2019;17:e1048-e1053. doi: 10.1016/j.clgc.2019.06.007.
48. Tan WS, Tan MY, Lamb BW, Sridhar A, Mohammed A, Baker H, et al. Intracorporeal robot-assisted radical cystectomy, together with an enhanced recovery programme, improves postoperative outcomes by aggregating marginal gains. BJU Int. 2018;121:632-9. doi: 10.1111/bju.14073.
49. Teishima J, Hieda K, Inoue S, Goto K, Ikeda K, Ohara S, et al. Comparison of initial experiences of robot-assisted radical cystectomy with those of laparoscopic for bladder cancer. Innovations (Phila). 2014;9:322-6. doi: 10.1097/IMI.0000000000000056.
50. Vejlgaard M, Maibom SL, Joensen UN, Thind PO, Rohrsted M, Aasvang EK, et al. Quality of life and secondary outcomes for open versus robot-assisted radical cystectomy: a double-blinded, randomised feasibility trial. World J Urol. 2022;40:1669-77. doi: 10.1007/s00345-022-04029-9.
51. Wang GJ, Barocas DA, Raman JD, Scherr DS. Robotic vs open radical cystectomy: prospective comparison of perioperative outcomes and pathological measures of early oncological efficacy. BJU Int. 2008;101:89-93. doi: 10.1111/j.1464-410X.2007.07212.x.
52. Yang R, Rac G, Felice MD, Pahouja G, Ko C, Okabe Y, et al. Robotic versus open radical cystectomy for bladder cancer: evaluation of complications, survival, and opioid prescribing patterns. J Robot Surg. 2024;18:10. doi: 10.1007/s11701-023-01749-x.
53. Zhang S, Lin T, Zhang Q, Zhang S, Liu G, Ji C, et al. Comparison of perioperative outcomes in robot-assisted radical cystectomy and laparoscopic radical cystectomy. Int J Med Robot. 2020;16:e2074. doi: 10.1002/rcs.2074.
54. Parra RO, Andrus CH, Jones JP, Boullier JA. Laparoscopic cystectomy: initial report on a new treatment for the retained bladder. J Urol. 1992;148:1140-4. doi: 10.1016/s0022-5347(17)36843-x.
55. Menon M, Hemal AK, Tewari A, Shrivastava A, Shoma AM, El-Tabey NA, et al. Nerve-sparing robot-assisted radical cystoprostatectomy and urinary diversion. BJU Int. 2003;92:232-6. doi: 10.1046/j.1464-410x.2003.04329.x.
56. Kimura S, Iwata T, Foerster B, Fossati N, Briganti A, Nasu Y, et al. Comparison of perioperative complications and health-related quality of life between robot-assisted and open radical cystectomy: A systematic review and meta-analysis. Int J Urol. 2019;26:760-74. doi: 10.1111/iju.14005.
57. Leow JJ, Reese SW, Jiang W, Lipsitz SR, Bellmunt J, Trinh QD, et al. Propensity-matched comparison of morbidity and costs of open and robot-assisted radical cystectomies: a contemporary population-based analysis in the United States. Eur Urol. 2014;66:569-76. doi: 10.1016/j.eururo.2014.01.029.
58. Fonseka T, Ahmed K, Froghi S, Khan SA, Dasgupta P, Shamim Khan M. Comparing robotic, laparoscopic and open cystectomy: a systematic review and meta-analysis. Arch Ital Urol Androl. 2015;87:41-8. doi: 10.4081/aiua.2015.1.41.
59. Cai PY, Khan AI, Shoag JE, Scherr DS. Robotic Radical Cystectomy in the Contemporary Management of Bladder Cancer. Urol Clin North Am. 2021;48:45-50. doi: 10.1016/j.ucl.2020.09.003.
60. Hong X, Li T, Ling F, Yang D, Hou L, Li F, et al. Impact of surgical margin status on the outcome of bladder cancer treated by radical cystectomy: a meta-analysis. Oncotarget. 2017;8:17258-69. doi: 10.18632/oncotarget.12907.
61. Yong C, Daihui C, Bo Z. Laparoscopic versus open radical cystectomy for patients with bladder cancer over 75-year-old: a prospective randomized controlled trial. Oncotarget. 2017;8:26565-26572. doi: 10.18632/oncotarget.15717.

62. Gastecka A, Hnatyszyn-Dzikowska A, Hejka P, Adamczyk P, Pokrywczynska M, Kloskowski M, et al. Cost comparison of laparoscopic versus robot-assisted radical cystectomy. [Internet]. Health Policy and Technology. 2018;4:420-6. Available at. https://www.sciencedirect.com/science/article/pii/S2211883718301047.doi:10.1016/j.hlpt.2018.10.008.
63. Guillotreau J, Gamé X, Mouzin M, Doumerc N, Mallet R, Sallusto F, et al. Radical cystectomy for bladder cancer: morbidity of laparoscopic versus open surgery. J Urol. 2009;181:554-9; discussion 559. doi: 10.1016/j.juro.2008.10.011.
64. Styn NR, Montgomery JS, Wood DP, Hafez KS, Lee CT, Tallman C, et al. Matched comparison of robotic-assisted and open radical cystectomy. Urology. 2012;79:1303-8. doi: 10.1016/j.urology.2012.01.055.

Correspondence address:
Wenhui Zhou, MD
Department of Urology,
Tianjin First Central Hospital, No.2,
Baoshanxi Road, Xiqing District,
Tianjin, 300112, China
Telephone: + 86 022 2638-1113
E-mail: zhouwenhuihn@126.com

REVIEW ARTICLE

Vol. 50 (6): 703-713, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.9920

Evidence of restorative therapies in the treatment of Peyronie disease: A narrative review

Francesco Costantini Mesquita [1], Rodrigo Barros [2], Thiago Fernandes Negris Lima [3], David Velasquez [3], Luciano A. Favorito [4], Edoardo Pozzi [1], James Dornbush [5], David Miller [1], Francis Petrella [1], Ranjith Ramasamy [1]

[1] Desai Sethi Urology Institute, University of Miami Miller School of Medicine, Miami, FL, USA; [2] Serviço de Urologia, Hospital Universitário Antônio Pedro - Universidade Federal Fluminense - UFF, Niterói, RJ, Brasil; [3] Serviço de Urologia, Hospital Memorial Arthur Ramos, Maceió, AL, Brasil; [4] Unidade de Pesquisa Urogenital, Universidade Estadual do Rio de Janeiro – UERJ, Rio de Janeiro, RJ, Brasil; [5] AU/UGA Medical Partnership, Athens, GA, USA

ABSTRACT

Objective: To describe the evidence of Platelet Rich Plasma (PRP), Stem cells therapy (SCT) and Extracorporeal shockwave therapy (ESWL) for the treatment of Peyronies disease (PD), including information from the main urological society guidelines.

Materials and Methods: A literature review of PubMed articles published between 2000 and 2023 was conducted, utilizing keywords such as "Peyronie's Disease", "Penile curvature", "Platelet Rich Plasma", "Stem cells", and "Extracorporeal shockwave therapy". Only full-text articles in English were included, excluding case reports and opinions.

Results: A considerable number of clinical trials were conducted using PRP penile injections for therapy of PD, showing reduction of curvature, plaque size and improvement in quality of life. Preclinical studies in rats have shown the potential benefit of adipose-derived stem cells, with improvements in erectile function and fibrosis. Human studies with mesenchymal stem cells demonstrated promising results, with reduction of curvature and plaque size. ESWL effects on PD were investigated in randomized clinical trials and demonstrated no significant impact in curvature or plaque size, but reasonable effect on pain control.

Conclusion: Restorative therapies has emerged as an innovative treatment option for PD and the results from current studies appear to be promising and demonstrated good safety profile. Unfortunately, due to scarce evidence, PRP and SCT are still considered experimental by American Urological Association (AUA) and European Association of Urology (EAU) guidelines. ESWT is recommended, by the same guidelines, for pain control only. More high-quality studies with long-term follow-up outcomes are needed to evaluate efficacy and reproducibility of those therapies.

ARTICLE INFO

Luciano Alves favorito
https://orcid.org/0000-0003-1562-6068

Keywords:
Penile Induration; Platelet-Rich Plasma; Extracorporeal Shockwave Therapy

Int Braz J Urol. 2024; 50: 703-13

Submitted for publication:
July 10, 2024

Accepted after revision:
August 05, 2024

Published as Ahead of Print:
August 10, 2024

INTRODUCTION

Peyronie's disease (PD) is a disorder of the penis resulting in pathological curvature which may be associated with painful erections, penile deformity, erectile dysfunction (ED) and impairing of penetrative sexual intercourse (1). Prevalence reported range from 0.4-20%, as higher in patients with prostate cancer or diabetes, in the fifth decade of life (2-4).

The treatment of PD is a challenge. There are many oral options such as potassium para-aminobenzoate (POTABA), pentoxifylline and colchicine, with limited data available and lack of proven benefit. Intralesional injections of Collagenase clostridium histolyticum (CCH) may be offered to patients who desire non-surgical treatment at an earlier stage in the disease process. However, it is a treatment indicated to selected patients, with high costs, diverse experience and the lack of ideal treatment regimen (5).

Penile injections of Platelet Rich Plasma (PRP) and Stem Cell Therapy (SCT), extracorporeal shockwave therapy (ESWT), are potential restorative therapies that gained popularity for the treatment of PD. In recent years, there has been a substantial increase in the number of studies involving the use of these restorative therapies for PD treatment (6-8).

In this review, we describe the evidence of PRP, SCT and ESWL for the treatment of PD, including information from the main urological society guidelines.

MATERIALS AND METHODS

We analyzed published papers contained in the PubMed between 2000 and 2023 searching by the following key words: "Peyronie's Disease"; "Penile curvature"; "Platelet Rich Plasma"; "Stem cells"; "Extracorporeal shockwave therapy". The literature sources were limited to full-text articles and open-access journals published in English publications. Case reports, editorials and opinions of specialists were excluded.

RESULTS

This narrative review provides an overview of the current literature involving the evidence of the restorative therapies for the treatment of PD.

Platelet Rich Plasma (PRP)

Autologous PRP therapy, enriched with growth factors and platelets, is currently being explored for its potential in treating PD. This therapy, while approved by the Food and Drug Administration (FDA) for orthopedic uses, is yet to receive approval for urological conditions (9). The presence of growth factors such as VEGF, PDGF, FGF, and TGF-β in PRP contributes to tissue regeneration by modulating processes like stem cell migration, inflammation, angiogenesis, and wound healing (10). PRP's mechanism of action suggests its potential effectiveness during the acute inflammatory stage of PD. This hypothesis is supported by studies in other fields of restorative medicine, where PRP has shown promise in enhancing wound healing and tissue repair (11). The anti-inflammatory properties of PRP, as evidenced in orthopedic literature, may contribute to its therapeutic effects in PD by reducing plaque-associated inflammation (12).

In terms of clinical application, the technique of PRP preparation and injection protocol is also a critical factor. Variability in PRP preparation methods can lead to differences in the concentration of platelets and growth factors, potentially influencing treatment outcomes (13, 14). Standardization of these protocols is essential for comparing results across studies and for the development of effective treatment guidelines.

The safety profile of PRP in this context appears favorable, with most studies indicating only minor side effects like slight pain, mild penile bruising, ecchymosis, hematomas as well as transient hypotension (15).

However, the efficacy of PRP in Peyronie's disease is less clear. Achraf et al. showed 65 patients with PD, divided into two groups based on the severity of penile curvature, the first with a curvature between 25 and 35° and the second between 35 and 45°. They underwent an average of 6.1 PRP injections each group. Results showed notable curvature reduction in both groups, with an average decrease of 16.8° in the first group and 17.3° in the second group, suggesting PRP's potential as a safe and effective PD treatment

(16). Another prospective study evaluated the tolerance and effects of intra-plaque PRP injections in men with PD. After three injections performed 15 days apart in 17 patients, a decrease of 11.8º of penile curvature was observed without any noted side effects (17). Other studies, with different protocols, demonstrated positive results with PRP in improvement in penile curvature and erections, reduction in plaque size and pain, and are depicted in Table-1 (16-24).

Ongoing clinical trials are further investigating PRP's therapeutic role in PD. Early findings from Chu et al. indicate no adverse events, highlighting its safety. However, these initial results, based on a small cohort, showed no significant improvement in penile curvature at the 3-month evaluation. The study's authors note the need for further research to draw more definitive conclusions (24). Furthermore, long-term follow-up studies are necessary to assess the durability of PRP treatment effects in PD.

While short-term results are promising, the chronic nature of PD necessitates examination of long-term outcomes to fully understand the efficacy and safety of PRP therapy in this context. The American Urological Association (AUA) and European Association of Urology (EAU) guidelines acknowledge the current gaps in understanding the physiological impact of PRP therapy in PD and should currently be considered as being experimental (1, 25). This underscores the necessity for more comprehensive research to validate PRP as a viable treatment option for PD.

Stem Cell Therapy (SCT)

The promise of restorative medicine, with a special emphasis on stem cells, lies in the fact that the ultimate measure of success, as defined by patients, is the achievement of a "cure" (27). Stem cells possess remarkable regenerative capabilities, primarily driven by their pleiotropic and paracrine effects (28). At present, mesenchymal stem cells (MSCs) represent the most widely used and accessible source of stem cells (29). Unlike embryonic derived stem cells, MSCs exhibit minimal tumorigenic potential and are not encumbered by ethical constraints (30). Initially characterized as a cell population with fibroblast-like properties originating from bone marrow (31), MSCs have subsequently been identified in various tissues, including muscle, brain, fallopian tubes, ligaments, synovium, and adipose tissue (32). Numerous preclinical in vitro and in vivo studies have demonstrated that these cells stimulate cell growth (via trophic effects), enhance cell survival and proliferation, facilitate neo-vascularization, promote re-epithelialization, and exert immunomodulatory effects by releasing a diverse array of cytokines (33).

Several studies have scrutinized the applicability of stem cells in rat models to address PD (34-37). These studies, collectively indicating improved erectile function and a reduction in PD associated alterations among rats subjected to stem cell treatment, highlight the potential benefits of this approach. In terms of ensuring the safety of stem cell administration, researchers have explored various routes, with the most prevalent approaches being intra scar-tissue or intracavernosal injection (38).

In 2013, a study used adipose tissue-derived stem cells (ADSCs) to treat PD in a rat model. Fibrosis was induced using TGF-β1 in the rat tunica albuginea (TA), followed by xenogeneic transplantation of human ADSCs within a day, resulting in notable improvements in penile fibrosis. This breakthrough marked the first successful instance of xenogeneic cell transplantation in immunocompetent animals without the need for immunosuppressants. ADSCs have demonstrated immunomodulatory and immunosuppressive properties in earlier research, including their effectiveness in reversing PD progression during the acute phase of TGF-β-induced inflammation and decreasing expression of tissue inhibitors of metalloproteinases. (35). In a related study simulating the chronic phase of PD, ADSCs were injected a month after TGF-β1 injection in a rat model. Remarkably, the rats exhibited reduced fibrosis, decreased collagen III expression, and lowered expression of fibrosis-related genes, indicating positive changes in biochemical fibrosis. Additionally, fibrotic plaques showed spontaneous partial regression after 60 days (34).

Another study was conducted utilizing stem cells to assess the potential of local autologous injection of the stromal vascular fraction (SVF) of adipose tissue in reducing established fibrosis in a rat model

Table 1 - Studies examining the effects of PRP on PD.

STUDY	YEAR	SAMPLE SIZE	STUDY DESIGN	INTERVENTION (PRP)	CONTROL GROUP	OUTCOME MEASURES	KEY FINDINGS	LIMITATIONS
Virag et al. (18)	2017	90 patients	Prospective Cohort Study	8 mL of PRP combined with HA, injected 4 times within 2 months, additional monthly sessions if necessary	None	Penile deformation, TA thickening, presence and size of calcifications, PD and sexual function questionnaires	Significant improvement in angulation and thickening after 4 sessions; 73.3% of patients showed satisfactory improvement; younger patients achieved better results; mean reduction in angle of 16.54°, representing an average reduction of 39.65%	No control group
Notsek, Boiko M. (19)	2019	59 patients	Randomized Controlled Trial	Intralesional PRP injections	Intralesional injections of 0.9% sodium chloride	Curvature angle, plaque size, plaque softness, IIEF-5, pain presence	In the PRP group: 50% angle decrease, 50% plaque size reduction, 59.4% achieved plaque softening, 56.3% enhancement in erectile function (IIEF-5), 84% pain reduction. Control group had significantly lower improvements in these areas.	Longer-term follow-up needed
Achraf et al. (16)	2022	65 patients	Prospective Study	Intralesional PRP injections	None	Curvature angle, erectile function, pain during intercourse	Angulation improved by an average of 16.8° in the first group (25-35° curvature) and 17.27° in the second group (35-45° curvature). Pain during sex decreased significantly; improvement in erectile function	No control group
Farrag et al. (20)	2022	50 patients	Prospective Interventional Randomized Comparative Trial	Intralesional PRP injections	Mitomycin-C plus Dexamethasone	Penile curvature, IIEF-5 score, PDQ, plaque size	Improvement in PDQ domains and IIEF scores; curvature and erectile dysfunction improved in both groups, but more in PRP for erectile function; plaque size reduction noted in both groups	Small sample size, short follow-up duration, no placebo arm or blinding

Virag, Sussman (21)	2016	50 patients	Interventional Series	Intralesional injections of PRP+HA under US guidance	None	PDQ, IIEF-5, angulation, maximum thickness, patient satisfaction	38% reduction in average angulation, maximum thickness decreased from 4.4mm to 3.3mm, average PDQ bother reduced from 10.5 to 5, IIEF-5 increased from 17.7 to 21.1. 84% of patients showed improvement	No control group, short follow-up period, industry-funded
Virag, Sussman (22)	2016	75 patients	Case Control Study	PRP+HA injections under US guidance	None	Angulation, albuginea thickness, sexual activity, ED, PDQ	36.9% average angulation decrease, 26.7% reduction in albuginea thickness, improvement in erections in 37% of ED patients, 82.7% self-reported improvement, better results in non-calcified and <60° angulation cases	No control group for comparison
Schirmann et al. (17)	2022	17 patients	Prospective Pilot Study	Intra-plate injections of PRP	None	PDQ, Angle of curvature, Erectile function (IIEF-EF, EHS, SEP)	No side effects; PDQ domains significantly improved; curvature decreased by 11.8°; IIEF-EF score improved by 5-7 points	Small sample size, lack of control group, short-term study
Alshuaibi et al. (23)	2023	36 patients	Prospective Case Series Study	Combination of PNT, PM, and PRP injections	None	Improvement in curvature	Mean curvature improved by 16.85° (47.7% improvement); no serious events reported; effective for penile deformity due to PD	No control group, short-term follow-up

of PD. While no significant differences in erectile function were observed, there was a noticeable reversal of fibrotic changes after the SVF injection, highlighting the potential of local SVF injection to reverse TA fibrosis in the chronic phase of PD in a rat model (37).

Human studies to evaluate the feasibility of stem cell therapy for PD are scarce. Levy et al. published a compelling human study examining five patients with PD and penile deformities/curvatures ranging from 0º to 120º. The study involved intra-plate injections of placental matrix-derived stem cells (PM-MSC) to address this condition. Besides providing a notable improvement in curvature (by 30º to 120º) and reduction of the number of plaques, no complications involving penile hematoma, corporal rupture or penile edema occurred (7). This research marked the first instance of utilizing PM-MSC to manage PD in humans, albeit with a limited sample of five subjects. Another study, combining autologous SVF injections isolated from lipoaspirate with a series of ESWT, evaluated subjective outcomes and safety of

this combined therapy in 11 men with stable PD. After a 6 months follow-up, all patients noted subjective improvement in curvature and subjective reduction in plaque size (38). The characteristics of the most relevant SCT studies are presented in Table-2.

The cost of the off-label treatment expenses exhibited considerable variability among different clinics, with an average expenditure of $5,291 per stem cell therapy injection in USA (39). The AUA guideline regards the use of stem cells as a promising approach; however, it has not yet incorporated this treatment modality into its recommendations (1). The EAU does not mention the use of stem cells in its guideline on penile curvature.

Extracorporeal shockwave therapy (ESWT)

The precise way in which ESWT impacts PD remains uncertain, despite numerous studies reporting positive outcomes. ESWT could potentially induce changes and restructuring in the penile plaque. Specifically, the application of ESWT might generate heat, leading to heightened local blood circulation (40). This, in turn, could trigger an inflammatory response, subsequently boosting macrophage activity. This cascade of events could eventually lead to the breakdown and absorption of the plaque (41).

Three studies (19, 42, 43) encompassing 225 patients were examined to gauge penile plaque size using

Table 2 - Studies examining the effects of SCT on PD.

STUDY	YEAR	STEM CELLS	HUMANS OR ANIMALS	RESULTS
Castiglione et al. (34)	2013	Humans adipose-derived stem cells	Animals	Erectile dysfunction improving during the acute phase of PD
Gokce et al. (35)	2014	Rat adipose-derived stem cells	Animals	Erectile dysfunction improving during the acute phase of PD
Gokce et al. (36)	2015	Genetically modified adipose tissue-derived stem cells with human alfa-2b	Animals	Erectile dysfunction improving during acute phase of PD
Milenkovic et al. (33)	2019	Humans adipose-derived stem cells	Animals	Tunica albuginea fibrosis decreased in a rat model of chronic PD
Hakim et al. (37)	2020	Rat adipose-derived stem cells	Animals	Local injection of SVF in a rat model of chronic PD significantly decreased collagen III concentration in the TA
Levy et al. (7)	2015	Placental matrix-derived mesenchymal stem cells	Humans	Peak systolic velocity and penile curvature improved signifcantly 6 weeks, 3 months and 6 months after treatment. 7 of 10 fibrotic plaques in the tunica albuginea disappeared completely at 3 months

ultrasonography. The results were compelling, showcasing a notable reduction in plaque size within the ESWT group when compared to the control group. Specifically, 39.8% of patients in the ESWT group experienced a reduction in plaque size compared to 30.3% observed in the control group. When it came to evaluating the improvement in penile curvature, researchers analyzed pre- and post-treatment photographs from three studies. According to the authors, 44% (37 of 84) of patients in the ESWT group reporting a significant improvement in penile curvature, slightly surpassing the 42.1% (48 of 114) noted in the control group. Additionally, the ESWT group demonstrated superior pain management, as 82.1% experienced pain relief and 61% achieved complete pain remission, surpassing the rates in the control group (51.6% for relief and 18.8% for complete remission).

In a study conducted by Di Mauro et al. analyzing 325 consecutive patients with PD in a multi-center single-arm clinical trial, notable improvements were observed. These improvements included a reduction in plaque size from 1.78 to 1.53 cm^2, an increase in erect penis length from 13 to 14 cm, a decrease in penile curvature from 30.4 to 25.0 degrees, and a reduction in reported pain on the Visual Analog Scale (VAS) from 7 to 3. Furthermore, improvements in discomfort caused by PD, as indicated by the Peyronie's Disease Questionnaire (PDQ), and enhanced sexual satisfaction measured by the International Index of Erectile Function (IIEF), were also noted (8).

In 2021, Backr et al. conducted a comprehensive meta-analysis that revealed notable heterogeneity in the outcomes of individuals with PD undergoing ESWT. A total of three randomized clinical trials, comprising of 117 men in the ESWT group and 121 in placebo group were reviewed. Their analysis suggests that ESWT does not yield significant improvements in penile curvature or pain among men with PD. Nevertheless, there is evidence to suggest that ESWT may have a potential positive impact on reducing plaque size in this specific patient population (44). Table-3 shows relevant studies examining the effects of ESWT on PD (8, 42-46).

According to the guidelines of the AUA, clinicians are advised to refrain from using ESWT for the purpose of reducing penile curvature or plaque size. However, healthcare professionals may consider the possibility of offering ESWT to alleviate penile pain. This is a conditional recommendation with an evidence strength grade of B (1). As per the EAU, ESWT may be offered only to treat penile pain in the acute phase of PD, with a level of evidence 2b. (26). Patients need vigilant monitoring for occurrences of localized pain, hematoma formation, neurapraxia, and other adverse events, despite complications not commonly manifesting (46). Further research is warranted to unravel ESWT's full potential and optimize its application in treating PD.

CONCLUSIONS

Restorative therapies have emerged as an innovative and less invasive treatment option for PD. Results from current studies appear to be promising and demonstrate good safety profile. However, at the moment, these treatments do not provide cure for men diagnosed with acute or chronic PD. Unfortunately, due to scarce evidence, PRP and SCT are still considered by AUA and EAU guidelines as experimental therapies. ESWT is recommended, by the same guidelines, for pain management. More high-quality studies with long-term follow-up outcomes are needed to evaluate efficacy, reproducibility and define evidenced-based protocols to standardize techniques.

Table 3 - Studies examining the effects of ESWT on PD.

AUTHOR	YEAR	STUDY TYPE	RESULTS
Palmieri et al. (43)	2009	Placebo- controlled randomized	ESWT treatment brought significant improvement in VAS, IIEF-5 and mean QoL scores. Mean plaque size and curvature were unchanged. ESWT leads to pain resolution and positively impacts erectile function and quality of life
Hatzichristodoulou et al. (42)	2013	Placebo controlled, randomized trial	ESWT is not recommend given the following: ESWT provide pain reduction by 85%. Pain resolution occurred in the placebo group by 48%. ESWT group showed no difference in plaque size reduction. Penile deviation worsened by 40% in ESWT group.
Gao et al. (46)	2016	Meta-Analysis	ESWT significantly increased the percentages in the following: lessening of penile plaques, pain relief and complete pain remission. There was insignificant improvement with penile curvature and sexual function in ESWT vs placebo.
Di Mauro et al. (8)	2019	Single-Arm Observational Study	ESWT treatment resulted in reduction in plaque size, penile curvature and pain. Penile lenght with erection increased after ESWT treatment
Bakr et al. (44)	2021	Systematic Review and Meta-Analysis	ESWT is associated with a reduction in plaque size but no significant difference in penile curvature, erection function or pain
Abdessater et al. (45)	2022	Retrospective Data Analysis	ESWT had positive impacts on penile pain, curvature, plaque size and erectile dysfunction in PD during the early inflammatory phase

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Nehra A, Alterowitz R, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh JJ, et al. Peyronie's Disease: AUA Guideline. J Urol. 2015;194:745-53. doi: 10.1016/j.juro.2015.05.098.
2. Stuntz M, Perlaky A, des Vignes F, Kyriakides T, Glass D. The Prevalence of Peyronie's Disease in the United States: A Population-Based Study. PLoS One. 2016;11:e0150157. doi: 10.1371/journal.pone.0150157.
3. Mulhall JP, Creech SD, Boorjian SA, Ghaly S, Kim ED, Moty A, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171(6 Pt 1):2350-3. doi: 10.1097/01.ju.0000127744.18878.f1.
4. Hellstrom WJ. History, epidemiology, and clinical presentation of Peyronie's disease. Int J Impot Res. 2003;15(Suppl 5):S91-2. doi: 10.1038/sj.ijir.3901081.
5. Babu A, Kayes O. Recent advances in managing Peyronie's disease. F1000Res. 2020;9:F1000 Faculty Rev-381. doi: 10.12688/f1000research.20557.1.
6. Yáñez-Castillo YM, Arrabal-Polo MÁ. Applications of Platelet Rich Plasma in Urology. Arch Esp Urol. 2022;75:669-83. doi: 10.56434/j.arch.esp.urol.20227508.98.

7. Levy JA, Marchand M, Iorio L, Zribi G, Zahalsky MP. Effects of Stem Cell Treatment in Human Patients With Peyronie Disease. J Am Osteopath Assoc. 2015;115:e8-13. doi: 10.7556/jaoa.2015.124.
8. Di Mauro M, Russo GI, Della Camera PA, Di Maida F, Cito G, Mondaini N, et al. Extracorporeal Shock Wave Therapy in Peyronie's Disease: Clinical Efficacy and Safety from a Single-Arm Observational Study. World J Mens Health. 2019;37:339-46. doi: 10.5534/wjmh.180100.
9. Israeli JM, Lokeshwar SD, Efimenko IV, Masterson TA, Ramasamy R. The potential of platelet-rich plasma injections and stem cell therapy for penile rejuvenation. Int J Impot Res. 2022;34:375-82. doi: 10.1038/s41443-021-00482-z.
10. Cecerska-Heryć E, Goszka M, Serwin N, Roszak M, Grygorcewicz B, Heryć R, et al. Applications of the regenerative capacity of platelets in modern medicine. Cytokine Growth Factor Rev. 2022;64:84-94. doi: 10.1016/j.cytogfr.2021.11.003.
11. Smith AJ, Duncan HF, Diogenes A, Simon S, Cooper PR. Exploiting the Bioactive Properties of the Dentin-Pulp Complex in Regenerative Endodontics. J Endod. 2016;42:47-56. doi: 10.1016/j.joen.2015.10.019.
12. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med. 2008;1:165-74. doi: 10.1007/s12178-008-9032-5.
13. Rossi L, Ranalletta M, Pasqualini I, Zicaro JP, Paz MC, Camino P, et al. Substantial Variability in Platelet-Rich Plasma Composition Is Based on Patient Age and Baseline Platelet Count. Arthrosc Sports Med Rehabil. 2023;5:e853-e858. doi: 10.1016/j.asmr.2023.03.017.
14. Khodamoradi K, Dullea A, Golan R, Molina M, Arora H, Masterson TA, et al. Platelet Rich Plasma (PRP) Growth Factor Concentration Varies in Men With Erectile Dysfunction. J Sex Med. 2022;19:1488-93. doi: 10.1016/j.jsxm.2022.06.003.
15. Alkandari MH, Touma N, Carrier S. Platelet-Rich Plasma Injections for Erectile Dysfunction and Peyronie's Disease: A Systematic Review of Evidence. Sex Med Rev. 2022;10:341-52. doi: 10.1016/j.sxmr.2020.12.004.
16. Achraf C, Abdelghani PA, Jihad PEA. Platelet-rich plasma in patients affected with Peyronie's disease. Arab J Urol. 2022;21:69-75. doi: 10.1080/2090598X.2022.2135284.
17. Schirmann A, Boutin E, Faix A, Yiou R. Tolerance and efficacy of platelet-rich plasma injections in Peyronie's disease: Pilot study. Prog Urol. 2022;32:856-61. doi: 10.1016/j.purol.2022.05.004.
18. Virag R, Sussman H, Lambion S, de Fourmestraux V. Evaluation of the benefit of using a combination of autologous platelet rich-plasma and hyaluronic acid for the treatment of Peyronie's disease. [Internet]. Sex Health Issues 2017, 1, 1–8. Available at. <https://www.oatext.com/pdf/SHI-1-102.pdf>
19. Notsek M, Boiko M. PO-01-083 Platelet-rich Plasma Therapy of Peyronie's Disease. [Internet]. J Sex Med. 2019 May 1;16(Supplement_2):S70. Available at. <https://academic.oup.com/jsm/article-abstract/16/Supplement_2/S70/7020341> doi: https://doi.org/10.1016/j.jsxm.2019.03.225
20. Farrag A, Awwad ahmad A, AL Mohsen AR, Fahmy S, Hassan M. Evaluation of Intralesional Injection of Platelet Rich Plasma Compared with Mitomycin-C plus Dexamesathone in Treatment of Peyronie's Disease. [Intenert] Al-Azhar Int Med J. 2022;3:90–6. Available at. <https://journals.ekb.eg/article_226863.html>
21. Virag R, Sussman H. 011 Ultrasound Guided Treatment of Peyronie's Disease with Plasma Rich Platelets (PRP) and Hyaluronic Acid (HA). [Internet] J Sex Med. 2016 May 1;13(Supplement_1):S5–6. Avaiable at. <https://academic.oup.com/jsm/article-abstract/13/Supplement_1/S5/7003634?redirectedFrom=fulltext> doi: https://doi.org/10.1016/j.jsxm.2016.02.013
22. Virag R, Sussman H. PS-05-007 Plasma Rich Platelets and Hyaluronic Acid Improves Peyronie's Disease: A Case Control Study of 75 Cases. [Internet]. J Sex Med. 2017 Apr 1;14(Supplement_4a):e121. Available at. <https://www.tandfonline.com/doi/full/10.1080/2090598X.2022.2135284> doi: 10.1080/2090598X.2022.2135284.
23. Alshuaibi M, Zugail AS, Lombion S, Beley S. New protocol in the treatment of Peyronie's disease by combining platelet-rich plasma, percutaneous needle tunneling, and penile modeling: Preliminary results. Fr J Urol. 2024;34:102526. doi: 10.1016/j.purol.2023.09.013.
24. Chu KY, Molina ML, Ledesma B, Zucker I, Saltzman RG, Masterson TA, et al. A Phase 2 Randomized, Placebo-controlled Crossover Trial to Evaluate Safety and Efficacy of Platelet-rich Plasma Injections for Peyronie's Disease: Clinical Trial Update. Eur Urol Focus. 2023;9:11-13. doi: 10.1016/j.euf.2022.08.017.

25. Hatzimouratidis K, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Salonia A, et al. EAU guidelines on penile curvature. Eur Urol. 2012;62:543-52. doi: 10.1016/j.eururo.2012.05.040.
26. Campbell JD, Milenkovic U, Usta MF, Albersen M, Bivalacqua TJ. The good, bad, and the ugly of regenerative therapies for erectile dysfunction. Transl Androl Urol. 2020;9(Suppl 2):S252-S261. doi: 10.21037/tau.2019.10.06.
27. Hanson-Divers C, Jackson SE, Lue TF, Crawford SY, Rosen RC. Health outcomes variables important to patients in the treatment of erectile dysfunction. J Urol. 1998;159:1541-7. doi: 10.1097/00005392-199805000-00037.
28. Soebadi MA, Milenkovic U, Weyne E, Castiglione F, Albersen M. Stem Cells in Male Sexual Dysfunction: Are We Getting Somewhere? Sex Med Rev. 2017;5:222-35. doi: 10.1016/j.sxmr.2016.11.002.
29. Leon-Rodriguez E, Rivera-Franco MM, Lacayo-Leñero D, Campos-Castro A, Meneses-Medina MI. First - line, non - cryopreserved autologous stem cell transplant for poor - risk germ - cell tumors: Experience in a developing country. Int Braz J Urol. 2019;45:74-82. doi: 10.1590/S1677-5538.IBJU.2017.0562.
30. Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell. 2008;2:313-9. doi: 10.1016/j.stem.2008.03.002.
31. Caplan AI. MSCs: The Sentinel and Safe-Guards of Injury. J Cell Physiol. 2016;231:1413-6. doi: 10.1002/jcp.25255.
32. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011;9:11-5. doi: 10.1016/j.stem.2011.06.008.
33. Milenkovic U, Albersen M, Castiglione F. The mechanisms and potential of stem cell therapy for penile fibrosis. Nat Rev Urol. 2019;16:79-97. doi: 10.1038/s41585-018-0109-7.
34. Castiglione F, Hedlund P, Van der Aa F, Bivalacqua TJ, Rigatti P, Van Poppel H, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. Eur Urol. 2013;63:551-60. doi: 10.1016/j.eururo.2012.09.034. Epub 2012 Sep 24. Erratum in: Eur Urol. 2013 Jul;64(1):e21.
35. Gokce A, Abd Elmageed ZY, Lasker GF, Bouljihad M, Kim H, Trost LW, et al. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease. Andrology. 2014;2:244-51. doi: 10.1111/j.2047-2927.2013.00181.x.
36. Gokce A, Abd Elmageed ZY, Lasker GF, Bouljihad M, Braun SE, Kim H, et al. Intratunical Injection of Genetically Modified Adipose Tissue-Derived Stem Cells with Human Interferon α-2b for Treatment of Erectile Dysfunction in a Rat Model of Tunica Albugineal Fibrosis. J Sex Med. 2015;12:1533-44. doi: 10.1111/jsm.12916.
37. Hakim L, Fiorenzo S, Hedlund P, Montorsi F, Bivalacqua TJ, De Ridder D, et al. Intratunical injection of autologous adipose stromal vascular fraction reduces collagen III expression in a rat model of chronic penile fibrosis. Int J Impot Res. 2020;32:281-8. doi: 10.1038/s41443-019-0136-9.
38. Lander EB, Berman MH, See JR. Stromal Vascular Fraction Combined with Shock Wave for the Treatment of Peyronie's Disease. Plast Reconstr Surg Glob Open. 2016;4:e631. doi: 10.1097/GOX.0000000000000622.
39. Thomas J, Sencaj M, Ghomeshi A, Zucker IJ, Best JC, Ramasamy R. Stem-Cell, Shockwave, and Platelet Rich Plasma Therapy for the Treatment of Erectile Dysfunction and Peyronie's Disease: A Survey of Clinics Across the USA. Urology. 2023;178:83-90. doi: 10.1016/j.urology.2023.01.061.
40. Vieiralves RR, Schuh MF, Favorito LA. Low-intensity extracorporeal shockwave therapy in the treatment of erectile dysfunction - a narrative review. Int Braz J Urol. 2023;49:428-40. doi: 10.1590/S1677-5538.IBJU.2023.9904.
41. Husain J, Lynn NN, Jones DK, Collins GN, O'Reilly PH. Extracorporeal shock wave therapy in the management of Peyronie's disease: initial experience. BJU Int. 2000;86:466-8. doi: 10.1046/j.1464-410x.2000.00827.x.
42. Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med. 2013;10:2815-21. doi: 10.1111/jsm.12275.

43. Palmieri A, Imbimbo C, Longo N, Fusco F, Verze P, Mangiapia F, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. Eur Urol. 2009;56:363-9. doi: 10.1016/j.eururo.2009.05.012. Erratum in: Eur Urol. 2009 Nov;56(5):e43-4.
44. Bakr AM, El-Sakka AI. Extracorporeal Shockwave Therapy in Peyronie's Disease: Systematic Review and Meta-Analysis. J Sex Med. 2021;18:1705-14. doi: 10.1016/j.jsxm.2021.06.012.
45. Abdessater M, Akakpo W, Kanbar A, Parra J, Seisen T, Chartier-Kastler E, et al. Low-intensity extracorporeal shock wave therapy for Peyronie's disease: a single-center experience. Asian J Androl. 2022;24:45-9. doi: 10.4103/aja.aja_40_21.
46. Gao L, Qian S, Tang Z, Li J, Yuan J. A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease. Int J Impot Res. 2016;28:161-6. doi: 10.1038/ijir.2016.24.

Correspondence address:
Rodrigo Barros, PhD
Serviço de Urologia,
Hospital Universitário Antônio Pedro - Universidade Federal Fluminense - UFF
Av. Marquês do Paraná, 303
Centro, Niterói, RJ, 24033-900. Brasil
Fax: +55 21 2629-9000
E-mail: rodrigo_brrs@yahoo.com.br

REVIEW ARTICLE

Vol. 50 (6): 714-726, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.9921

Endoscopic Combined Intrarenal Surgery: best practices and future perspectives

Anderson B. Pellanda [1], Fabio C. M. Torricelli [1], John Denstedt [2], Alexandre Danilovic [1], Giovanni S. Marchini [1], Fabio C. Vicentini [1], Carlos A. Batagello [1], William C. Nahas [1], Eduardo Mazzucchi [1]

[1] Divisão de Urologia, Departamento de Cirurgia, Faculdade de Medicina da Universidade de São Paulo - USP, São Paulo, SP, Brasil; [2] University of Western Ontario in London, Canada

ABSTRACT

Introduction: Endoscopic Combined Intrarenal Surgery (ECIRS) has emerged as a promising technique for the management of large and complex kidney stones, potentially offering advantages over traditional Percutaneous Nephrolithotomy (PCNL). This study aims to evaluate best practices, outcomes, and future perspectives associated with ECIRS.

Materials and Methods: A comprehensive PubMed search was conducted from 2008 to 2024, using MESH terms and the following key words: "ECIRS" and "Endoscopic Combined Intrarenal Surgery" The search yielded 157 articles, including retrospective cohort studies, two randomized controlled trials (RCTs), and four meta-analyses comparing ECIRS with PCNL. Most important findings were summarized regarding indications, patient positioning, kidney access, tract size, surgical outcomes, and complications.

Results: ECIRS demonstrated higher stone-free rate, lower complication rate, and a reduced need for multiple procedures compared to traditional PCNL. Additionally, ECIRS has the potential to integrate new technologies to further enhance outcomes.

Conclusion: ECIRS demonstrates significant advantages in the management of large kidney stones. Future research should focus on well-designed RCTs to provide robust evidence of its efficacy, safety, and cost-effectiveness, potentially establishing ECIRS as the first option treatment for complex kidney stones.

ARTICLE INFO

Anderson Pellanda
https://orcid.org/0000-0002-6527-1528

Keywords:
Kidney; Lithotripsy; Urinary Calculi

Int Braz J Urol. 2024; 50: 714-26

Submitted for publication:
July 25, 2024

Accepted after revision:
August 10, 2024

Published as Ahead of Print:
August 25, 2024

INTRODUCTION

Complex and large kidney stones pose a significant challenge in urology, necessitating a careful balance between effectiveness and safety when selecting the optimal surgical approach. Prior to the development of endoscopic and percutaneous techniques, open and laparoscopic surgeries were commonly utilized, yielding good outcomes in stone clearance but also carrying high morbidity. Since its initial description by Fernstrom in 1976 (1), percutaneous nephrolithotomy (PCNL) has emerged as the gold standard treatment modality for large kidney stones (>2cm) (2, 3). Over the past decades, PCNL has undergone numerous advancements and refinements. These include enhancements in patient positioning (4-6), improvements in kidney puncture guidance (7-9), advancements in energy delivery systems (10, 11), development of effective suction devices (11, 12), and utilization of flexible (13-15) and miniaturized instruments (16).

Among these innovations, the integration of retrograde flexible nephroscopy with standard PCNL stands out significantly. This approach facilitates surgeon access to all calices (14) and reduces the requirement for aggressive kidney instrumentation (13), leading to improved outcomes (17). Despite recommendations for routine use of flexible scopes alongside standard PCNL (2), many studies still report the exclusive use of rigid nephroscopes (18, 19). Flexible ureteroscopes have supported percutaneous procedures since 1995 (20). However, it was not until 2008 that Scoffone et al. (21) introduced the term Endoscopic Combined Intrarenal Surgery (ECIRS) to describe the simultaneous use of rigid nephroscopy and retrograde flexible ureteroscopy. Subsequently, several studies have aimed to compare traditional PCNL with ECIRS, but high-quality research is needed to establish ECIRS as the new standard treatment for large kidney stones (3, 18, 22-25).

ECIRS presents distinct features and challenges. One notable concern is the requirement for two surgeons and two video systems, which can pose logistical and financial burdens, particularly in settings with limited resources. Moreover, the cost-effectiveness of this simultaneous endoscopic approach remains uncertain, prompting questions about its economic viability. The complexity of ECIRS, which involves both antegrade and retrograde accesses, demands considerable skill and coordination, thereby limiting its broader adoption.

Despite these challenges, ECIRS offers potential benefits that makes it an attractive option for treating large kidney stones. These include a high stone-free rate, lower morbidity, and fewer procedures required per patient to achieve the surgical goal. The ability of ECIRS to access all calices using flexible instruments and its potential to minimize kidney trauma can lead to improved patient outcomes. This includes reduced complication rate and faster recovery time compared to traditional approaches.

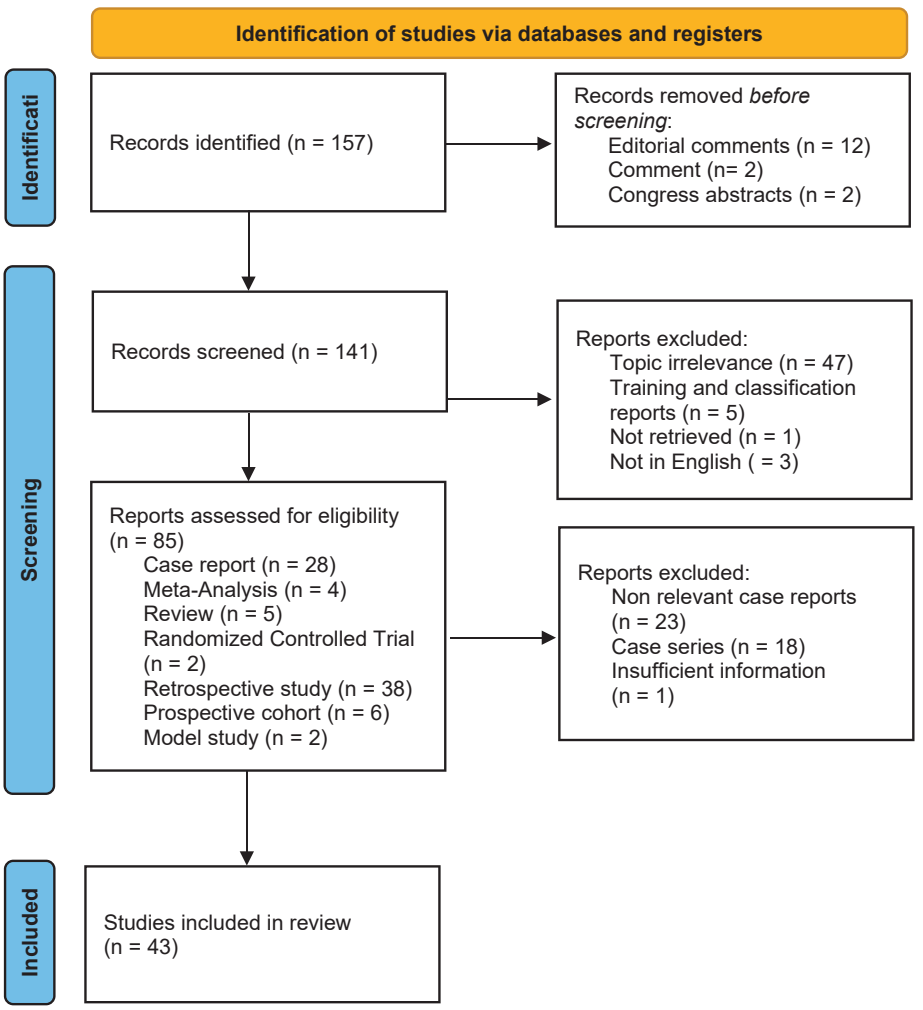
This study aims to discuss the best practices in surgical techniques and present the outcomes associated with ECIRS in the management of large kidney stones. By critically analyzing the available evidence, our goal is to assess whether the advantages of ECIRS outweigh its drawbacks. This will provide valuable insights for urologists considering ECIRS as a treatment option for their patients.

DATA ACQUISITION

We conducted an extensive PubMed search covering the period from 2008 to 2024, using MESH terms and key words such as “ECIRS” and “Endoscopic Combined Intrarenal Surgery” (Figure-1).

Our PubMed search yielded 157 articles on ECIRS. Among these, most were retrospective cohort studies. There were only two prospective randomized controlled trials (RCTs) identified: one RCT compared the efficacy and safety of mini-ECIRS versus a combination of PCNL and mini-PCNL for treating staghorn calculi (18); the second RCT examined the outcomes of mini-ECIRS in different patient positions (26). Despite the limited number of RCTs, four meta-analyses were published in 2022 (22-25), comparing ECIRS with PCNL. These systematic reviews encompassed a variety of study designs, including retrospective

Figure 1 – Flowchart.



studies with both supine and prone patient positioning, and evaluations of both standard and miniaturized ECIRS techniques. The summaries of these meta-analyses provided insights into several critical aspects of ECIRS versus PCNL, including efficacy, safety, and procedural outcomes. These findings are essential for understanding the comparative effectiveness of ECIRS in managing large kidney stones and can guide clinical decision-making in urology.

Table 1 and 2 summarize data from meta-analyses.

INDICATIONS

ECIRS shares similar indications with PCNL but offers the potential benefit of reducing the number of percutaneous tracts required to manage large or complex kidney stones (27). Moreover, ECIRS may present advantages in specific clinical scenarios, including:

1. Pediatric patients (28)
2. Transplanted kidney (29)
3. Management of encrusted ureteral stents (30)

Table 1 – Data from Meta-Analyses

				Patient positioning					
Meta Analysis	Patients (n)	Studies included	Type of study	ECIRS	PCNL	ECIRS (n)	PCNL (n)	Tract size	Objective comparison
Abdullatif et al. 2022 (25)	546	Wen, et al. 2016 (18)	RCT	GMSV	Prone	33	34	20 Fr	mini-ECIRS vs mini-PCNL
		Nuño de la Rosa, et al. 2014 (50)	Retrospective	GMSV	Supine	73	98	24-30 Fr	ECIRS vs PCNL
		Hamamoto, et al 2014 (19)	Retrospective	Prone splitleg	Prone	60	101	18 Fr (mini) / 30 Fr (PCNL)	mini-ECIRS vs mini-PCNL vs PCNL
		Leng, et al. 2018 (51)	Retrospective	Oblique supine lithotomic	Oblique supine lithotomic	44	43	16-18 Fr	mini-ECIRS vs mini-PCNL
		Zhao, et al. 2021 (52)	Retrospective	GMSV	Prone	66	74	16-18 Fr	mini-ECIRS vs mini-PCNL
Widyokirono et al. 2022 (22)	614	Wen, et al. 2016 (18)	RCT	GMSV	Prone	33	34	20 Fr	mini-ECIRS vs mini-PCNL
		Nuño de la Rosa, et al. 2014 (50)	Retrospective	GMSV	Supine	73	98	24-30 Fr	ECIRS vs PCNL
		Hamamoto, et al. 2014 (19)	Retrospective	Prone splitleg	Prone	60	101	18 Fr (mini) / 30 Fr (PCNL)	mini-ECIRS vs mini-PCNL vs PCNL
		Leng, et al. 2018 (51)	Retrospective	Oblique supine lithotomic	Oblique supine lithotomic	44	43	16-18 Fr	mini-ECIRS vs mini-PCNL
		Zhao, et al. 2021 (52)	Retrospective	GMSV	Prone	66	74	16-18 Fr	mini-ECIRS vs mini-PCNL
		Kontos, et al. 2018 (53)	Retrospective	Supine	Supine	33	35	NA	ECIRS vs PCNL
Liu et al. 2022 (23)	919	Wen, et al. 2016 (18)	RCT	GMSV	Prone	33	34	20 Fr	mini-ECIRS vs mini-PCNL
		Nuño de la Rosa, et al. 2014 (50)	Retrospective	GMSV	Supine	73	98	24-30 Fr	ECIRS vs PCNL
		Hamamoto, et al. 2014 (19)	Retrospective	Prone splitleg	Prone	60	101	18 Fr (mini) / 30 Fr (PCNL)	mini-ECIRS vs mini-PCNL vs PCNL
		Leng, et al. 2018 (51)	Retrospective	Oblique supine lithotomic	Oblique supine lithotomic	44	43	16-18 Fr	mini-ECIRS vs mini-PCNL
		Zhao, et al. 2021 (52)	Retrospective	GMSV	Prone	66	74	16-18 Fr	mini-ECIRS vs mini-PCNL
		Isac, et al. 2013 (54)	Retrospective	Prone splitleg	Prone	62	96	30 Fr	Endoscopic-guided versus fluoroscopic-guided renal access in PCNL
		Xu, et al. 2019 (55)	Retrospective Meeting abstract	NA	NA	61	74	16-22 Fr	mini-ECIRS vs mini-PCNL

				Patient positioning					
Meta Analysis	Patients (n)	Studies included	Type of study	ECIRS	PCNL	ECIRS (n)	PCNL (n)	Tract size	Objective comparison
Gauhar et al. 2022 (24)	2054	Wen, et al. 2016 (18)	RCT	GMSV	Prone	33	34	20 Fr	mini-ECIRS vs mini-PCNL
		Nuño de la Rosa, et al. 2014 (50)	Retrospective	GMSV	Supine	73	98	24-30 Fr	ECIRS vs PCNL
		Hamamoto et al. 2014 (19)	Retrospective	Prone splitleg	Prone	60	101	18 Fr (mini) / 30 Fr (PCNL)	mini-ECIRS vs mini-PCNL vs PCNL
		Leng, et al. 2018 (51)	Retrospective	Oblique supine lithotomic	Oblique supine lithotomic	44	43	16-18 Fr	mini-ECIRS vs mini-PCNL
		Zhao, et al. 2021 (52)	Retrospective	GMSV	Prone	66	74	16-18 Fr	mini-ECIRS vs mini-PCNL
		Isac, et al. 2014 (54)	Retrospective	Prone splitleg	Prone	62	96	30 Fr	Endoscopic-guided versus fluoroscopic-guided renal access in PCNL
		Mami, et al. 2021 (56)	Retrospective	Prone	Prone	18	52	NA	ECIRS vs PCNL vs RIRS
		Kawahara, et al. 2012 (57)	Retrospective	GMSV	Prone	27	23	24-30 Fr	Endoscopic-guided versus ultrasound-guided renal access in PCNL
		Hong, et al. 2016 (58)	Retrospective	GMSV	Prone	78	90	> 20 Fr	ECIRS vs PCNL
		Gao, et al. 2019 (59)	Retrospective	Prone splitleg	Prone	45	40	18 Fr	mini-ECIRS vs RIRS vs miniPCNL
		Xu, et al. 2019 (55)	Retrospective Meeting abstract	NA	NA	61	74	16-22 Fr	mini-ECIRS vs mini-PCNL
		Beck, et al. 2009 (60)	Retrospective Meeting abstract	NA	NA	51	70	NA	Endoscopic-guided renal access in PCNL
		Zelvys, et al. 2014 (61)	Retrospective Meeting abstract	Supine	Supine or prone	22	113	NA	ECIRS vs PCNL
		Zhang, et al. 2016 (62)	Retrospective Meeting abstract	NA	NA	84	197	NA	Supermini-ECIRS vs mini-PCNL
		Yong, et al. 2017 (63)	Retrospective Meeting abstract	Supine	Supine or prone	16	91	NA	ECIRS vs PCNL
		Kavaliauskaite, et al. 2018 (64)	Retrospective Meeting abstract	NA	NA	37	93	NA	ECIRS vs PCNL

ECIRS = Endoscopic Combined Intrarenal Surgery; PCNL = percutaneous nephrolithotomy; mini-PCNL = miniaturized percutaneous nephrolithotomy; mini-ECIRS = miniaturized Endoscopic Combined Intrarenal Surgery; RCT = Randomized Controled Trial; GMSV = Galdakao-modified supine Valdivia; Fr = French

Table 2 – Outcomes from Meta-Analyses

		Result							
Meta-Analysis	SFR	Operative time	Blood loss	Transfusions	Complications	Hospital Stay	Sepsis	Fever	Auxiliary procedures
Abdullatif et al. 2022 (25)	Favors ECIRS	NS	NS	NS	Favors ECIRS	Favors ECIRS	NA	NA	NA
Widyokirono et al. 2022 (22)	Favors ECIRS	NS	NS	NA	Favors ECIRS	NA	Favors ECIRS over PCNL / = mini-PCNL	NA	Favors ECIRS
Liu et al. 2022 (23)	Favors ECIRS	NS	NS	Favors ECIRS	Favors ECIRS	NS	NA	NS	NA
Gauhar et al. 2022 (24)	Favors ECIRS*	NS	Favors ECIRS	NS	NA	NS	NS	NS	Favors ECIRS

*Forrest plot table favors ECIRS, but plot diagram is inverted; NS = not statistically significant; NA = data not available; ECIRS = Endoscopic Combined Intrarenal Surgery; PCNL = percutaneous nephrolithotomy; mini-PCNL = miniaturized percutaneous nephrolithotomy

4. Treatment of large ureteral stones (31)
5. Simultaneous management of renal and ureteral stones (32)
6. Treatment of upper urinary tract urothelial carcinoma (33)

These specialized applications highlight the versatility of ECIRS across various challenging urological conditions, underscoring its potential as a preferred or complementary approach in specific patient populations and clinical settings.

POSITIONING AND PREPARATION OF THE PATIENT

Initially, ECIRS was described in the Galdakao-modified supine Valdivia (GMSV) position (4, 21). Over time, various alternative patient positions have been explored, including:

- **Prone Split-Leg Position:** This position involves placing the patient prone with the legs split apart, facilitating access to the kidney and improving stone clearance (19).
- **Barts "Flank-Free" Modified Supine Position:** In this position, the patient is placed supine with modifications to allow flank-free access to the kidney, which can simplify the procedure (5, 8).
- **Intermediate or Fully Supine Positions:** Some variations include intermediate or fully supine positions, which may offer advantages in specific patient populations or procedural preferences (34).

Abouelgreed et al. conducted a RCT comparing the GMSV and prone positions and found no significant differences in success rates, complication rates, operative time, blood loss, or the need for additional procedures (26). There is a hypothesis that higher intrarenal pressure in prone positions during PCNL may lead to increased rates of postoperative infectious complications (35). However, in ECIRS, the dual drainage through both the ureteral access sheath and the percutaneous sheath likely mitigates this risk. This dual drainage system helps maintain adequate irrigation and drainage, potentially reducing the risk of complications associated with increased intrarenal pressure. Overall, the choice of patient positioning in ECIRS should consider the specific advantages and potential risks associated with each position, aiming to optimize procedural outcomes while ensuring patient safety and comfort.

One of the primary objectives of ECIRS is to reduce the number of access tracts required during the procedure, which helps minimize intraoperative bleeding and associated risks. An additional intervention that may be considered to further mitigate the risk of bleeding is the perioperative use of tranexamic acid. It is a synthetic derivative of the amino acid lysine, known for its antifibrinolytic properties. It works by inhibiting the breakdown of fibrin clots, thereby reducing bleeding. While specific studies on the use of tranexamic acid in ECIRS are limited, its effectiveness in reducing bleeding complications has been well-documented in other surgical settings, including PCNL. In PCNL, tranexamic acid has been recommended in guidelines based on evidence from several studies and meta-analyses (3, 36). These studies have demonstrated that tranexamic acid can effectively reduce blood loss during and after PCNL, potentially decreasing the need for blood transfusions and improving patient outcomes.

Given the similarities in procedural techniques and potential for bleeding between PCNL and ECIRS, the perioperative use of tranexamic acid in ECIRS may offer similar benefits. However, further research specifically focusing on ECIRS is necessary to establish its efficacy and safety profile in this context.

KIDNEY ACCESS

The flexible ureteroscope used during ECIRS plays a crucial role in enhancing precision and safety by providing direct visualization and monitoring during kidney access procedures. Here are some key points regarding its benefits and recent advancements:

1. **Precise Kidney Access:** The flexible ureteroscope allows for precise localization and monitoring of the puncture site and tract dilation. By placing the ureteroscope tip in the targeted calyx, it helps guide the needle during both fluoroscopy-guided and ultrasound-guided procedures, thereby reducing puncture time and improving accuracy (8, 9).
2. **Clinical Outcomes:** A multi-institutional retrospective cohort study by Taguchi et al demonstrated that ureteroscopy-assisted puncture reduces the risk of additional surgical interventions and decreases overall procedure time, fluoroscopy exposure, and the duration of postoperative ureteral stent placement (37).
3. **Advancements in Guidance Techniques:**
   3a - Real-time Virtual Sonography: This technique synchronizes real-time ultrasound images with preoperative CT scans, allowing for precise localization and guidance during renal access procedures (38).
   3b - Three-Dimensional Mixed-Reality Hologram Guidance: Emerging technologies like mixed-reality hologram guidance provide three-dimensional visualization and guidance, enhancing procedural accuracy (7).
   3c - Automated Needle Targeting with X-ray (ANT-X): This innovative method aims to automate needle targeting using X-ray guidance, potentially improving procedural efficiency and accuracy (39). However, further research is needed to validate its effectiveness in clinical practice.

These advancements underscore the continuous evolution of ECIRS techniques towards improving outcomes and patient safety through enhanced precision, reduced procedural complexity, and optimized resource utilization. Continued research and clinical validation of these innovative approaches will be critical in further establishing their role in enhancing the efficacy and safety of ECIRS procedures.

Although not universally required, most studies in the literature describe the use of ureteral access sheaths (UAS) during flexible ureteroscopy, particularly in procedures like ECIRS. The UAS offers several advantages:

1. **Improved Kidney Drainage and Lower Intrarenal Pressure:** The presence of a UAS facilitates better drainage of the kidney during the procedure. It helps maintain a lower intrarenal pressure, which is

beneficial in reducing the risk of complications such as fluid extravasation and postoperative infections (40, 41).

2. **Facilitation of Ureteroscope Navigation:** The UAS provides a smooth pathway for the ureteroscope to navigate into the kidney. This is particularly advantageous in cases involving large-volume or impacted pelvic stones, where simultaneous lithotripsy through both antegrade and retrograde accesses can be performed effectively.
3. **Simultaneous Treatment of Stones:** In scenarios where both antegrade and retrograde accesses are utilized (as in ECIRS), the UAS allows for efficient simultaneous treatment of stones located in different parts of the kidney. This approach enhances procedural efficiency and may reduce the total operative time.

Overall, while the use of ureteral access sheaths is not mandatory, their adoption during flexible ureteroscopy, including in ECIRS, is widely recommended due to the aforementioned benefits. They contribute to improved drainage, lower intrarenal pressure, facilitate ureteroscope navigation, and enable simultaneous management of complex stone burdens, thereby enhancing the overall effectiveness and safety of the procedure.

Tract size and equipment choice

ECIRS, similarly to PCNL, can be performed using various sizes of nephrostomy tracts. The choice of tract size is an important consideration as it can influence intraoperative bleeding and the feasibility of different lithotripsy modalities. Reducing the tract size in ECIRS may potentially minimize bleeding during the procedure. However, it's important to note that not all energy modalities used for lithotripsy are compatible with smaller endoscopes. Recent advancements in laser platforms have contributed to the trend towards instrument miniaturization, which has implications for both ECIRS and PCNL procedures. While there are no prospective studies directly comparing conventional ECIRS to mini-ECIRS, there have been two retrospective studies that have attempted to assess this comparison. Both show potential benefits such as reduced morbidity, shorter hospital stays, and faster recovery time with miniaturization. Future research, including prospective studies, is needed to systematically evaluate the advantages and limitations of mini-ECIRS compared to conventional ECIRS. This includes assessing factors such as stone clearance rate, complication rate, procedural time, and overall patient outcomes.

Usui et al. retrospectively analyzed 144 patients in matched pairs undergoing 24 or 30 Fr ECIRS versus 16.5 Fr mini-ECIRS, finding similar stone-free rate (SFR), complications and severe complications. While there was no statistically significant difference in bleeding-related complications between the groups (2.6% vs. 6.5%, p = 0.442), only the ECIRS group had cases of pseudoaneurysm or required blood transfusion. Additionally, the mini-ECIRS group experienced less pain in the perioperative period (42). Similarly, Moon et al. retrospectively compared standard (20Fr) to mini (12 Fr) ECIRS, both performed using a holmium:YAG laser for lithotripsy. Before matching, the standard ECIRS group had larger and more complex stones, as well as a higher estimated blood loss. After propensity-score matching, the only statistically significant difference that remained was the higher estimated blood loss in the standard ECIRS group (43). A meta-analysis published in 2022 by Liu et al. performed a subgroup analysis comparing mini-ECIRS to mini-PCNL. This analysis found that mini-ECIRS had a higher SFR, fewer overall and severe complications, and shorter hospital stay, while no difference was found in operative time, hemoglobin drop or blood transfusions between the two groups (23).

Vacuum-assisted procedures have recently been thoroughly studied for retrograde intrarenal surgery (RIRS) and mini-PCNL. However, only one retrospective cohort study has described the use of suctioning percutaneous sheaths in ECIRS (44). The authors reported a 91.8% final SFR after an average of 1.54 procedures for staghorn calculi. In this study

authors also describe a high rate of postoperative fever, achieving 29.5%. Positive urine culture was identified as the only significant risk factor for postoperative fever, while body mass index and stone volume were significant risk factors for achieving initial stone-free status.

SURGICAL RESULTS

Despite its more complex nature, most studies did not report longer operative time for ECIRS compared to PCNL (22-25). Gauhar et al. found a trend towards shorter operative time in the ECIRS group, but the difference was not statistically significant (24). Among the four meta-analyses published, only Abdullatif et al. (25) found that patients undergoing ECIRS had shorter hospital stays, while the other three reported no differences between the groups.

The evaluation of stone-free status in endourology papers indeed sparks considerable debate, primarily focusing on two key aspects: the threshold size of residual fragments and the imaging techniques employed for assessment (45). Most studies consider fragments up to 4 mm as clinically insignificant, but other cut-offs, such as 2 mm, 3 mm, or even the total absence of residual fragments are also used. The imaging techniques most employed are kidney–ureter–bladder (KUB) X-ray and/or ultrasound (US), with fewer studies using computed tomography scan (CT). The variability in follow-up durations across studies also complicates the ability to draw broad conclusions. Some studies differentiate initial and final SFR. Initial SFR refers to the evaluation after a single session of the procedure, while final SFR includes the assessment after any additional auxiliary procedures (i.e., shock wave lithotripsy, PCNL or RIRS). Recent studies have even advocated for the use of intraoperative CT during endourological procedures, though its application in ECIRS has yet to be assessed (46). Despite this variability, most papers report better initial (22, 23, 25) and final (23) SFRs with ECIRS. Additionally, Gauhar and Widyokirono reported lower retreatment rate in the ECIRS group in their analysis (22, 24).

Postoperative drainage

In a recent review encompassing 33 studies, Nedbal et al. highlighted the lack of standardization regarding the placement of postoperative nephrostomy tubes (47). Common reasons for placing nephrostomy tubes included managing bleeding, cases involving a solitary kidney, residual stones, multiple access points (48), or infection stones obstructing the calyces. However, using a nephrostomy tube may result in increased postoperative pain and delayed hospital discharge (49). Therefore, its routine use is typically not recommended unless there is a specific clinical indication. Conversely, many authors advocate for the postoperative placement of ureteral stents, especially when using a UAS.

Complications

All four meta-analyses reported fewer complications with ECIRS compared to PCNL (22-25). Liu et al. categorized complications by severity and found more overall and severe complications in the PCNL group (23). The most undesired complications in endourologic percutaneous procedures are bleeding requiring transfusion, infectious events and adjacent organ injury (17). The latter is fortunately rare due to improved access techniques, as previously discussed. Gauhar et al. found a lower hemoglobin drop in the ECIRS group but similar blood transfusion rates (24), whereas Liu et al. found similar hemoglobin drop rates but lower transfusion rates (23). However, Liu et al. acknowledged that the sample size was insufficient to ensure significance and concluded that further studies are needed for a more definitive conclusion. The other two meta-analyses found no statistical difference between the groups regarding estimated blood loss and transfusion rates. Widyokirono et al. reported a significantly lower incidence of urosepsis with ECIRS compared to conventional PCNL, but no difference when compared to mini-PCNL (22). Gauhar et al. noted a trend towards a lower incidence of fever in the ECIRS group, but this was not statistically significant, and there was no difference in sepsis (24). Liu et al. also reported no difference in postoperative fever between the groups (23).

CONCLUSIONS

In recent years, ECIRS has demonstrated significant advantages in treating large and complex kidney stones, including improved stone-free rate, reduced need for auxiliary procedures, and lower complication rate compared to traditional PCNL. Future research should focus on well-designed RCTs to provide robust evidence on the efficacy, safety, and cost-effectiveness of ECIRS, potentially establishing it as the new standard treatment.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10:257-9. doi: 10.1080/21681805.1976.11882084.
2. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol. 2016;196:1161-9. doi: 10.1016/j.juro.2016.05.091.
3. Skolarikos A, Jung H, Neisius A, Petřík A, Somani B, Tailly T, et al. EAU Guidelines on Urolithiasis. Edn. presented at the EAU Annual Congress Paris 2024. [Internet]. Avaliable at. <https://uroweb.org/guidelines/urolithiasis>
4. Ibarluzea G, Scoffone CM, Cracco CM, Poggio M, Porpiglia F, Terrone C, et al. Supine Valdivia and modified lithotomy position for simultaneous anterograde and retrograde endourological access. BJU Int. 2007;100:233-6. doi: 10.1111/j.1464-410X.2007.06960.x.
5. Bach C, Goyal A, Kumar P, Kachrilas S, Papatsoris AG, Buchholz N,et al. The Barts 'flank-free' modified supine position for percutaneous nephrolithotomy. Urol Int. 2012;89:365-8. doi: 10.1159/000341430.
6. Batagello CA, Barone Dos Santos HD, Nguyen AH, Alshara L, Li J, Marchini GS, et al. Endoscopic guided PCNL in the prone split-leg position versus supine PCNL: a comparative analysis stratified by Guy's stone score. Can J Urol. 2019;26:9664-74.
7. Porpiglia F, Checcucci E, Amparore D, Peretti D, Piramide F, De Cillis S, et al. Percutaneous Kidney Puncture with Three-dimensional Mixed-reality Hologram Guidance: From Preoperative Planning to Intraoperative Navigation. Eur Urol. 2022;81:588-97. doi: 10.1016/j.eururo.2021.10.023.
8. Vicentini FC, El Hayek KKR, Szwarc M, Perrella R, Kuriki P, Cohen D, et al. Ultrasound guided endoscopic combined Intrarenal surgery - 10 steps for the success. Int Braz J Urol. 2022;48:874-5. doi: 10.1590/S1677-5538.IBJU.2022.0029.
9. Marchini GS, Lima FS, Campos MEC, Maroccolo MVO, Reggio E, Mazzucchi E, et al. Modified biplanar (0-90°) endoscopic-guided puncture technique for percutaneous nephrolithtomy: refinement with endoscopic combined intrarrenal surgery to reduce fluoroscopy and operative time. Int Braz J Urol. 2023;49:785-6. doi: 10.1590/S1677-5538.IBJU.2023.0346.
10. Bergmann J, Rosenbaum CM, Netsch C, Gross AJ, Becker B. First Clinical Experience of a Novel Pulsed Solid-State Thulium:YAG Laser during Percutaneous Nephrolithotomy. J Clin Med. 2023;12:2588. doi: 10.3390/jcm12072588.
11. Patil A, Sharma R, Shah D, Gupta A, Singh A, Ganpule A, et al. A prospective comparative study of mini-PCNL using Trilogy™ or thulium fibre laser with suction. World J Urol. 2022;40:539-43. doi: 10.1007/s00345-021-03881-5.
12. De Stefano V, Castellani D, Somani BK, Giulioni C, Cormio A, Galosi AB, et al. Suction in Percutaneous Nephrolithotripsy: Evolution, Development, and Outcomes from Experimental and Clinical studies. Results from a Systematic Review. Eur Urol Focus. 2024;10:154-68. doi: 10.1016/j.euf.2023.06.010.
13. Gücük A, Kemahlı E, Üyetürk U, Tuygun C, Yıldız M, Metin A. Routine flexible nephroscopy for percutaneous nephrolithotomy for renal stones with low density: a prospective, randomized study. J Urol. 2013;190:144-8. doi: 10.1016/j.juro.2013.01.009.

14. Gökce Mİ, Gülpinar O, Ibiş A, Karaburun M, Kubilay E, Süer E. Retrograde vs. antegrade fl exible nephroscopy for detection of residual fragments following PNL: A prospective study with computerized tomography control. Int Braz J Urol. 2019;45:581-7. doi: 10.1590/S1677-5538.IBJU.2018.0695.
15. Cracco CM, Knoll T, Liatsikos EN, Osther PJ, Smith AD, Scarpa RM, et al. Rigid-only versus combined rigid and flexible percutaneous nephrolithotomy: a systematic review. Minerva Urol Nefrol. 2017;69:330-41. doi: 10.23736/S0393-2249.17.02841-7.
16. Qin P, Zhang D, Huang T, Fang L, Cheng Y. Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis. Int Braz J Urol. 2022;48:637-48. doi: 10.1590/S1677-5538.IBJU.2021.0347.
17. Cracco CM, Scoffone CM. ECIRS (Endoscopic Combined Intrarenal Surgery) in the Galdakao-modified supine Valdivia position: a new life for percutaneous surgery? World J Urol. 2011;29:821-7. doi: 10.1007/s00345-011-0790-0.
18. Wen J, Xu G, Du C, Wang B. Minimally invasive percutaneous nephrolithotomy versus endoscopic combined intrarenal surgery with flexible ureteroscope for partial staghorn calculi: A randomised controlled trial. Int J Surg. 2016;28:22-7. doi: 10.1016/j.ijsu.2016.02.056.
19. Hamamoto S, Yasui T, Okada A, Taguchi K, Kawai N, Ando R, et al. Endoscopic combined intrarenal surgery for large calculi: simultaneous use of flexible ureteroscopy and mini-percutaneous nephrolithotomy overcomes the disadvantageous of percutaneous nephrolithotomy monotherapy. J Endourol. 2014;28:28-33. doi: 10.1089/end.2013.0361.
20. Grasso M, Lang G, Taylor FC. Flexible ureteroscopically assisted percutaneous renal access. Tech Urol. 1995Spring;1:39-43.
21. Scoffone CM, Cracco CM, Cossu M, Grande S, Poggio M, Scarpa RM. Endoscopic combined intrarenal surgery in Galdakao-modified supine Valdivia position: a new standard for percutaneous nephrolithotomy? Eur Urol. 2008;54:1393-403. doi: 10.1016/j.eururo.2008.07.073.
22. Widyokirono DR, Kloping YP, Hidayatullah F, Rahman ZA, Ng AC, Hakim L. Endoscopic Combined Intrarenal Surgery vs Percutaneous Nephrolithotomy for Large and Complex Renal Stone: A Systematic Review and Meta-Analysis. J Endourol. 2022;36:865-76. doi: 10.1089/end.2021.0761.
23. Liu YH, Jhou HJ, Chou MH, Wu ST, Cha TL, Yu DS, et al. Endoscopic Combined Intrarenal Surgery Versus Percutaneous Nephrolithotomy for Complex Renal Stones: A Systematic Review and Meta-Analysis. J Pers Med. 2022;12:532. doi: 10.3390/jpm12040532.
24. Gauhar V, Castellani D, Cracco CM, Scoffone CM, Lim EJ, Rubilotta E, et al. Is endoscopic combined intrarenal surgery ready for primetime in endourology? Outcomes from a systematic review and meta-analysis. Cent European J Urol. 2022;75:171-81. doi: 10.5173/ceju.2022.0049.
25. Abdullatif VA, Sur RL, Abdullatif ZA, Szabo SR, Abbott JE. The Safety and Efficacy of Endoscopic Combined Intrarenal Surgery (ECIRS) versus Percutaneous Nephrolithotomy (PCNL): A Systematic Review and Meta-Analysis. Adv Urol. 2022;2022:1716554. doi: 10.1155/2022/1716554.
26. Abouelgreed TA, Abdelaal MA, Amin MM, Elatreisy A, Shalkamy O, Abdrabuh AM, et al. Endoscopic combined intrarenal surgery in the prone split-leg position versus Galdakao-modified supine Valdivia position for the management of partial staghorn calculi. BMC Urol. 2022;22:163. doi: 10.1186/s12894-022-01115-3.
27. Estrade V, Meria P, Almeras C; Lithiasis Committee of the French Association of Urology (CLAFU). 2022 Recommendations of the AFU Lithiasis Committee: Combined approach for the management of kidney and ureteral stones (Endoscopic Combined IntraRenal Surgery, ECIRS). Prog Urol. 2023;33:871-4. doi: 10.1016/j.purol.2023.08.009.
28. Tanidir Y, Sekerci CA, Genc YE, Gokmen E, Arslan F, Yucel S, et al. Endoscopic combined intrarenal surgery versus percutaneuos nephrolithotomy for complex pediatric stone disease: A comparative analysis of efficacy and safety. J Pediatr Urol. 2024;20:606.e1-606.e7. doi: 10.1016/j.jpurol.2024.05.025.
29. Sugino F, Nakane K, Kawase M, Iinuma K, Kawase K, Koie T. Endoscopic combined intrarenal surgery for renal allograft lithiasis using "sheath-connection technique": A case report. Urol Case Rep. 2023;47:102331. doi: 10.1016/j.eucr.2023.102331.
30. Tsaturyan A, Faria-Costa G, Peteinaris A, Lattarulo M, Martinez BB, Vrettos T, et al. Endoscopic management of encrusted ureteral stents: outcomes and tips and tricks. World J Urol. 2023;41:1415-21. doi: 10.1007/s00345-023-04361-8.
31. Limudomporn P, Phengsalae Y, Ketsuwan C. A giant ureteric calculus successfully removed by mini-endoscopic combined intrarenal surgery: A case report. Urol Case Rep. 2022;45:102270. doi: 10.1016/j.eucr.2022.102270.

32. Manikandan R, Mittal JK, Dorairajan LN, Mishra AK, Sreerag KS, Verma A. Endoscopic Combined Intrarenal Surgery for Simultaneous Renal and Ureteral Stones: A Retrospective Study. J Endourol. 2016;30:1056-61. doi: 10.1089/end.2016.0329.
33. Grande MS, Campobasso D, Inzillo R, Moretti M, Facchini F, et al. The use of endoscopic combined intrarenal surgery as an additional approach to upper urinary tract urothelial carcinoma: Our Experience. Indian J Urol. 2021;37:187-8. doi: 10.4103/iju.IJU_71_20.
34. Jung HD, Kim JC, Ahn HK, Kwon JH, Han K, Han WK, et al. Real-time simultaneous endoscopic combined intrarenal surgery with intermediate-supine position: Washout mechanism and transport technique. Investig Clin Urol. 2018;59:348-54. doi: 10.4111/icu.2018.59.5.348.
35. Perrella R, Vicentini FC, Paro ED, Torricelli FCM, Marchini GS, Danilovic A, et al. Supine versus Prone Percutaneous Nephrolithotomy for Complex Stones: A Multicenter Randomized Controlled Trial. J Urol. 2022;207:647-56. doi: 10.1097/JU.0000000000002291.
36. Cleveland B, Norling B, Wang H, Gandhi V, Price CL, Borofsky MS, et al. Tranexamic acid for percutaneous nephrolithotomy. Cochrane Database Syst Rev. 2023;10:CD015122. doi: 10.1002/14651858.CD015122.pub2.
37. Taguchi K, Yamashita S, Hamamoto S, Deguchi R, Kawase K, Okada T, et al. Ureteroscopy-assisted puncture for ultrasonography-guided renal access significantly improves overall treatment outcomes in endoscopic combined intrarenal surgery. Int J Urol. 2021;28:913-9. doi: 10.1111/iju.14603.
38. Hamamoto S, Unno R, Taguchi K, Ando R, Hamakawa T, Naiki T, et al. A New Navigation System of Renal Puncture for Endoscopic Combined Intrarenal Surgery: Real-time Virtual Sonography-guided Renal Access. Urology. 2017;109:44-50. doi: 10.1016/j.urology.2017.06.040.
39. Taguchi K, Hamamoto S, Kato T, Iwatsuki S, Etani T, Okada A, et al. Robot-assisted fluoroscopy-guided renal puncture for endoscopic combined intrarenal surgery: a pilot single-centre clinical trial. BJU Int. 2021;127:307-10. doi: 10.1111/bju.15291.
40. Doizi S, Uzan A, Keller EX, De Coninck V, Kamkoum H, Barghouthy Y, et al. Comparison of intrapelvic pressures during flexible ureteroscopy, mini-percutaneous nephrolithotomy, standard percutaneous nephrolithotomy, and endoscopic combined intrarenal surgery in a kidney model. World J Urol. 2021;39:2709-17.
41. Santa Cruz JAC, Danilovic A, Vicentini FC, Brito AH, Batagello CA, Marchini GS, et al. Ureteral access sheath. Does it improve the results of flexible ureteroscopy? A narrative review. Int Braz J Urol. 2024;50:346-58. doi: 10.1590/S1677-5538.IBJU.2024.9907.
42. Usui K, Komeya M, Taguri M, Kataoka K, Asai T, Ogawa T, et al. Minimally invasive versus standard endoscopic combined intrarenal surgery for renal stones: a retrospective pilot study analysis. Int Urol Nephrol. 2020;52:1219-25. doi: 10.1007/s11255-020-02433-x.
43. Moon YJ, Cho KS, Jung DC, Chung DY, Lee JY. The Consecutive 200 Cases of Endoscopic-Combined Intrarenal Surgery: Comparison between Standard and Miniature Surgeries. Medicina (Kaunas). 2023;59:1971. doi: 10.3390/medicina59111971.
44. Tominaga K, Inoue T, Yamamichi F, Fujita M, Fujisawa M. Impact of Vacuum-Assisted Mini-Endoscopic Combined Intrarenal Surgery for Staghorn Stones: Analysis of Perioperative Factors of Postoperative Fever and Stone-Free Status. J Endourol. 2023;37:400-6. doi: 10.1089/end.2022.0579.
45. Higgins AM, Ganesan V, Ghani KR, Agarwal DK, Borofsky MS, Dauw CA. The 2023 Stone-Free CT Mandate: Addressing the Two Sides of the Debate. J Endourol. 2022;36:1522-5. doi: 10.1089/end.2022.0610.
46. Lepine HL, Vicentini FC, Mazzucchi E, Molina WR, Marchini GS, Torricelli FC, et al. Intraoperative computed tomography for detection of residual stones in endourology procedures: systematic review and meta-analysis. Int Braz J Urol. 2024;50:250-60. doi: 10.1590/S1677-5538.IBJU.2024.0092.
47. Nedbal C, Jahrreiss V, Cerrato C, Castellani D, Kamal WK, Hameed Z, et al. Current role of endoscopic combined intrarenal surgery in the management of renal stones: A scoping review. Indian J Urol. 2023;39:274-84. doi: 10.4103/iju.iju_249_23.
48. Batagello CA, Vicentini FC, Monga M, Miller AW, Marchini GS, Torricelli FCM, et al. Tranexamic acid in patients with complex stones undergoing percutaneous nephrolithotomy: a randomised, double-blinded, placebo-controlled trial. BJU Int. 2022;129:35-47. doi: 10.1111/bju.15378.
49. Isac W, Rizkala E, Liu X, Noble M, Monga M. Tubeless percutaneous nephrolithotomy: outcomes with expanded indications. Int Braz J Urol. 2014;40:204-11. doi: 10.1590/S1677-5538.IBJU.2014.02.10.

50. Nuño de la Rosa I, Palmero JL, Miralles J, Pastor JC, Benedicto A. A comparative study of percutaneous nephrolithotomy in supine position and endoscopic combined intrarenal surgery with flexible instrument. Actas Urol Esp. 2014;38:14-20. English, Spanish. doi: 10.1016/j.acuro.2013.06.002.
51. Leng S, Xie D, Zhong Y, Huang M. Combined Single-Tract of Minimally Percutaneous Nephrolithotomy and Flexible Ureteroscopy for Staghorn Calculi in Oblique Supine Lithotomy Position. Surg Innov. 2018;25:22-27. doi: 10.1177/1553350617741023.
52. Zhao F, Li J, Tang L, Li C. A comparative study of endoscopic combined intrarenal surgery (ECIRS) in the galdakao-modified supine valdivia (GMSV) position and minimally invasive percutaneous nephrolithotomy for complex nephrolithiasis: a retrospective single-center study. Urolithiasis. 2021;49:161-6. doi: 10.1007/s00240-020-01207-5.
53. Kontos S, Papatsoris A, Nalagatla SK. ECIRS (endoscopic combined intrarenal surgery) versus fluoroscopic-guided renal access during supine percutaneous nephrolithotomy (PCNL): A comparative study. [Internet] Hell Urol 2018;30:43–48. Available at. <https://api.semanticscholar.org/CorpusID:87388184>
54. Isac W, Rizkala E, Liu X, Noble M, Monga M. Endoscopic-guided versus fluoroscopic-guided renal access for percutaneous nephrolithotomy: a comparative analysis. Urology. 2013;81:251-6. doi: 10.1016/j.urology.2012.10.004.
55. Xu K, Li Z. Comparison of Multi-tract minimally invasive percutaneous nephrolithotomy and Endoscopic Combined Intrarenal Surgery for Staghorn Renal Calculi: A single institution experience. In Proceedings of the 37th World Congress of Endourology, Abu Dhubi, United Arab Emirates, 31 October 2019; p. 235.
56. Mami D, Alchinbayev M, Kazachenko A. Comparison of minimally invasive treatment methods for urinary stones: A retrospective analysis. [Internet]. Electron J Gen Med. 2021; 18: em321. Available at. < https://www.ejgm.co.uk/article/comparison-of-minimally-invasive-treatment-methods-for-urinary-stones-a-retrospective-analysis-11252>
57. Kawahara T, Ito H, Terao H, Yoshida M, Ogawa T, Uemura H, et al. Ureteroscopy assisted retrograde nephrostomy: a new technique for percutaneous nephrolithotomy (PCNL). BJU Int. 2012;110:588-90. doi: 10.1111/j.1464-410X.2011.10795.x.
58. Gauhar V, Castellani D, Cracco CM, Scoffone CM, Lim EJ, Rubilotta E, et al. Is endoscopic combined intrarenal surgery ready for primetime in endourology? Outcomes from a systematic review and meta-analysis. Cent European J Urol. 2022;75:171-81. doi: 10.5173/ceju.2022.0049.
59. Gao H, Zhang H, Wang Y, Li K, Du W, Wang X, et al. Treatment of Complex Renal Calculi by Digital Flexible Ureterorenoscopy Combined with Single-Tract Super-Mini Percutaneous Nephrolithotomy in Prone Position: A Retrospective Cohort Study. Med Sci Monit. 2019;25:5878-85. doi: 10.12659/MSM.915034.
60. Beck S, Jain N, Kaplan A, Box G, Clayman R, Mcdougall E. Endoscopic guided percutaneous access during percutaneous nephrolithotomy: Is it of any clinical advantage? J Endourol. 2009; 23: A154-A155.
61. Zelvys A, Cekauskas A, Jankevicius F. B71 - Role of combined intrarenal surgery (ECIRS) in management of large/complex kidney stones. Eur Urol Suppl. 2014; 13: e1192.
62. Zhang W, Lu P. Super-mini percutaneous nephrolithotomy combined with flexible ureteroscopy versus the Chinese minimally invasive percutaneous nephrolithotomy: An efficacy analysis in patients with renal stones 2.5-4.0 cm. J Endourol. 2016; 30 (S2): A207-A208.
63. Yong D, Koh S, Tan Y. Supine percutaneous nephrolithotomy is safe and achieves higher stone free rates when combined with retrograde intrarenal surgery (endoscopic combined intra renal surgery). J Endourol. 2017; 31 (S2): A42-A43
64. Kavaliauskaite R, Želvys A. 65 – Endoscopic combined intrarenal surgery value in multiple renal stones treatment. Eur Urol Suppl. 2018; 17: e2232.

Correspondence address:
Fábio César Miranda Torricelli, MD
Divisão de Urologia, Departamento de Cirurgia,
Faculdade de Medicina da Universidade
de São Paulo - USP
Rua Barata Ribeiro, 380 / 74
São Paulo, SP, 01308-000, Brasil
Telefophone: +55 11 2768-4552
E-mail: fctorricelli@yahoo.com.br

ORIGINAL ARTICLE

Vol. 50 (6): 727-736, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0230

Robot-assisted radical nephroureterectomy using the KangDuo Surgical Robot-01 System versus the da Vinci System: a multicenter prospective randomized controlled trial

Zhongyuan Zhang [1], Zhenyu Li [1], Weifeng Xu [2], Xuan Wang [3], Shengcai Zhu [3], Jie Dong [2], Xiaojun Tian [4], Wei Zuo [1], Qi Tang [1], Zhihua Li [1], Kunlin Yang [1], Xiaoqiang Xue [2], Yingjie Li [2], Hongxian Zhang [4], Qiming Zhang [4], Silu Chen [1], Zhaoheng Jin [2], Xuesong Li [1], Zhigang Ji [2], Lulin Ma [4], Ming Liu [3]

[1] Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, National Urological Cancer Center, Beijing, China; [2] Department of Urology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China; [3] Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China; [4] Department of Urology, Peking University Third Hospital, Beijing, China

ABSTRACT

Introduction: We aim to compare the safety and effectiveness of the KangDuo (KD)-Surgical Robot-01 (KD-SR-01) system and the da Vinci (DV) system for robot-assisted radical nephroureterectomy (RARNU).

Materials and Methods: This multicenter prospective randomized controlled trial was conducted between March 2022 and September 2023. Group 1 included 29 patients undergoing KD-RARNU. Group 2 included 29 patients undergoing DV-RARNU. Patient demographic and clinical characteristics, perioperative data, and follow-up outcomes were collected prospectively and compared between the two groups.

Results: There were no significant differences in patient baseline demographic and preoperative characteristics between the two groups. The success rates in both groups were 100% without conversion to open or laparoscopic surgery or positive surgical margins. No significant difference was observed in docking time [242 (120-951) s vs 253 (62-498) s, P = 0.780], console time [137 (55-290) min vs 105 (62-220) min, P = 0.114], operative time [207 (121-460) min vs 185 (96-305) min, P = 0.091], EBL [50 (10-600) mL vs 50 (10-700) mL, P = 0.507], National Aeronautics and Space Administration Task Load Index scores, and postoperative serum creatinine levels between the two groups. None of the patients showed evidence of distant metastasis, local recurrence, or equipment-related adverse events during the four-week follow-up. One (3.4%) patient in Group 2 experienced postoperative enterovaginal and enterovesical fistulas (Clavien-Dindo grade III).

Conclusions: The KD-SR-01 system is safe and effective for RARNU compared to the DV Si or Xi system. Further randomized controlled studies with larger sample sizes and longer durations are required.

ARTICLE INFO

Zhenyu Li
https://orcid.org/0000-0002-9319-2536

Keywords:
Robotic Surgical Procedures;
Nephroureterectomy;
Multicenter Studies as Topic

Int Braz J Urol. 2024; 50: 727-36

Submitted for publication:
April 22, 2024

Accepted after revision:
June 22, 2024

Published as Ahead of Print:
August 10, 2024

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy, accounting for only 5-10% of all urothelial carcinomas (1). The gold standard treatment for localized high-risk UTUC has been radical nephroureterectomy (RNU) via an open approach with bladder cuff excision (BCE). However, due to concerns regarding perioperative morbidity, there has been a growing interest in exploring minimally invasive approaches as alternative treatment options (2-4).

Since its initial documentation by Clayman et al. in 1991 (5), laparoscopic RNU (LSRNU) has demonstrated comparable oncologic outcomes, reduced morbidity and improved perioperative outcomes compared to the open approach (6). Over the past two decades, robot-assisted RNU (RARNU) has also gained attraction, showing satisfactory oncologic outcomes and improved visualization, dexterity and ergonomics (3, 7-10). Although several newly developed robotic surgical systems such as the Revo-I, Senhance and Versius systems have emerged (11-13), the da Vinci (DV) system (Intuitive Surgical, Sunnyvale, CA, USA) remains dominant in the market. Recently, a novel robotic platform called the KangDuo (KD)-Surgical robot-01 (KD-SR-01) (Suzhou KangDuo Robot Co., Ltd., Suzhou, China), has been introduced in China. Preliminary investigations of the KD system have shown excellent performance in pyeloplasty, partial nephrectomy, and radical prostatectomy (14-17). However, no comparative study has yet been conducted to assess the utilization of the KD and DV systems in RARNU.

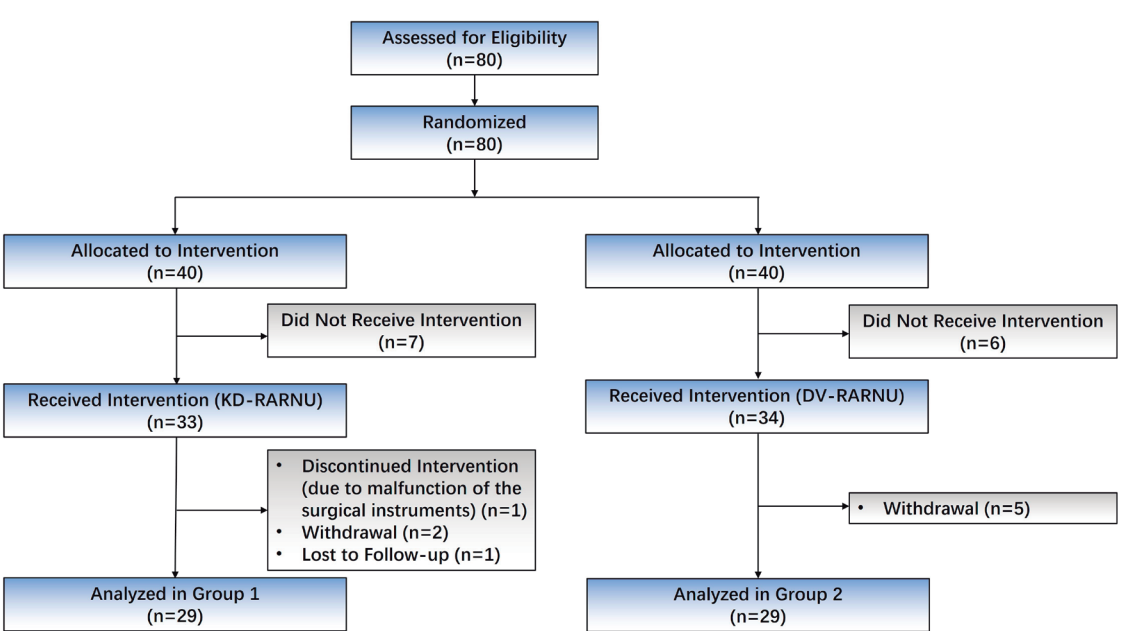
To our knowledge, this study is the first multicenter prospective randomized controlled trial aiming to compare the safety and effectiveness of the KD system with the DV system in the context of RARNU. We hypothesize that the KD-SR-01 system is safe and effective for RARNU compared to the DV system.

MATERIALS AND METHODS

Patient selection

The protocol of the multicenter randomized controlled trial was approved by the ethics committees of all participating centers. The study was registered at www.chictr.org.cn (ChiCTR2200056672). Between March 2022 and September 2023, patients aged between 18-85 years with a suspicion of ≤T1-3N0M0 UTUC requiring RNU were prospectively included (Figure-1). Exclusion criteria included a history of ipsilateral abdominal

Figure 1 - Trial profile.



surgery, concomitant uncontrolled diseases or urinary tract infection, pregnancy or lactation, relatively high surgical risk or inability to tolerate surgery, and inability or reluctance to cooperate during follow-up. All surgeries were performed by expert surgeons from large tertiary centers with experience with >100 standard robotic surgical procedures, primarily using the DV system. These surgeons had received sufficient training for the KD system, which involved a structured curriculum encompassing comprehensive didactic education, simulation-based training, proctorship under experienced mentors, and hands-on practice in standardized surgical techniques. Prior to the surgery, written informed consent was obtained from all patients, and imaging studies involving chest X-ray, urinary ultrasound, and computed tomography (CT) were performed.

Randomization and intervention

With randomized block design, the random allocation sequence was generated by the statist using SAS 9.4 and then put in opaque sealed envelopes. The investigator opened an envelope when a new patient entered the study after full communication. Treatment allocation remained masked to both the patients and the investigators until the envelope was opened. The treatment allocation was also masked to the pathologists and individuals who assessed the outcomes for the whole course of study.

Patients were assigned to two groups: Group 1 comprised 29 patients undergoing RARNU with the KD-SR-01 system (KD-RARNU) (Figure-2A), and Group 2 included 29 patients undergoing RARNU with the da Vinci Surgical Si or Xi System (DV-RARNU). The case report form was completed for each patient.

Surgical procedures

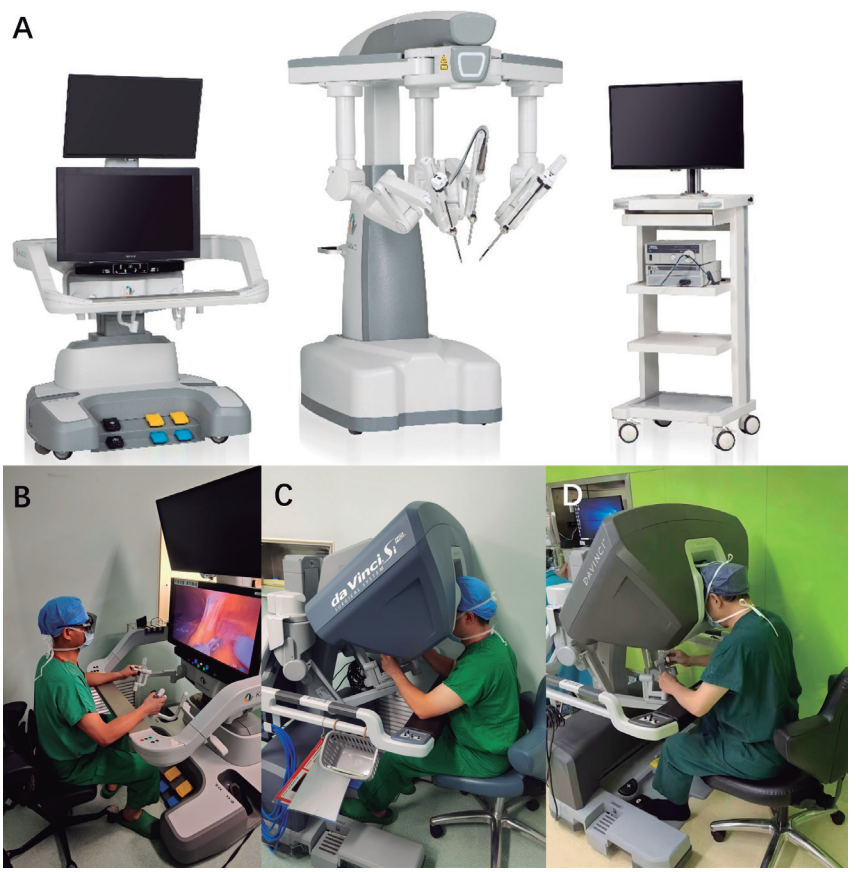
Under general anesthesia, the patient was positioned in the 45°-60° lateral decubitus position with the lesion side facing upward. The surgeon was sitting in front of the console (Figures 2 B-D), and the assistant was stationed at the patient cart. Three trocars, consisting of two operative trocars and one camera trocar, were used in both robotic systems. Additionally, two assistant trocars were used for suction, retraction, and suture retrieval in both groups (Figure-3). KD-RARNU procedures were performed using either the double-docking technique or the single-docking technique, while DV-RARNU procedures were performed using the single-docking technique only. The double-docking technique necessitated a transition from proximal upper tract dissection to lower tract dissection. The port placement and the robotic docking place were depicted in Figure-3 A-C (first docking) and Figures 3 D-F (second docking). Subsequently, the robotic cart was redocked from a 45° angle entering over the ipsilateral shoulder to a 45° angle entering over the ipsilateral hip. The single-docking technique required the trocar configuration and the robot docking in Figures-3 G-I.

Transperitoneal RARNU was performed in both groups using previously described techniques in LSRNU (18, 19). After mobilization of the colon, the renal vein and the renal artery were identified (Figure-4A). The renal hilum was carefully dissected, clipped, and transected using Hem-o-lock or endovascular gastrointestinal anastomosis (Endo-GIA) (Figure-4B). The kidney and the proximal ureter were then dissected (Figure-4C). If necessary, redocking was performed before clipping the ureter distal to the tumor site using Hem-o-lock to prevent tumor seeding. The ureter was meticulously dissected caudally until the ureterovesical junction (Figure-4D). The bottom of the tent-shaped structure was visualized with the retraction of the ureter in the superior and lateral directions. BCE was employed with endoscissors (Figure-4E). Bladder closure could alternatively be achieved by Hem-o-lock clipping or a two-layer running manner using a barbed suture (Figure-4F). Finally, the dissected specimen was extracted en bloc. Lymph node dissection was performed in cases where lymph node metastasis was suspected in the preoperative evaluation or enlarged lymph nodes were found during surgery.

Data collection and follow-up

Patient demographic and clinical characteristics, perioperative data, and follow-up outcomes were collected prospectively and compared between the two groups. Patient demographic and clinical characteristics included age, gender, body mass index (BMI), laterality, clinical T stage (according to the 2004 World

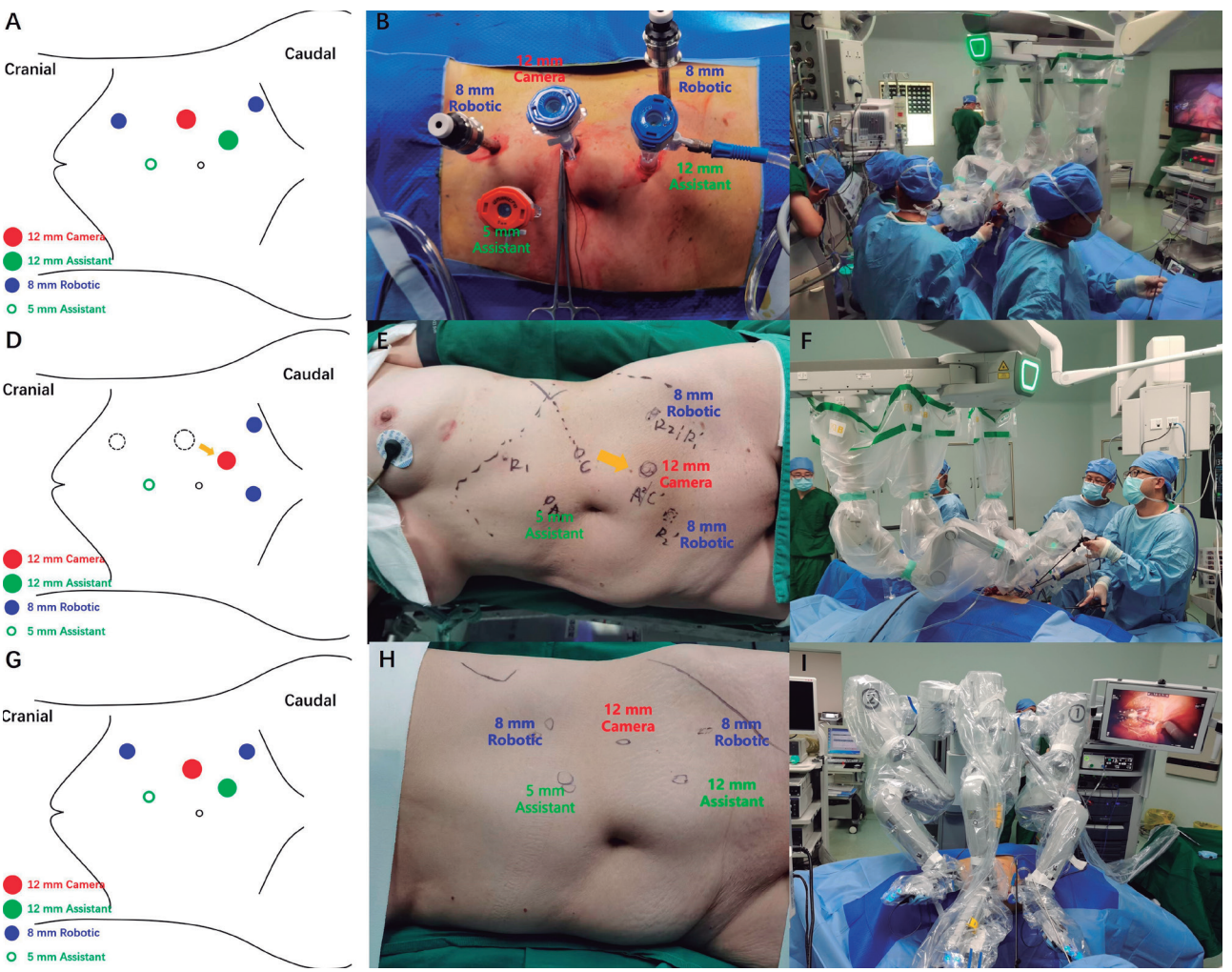
Figure 2 - The KD-SR-01 system and the interactions between the surgeon and the consoles of the KD-SR-01 and the DV systems.



(A) The KD-SR-01 system included the surgeon console, the patient cart, and the vision cart. (B) The surgeon was able to control the open console of the KD-SR-01 system. (C) The surgeon was sitting at the immersive console of the DV Si System. (D) The surgeon was sitting at the immersive console of the DV Xi System.

Health Organization grade classification), and preoperative serum creatinine levels. Perioperative data included conversion to open or laparoscopic surgery, docking time, console time, operative time, estimated blood loss (EBL) and the National Aeronautics and Space Administration task load index (NASA-TLX) scores. The docking process was precisely measured from the initiation of the robotic cart to the attachment of the final cannula to the manipulator arm. In cases where the double-docking technique was used, docking time specifically referred to the first-docking time. Console time was defined as the duration spent operating the console to complete the surgical procedures. Subjective evaluation of an estimate of global workload was conducted using the Paper/Pencil Version of the NASA-TLX scores, which was modified from original NASA-TLX continuous rating scale (0-100) to a 20-point scale with the weighting process eliminated and the ratings to simplify the application. Patients were followed up on postoperative day (POD) 1, POD 7, and postoperative week (POW) 4, during which blood and urine tests and physical examinations were conducted. Imaging evaluations such as computed tomography or magnetic resonance imaging were performed on POW 4. The primary endpoint was the success rate of operation determined by the absence of conversion to open or laparoscopic surgery and the presence of negative surgical margins. The secondary endpoint was the postoperative serum creatinine levels.

Figure 3 - Port placement and robot docking place for KD-RARNU and DV-RARNU.



(A and B) The port placement of the first docking. (C) The robotic cart was first docked at a 45° angle entering over the ipsilateral shoulder. (D and E) The port placement of the second docking. (F) The robotic cart was redocked at a 45° angle entering over the ipsilateral hip. (G-I) Single-docking technique for KD-RARNU or DV-RARNU. (G and H) The port placement of the single-docking technique. (I) The robot docking place of the single-docking technique.

Postoperative complications were categorized according to the Clavien-Dindo system (20).

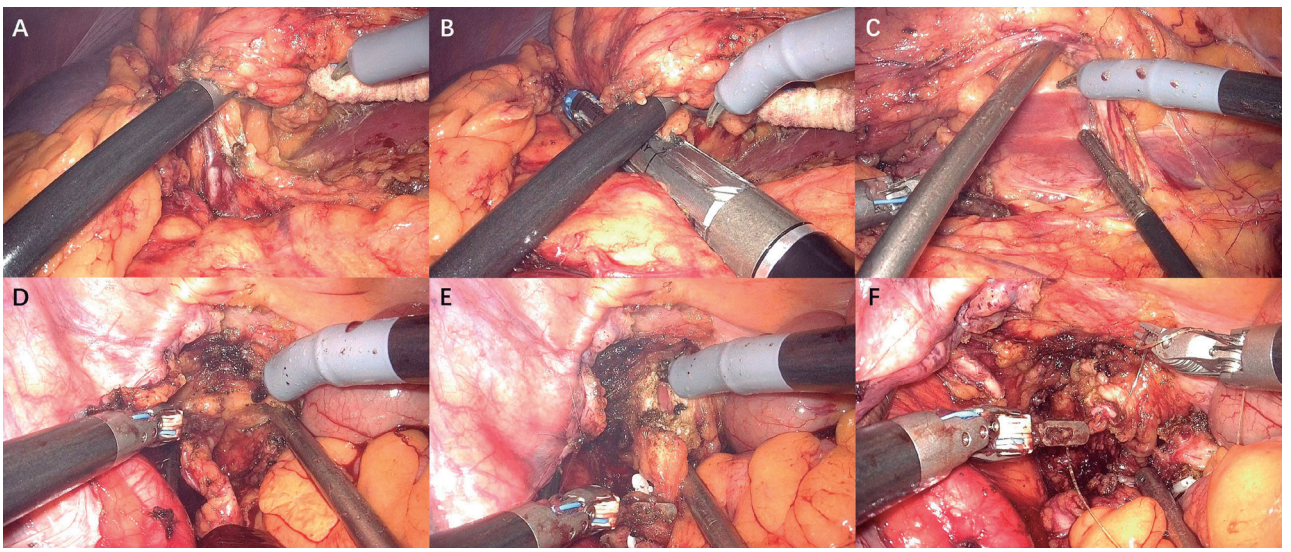
Statistical analysis

All statistical analyses were performed using SPSS 27.0 software. The Fisher's exact test or Pearson's chi-square test were used for categorical variables, while the Student t-test or Mann–Whitney U test were used for continuous variables. A probability (P) value of <0.05 was considered significant.

RESULTS

As shown in Figure-1, a total of 58 patients were included for analysis (n=29 per each group). Patient

Figure 4 - Surgical procedures of RARNU.



(A) The renal hilum was identified and dissected. (B) The renal artery and the renal vein were transected using Endo-GIA. (C) The kidney and the proximal ureter were dissected. (D) The ureter was dissected carefully caudally until the ureterovesical junction. (E) BCE was performed with endoscissors. (F) The bladder was closed with a two-layer running manner using a barbed suture.

baseline demographic and preoperative characteristics of the two groups are displayed in Table-1. There were no statistically significant differences regarding age, gender, BMI, laterality, clinical tumor stage, and preoperative serum creatinine levels between the two groups.

Perioperative data and follow-up outcomes are presented in Table-2. All RARNU procedures were completed without conversion to open or laparoscopic surgery, and positive surgical margins were not noted, resulting in a 100% success rate for both groups. There were no significant differences observed in docking time [242 (120-951) s vs 253 (62-498) s, P = 0.780], console time [137 (55-290) min vs 105 (62-220) min, P = 0.114], operative time [207 (121-460) min vs 185 (96-305) min, P = 0.091], and EBL [50 (10-600) mL vs 50 (10-700) mL, P = 0.507] between the two groups. The global, mental demand, physical demand, temporal demand, performance, effort and frustration of the NASA-TLX scores of Group 1 were

Table 1 - Patient baseline demographic and preoperative characteristics.

Variables	Group 1 (n=29)	Group 2 (n=29)	*P* value
Age, years, mean ± SD	63.62±10.34	67.31±6.44	0.109
Gender, male/female, n	21/8	14/15	0.060
BMI, kg/m^2, mean ± SD	25.33±3.32	24.83±3.61	0.582
Laterality, right/left, n	10/19	16/13	0.113
Clinical tumor stage, n (%)			0.929
T1	13 (44.8%)	14 (48.3%)	
T2	11 (37.9%)	11 (37.9%)	
T3	5 (17.2%)	4 (13.8%)	
Preoperative serum creatinine levels, μmol/L, mean ± SD	100.90±35.43	101.89±35.53	0.916

SD = standard deviation; BMI = body mass index.

Table 2 - Perioperative data and follow-up outcomes.

Variables	Group 1 (n=29)	Group 2 (n=29)	P value
Conversion, n	0	0	-
Success rate	100%	100%	-
Docking time. s, median (range)	242 (120-951)	253 (62-498)	0.780
Console time, min, median (range)	137 (55-290)	105 (62-220)	0.114
Operative time, min, median (range)	207 (121-460)	185 (96-305)	0.091
EBL, ml, median (range)	50 (10-600)	50 (10-700)	0.507
NASA-TLX scores, mean ± SD			
Global	14.38±15.57	13.86±13.50	0.893
Mental demand	2.59±2.97	3.00±3.76	0.644
Physical demand	2.97±3.82	3.03±3.91	0.946
Temporal demand	2.93±4.28	2.55±3.14	0.701
Performance	1.38±0.98	1.24±0.87	0.573
Effort	2.66±2.94	2.38±2.56	0.705
Frustration	1.86±1.58	1.66±1.42	0.601
Serum creatinine levels, μmol/L, mean ± SD			
POD 1	111.93±38.20	115.08±43.67	0.864
POD 7	116.48±43.23	116.92±51.07	0.972
POW 4	120.70±47.94	120.53±58.06	0.990
Equipment-related adverse events, n	0	0	-
Postoperative complications of Clavien-Dindo grade ≥ III, n (%)	0 (0)	1 (3.4)	1.000

EBL = estimated blood loss; NASA-TLX = National Aeronautics and Space Administration task load index; SD = standard deviation; POD = postoperative day; POW = postoperative week.

14.38±15.57, 2.59±2.97, 2.97±3.82, 2.93±4.28, 1.38±0.98, 2.66±2.94, and 1.86±1.58, respectively. These scores were comparable to those of Group 2 which were 13.86±13.50, 3.00±3.76, 3.03±3.91, 2.55±3.14, 1.24±0.87, 2.38±2.56, and 1.66±1.42, respectively. Postoperative serum creatinine levels on POD 1 (111.93±38.20 μmol/L vs 115.08±43.67 μmol/L, P = 0.864), POD 7 (116.48±43.23 μmol/L vs 116.92±51.07 μmol/L, p=0.972), and POW 4 (120.70±47.94 μmol/L vs 120.53±58.06 μmol/L, P = 0.990) showed no difference statistically significant between the two groups. No evidence of distant metastasis or local recurrence were found based on imaging evaluation conducted on POW 4.

No equipment-related adverse events were reported during the follow-up period. No major postoperative complications (Clavien-Dindo grade ≥ III) were noted in Group 1. One (3.4%) patient in Group 2 experienced enterovaginal and enterovesical fistulas (Clavien-Dindo grade III) after surgery, which were repaired by surgical intervention.

DISCUSSION

RARNU has gained increasing popularity in robotic surgery. The study represents the first multi-center

prospective randomized controlled trial to compare the safety and effectiveness of the innovative KD system with the DV system for RARNU. All surgical procedures were successfully completed without open or laparoscopic conversion, and no positive surgical margins were observed, indicating comparable effectiveness profiles. No significant differences were observed in docking time, console time, operative time, EBL, and serum creatinine levels on POD 1, POD 7, and POW 4 between the two groups. Group 1 experienced no equipment-related adverse events or severe (Clavien-Dindo grade ≥ III) postoperative complications, affirming the safety of the KD system.

Regarding the trocar placement and docking techniques, the KD system introduced an additional trocar at the midline of the lower abdomen, and the laparoscopic instruments were shifted between ports during the double-docking procedures, which enabled the transition from the dissociation of the kidney and proximal ureter to the dissociation of the distal ureter and BCE without patient repositioning. In cases where the patient's abdomen was relatively short and the laparoscopic instruments were of sufficient length, the single-docking technique was recommended, especially for DV-RARNU, to alleviate the additional burden of redocking and repositioning. In terms of the BCE technique, a tent-shaped bladder mucosal cuff and intramural ureter could be visualized by retraction in the superior and lateral directions, facilitating en bloc BCE with clear surgical margins both at the base and border of the specimen without urinary spillage (18, 19).

There are several noteworthy features of the KD system. The open surgeon console of the KD system serves to alleviate neck fatigue of the surgeons and enhance communications between surgeons and assistants (16). Furthermore, the KD system is equipped with three suspended arms with synchronous rotation capabilities to accommodate patient position without repositioning. The force sensor technology and the cross-laser design also enhanced the convenience of docking and undocking procedures. In addition, the KD system utilizes a foot clutch, which requires additional training for surgeons familiar with the manual clutch of the DV system to adapt to this new feature. However, the ergonomics of the KD system are comparable to the DV system based on NASA-TLX scores.

Similar to the DV system, the KD system lacks tactile feedback systems, which can be partially compensated by a high-resolution three-dimensional laparoscope for procedures within the deep and confined areas (21). The utilization of single-site technology and remote surgery in the KD system has also been limited. Single-site technology is associated with better cosmetic outcomes (22), and remote surgery eliminates geographical barriers among surgeons, assistants and patients (23). All of these innovations merit further exploration for the advancement of robotic systems, particularly for RARNU.

This study certainly has some limitations. The sample size was relatively small in both groups, which may impact the generalizability of the findings. Additionally, the limited four-week postoperative follow-up period prevents an assessment of long-term oncological outcomes and renal function status after RARNU. Furthermore, although KD-SR-01 is a self-developed Chinese system with a lower estimated cost compared to the DV system, which could potentially benefit more patients by driving prices down, a cost-effective analysis comparing different robotic systems was not conducted.

CONCLUSIONS

The KD-SR-01 system manifests the safety and effectiveness for RARNU in comparison with the DV Si or Xi system. However, larger-sample and longer-term prospective randomized controlled trials are warranted to assess the oncologic outcomes and renal function status.

ABBREVIATIONS

BCE = bladder cuff excision
BMI = body mass index
CT = computed tomography
DV = da Vinci
EBL = estimated blood loss
Endo-GIA = endovascular gastrointestinal anastomosis
KD = KangDuo

KD-SR-01 = KangDuo-Surgical Robot-01
LSRNU = laparoscopic radical nephroureterectomy
NASA-TLX = National Aeronautics and Space Administration task load index
POD = postoperative day
POW = postoperative week
RARNU = robot-assisted radical nephroureterectomy
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGEMENTS

Zhongyuan Zhang, Zhenyu Li, Weifeng Xu, Xuan Wang contributed similarly as first author
The authors are grateful to Shubo Fan, Gang Wang, Yi Xie, and Yaoguang Zhang who have made substantial contributions to this study.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71:7-33. doi: 10.3322/caac.21654. Erratum in: CA Cancer J Clin. 2021 Jul;71(4):359. doi: 10.3322/caac.21669.
2. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020 Update. Eur Urol. 2021;79:62-79. doi: 10.1016/j.eururo.2020.05.042.
3. Saini S, Pathak RA, Hemal AK. Robotic nephroureterectomy in the management of upper tract urothelial cancer: inching toward standard of care? Int Urol Nephrol. 2022;54:1777-85. doi: 10.1007/s11255-022-03225-1.
4. Lo EM, Kim HL. Robot-Assisted Surgery for Upper Tract Urothelial Carcinoma. Urol Clin North Am. 2021;48:71-80. doi: 10.1016/j.ucl.2020.09.011.
5. Clayman RV, Kavoussi LR, Figenshau RS, Chandhoke PS, Albala DM. Laparoscopic nephroureterectomy: initial clinical case report. J Laparoendosc Surg. 1991;1:343-9. doi: 10.1089/lps.1991.1.343.
6. Ni S, Tao W, Chen Q, Liu L, Jiang H, Hu H, et al. Laparoscopic versus open nephroureterectomy for the treatment of upper urinary tract urothelial carcinoma: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2012;61:1142-53. doi: 10.1016/j.eururo.2012.02.019.
7. Clements MB, Krupski TL, Culp SH. Robotic-Assisted Surgery for Upper Tract Urothelial Carcinoma: A Comparative Survival Analysis. Ann Surg Oncol. 2018;25:2550-62. doi: 10.1245/s10434-018-6557-8.
8. Rodriguez JF, Packiam VT, Boysen WR, Johnson SC, Smith ZL, Smith ND, et al. Utilization and Outcomes of Nephroureterectomy for Upper Tract Urothelial Carcinoma by Surgical Approach. J Endourol. 2017;31:661-5. doi: 10.1089/end.2017.0086.
9. Aboumohamed AA, Krane LS, Hemal AK. Oncologic Outcomes Following Robot-Assisted Laparoscopic Nephroureterectomy with Bladder Cuff Excision for Upper Tract Urothelial Carcinoma. J Urol. 2015;194:1561-6. doi: 10.1016/j.juro.2015.07.081.
10. Medina LG, Alsyouf M, Ghoreifi A, Sayegh AS, Koh K, Yu W, et al. Distal ureter and bladder cuff excision using the "Keyhole Technique" during Robotic Radical Nephroureterectomy. Int Braz J Urol. 2022;48:876-7. doi: 10.1590/S1677-5538.IBJU.2022.0147.
11. Chang KD, Abdel Raheem A, Choi YD, Chung BH, Rha KH. Retzius-sparing robot-assisted radical prostatectomy using the Revo-i robotic surgical system: surgical technique and results of the first human trial. BJU Int. 2018;122:441-8. doi: 10.1111/bju.14245.
12. Venckus R, Jasenas M, Telksnys T, Venckus M, Janusonis V, Dulskas A, et al. Robotic-assisted radical prostatectomy with the Senhance® robotic platform: single center experience. World J Urol. 2021;39:4305-10. doi: 10.1007/s00345-021-03792-5.
13. Borse M, Godbole G, Kelkar D, Bahulikar M, Dinneen E, Slack M. Early evaluation of a next-generation surgical system in robot-assisted total laparoscopic hysterectomy: A prospective clinical cohort study. Acta Obstet Gynecol Scand. 2022;101:978-86. doi: 10.1111/aogs.14407.

14. Fan S, Xiong S, Li Z, Yang K, Wang J, Han G, et al. Pyeloplasty with the Kangduo Surgical Robot vs the da Vinci Si Robotic System: Preliminary Results. J Endourol. 2022;36:1538-44. doi: 10.1089/end.2022.0366.
15. Li X, Xu W, Fan S, Xiong S, Dong J, Wang J, et al. Robot-assisted Partial Nephrectomy with the Newly Developed KangDuo Surgical Robot Versus the da Vinci Si Surgical System: A Double-center Prospective Randomized Controlled Noninferiority Trial. Eur Urol Focus. 2023;9:133-40. doi: 10.1016/j.euf.2022.07.008.
16. Fan S, Zhang Z, Wang J, Xiong S, Dai X, Chen X, et al. Robot-Assisted Radical Prostatectomy Using the KangDuo Surgical Robot-01 System: A Prospective, Single-Center, Single-Arm Clinical Study. J Urol. 2022;208:119-27. doi: 10.1097/JU.0000000000002498. Erratum in: J Urol. 2022 Sep;208(3):744. doi: 10.1097/JU.0000000000002838.
17. Fan S, Hao H, Chen S, Wang J, Dai X, Zhang M, et al. Robot-Assisted Laparoscopic Radical Prostatectomy Using the KangDuo Surgical Robot System vs the da Vinci Si Robotic System. J Endourol. 2023;37:568-74. doi: 10.1089/end.2022.0739.
18. Liu P, Fang D, Xiong G, Yang K, Zhang L, Yao L, et al. A Novel and Simple Modification for Management of Distal Ureter During Laparoscopic Nephroureterectomy Without Patient Repositioning: A Bulldog Clamp Technique and Description of Modified Port Placement. J Endourol. 2016;30:195-200. doi: 10.1089/end.2015.0603.
19. Yuan C, Xu C, Li Z, Meng C, Du Y, Zhang C, et al. Surgical techniques and oncological outcomes of pure transperitoneal laparoscopic radical nephroureterectomy for upper urinary tract urothelial carcinoma. Transl Androl Urol. 2023;12:952-9. doi: 10.21037/tau-22-653.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13. doi: 10.1097/01.sla.0000133083.54934.ae.
21. Fan S, Dai X, Yang K, Xiong S, Xiong G, Li Z, et al. Robot-assisted pyeloplasty using a new robotic system, the KangDuo-Surgical Robot-01: a prospective, single-centre, single-arm clinical study. BJU Int. 2021;128:162-5. doi: 10.1111/bju.15396.
22. Buffi NM, Lughezzani G, Fossati N, Lazzeri M, Guazzoni G, Lista G, et al. Robot-assisted, single-site, dismembered pyeloplasty for ureteropelvic junction obstruction with the new da Vinci platform: a stage 2a study. Eur Urol. 2015;67:151-6. doi: 10.1016/j.eururo.2014.03.001.
23. Fan S, Xu W, Diao Y, Yang K, Dong J, Qin M, et al. Feasibility and Safety of Dual-console Telesurgery with the KangDuo Surgical Robot-01 System Using Fifth-generation and Wired Networks: An Animal Experiment and Clinical Study. Eur Urol Open Sci. 2023;49:6-9. doi: 10.1016/j.euros.2022.12.010.

Correspondence address:
Xuesong Li, MD
Department of Urology,
Peking University First Hospital, Beijing, China
E-mail: pineneedle@sina.com

ORIGINAL ARTICLE

Vol. 50 (6): 737-745, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0308

Safety and efficacy of vacuum-assisted mini-percutaneous nephrolithotomy for the treatment of renal stone disease: an analysis of stone free status and postoperative infectious complications

Kaushik P. Kolanukuduru [1], Osama Zaytoun [1, 2], Neeraja Tillu [1], Asher Mandel [1], Zachary Dovey [1], Maurizio Buscarini [1]

[1] Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2] Department of Urology, University of Alexandria, Alexandria, Egypt

ABSTRACT

Purpose: Vacuum-assisted mini-percutaneous nephrolithotomy (vmPCNL) is being increasingly adopted due to its faster operating times and lower incidence of postoperative infectious complications (IC), however, studies have been limited by small sample sizes. We hypothesize that vmPCNL is an efficacious treatment for renal stone disease with acceptable stone-free rates (SFR) and low incidence of IC. The objectives of this study were to measure SFR three months after surgery, determine the factors influencing SFR, and determine the rates of postoperative IC after vmPCNL.

Materials and Methods: Seven hundred and sixty seven patients underwent vmPCNL for the treatment of renal stones > 20 mm at a single institution. Patients underwent postoperative computed tomography at three months to assess SFR. Postoperative fever and SIRS/Sepsis were recorded for individual patients. Multivariate logistics regression was performed to assess predictors of SFR.

Results: The SFR was found to be 73.7% at three months. Stone burden (OR 0.39, 95% CI [0.33-0.46]) and age (OR 1.03, 95% CI [1.01-1.04]) emerged as statistically significant predictors of SFR on multivariate analysis. 5.5% of patients experienced postoperative fever, while 2.9% experienced SIRS/Sepsis.

Conclusions: This is the largest continuous cohort of patients to undergo vmPCNL for stone disease and demonstrates that vmPCNL is safe and efficacious, with an SFR of 74% at three months. The incidence of postoperative fever and SIRS/Sepsis is 5.5% and 2.9% respectively. Further randomized studies with large sample sizes are required to ascertain the rates of these complications in comparison to conventional approaches.

ARTICLE INFO

Kaushik Prabhav Kolanukuduru
https://orcid.org/0009-0001-9525-2600

Keywords:
Nephrolithotomy, Percutaneous; Nephrolithiasis; Kidney Calculi

Int Braz J Urol. 2024; 50: 737-45

Submitted for publication:
May 25, 2024

Accepted after revision:
July 03, 2024

Published as Ahead of Print:
August 10, 2024

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the surgical treatment of choice for patients with renal stones > 20 mm or lower pole stones > 10 mm (1). Mini-PCNL (mPCNL) involves the use of a miniature endoscope passed through a percutaneous tract (14 – 22 Fr) to access the renal collecting system to perform lithotripsy (2). mPCNL has similar efficacy to traditional PCNL approaches, with a superior safety profile and a reduced need for transfusion after surgery (3, 4). mPCNL has also been shown to be superior to retrograde intrarenal surgery (RIRS) in the context of postoperative stone-free rate (SFR), with similar rates of postoperative complications (5). However, a potential disadvantage to mPCNL is the longer operating times and the increased intrarenal pressures (IRP) (6).

Vacuum-assisted mPCNL (vmPCNL) is being increasingly adopted due to its faster operating times, high SFR, and low incidence of complications. The lower IRP during vmPCNL prevents excessive pyelic-venous backflow and renal pelvis damage (7).

Studies on the outcomes of vmPCNL have been limited by small sample sizes, with limited evidence on SFR and infectious complications (IC). We hypothesize that vmPCNL has acceptable SFR with a low incidence of IC and sought to determine SFR and IC rate in a contemporary cohort of patients. To our knowledge, this study represents the largest continuous cohort of patients to undergo vmPCNL for renal stone disease.

MATERIALS AND METHODS

Study setting, design, and participants:

This prospective study was performed after obtaining institutional review board approval at the institution where the study took place (IRB ITCBM44678/12012). Between 2016 and 2022, patients with renal stone disease were offered vmPCNL for definitive surgical treatment after a shared decision-making process. After clinical examination, patients underwent routine preoperative assessments including contrast/non-contrast computerized tomography (CT), renal ultrasound (RUS), preoperative creatinine, urinalysis, and urine culture. Patients with suspicion of urinary tract obstruction or infection were stented prior to surgery. All procedures were performed by a single surgeon (MB).

Surgical Technique

Following anesthetic induction and routine ureteral occlusion balloon placement (Boston Scientific™), patients were placed in either prone or supine position depending on individual patient characteristics (such as patient BMI, cardiorespiratory status, and high-risk for anesthetic complications), stone location, and the surgeon's decision on a case-to-case basis. Percutaneous renal access was obtained with an 18-gauge diamond-tipped needle on the appropriate calyx using standard fluoroscopic guidance. The surgical equipment used included the 12F mini-nephroscope (MIP, Karl Storz™) and the 16F ClearPetra® vacuum suction sheath (Well Lead Medical Co.™). A holmium laser was used to perform stone fragmentation and dusting (Ho:YAG laser, Lumenis/Boston Scientific™, 550 µm fiber, 100 W). Irrigation was performed with a normal saline bag placed 1.5 meters above the site of nephroscope insertion. After introducing the nephroscope and suction sheath, the negative pressure was switched on to ensure a suction effect. The vacuum pressure was set at 200 mm Hg. Stone clearance was performed until no stones could be visualized by the surgeon. Basketing was employed in select cases where the fragments were only reachable with the nephroscope. At the end of the procedure, all calyces were routinely inspected with a flexible scope passed through the sheath. An antegrade double-J stent was placed after surgery at the surgeon's discretion, which was removed between one and two weeks after surgery. All procedures were performed under fluoroscopic guidance. In cases where the total stone burden was high due to stones present in different anatomical locations of the kidney, a multistage approach was used to decrease the operative time of any single procedure, thus minimizing patient risk (42 patients [5.5%]). The surgical technique was standardized across all cases to maintain consistency in patient care.

Data Variables and Study Measures

Preoperative variables collected included age, sex, body mass index (BMI), preoperative creatinine, and preoperative stent placement. Stone-specific characteristics like laterality, location, stone burden (mm), and stone density (measured in Hounsfield Units, HU) were also collected simultaneously. Operative characteristics included for the analysis were operative time (induction of anesthesia to end of surgery), lithotripsy time, position of vmPCNL, use of basket, stent placement after surgery, and duration of postoperative stay. Postoperative variables analyzed included postoperative creatinine, postoperative complications within 90 days (if any), postoperative fever (within 48 hours), and SIRS/Sepsis. We defined SIRS as the presence of two or more of the following: body temperature >38°C or <36°C, white blood cell count >12×109, or heart rate > 90 beats/minute. Patients with SIRS were diagnosed with sepsis if they also had a positive blood culture. Finally, we measured the stone-free rate (SFR) after vmPCNL, defined as the absence of any residual fragments on postoperative CT scan three months after surgery.

Statistical analysis

Means with standard deviations were measured for continuous variables, while categorical variables were reported as absolute numbers and percentages. Logistic regression analysis was initially performed on relevant perioperative variables to determine predictors of SFR. Subsequent to this, a multivariate analysis was performed using those variables that demonstrated statistical significance ($p < 0.05$). Odds ratios (OR) were calculated for variables in the multivariate model along with 95% confidence intervals (CI). All analysis was performed on R programming software version 4.3.3.

RESULTS

Baseline, Stone and Operative Characteristics

Seven hundred and sixty seven patients underwent vmPCNL for the treatment of renal stones. 57% of patients were male, while 43% were female. The mean age and BMI of the group were 49.9 ± 14.61 years and 29.7 ± 6.05 kg/m^2 respectively. The mean preoperative creatinine was 1.41 ± 0.36 gm/dL. 50.1% of patients had a stent placed preoperatively due to suspicion of infection or urinary tract obstruction. 63.6% and 36.4% of patients had left-sided and right-sided renal stone disease respectively, with 53.6% of patients having lower pole stone disease. The mean stone burden for this group was 32.4 ± 15.6 mm. 22% of patients had high-density stones as measured by preoperative CT (HU > 950). The mean operative and lithotripsy time was 117.6 ± 43.4 and 68.9 ± 38.3 minutes respectively. 77.1% of vmPCNL were performed in prone position. Intraoperative basketing was performed in 7.95% of cases due to inadequate stone clearance using the suction evacuation alone. Following surgery, a stent was left in place in 67.5% of procedures. 96.3% of patients were admitted to the hospital overnight (Table-1).

Postoperative complications and outcomes after vmPCNL

The mean postoperative creatinine in this cohort was 1.18 ± 0.33 gm/dL, thus resulting in a mean creatinine change of -0.23 ± 0.49 gm/dL (postoperative - preoperative). 12.9% of patients experienced at least one complication within 90 days after surgery. Urinoma was noted after surgery in 1.4% of patients, while 2.3% of patients required transfusion after surgery. 3.4% and 1.4% of all patients experienced Clavien-Dindo 3 and Clavien-Dindo 4 complications respectively. The mortality rate in this study was 0.26%. At three months, 73.7% of all patients were stone-free after vmPCNL (Table-2).

Predictors of Stone Free Rate at three months

On univariate analysis, age, lower pole disease, stone burden, and position of vmPCNL (supine vs. prone) showed statistically significant associations with SFR. Including these variables in a multivariate model revealed that stone burden (OR 0.39, 95% CI [0.33-0.46], $p < 0.001$) was inversely related to SFR, while SFR increased with age (OR 1.03, 95% CI [1.01-1.04], $p < 0.001$). Lower pole disease (OR 1.39, 95% CI [0.92-2.1], $p=0.11$) and position of the patient (supine vs. prone) during vmPCNL (OR 0.57, 95% CI [0.31-1.05], $p=0.07$) did not yield any statistical significance when controlling for confounders in the multivariate model (Table-3).

Table 1 - Baseline, stone, and operative characteristics of patients undergoing vmPCNL (vacuum-assisted mini-percutaneous nephrolithotomy).

PARAMETER	RESULT
Number of patients, n	767
Sex, n (%):	
Male	437 (57%)
Female	330 (43%)
Age, mean ± SD	49.9 ± 14.61
Body Mass Index, mean ± SD	29.71 ± 6.05
Preoperative Creatinine (gm/dL), mean ± SD	1.41 ± 0.36
Preoperative Stent Placed, n (%)	385 (50.1%)
Laterality, n (%):	
Right	279 (36.4%)
Left	488 (63.6%)
Stone Location, n (%):	
Upper Pole and Pelvis	356 (46.4%)
Lower Pole	411 (53.6%)
Stone burden (mm), mean ± SD	32.4 ± 15.6
Stone Density, Hounsfield Units (HU), n (%)	
< 600	298 (38.9%)
600 - 950	300 (39.1%)
>950	169 (22%)
Operative time (minutes), mean ± SD	117.6 ± 43.4
Prone position, mean ± SD	131.5 ± 22.1
Supine position, mean ± SD	105 ± 43.7
Lithotripsy time (minutes), mean ± SD	68.9 ± 38.3
Position, n (%):	
Prone	591 (77.1%)
Supine	176 (22.9%)
Use of basket intraoperatively, n (%)	61 (7.95%)
Intraoperative stent placement, n (%)	518 (67.5%)
Postoperative stay, n (%):	
< 1 day	28 (3.7%)
≥ 1 day	739 (96.3%)

DISCUSSION

To our knowledge, this is the largest continuous series of patients to undergo vmPCNL with the ClearPetra® system for the treatment of renal stone disease. We found that 73.7% of patients were stone-free three months after surgery. Stone burden was the only clinically significant predictor of SFR in this patient cohort. While age was also identified to be a predictor of SFR after surgery, the OR for this association tended to one (OR=1.03), thus suggesting that the significance we found was only a statistical one, with little clinical relevance. Nonetheless, further studies are required to truly ascertain the role of age as a predictive factor for SFR in the setting of vmPCNL. As the study evolved, we progressed from using intermittent suction evacuation

Table 2 - Postoperative characteristics and complications of patients undergoing vmPCNL (vacuum-assisted mini-percutaneous nephrolithotomy).

PARAMETER	RESULT
Postoperative Creatinine (gm/dL), mean ± SD	1.18 ± 0.33
Change in Creatinine (gm/dL), mean ± SD (postoperative - preoperative)	-0.23 ± 0.49
Total Number of postoperative complications, n (%)	99 (12.9%)
Postoperative Fever (within 48 hours), n (%)	42 (5.5%)
Postoperative SIRS/Sepsis, n (%)	22 (2.9%)
Urinoma, n (%)	11 (1.43%)
Postoperative transfusion, n (%)	18 (2.3%)
Postoperative Complications within 90 days, n (%):	
Clavien-Dindo 1	34 (4.4%)
Clavien-Dindo 2	25 (3.3%)
Clavien-Dindo 3	26 (3.4%)
Clavien-Dindo 4	12 (1.5%)
Clavien-Dindo 5	2 (0.26%)
Stone free at three months, n (%)	565 (73.7%)

to continuous suctioning, which we felt improved intraoperative visualization without compromising stone fragmentation and clearance if a steady flow of irrigation was maintained. The use of intraoperative basketing decreased as the study progressed and the team became more comfortable with the use of the ClearPetra® system. Additionally, we employed retrograde nephroscopy to visualize renal calyces in specific cases to confirm adequate stone clearance.

We noted that approximately 13% of patients in our cohort experienced a postoperative complication; most complications were Clavien-Dindo 1 (4.4% of the whole cohort). 5.16% of patients experienced a complication ≥ Clavien-Dindo 3. 2.3% required postoperative blood transfusion. Two patients in this study died after surgery (0.26%). Both patients had multiple comorbidities prior to surgery and were of advanced age (67 and 72 years respectively). One of these patients died due to sepsis, while the other died due to anesthetic complications. This mortality rate is in concordance with previously reported mortality rates of 0.2% after PCNL (8). These findings suggest that vmPCNL may not contribute to decreased mortality or transfusion rate when compared to PCNL, and thus, may only be useful in promoting SFR and lowering the incidence of IC after surgery. It is essential to identify the risk of postoperative complications prior to surgery and tailor the treatment approach to individual cases based on the probability of postoperative complications. Many studies have explored the use of the Charlson Comorbidity Index, Guy's Stone score, S.T.O.N.E. score, and other relevant perioperative variables to generate nomograms predictive of SFR and postoperative complications after PCNL (9-12). The published data surrounding this, however, seems to be contradictory, and many studies are limited by small sample sizes with no external validation. Further studies are essential to develop preoperative predictive models to assess the probability of SFR and postoperative complications after vmPCNL.

Five.five percent of patients in this study developed fever within 48 hours of vmPCNL, while 2.9% of all patients went on to develop SIRS/Sepsis. The suction effect of the vacuum sheath plays an important role in decreasing pyelo-venous backflow by decreasing IRP (13). Fewer microbes are translocated across the pelvis into the vasculature, resulting in a decreased incidence of postoperative IC. A recent study by Marmiroli et al. showed that vacuum-assisted procedures and decreased operative time were associated with a lower risk of IC in mPCNL patients, and that 30% of patients

Table 3 - Univariate and multivariate analysis of perioperative factors influencing stone-free rate at three months.

PARAMETER	UNIVARIABLE			MULTIVARIABLE	
	Stone Free at three months	Residual Stone Disease at three months	p-value	Odds Ratio (95% CI)	p-value
Age, mean ± SD	51.2 ± 15.1	46.4 ± 12.6	<0.001	1.03 (1.01 - 1.04)	<0.001
BMI, mean ± SD	29.7 ± 6.14	29.7 ± 5.81	0.96		
Sex, n (%)					
Male	316 (41.1%)	121 (15.8%)	Ref.		
Female	249 (32.5%)	81 (10.6%)	0.33		
Preoperative Creatinine, mean ± SD	1.41 ± 0.36	1.42 ± 0.39	0.69		
Preoperative Stent Placed, n (%):	279 (36.4%)	106 (13.8%)	0.45		
Lower Pole Stone, n (%):	289 (37.7%)	122 (15.9%)	0.02	1.39 (0.92 – 2.1)	0.11
Stone Burden (mm), mean ± SD	28 ± 14.8	44.9 ± 10.8	<0.001	0.39 (0.33 - 0.46)	<0.001
Stone Density, HU, n (%)					
<600	211 (27.5%)	87 (11.3%)	Ref.		
600 - 950	228 (29.7%)	72 (9.4%)	0.15		
> 950	126 (16.4%)	43 (5.6%)	0.38		
Lithotripsy time, mean ± SD	68.42 ± 37.5	70.4 ± 40.4	0.53		
Use of basket, n (%):	61 (7.95%)	0 (0%)	0.97		
Intraoperative stent placed, n (%):	377 (49.2%)	141 (18.4%)	0.42		
Postoperative Creatinine, mean ± SD	1.18 ± 0.33	1.18 ± 0.34	0.86		
Change in creatinine (postoperative - preoperative), mean ± SD	-0.23 ± 0.48	-0.24 ± 0.49	0.87		
Position, n (%)					
Prone	425 (55.4%)	166 (21.6%)	Ref.	-	
Supine	140 (18.3%)	36 (4.7%)	0.04	0.57 (0.31 - 1.05)	0.07

experience some form of IC after surgery (14). This study, however, was limited by its retrospective nature and relatively small sample size. A propensity-matched analysis by Lievore et al. noted significantly lower SFR and IC rates in the vmPCNL group when compared to mPCNL (SFR: 89.4% vs. 78.8%, Infectious complications: 7.7% vs. 25%) (15). The reporting of IC across the literature is heterogeneous and is dependent on the study population, preoperative stone characteristics, PCNL technique, postoperative antibiotic protocols, and the definitions used for these complications. While the utility of preoperative antibiotics has been well established for PCNL treatment (16, 17), further studies are required to truly ascertain the role of perioperative antibiotics in the context of vmPCNL.

Other prospective cohort studies have also explored the SFR and postoperative IC of patients undergoing vmPCNL. Zanetti et al. found that 71.3% of patients were stone-free at 1 – 3 months, while 7.4% of patients experienced fever after surgery (18). Reddy et al. noted an SFR of 77.3% of patients and a Clavien-Dindo 2 postoperative IC rate of 3.6% (19). For comparison, we noted an SFR of 73.7%, and an incidence of postoperative fever and SIRS/Sepsis of 5.3% and 2.9% respectively, thus confirming the findings of these prospective studies.

To our knowledge, three randomized controlled trials (RCTs) have compared the postoperative outcomes of the ClearPetra® system for vmPCNL (Supplementary Table-1). The study by Lai et al. had 38 patients in each arm and noted that the use of vmPCNL

Supplementary Table 1 - Randomized controlled trials comparing outcomes between conventional mini-percutaneous nephrolithotomy (mPCNL) and vacuum-assisted mini-percutaneous nephrolithotomy (vmPCNL).

AUTHOR (YEAR)	CHARACTERISTICS		NUMBER IN EACH GROUP		STONE SIZE (MM)		TRACT SIZE	STONE TREATMENT TIME		POSTOPERATIVE COMPLICATIONS		SFR DEFINITION	SFR	
	Group A	Group B	Group A	Group B	Group A	Group B		Group A	Group B	Group A	Group B		Group A	Group B
Lai et al. (2020) (20)	mPCNL	vmPCNL	38	38	20.2 ± 6.5	23.4 ± 7.3	18 Fr	70.4 ± 14.8	56.3 ± 19.8	Fever: 21.1% Transfusion: 2.7%	Fever: 13.2% Transfusion: 2.7%	Absence of residual fragments on NCCT, 30 d after surgery	86.80%	94.40%
Xu et al. (2020) (21)	mPCNL	vmPCNL	30	30	38 ± 14	42 ± 10	20 Fr	69.5 ± 29.4	54.2 ± 28.7	Grade 1: 20% Grade 2: 13.3% Grade 3: 3.3%	Grade 1: 6.6% Grade 2: 6.6% Grade 3: -	Absence of residual fragments > 4 mm on NCCT, 3 months after surgery	76.60%	90%
Liang et al. (2023) (22)	vmPCNL	mPCNL	59	58	27.7 ± 5.7	28.8 ± 5.5	18 Fr	26.9 ± 14.3	35.7 ± 11.8	Grade 1: 5.1% Grade 3: -	Grade 1: 10.3% Grade 3: 1.7%	Absence of residual fragments > 4 mm on NCCT, 1 month after surgery	96.60%	89.70%

increased SFR (94.4% in vmPCNL vs 86.8% in mPCNL) and decreased the incidence of Clavien-Dindo 2 postoperative fever (15.8% in vmPCNL vs. 21.1% in mPCNL) (20). Xu et al. explored SFR and postoperative fever rates between the two techniques in the context of staghorn calculi, with 30 patients randomized to each arm. The authors found that while vmPCNL was associated with a lower incidence of postoperative fever (6.6% vs. 20%), there was no difference in SFR at three months (21). Finally, an RCT by Liang et al. randomized 59 and 58 patients to vmPCNL and mPCNL respectively. The authors found that there was no significant difference in SFR at 30 days postoperatively. While they did note a trend of higher incidence of postoperative fever in the mPCNL group, the study had too few events to draw any meaningful conclusions from these results (22). These studies, while randomized in nature, are limited by their small numbers, and thus preclude the need for trials with larger sample sizes. The trends identified in our study may serve as a reference point for statistical powering of future RCTs.

Our study, however, has notable limitations. Firstly, given that this was a prospective single-arm study, we did not have a comparator group of patients who underwent mPCNL. Instead, we opted to focus on the surgical technique and the postoperative outcomes after vmPCNL alone. Additionally, we did not record IRP during this study and thus were not able to test the association between IRP and IC. Finally, we did not report on the antibiotic protocols used in the study as these changed over time with changes in antibiotic resistance patterns and hospital protocols at the center where the study was performed.

Despite these limitations, we believe this study is of value, as it represents the largest continuous series of patients to undergo vmPCNL. The results of this study demonstrate that vmPCNL is a safe and efficacious technique for stone clearance, with an acceptable SFR and a

low incidence of postoperative infectious complications. Stone burden is a clinically meaningful predictor of SFR in this population of patients.

CONCLUSIONS

vmPCNL is a safe and efficacious technique for stone clearance in patients with renal stone disease, due to the low incidence of serious complications, IC, and an SFR of 73.7% at three months. Stone burden is a significant predictor of SFR. 5.5% of patients experience fever after surgery, while 2.9% of patients develop SIRS/Sepsis. Further randomized studies with large sample sizes are necessary to truly ascertain the differences between vacuum-assisted and conventional approaches.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Skolarikos A, Jung H, Neisius A, Petřík A, Somani B, Tailly T. et al. EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. [Internet], Available at. <https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urolithiasis-2024.pdf>
2. Sadiq AS, Atallah W, Khusid J, Gupta M. The Surgical Technique of Mini Percutaneous Nephrolithotomy. J Endourol. 2021;35(S2):S68-S74. doi: 10.1089/end.2020.1080.
3. Sharma G, Sharma A, Devana SK, Singh SK. Mini Versus Standard Percutaneous Nephrolithotomy for the Management of Renal Stone Disease: Systematic Review and Meta-analysis of Randomized Controlled Trials. Eur Urol Focus. 2022;8:1376-85. doi: 10.1016/j.euf.2021.07.014.
4. Qin P, Zhang D, Huang T, Fang L, Cheng Y. Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis. Int Braz J Urol. 2022;48:637-48. doi: 10.1590/S1677-5538.IBJU.2021.0347.
5. Dorantes-Carrillo LA, Basulto-Martínez M, Suárez-Ibarrola R, Heinze A, Proietti S, Flores-Tapia JP, et al. Retrograde Intrarenal Surgery Versus Miniaturized Percutaneous Nephrolithotomy for Kidney Stones >1cm: A Systematic Review and Meta-analysis of Randomized Trials. Eur Urol Focus. 2022;8:259-70. doi: 10.1016/j.euf.2021.02.008.
6. Doizi S. Intrarenal Pressure: What Is Acceptable for Flexible Ureteroscopy and Percutaneous Nephrolithotomy? Eur Urol Focus. 2021;7:31-3. doi: 10.1016/j.euf.2021.01.010.
7. Tokas T, Herrmann TRW, Skolarikos A, Nagele U; Training and Research in Urological Surgery and Technology (T.R.U.S.T.)-Group. Pressure matters: intrarenal pressures during normal and pathological conditions, and impact of increased values to renal physiology. World J Urol. 2019;37:125-31. doi: 10.1007/s00345-018-2378-4.
8. Armitage JN, Withington J, van der Meulen J, Cromwell DA, Glass J, Finch WG, et al. Percutaneous nephrolithotomy in England: practice and outcomes described in the Hospital Episode Statistics database. BJU Int. 2014;113:777-82. doi: 10.1111/bju.12373.
9. Unsal A, Resorlu B, Atmaca AF, Diri A, Goktug HN, Can CE, et al. Prediction of morbidity and mortality after percutaneous nephrolithotomy by using the Charlson Comorbidity Index. Urology. 2012;79:55-60. doi: 10.1016/j.urology.2011.06.038.
10. Sahan M, Yarimoglu S, Polat S, Nart B, Koras O, Bozkurt IH, et al. A novel nomogram and a simple scoring system for urinary leakage after percutaneous nephrolithotomy. Int Braz J Urol. 2022;48:817-27. doi: 10.1590/S1677-5538.IBJU.2022.0091.
11. Shahabi A, Aali S. An insight into the Nomogram of Percutaneous Nephrolithotomy. Int Braz J Urol. 2023;49:789-90. doi: 10.1590/S1677-5538.IBJU.2023.0398.
12. Xie F, Deng S, Fei K, Xu H, Zhang H. Nomogram to predict the risk of adverse outcomes in patients with residual stones following percutaneous nephrolithotomy. Int Braz J Urol. 2023;49:599-607. doi: 10.1590/S1677-5538.IBJU.2023.0111.
13. Kreydin EI, Eisner BH. Risk factors for sepsis after percutaneous renal stone surgery. Nat Rev Urol. 2013;10:598-605. doi: 10.1038/nrurol.2013.183.

14. Marmiroli A, Nizzardo M, Zanetti SP, Lucignani G, Turetti M, Silvani C, et al. Vacuum-assisted mini-percutaneous nephrolithotomy is associated with lower rates of infectious complications compared to vacuum-cleaner procedure in patients at high risk for infections: a single-center experience. World J Urol. 2024;42:200. doi: 10.1007/s00345-024-04897-3.
15. Lievore E, Boeri L, Zanetti SP, Fulgheri I, Fontana M, Turetti M, et al. Clinical Comparison of Mini-Percutaneous Nephrolithotomy with Vacuum Cleaner Effect or with a Vacuum-Assisted Access Sheath: A Single-Center Experience. J Endourol. 2021;35:601-8. doi: 10.1089/end.2020.0555.
16. Talizin TB, Danilovic A, Torricelli FCM, Marchini GS, Batagello C, Vicentini FC, et al. Postoperative antibiotic prophylaxis for percutaneous nephrolithotomy and risk of infection: a systematic review and meta-analysis. Int Braz J Urol. 2024;50:152-63. doi: 10.1590/S1677-5538.IBJU.2023.0626.
17. Danilovic A, Talizin TB, Torricelli FCM, Marchini GS, Batagello C, Vicentini FC, et al. One week pre-operative oral antibiotics for percutaneous nephrolithotomy reduce risk of infection: a systematic review and meta-analysis. Int Braz J Urol. 2023;49:184-93. doi: 10.1590/S1677-5538.IBJU.2022.0544.
18. Zanetti SP, Lievore E, Fontana M, Turetti M, Gallioli A, Longo F, et al. Vacuum-assisted mini-percutaneous nephrolithotomy: a new perspective in fragments clearance and intrarenal pressure control. World J Urol. 2021;39:1717-23. doi: 10.1007/s00345-020-03318-5.
19. Reddy NK, Patil AP, Tak GR, Shah D, Singh AG, Ganpule AP, et al. Size Distribution of Fragments by High-power Holmium Laser Lithotripsy in MiniPCNL with Suction. Curr Urol Rep. 2021;22:64. doi: 10.1007/s11934-021-01072-8.
20. Lai D, Xu W, Chen M, He Y, Li X, Sheng M, et al. Minimally Invasive Percutaneous Nephrolithotomy with a Novel Vacuum-assisted Access Sheath for obstructive calculous pyonephrosis A Randomized Study. Urol J. 2020;17:474-9. doi: 10.22037/uj.v16i7.5577.
21. Xu G, Liang J, He Y, Li X, Yang W, Lai D, et al. Comparison of two different minimally invasive percutaneous nephrostomy sheaths for the treatment of staghorn stones. BJU Int. 2020;125:898-904. doi: 10.1111/bju.15031.
22. Liang S, Duan X, Liu J, Zhang X, Liang R, Zhao Y, et al. Vacuum-Assisted vs Conventional Minimally Invasive Percutaneous Nephrolithotomy for the Treatment of Two-to-Four-Centimeter Stones: A Multicenter Prospective and Randomized Trial. J Endourol. 2023;37:1241-7. doi: 10.1089/end.2023.0324.

Correspondence address:
Kaushik Prabhav Kolanukuduru, MD
Department of Urology,
Icahn School of Medicine at Mount Sinai
142,5 Madison Ave,
New York, NY, 10029, USA
E-mail: kaushik.kolanukuduru@mountsinai.org

ORIGINAL ARTICLE

Vol. 50 (6): 746-753, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0341

Are very thin patients at a higher risk of complications when submitted to percutaneous nephrolithotomy?

Priscila Kuriki Vieira Mota [1], Daniel Beltrame Ferreira [1], Rafael Felisberto Dias Florencio [1], David Jacques Cohen [1], Rodrigo Perrella [2], Carlos Alfredo Batagello [3], Claudio Bovolenta Murta [3], Joaquim Francisco de Almeida Claro [1], Fabio C. Vicentini [1, 3]

[1] Divisão de Urologia, Hospital Brigadeiro, São Paulo, SP, Brasil; [2] Divisão de Urologia, Hospital Militar de Área de São Paulo, São Paulo, SP, Brasil; [3] Divisão de Urologia, Hospital das Clínicas, São Paulo, SP, Brasil

ABSTRACT

Purpose: To assess the impact of thinness on the outcome of the percutaneous nephrolithotomy (PCNL).

Materials and Methods: A matched case–control study was performed using a prospectively collected database of all patients who underwent PCNL between June 2011 and October 2021. The patients were stratified into two groups according to their phenotypic characteristics, arbitrarily defined according to their body mass index (BMI): <20 kg/m^2 (Group 1, very thin patients, G<20) and ≥25 kg/m^2 (Group 2, non-thin patients, G≥25). Patients were randomly matched based on Guy's Stone Score (GSS) according to case complexity at a ratio of 1:3.

Results: A total of 204 patients were enrolled in this study: 51 patients (G<20) and 153 controls (G≥25). Complications occurred in 15.2% of the patients, with 5.4% of these complications classified as major complications (Clavien grade ≥ 3). According to complications there were no significant differences between the groups. The overall complication rates were 17.6% in the G<20 and 14.4% in the G≥25 (p = 0.653). The major complication rates were 3.9% in the G<20 and 5.8% in the G≥25 (p=0.429). No differences in transfusion or urinary fistula rates were found.

Conclusions: In this study, very thin patients were not at a higher risk of complications when submitted to PCNL than in those with a BMI of ≥25 kg/m2. Apparently, this technique can be used in these patients, just as it is used in any other type of patient, independently of their BMI.

ARTICLE INFO

Fabio Vicentini
https://orcid.org/0000-0003-3745-341X

Keywords:
Urolithiasis; Nephrolithotomy, Percutaneous; Body Mass Index

Int Braz J Urol. 2024; 50: 746-53

Submitted for publication:
June 13, 2024

Accepted after revision:
August 13, 2024

Published as Ahead of Print:
August 25, 2024

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the gold standard treatment for large renal stones, according to the American, and the European guidelines (1-3). Nephrolithiasis has been associated to obesity in several epidemiologic studies (4, 5); therefore, several studies have evaluated the impact of high body mass index (BMI) on PCNL outcomes (6-8). However, there are no data evaluating the impact of a low BMI on PCNL complications.

According to some expert opinions, very thin patients are at a greater risk due to the lower perirenal adipose tissue, the higher kidney mobility, the retro-renal position of the colon, and even the lower functional capacity, which could predispose them to a higher complication rate. Currently, there are no studies in the literature investigating the outcomes of very thin patients undergoing PCNL in terms of complications and perioperative outcomes. The hypothesis is that these patients could have an increased risk of complications and worse outcomes from PCNL compared to non-thin patients.

This study aimed to evaluate if very thin patients are at higher risk of complications when submitted to PCNL in a single tertiary center.

MATHERIALS AND METHODS

A matched case–control study was performed from June 2011 to October 2021 using a prospectively collected database of all patients who underwent PCNL. Informed consent was obtained from the patients, and the study protocol was approved by the local ethics committee (Institutional Review Board number: IRB: 8258117.8.0000.0091).

The patients were stratified according to their phenotypic characteristics, in two groups: very thin patients, arbitrarily defined as having BMI less than 20 kg/m2 (G<20) and non-thin patients, also arbitrarily defined as having a BMI equal or higher than 25 kg/m2 (Control group or G>25), in order to have two distinct groups regarding thinness. Patients were randomly matched based on Guy's Stone Score (GSS) according to case complexity at a ratio of 1:3.

The inclusion criteria were patients over 18 years old, with single or multiple renal stones >2 cm in size and symptomatic stones <2 cm in size, wherein first-line techniques (shockwave lithotripsy and ureteroscopy) failed. Patients excluded included pregnant women, patients with congenital or skeletal abnormalities, patients with refractory urinary tract infection, patients with coagulopathies, and those who refused to be included in the study. All patients underwent non-contrast computed tomography (CT) at least 6 months before the surgical procedure. Demographic data (age, gender, BMI, ASA score, and GSS) were analyzed. The GSS (9), routinely evaluated in all cases, was determined by a urologist during the preoperative consultation by CT scan analysis and was confirmed immediately before surgery. All urologists were trained in GSS, a nephrolithometry score known for its rapid application and reliable prediction of PCNL outcomes, compared to other nephrolithometry scores and nomograms (10-12). The intra- and post-operative data analyzed were operative time (defined as the time from cystoscopy until kidney drainage), fluoroscopy time, transfusion rates (intraoperatively and until discharge), tubeless approach (yes/no), complication rates, and length of hospital stay. The immediate success rate was defined as the absence of residual fragments >4 mm on CT scan performed in the first postoperative day (POD1). Complications were classified according to the Clavien-modified system, and complications with scores of ≥3 points were considered major complications (12).

Surgical technique

All patients received general anesthesia during the procedure. The surgical technique was similar in all cases. Patients were placed in the prone or supine position, according to surgeons' preference. A 6-Fr ureteral catheter was inserted through cystoscopy. After retrograde pyelography, the selected calyx was punctured under fluoroscopy guidance. Puncture was performed using an 18-gauge needle

and a hydrophilic guidewire was inserted and passed through the ureter.

In cases in which multiple tracts were planned, all punctures and guidewire placements were performed prior to tract dilation. The tract was dilated using fascial dilators, and a 30 Fr Amplatz sheath was placed in all cases. A 26 Fr nephroscope (Karl Storz Germany®) and an ultrasonic device (Lithoclast Master, EMS®) were used for navigation and lithotripsy. An 18 Fr nephrostomy tube was placed at the end of the procedure in cases of bleeding, residual stones, renal pelvis perforation, or multiple accesses. In the absence of these findings, a double-J stent was placed for 2 weeks. The operation time was recorded from the beginning of cystoscopy to the end of nephrostomy tube placement or stent placement.

Statistical analysis

Software R Core 3.5.1 was used for statistical analysis. Continuous variables were described by mean and standard deviations and were compared using Student's t-test. Categorical variables were described by simple and relative frequencies and were compared using the chi-square and Fisher's exact tests. Statistical significance was set at 0.05.

RESULTS

A total of 204 patients were enrolled in this study: 51 patients (G<20) and 153 controls (G≥25). The median BMI was 27.23±2.81 Kg/m2, and the median age was 50.51±13.33 years. Complex stones (GSS 3 or 4) were 66.66% of the cases. The groups were similar according to demographic characteristics, being the BMI the only difference between the groups. The mean BMI was 18.43±1.03 Kg/m^2 for G<20 and 30.29±4.60 Kg/m^2 for G≥25, (p<0.001) (Table-1).

Regarding operative variables, there were no statistically significant differences in the success rates, number of renal accesses, upper pole access, or operative time (Table-2).

Complications were observed in 15.2% of the patients. Among the complications, 5.4% were major complications. There were no significant differences between the groups according to complications; overall complication rates were 17.6% and 14.4% in the G<20 and G≥25 groups, respectively (p=0.653), and major complications rates were 3.9% for G<20 and 5.8% for G≥25 (p=0.429). No differences in transfusion or urinary fistula rates were found (Table-3).

DISCUSSION

Urolithiasis is one of the most common urological diseases and a frequent cause of morbidity and impaired quality of life worldwide (13). The management of urolithiasis has changed dramatically over the last three decades with the emergence of new technologies in endourology (2, 14, 15).

Obesity is a risk factor for the development of urinary stones, the role of a high BMI in treatment modalities for urolithiasis has been studied (7, 13, 16). The impact of obesity on PCNL does not seem to be important, since studies have shown that prone PCNL in normal-weight, obese, and super-obese individuals have similar outcomes (17, 18). In a publication of the CROES Percutaneous Nephrolithotomy Global Study a longer operation time, an inferior stone-free rate, and a higher re-intervention rate in obese patients were reported (19), however, this study did not standardize the PCNL technique. Ferreira et al. found no difference in outcomes and postoperative complications between obese and nonobese individuals who underwent a complete supine PCNL (8).

Conversely, there have been no comparative studies on how thinness may impact PCNL outcomes. Some endourologists have expressed concerns regarding PCNL in very thin patients, as they could carry a higher chance of complications due to difficult access linked to increased kidney mobility or a lack of perirenal fat. This could lead to poorer entrance orifice occlusion and, consequently, higher rates of bleeding or fistula formation. To the best of our knowledge, this is the first study to evaluate the impact of thinness on PCNL complications. We compared the data of 204 patients who underwent PCNL matched based on GSS at a ratio of 3:1. We arbitrari-

Table 1 - Characteristics and demographic variables.

	G<20	G≥25	*P* value
	(n = 51)	(n = 153)	
Gender; n (%)			
Male	23 (45.1)	61 (39.9)	0.516
Female	28 (54.9)	92 (60.1)	
Age (years)			
Mean (SD)	44.7 ± 14.4	49.6 ± 12.2	0.066
BMI (kg/m²)			
Mean (SD)	18.4 ± 1.1	30.3 ± 4.6	<0.001
ASA Score; n (%)			
I	23 (45.1)	42 (27.4)	0.473
II	21 (41.2)	93 (60.8)	
III	7 (13.7)	18 (11.8)	
GSS; n (%)			
1	9 (17.7)	27 (17.7)	
2	8 (15.7)	24 (15.7)	
3	17 (33.3)	51 (33.3)	
4	17 (33.3)	51 (33.3)	
Stone size (mm); mean (SD)	26.7 ± 15.1	27.2 ± 13.7	0.239

Data are presented as median (first quartile, third quartile) or number (proportion).
SD = standard deviation; BMI = body mass index; ASA = American Society of Anesthesiologists; GSS = Guy's stone score; HU: Hounsfield unit

ly selected BMI values of <20 based on the group's experience in visually classifying these patients as thin and associating this phenotype with a greater chance of complications. Conversely, patients with a BMI of ≥25 were visually classified as definitely non-thin, representing a different group from those with a BMI of <20, where potential surgical difficulties would not be encountered. All patients underwent a CT scan both before and after surgery, allowing surgeons to reliably evaluate their stone-free status and complications.

In the present study, the overall complication rate was low and not significantly different between thin and non-thin groups (17.6% and 14.4%, respectively, p=0.653), and major complications were predominant in the control group (40.9%, p=0.429). There was, also, no significant difference in the immediate success rate between the two groups (37.3% vs. 34.0%, p=0.735). A stone size of ≤4 mm was used as the threshold to determine immediate success. It has been found to be a cost-effective threshold for the management of patients with residual fragments after PCNL (20). A POD1 CT scan ensured a high level of imaging accuracy. Vicentini et al., in a large descriptive study validating GSS involving more than 1,000 PCNL procedures, reported that the stone-free rate was inversely proportional to stone complexity, with GSS grades 1, 2, 3, and 4 having stone-free rates of 85%, 60%, 45%, and 25%, respectively (21). The high number of complex stones in our series (approx-

Table 2 - Operative variables.

	G<20	G≥25	*P* value
	(n = 51)	(n = 153)	
Operative time (min); mean (SD)	120.4 ± 46.6	121.21 ± 51.1	0.925
Number of accesses; n (%)			
1	35 (68.6)	108 (70.6)	0.699
2	13 (25.5)	32 (20.9)	
3 or more	3 (5.9)	13 (8.5)	
Upper calyx access			
n (%)	9 (17.6)	32 (20.9)	0.690
Fluoroscopy time (min)			
Mean ± SD	14.92 (9.47)	14.42 (7.55)	0.735
Tubeless			
n (%)	12 (23.5)	25 (16.3)	0.294
Hospital stay (hour)			
Mean ± SD	67.53 (82.19)	63.90 (59.77)	0.772
Overall success rate; n (%)	19 (37.3)	52 (34)	0.735

Data are presented as median (first quartile, third quartile) or number (proportion).
SD = standard deviation

Table 3 - Intra- and post-operative complications.

	G<20	G≥25	*P* value
	(n = 51)	(n = 153)	
Overall complication rate; n (%)	9 (17.6)	22 (14.4)	0.653
Major complication rate; n (%)	2 (3.9)	9 (5.8)	0.429
Type of complication; n (%)			
Severe bleeding (transfusion)	2 (3.9)	8 (5.2)	0.728
Urinary tract infection	1 (1.9)	5 (3.2)	
Tract leakage (persistent fistula)	1 (1.9)	2 (1.3)	
Pain	2 (3.9)	3 (1.9)	
Stone migration to ureter	0 (0)	2 (1.3)	
Acute kidney injury	1 (1.9)	1 (0.6)	
Pleural injury	0 (0)	1 (0.6)	
Bronchospasm	0 (0)	1 (0.6)	
Hydrothorax	1 (1.9)	0 (0)	

Data are presented as number (proportion).
SD = standard deviation.

imately 66% GSS of 3 and 4) is consistent with the observed stone-free rates in our patients (22).

Certain aspects may differ between thin and obese patients who have undergone PCNL. Based on our experience, we advocate for specialized care for this group of patients. Kidney movement during puncture seems to be more pronounced when patients are in a supine position, and it is not uncommon to manually stabilize the kidney while dilating it by applying pressure to the medial side with the hand not holding the needle. A smaller sheath caliber appears to be more suitable for these patients, as they typically have a lower total blood volume. Using a sheath caliber greater than 24 Fr is associated with a more significant decrease in hemoglobin levels (23). In these patients, it is important to have the sheath adequately inserted inside the calyx to avoid perirenal liquid leakage due to lack of fat for blockage (24). Nephrostomy tubes do not seem to avoid fistula, and it is not indicated as usual for any patient.

Our study has some limitations. First, this was a retrospective study, despite the database being collected prospectively, and a matched-paired comparison was performed to decrease confounders. Second, the number of enrolled patients was relatively small to draw strong conclusions. At the time of the study, miniaturized PCNL, endoscopic combined intrarenal surgery or ultrasound-guided puncture were not routinely performed at our institution, and some endpoints could be different today, reducing bleeding complications and the fluoroscopy time (23, 25, 26). In this study a 30 Fr accesses were performed for the use of a 26 Fr nephroscope.

Until more studies with a higher number of enrolled patients are available, our study does not support the impression that thinness has a negative impact on the PCNL outcomes.

CONCLUSIONS

Thinness (BMI less than 20 kg/m^2) was not associated with higher complication rates in patients who underwent PCNL compared to those with a BMI of 25 kg/m^2 or more. This technique appears to be safely applicable in very thin patients.

ABBREVIATIONS

PCNL = Percutaneous nephrolithotomy
BMI = Body Mass Index
G<20 = Very thin patients, body mass index <20 kg/m^2
G≥25 = Non-thin patients, body mass index ≥25 kg/m2
GSS = Guy´s Stone Score
ASA = Anesthesiologists physical status classification
CT = Computed tomography
POD1 = First postoperative day

COMPLIANCE WITH ETHICAL STANDARDS

Data sharing policy
REDCap® software.

Ethical approval

All procedures performed in the study were in accordance with the ethical standards of the local research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent

Informed consent was obtained from patients.

Availability of data and material

All data are filed in a database (REDCap® software).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82. doi: 10.1016/j.eururo.2015.07.041.
2. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016;196:1153-60. doi: 10.1016/j.juro.2016.05.090.
3. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10:257-9. doi: 10.1080/21681805.1976.11882084.
4. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293:455-62. doi: 10.1001/jama.293.4.455.
5. Taylor EN, Stampfer MJ, Mount DB, Curhan GC. DASH-style diet and 24-hour urine composition. Clin J Am Soc Nephrol. 2010;5:2315-22. doi: 10.2215/CJN.04420510.
6. Vicentini FC, Perrella R, Souza VMG, Hisano M, Murta CB, Claro JFA. Impact of patient position on the outcomes of percutaneous neprolithotomy for complex kidney stones. Int Braz J Urol. 2018;44:965-971. doi: 10.1590/S1677-5538.IBJU.2018.0163.
7. Melo PAS, Vicentini FC, Perrella R, Murta CB, Claro JFA. Comparative study of percutaneous nephrolithotomy performed in the traditional prone position and in three different supine positions. Int Braz J Urol. 2019;45:108-117. doi: 10.1590/S1677-5538.IBJU.2018.0191.
8. Ferreira TAC, Dutra MMG, Vicentini FC, Szwarc M, Mota PKV, Eisner B, et al. Impact of Obesity on Outcomes of Supine Percutaneous Nephrolithotomy. J Endourol. 2020;34:1219-22. doi: 10.1089/end.2020.0576.
9. Thomas K, Smith NC, Hegarty N, Glass JM. The Guy's stone score--grading the complexity of percutaneous nephrolithotomy procedures. Urology. 2011;78:277-81. doi: 10.1016/j.urology.2010.12.026.
10. Vicentini FC, Serzedello FR, Thomas K, Marchini GS, Torricelli FCM, Srougi M, et al. What is the quickest scoring system to predict percutaneous nephrolithotomy outcomes? A comparative study among S.T.O.N.E score, guy's stone score and croes nomogram. Int Braz J Urol. 2017;43:1102-9. doi: 10.1590/S1677-5538.IBJU.2016.0586.
11. Xie F, Deng S, Fei K, Xu H, Zhang H. Nomogram to predict the risk of adverse outcomes in patients with residual stones following percutaneous nephrolithotomy. Int Braz J Urol. 2023;49:599-607. doi: 10.1590/S1677-5538.IBJU.2023.0111.
12. Shahabi A, Aali S. An insight into the Nomogram of Percutaneous Nephrolithotomy. Int Braz J Urol. 2023;49:789-90. doi: 10.1590/S1677-5538.IBJU.2023.0398.
13. de la Rosette JJ, Zuazu JR, Tsakiris P, Elsakka AM, Zudaire JJ, Laguna MP, et al. Prognostic factors and percutaneous nephrolithotomy morbidity: a multivariate analysis of a contemporary series using the Clavien classification. J Urol. 2008;180:2489-93. doi: 10.1016/j.juro.2008.08.025.
14. Seike K, Ishida T, Taniguchi T, Fujimoto S, Kato D, Takai M, et al. Low Body Mass Index as a Predictive Factor for Postoperative Infectious Complications after Ureterorenoscopic Lithotripsy. Medicina (Kaunas). 2021;57:1100. doi: 10.3390/medicina57101100.
15. Skolarikos A. Medical treatment of urinary stones. Curr Opin Urol. 2018;28:403-7. doi: 10.1097/MOU.0000000000000523.
16. Ozgor F, Sahan M, Cubuk A, Ortac M, Ayranci A, Sarilar O. Factors affecting infectious complications following flexible ureterorenoscopy. Urolithiasis. 2019;47:481-6. doi: 10.1007/s00240-018-1098-y.
17. Trinchieri A, Croppi E, Montanari E. Obesity and urolithiasis: evidence of regional influences. Urolithiasis. 2017;45:271-8. doi: 10.1007/s00240-016-0908-3.
18. Zhou X, Sun X, Chen X, Gong X, Yang Y, Chen C, et al. Effect of Obesity on Outcomes of Percutaneous Nephrolithotomy in Renal Stone Management: A Systematic Review and Meta-Analysis. Urol Int. 2017;98:382-90. doi: 10.1159/000455162.
19. Dauw CA, Borofsky MS, York N, Lingeman JE. Percutaneous Nephrolithotomy in the Superobese: A Comparison of Outcomes Based on Body Mass Index. J Endourol. 2016;30:987-91. doi: 10.1089/end.2016.0437.
20. Fuller A, Razvi H, Denstedt JD, Nott L, Pearle M, Cauda F, et al. The CROES percutaneous nephrolithotomy global study: the influence of body mass index on outcome. J Urol. 2012;188:138-44. doi: 10.1016/j.juro.2012.03.013.

21. Raman JD, Bagrodia A, Bensalah K, Pearle MS, Lotan Y. Residual fragments after percutaneous nephrolithotomy: cost comparison of immediate second look flexible nephroscopy versus expectant management. J Urol. 2010;183:188-93. doi: 10.1016/j.juro.2009.08.135.
22. Vicentini FC, Marchini GS, Mazzucchi E, Claro JF, Srougi M. Utility of the Guy's stone score based on computed tomographic scan findings for predicting percutaneous nephrolithotomy outcomes. Urology. 2014;83:1248-53. doi: 10.1016/j.urology.2013.12.041.
23. de Souza Melo PA, Vicentini FC, Beraldi AA, Hisano M, Murta CB, de Almeida Claro JF. Outcomes of more than 1 000 percutaneous nephrolithotomies and validation of Guy's stone score. BJU Int. 2018;121:640-6. doi: 10.1111/bju.14129.
24. Qin P, Zhang D, Huang T, Fang L, Cheng Y. Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis. Int Braz J Urol. 2022;48:637-48. doi: 10.1590/S1677-5538.IBJU.2021.0347.
25. Sahan M, Yarimoglu S, Polat S, Nart B, Koras O, Bozkurt IH, et al. A novel nomogram and a simple scoring system for urinary leakage after percutaneous nephrolithotomy. Int Braz J Urol. 2022;48:817-27. doi: 10.1590/S1677-5538.IBJU.2022.0091.
26. Marchini GS, Lima FS, Campos MEC, Maroccolo MVO, Reggio E, Mazzucchi E, et al. Modified biplanar (0-90°) endoscopic-guided puncture technique for percutaneous nephrolithtomy: refinement with endoscopic combined intrarrenal surgery to reduce fluoroscopy and operative time. Int Braz J Urol. 2023;49:785-6. doi: 10.1590/S1677-5538.IBJU.2023.0346.

Correspondence address:
Priscila Kuriki Vieira Mota, MD, PhD
Divisão de Urologia, Hospital Brigadeiro
Av. Brigadeiro Luís Antônio, 2651
São Paulo, SP, 01401-901, Brasil
Telephone: +55 11 99434-2731
E-mail: prikuriki@yahoo.com.br

ORIGINAL ARTICLE

Vol. 50 (6): 754-763, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0458

First impressions of Telesurgery robotic-assisted radical prostatectomy using the Edge medical robotic platform

Marcio Covas Moschovas [1, 2], Travis Rogers [1], Wanhai Xu [3], Roshane Perera [1], Xu Zhang [3], Vipul Patel [1, 2]

[1] AdventHealth Global Robotics Institute, Florida, USA; 2 University of Central Florida - UCF, Florida, USA; 3 Chinese PLA General Hospital, Beijing, China

ABSTRACT

Purpose: We reported, as a referral center in prostate cancer, our perspectives and experience performing Telesurgery using robotic surgery and 5G network.

Material and methods: We described and illustrated the Telesurgery applications and outcomes to treat a patient with prostate cancer located 1300 kilometers away from the surgeon (Beijing-Harbin) in China. We used the Edge Medical Robot (MP1000) in November 2023 in a 71-year-old patient with Gleason 6 (ISUP 1) in 8 cores from 13, PSA of 14 ng/dL, and clinical stage cT2a. MRI described a PIRADS 5 nodule on the left peripheral zone at the base, and 20gr prostate. We described details about the connection between centers, perioperative outcomes, and our perspectives as a referral center in prostate cancer.

Results: We had no delays, or problems with network connection between the centers. The procedure was performed in 60 minutes, with no intra- or postoperative complications. Estimated blood loss was 100 mL. The patient was ambulating soon after anesthesia recovery. Final pathology described a Gleason 6 (ISUP 1) involving the left base and left seminal vesicle, negative surgical margins, and no lymph node involvement (pT3bN0). The patient was continent soon after catheter removal (7 days).

Conclusion: As technological progress introduced novel robotic platforms and high-speed networks, the concept of Telesurgery became a tangible reality while 5G technology solved latency and transmission concerns. However, with these advancements, ethical considerations and regulatory frameworks should underline the importance of transparency and patient safety with responsible innovation in the field.

ARTICLE INFO

Marcio Covas Moschovas
https://orcid.org/0000-0002-3290-7323

Keywords:
Minimally Invasive Surgical Procedures; Robotic Surgical Procedures; Inventions

Int Braz J Urol. 2024; 50: 754-63

Submitted for publication:
August 08, 2024

Accepted after revision:
August 12, 2024

Published as Ahead of Print:
August 25, 2024

INTRODUCTION

In the relentless pursuit of medical and technological progress, the field of surgery has undergone a profound transition, transcending the confines of traditional operating rooms and approximating surgeons and patients from different cities and continents (1). In this scenario, Telesurgery appears as an innovative association between medicine and technology that has rewritten the history of surgical practice (2). From its landmark start with the first transatlantic procedure in 2001, where a surgeon in New York operated on a patient in Strasbourg ("Lindberg operation"), Telesurgery has become a symbol of the remarkable synergy between human expertise and digital precision (1, 3, 4). However, it was only in the last few years that a fusion of robotic surgery and a high-quality internet network enabled the expansion of Telesurgery (5–7).

Since the "Lindberg operation" that paved the way for transcontinental surgical interventions to the latest communication advancements with the 5G network, geographical limitations have been modified while we navigate through the historical landscape that redefines the current status of Telesurgery (8). In the past three years, several groups have described different long-distance procedures in animal models and humans with optimal rates of success (9, 10).

Telesurgery brings tremendous humanitarian potential to underserved areas with restricted access to surgical specialties (11). With this technology, patients can be treated by an expert located thousands of kilometers away, and the same surgeon can operate on patients from different cities or countries on the same day. In this scenario, after having experience with several robotic platforms (12,13), we described our perspectives and experience performing a robotic-assisted radical prostatectomy using Telesurgery with the Edge robot.

MATERIAL AND METHODS

We performed a Telesurgery robotic-assisted radical prostatectomy on a 71-year-old patient with Gleason 6 (ISUP 1) in 8 cores from 13, PSA of 14 ng/dL, and clinical stage cT2a. MRI described a PIRADS 5 nodule on the left peripheral zone at the base, and 20gr prostate. We described details about the connection between centers, perioperative outcomes, and our perspectives as a referral center in prostate cancer.

Network technology and data management

In Telesurgery, network technology is essential to guarantee the feasibility and success of the surgical procedure. The data transmission is performed with 4G or 5G internet technology with or without exclusive optical fiber (wired transmission) support as a backup in case of issues with the Wi-Fi connection (14, 15). In this scenario, several variables are monitored during the procedure while the remote surgeon is operating. Every 2 minutes, the roundtrip network latency is calculated to ensure the transmission quality because, usually, delays higher than 100 to 300ms could compromise the synchrony between surgeon and remote patient (16). Round trip latency refers to the time it takes for data to travel from the remote operating console to the surgical site and back, encompassing the entire communication cycle. In Telesurgery, where precision and real-time response are imperative, understanding and minimizing roundtrip latency becomes vital.

Time-to-live (TTL) represents the duration or maximum number of hops a data packet can undertake before being discarded. This parameter plays a pivotal role in maintaining the integrity and efficiency of communication between the surgical site and the remote operating console. In this context, understanding the significance of TTL becomes essential for protecting the information flow and ultimately ensuring the success and precision of remote surgical interventions.

Frame loss (expressed in dB/km or dB/m) is another crucial parameter to establish the performance of an optical fiber. In a machine vision system, the main consideration is to guarantee the stable and swift transmission of each frame's image to the computer equipment. However, due to frequent issues arising from inadequate hardware and software com-

patibility, image data loss, commonly called dropped frames (Frame loss), occurs during transmission. This frame loss manifests as abnormal data processing, display results freezing, and image faults.

In our experience, the connection between Beijing (Chinese PLA General Hospital) and Harbin (Harbin Medical University Cancer Hospital) used a 5G network and OTN (optical transport network) dedicated line with low latency, large bandwidth, high reliability, and high security.

Robotic platform and surgical technique

In addition to the transmission technology, a robotic platform able to connect and perform Telesurgery is also needed. We used the Edge Medical robotic platform MP1000 (Shenzhen Edge Medical Co., Ltd., Shenzhen, China), a multiport platform composed of four arms attached to a single tower (Figure-1) (17).

The trocar placement followed a conventional multiport position with four robotic trocars and two additional trocars for the assistant (Figure-2). This platform provides three instruments with 8mm and a 3D endoscope with 8mm. After placing the trocars, the robot is docked (Figure-3), the instruments are placed (Scissors, Prograsp, and Maryland), and the procedure follows our conventional robotic-assisted radical prostatectomy technique (18–23) with the following sequence:

1. Bladder detachment
2. Anterior Bladder neck dissection
3. Posterior Bladder neck dissection
4. Seminal vesicles control with athermal technique and Hem-o-lok clips
5. Posterior prostate dissection and nerve-sparing between Denonvilliers layers
6. Lateral prostate dissection communicating lateral and posterior planes of the prostate
7. Prostate arterial pedicle control with Hem-o-lok clips

Figure 1 - Edge robot console and multiport patient cart.

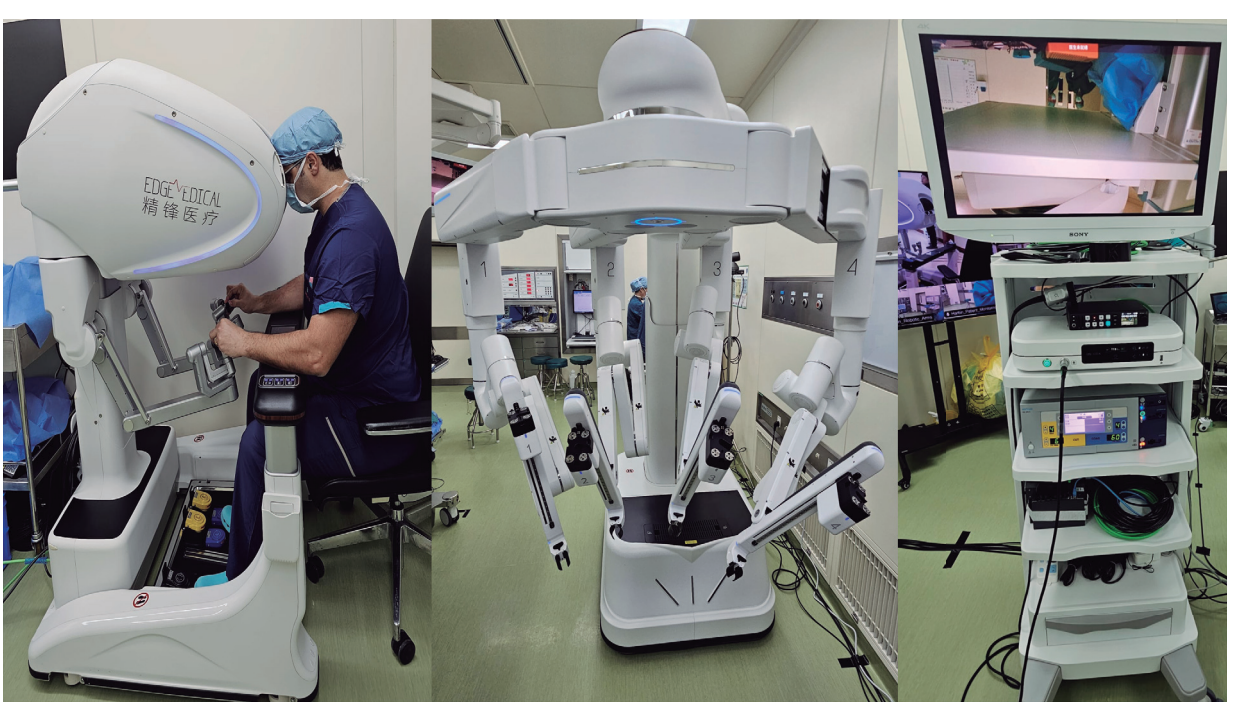


Figure 2 - Trocar placement.

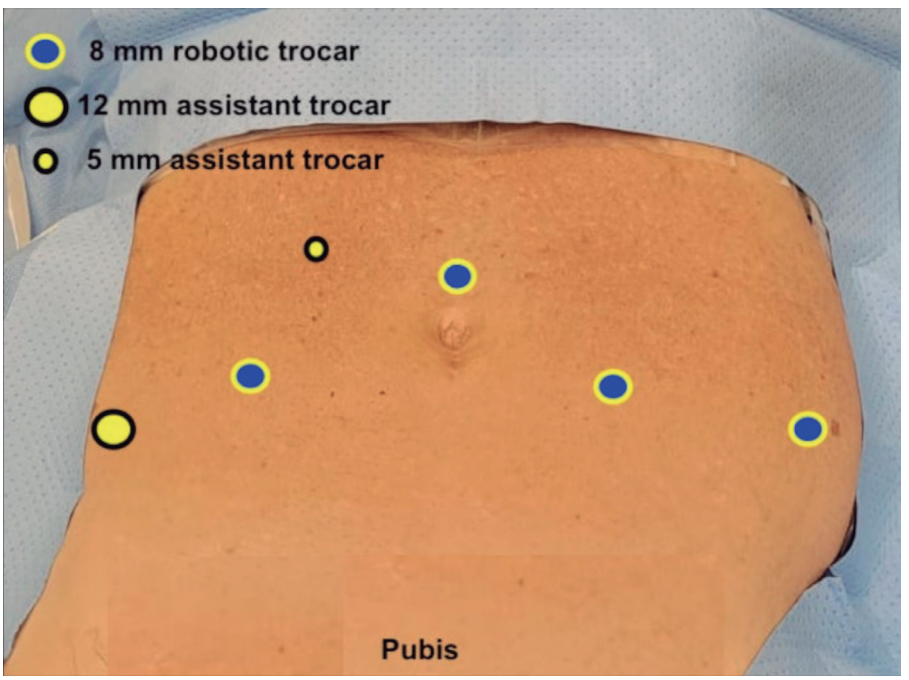
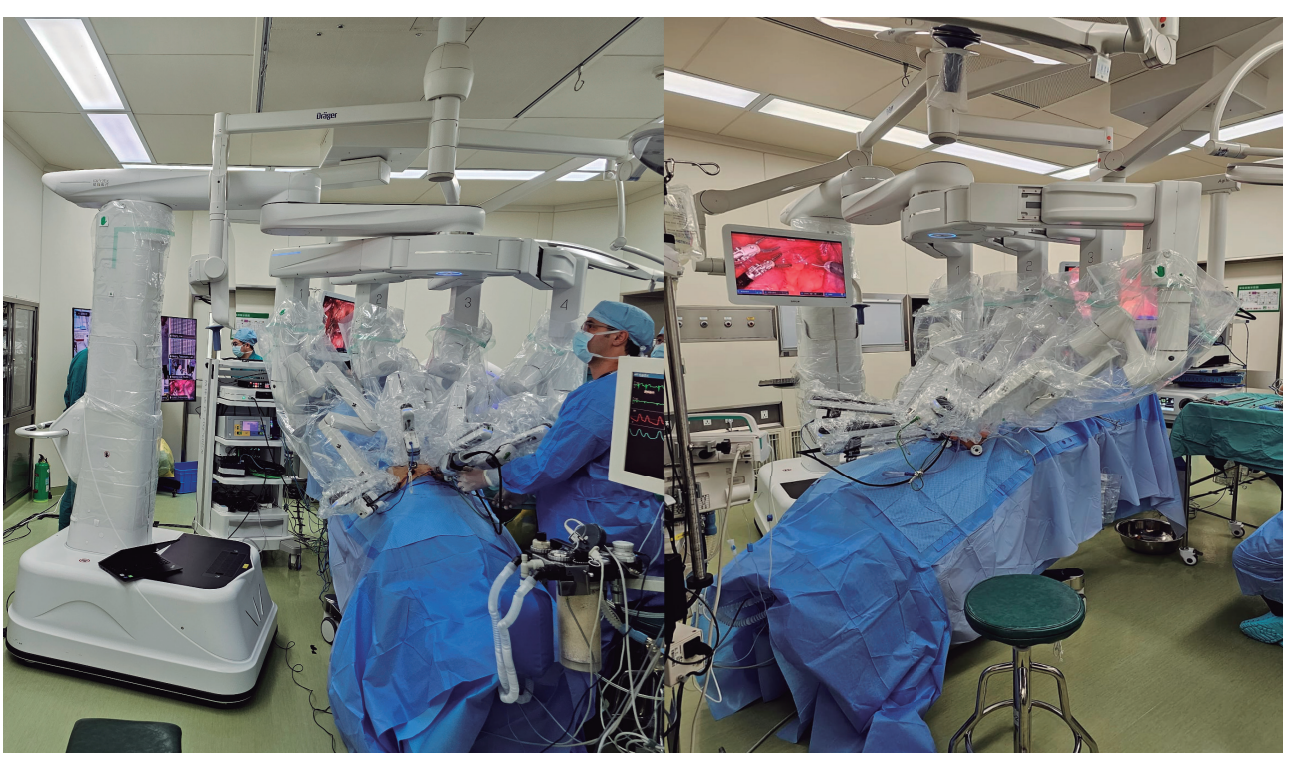


Figure 3 - Operation Room setup during surgery.



8. Minimal Apical Dissection and DVC control with running suture
9. Urethra division and hemostasis
10. Posterior reconstruction (Rocco's stitch) and Anastomosis with barbed suture
11. Pelvic Lymph node dissection

Telesurgery Logistics between centers

We performed a robotic-assisted radical prostatectomy between Beijing (Chinese PLA General Hospital) and Harbin (Harbin Medical University Cancer Hospital). All telesurgery procedures are approved by the Institutional review board and administrative bodies of both centers involved in the patient care. The patient was located in Harbin, while the main surgeon was in Beijing, approximately 1300 kilometers away.

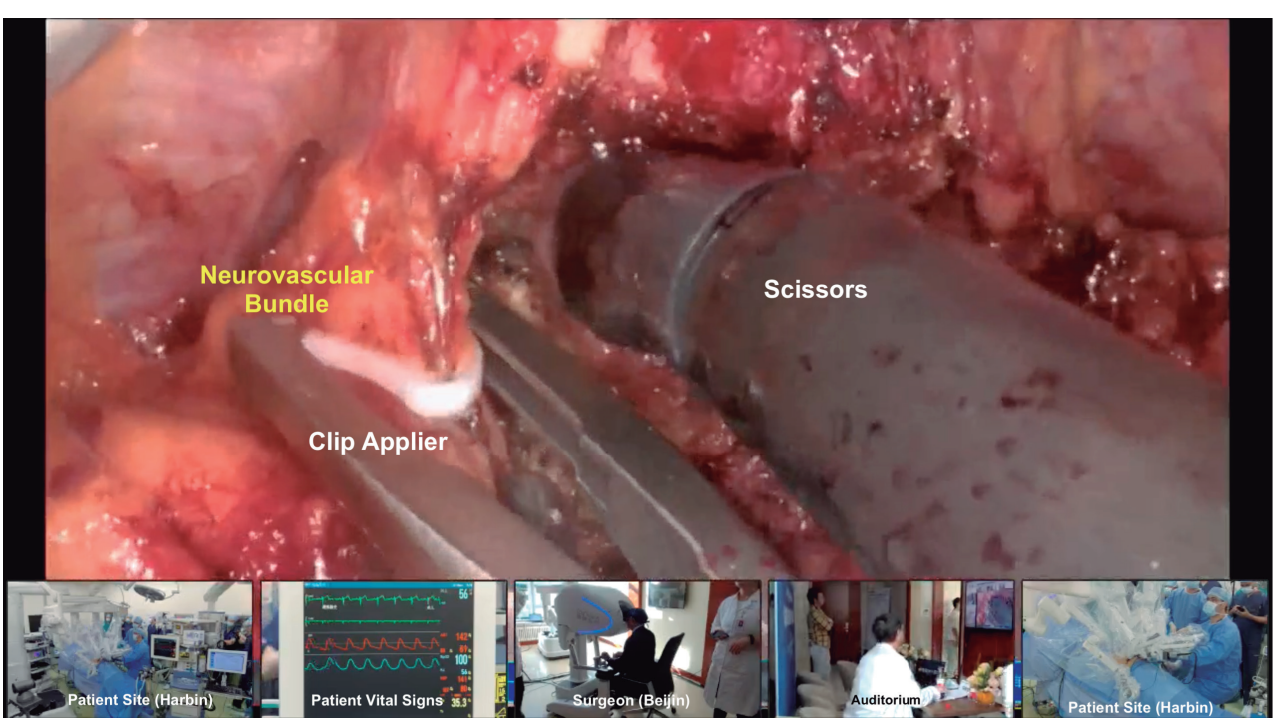
It is important to note that, on the patient side of the transmission, the tableside assistant was also an expert robotic surgeon (MCM) who would finish the procedure in case of any transmission issues. This is crucial to guarantee patient security and optimal outcomes in case of technological problems during the surgery, especially during the implementation of Telesurgery. The imaging and audio communication between both surgeons is smoothly performed like a conventional robotic surgery, with a microphone and speakers on the surgeon's console and assistant's room. We had no pertinent delays in the data transmission; audio and video were not compromised at any moment of the surgery. During the broadcast, we had cameras filming the surgeon, patient, vital signs monitor, and staff from both centers (Figure-4).

RESULTS

Patient demography and perioperative data

The digital rectal exam described a T2a on the left side. The patient had a preoperative MRI showing a PIRADS 5 lesion on the left apex and mid

Figure 4 - Transmission setup showing surgeon, remote team with the patient, patient vital signs, and auditorium.



(Peripheral zone). The procedure was performed in 60 minutes with no intra- or postoperative complications and an estimated blood loss of 100 mL. The patient was ambulating soon after anesthesia recovery (approximately 4 hours after surgery). However, he stayed in the hospital for four days due to the postoperative routine of the local team. The Foley catheter was removed seven days after surgery, and the patient was continent soon after catheter removal. We define continence as the full capacity to hold the urine (no use of pads) after removing the catheter.

Final pathology described a Gleason 6 (ISUP 1) involving the left seminal vesicle, negative surgical margins, and no lymph node involvement (pT3bN0).

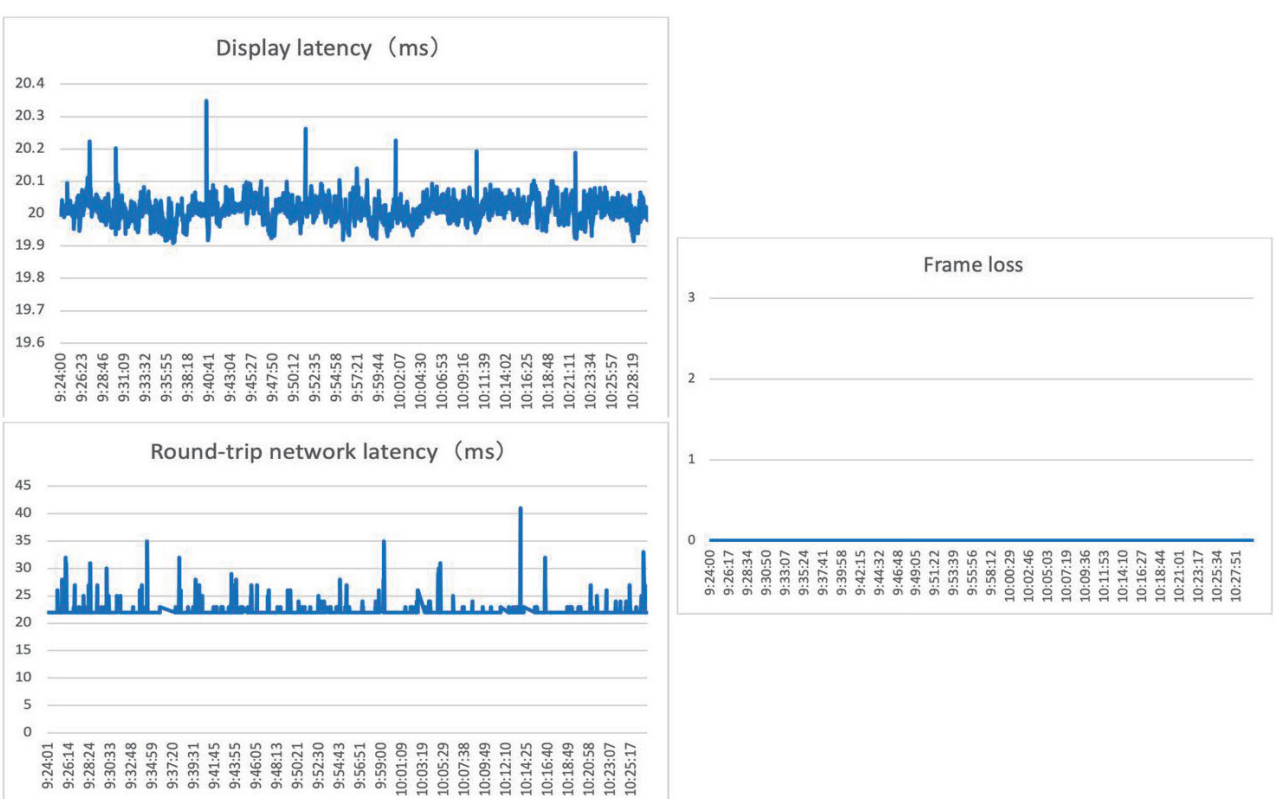
Data transmission and network details

The network was collected as the median value and interquartile range (IQR) of transmission data. The Roundtrip network latency was 22 (22-22) milliseconds, Time to Live (TTL) was 64 (64-64) bits, and no Frame Loss in decibels per kilometer (dB/km) was recorded. Figure-5 illustrates a graphical analysis of these variables.

DISCUSSION

The current scenario of Telesurgery integrates medical expertise and advanced robotic and telecommunication technology, with many advantages that have reshaped the landscape of surgical practice (2). One of its primary merits lies in the democratization of specialized surgical care, as it allows skilled surgeons to perform procedures remotely, overcoming geographical barriers and extending their reach to underserved or remote regions. This not only enhances accessibility but also facilitates timely interventions, particularly in emergencies. Additionally, Telesurgery contributes to the globalization

Figure 5 - Connection details showing the Display Latency, Frame loss, and Round-trip network latency.



of medical expertise, enabling collaboration between renowned surgeons in challenging cases, regardless of their physical locations (24). The precision and dexterity of robotic systems utilized in Telesurgery enhance the surgeon's capabilities, improving patient outcomes and minimizing the invasiveness of procedures. Moreover, the technology facilitates real-time consultation and guidance, promoting continuous learning and skill development within the medical community. As Telesurgery continues to evolve, its advantages promise to transform the traditional paradigms of surgery, making specialized care more accessible, efficient, and globally interconnected.

We described our initial Telesurgery experience in patients undergoing robotic-assisted radical prostatectomy. After years of using robotic technology to operate on patients in the Urology field, our first impression of remote surgery was very optimistic. Initially, our major concern was the potential surgery transmission and communication issues between both centers 1300 km apart. Therefore, to assist with the procedure, we sent an experienced robotic surgeon from our team to the patient site who was able to finish the surgery locally in case of any technical problems. However, in our experience, we could not detect transmission delays or any technological issues that could compromise the patient's care and the optimal quality of the surgery. At all times, even in specific moments that need synchrony between surgeon and assistant, such as prostate pedicle clipping, we could perform our surgical technique and communicate in the same way we do in our robotic surgery routine without imagining our audio issues.

This synchrony of audio and video between the console and the robotic platform is only possible with optimal connection provided by the 5G, optic fiber, or both combined (2, 25). Telesurgery transmission is a pivotal component in remote surgical interventions, where fast communication between the surgical site and the remote operating console is essential. The transmission process involves real-time data exchange over a network, including high-definition images and vital surgical information. The reliability and efficiency of this data transfer are critical for ensuring the precision and success of telesurgery procedures. Time to Live (TTL) plays a crucial role in selecting the duration or maximum number of hops a data packet can undergo before potential loss. Round trip latency, encompassing the time taken for data to travel from the remote console to the surgical site and back, directly influences the responsiveness and real-time nature of the surgical interaction. The continuous advancement of technology in telesurgery transmission not only addresses these challenges but also holds the promise of further optimizing the remote surgical experience, pushing the boundaries of what is achievable in remote surgical routine.

During the Telesurgery implementation, learning phase, and maintenance, we believe designing a surgical program focused on patient safety and ethical standards is crucial. As we navigate this new technological approach, we should avoid potential negative impacts on the patient's safety and operative outcomes. Therefore, we believe the first step is to provide a local team that is proficient in robotic surgery and can place the trocars, dock the robot, insert the instruments, and even finish the surgery in case of connection issues with the main surgeon. In addition, in some cases of patients with previous surgeries and bowel adhesions, the local team should have the expertise to perform the lysis of adhesions before placing the trocars. Therefore, in the current Telesurgery stage, we still need considerable training and expertise from the local team side of transmissions to provide optimal patient care.

It is crucial to acknowledge that, before performing the case, extensive preoperative testing ensured optimal connectivity. Successful telesurgery involves a collaborative community of experts to optimize connectivity and uphold ethical standards for the best patient outcomes. Telesurgery demands significant collaboration from government bodies and a diverse community of specialists. No single entity can succeed independently; it requires collective effort with coordination among robotic companies, surgeons, patients, patient advocates, telecom companies, hospital teams, administration, licensing committees, medical societies, governing bodies,

healthcare payors, and legal experts. Without a clear understanding and coordination of these components, telesurgery risks causing harm and likely will fail over time. In this scenario, our collaborative community described the 10 commandments of a safe and ethical exploration of telesurgery (26–28).

Besides the data transmission, security, and robotic surgery expertise, it is crucial to have a robotic platform with connectivity capacity to perform Telesurgery. In our remote surgery experience, the case was performed using the MP1000 (multiport) robot from Edge Medical, which has similar port placement, docking, instrumentation, and operative performance compared to the conventional multiport platform in the market in which we have thousands of cases of experience. We could replicate and maintain all steps of our surgical technique from the trocar placement until the end of the surgery. This is crucial to maintain our surgical standards and guarantee optimal performance, patient security, and satisfactory operative outcomes.

During the case, the surgeon on the console (VP) experienced no delays in moving the instruments or communicating with the remote assistant (MCM). The sensation was identical to our routine cases where the surgeon and assistant are working in the same room. The machine's performance during different surgical steps of this remote surgery was consistent. We detected no delays or issues when swapping the 3rd and 4th arms or adjusting the scope 30 up or down. In scenarios of increased delays, it is possible to visualize a delay difference while pressing the energy pedal and watching the tissue reaction on the console screen. In our experience, the energy was applied instantaneously to the tissues upon using the bipolar or monopolar pedals, just like in non-telesurgical cases. Additionally, the needle drivers, with their wrist-like angulation, enabled us to perform the anastomosis in the same conventional manner as with other platforms. In this scenario, we believe that recent advancements in data transmission associated with the new robotic platforms in the market enabled Telesurgery to become a reality in different countries, which implicates a huge humanitarian potential to further approximate surgeons and patients while providing a step forward on the healthcare quality, especially on underserved areas.

CONCLUSIONS

The future of Telesurgery holds the transformative potential to redefine the status of surgical practice in unprecedented ways. As technology advances, we anticipate increasingly sophisticated robotic systems with enhanced precision and sensory capabilities, offering surgeons an augmented range of motion and improved real-time feedback. Furthermore, virtual and augmented reality integration may engage surgeons in immersive environments, enhancing their situational awareness and dexterity during remote procedures. The advent of 5G technology promises to address latency issues, ensuring faster and more reliable data transmission for optimal telesurgical experience. Additionally, the global collaboration among medical experts, surgical societies, and healthcare authorities will likely intensify, promoting collaborations and expertise that transcend geographical boundaries. Ethical considerations and regulatory frameworks will continue to evolve with technological progress, emphasizing the need for transparency, patient safety, and responsible innovation.

CONFLICT OF INTEREST

None declared.

REFERENCES

12. Noël J, Reddy S, Giedelman C, Swarovski-Adams RCD, Patel E, Satava RM. History of Robotic Surgery. In: Robotic Urologic Surgery. Cham: Springer International Publishing. 2022: pp. 3–10.
13. Patel V, Saikali S, Moschovas MC, Patel E, Satava R, Dasgupta P, et al. Technical and ethical considerations in telesurgery. J Robot Surg. 2024;18:40. doi: 10.1007/s11701-023-01797-3.

14. Marescaux J, Leroy J, Rubino F, Smith M, Vix M, Simone M, et al. Transcontinental robot-assisted remote telesurgery: feasibility and potential applications. Ann Surg. 2002;235:487-92. doi: 10.1097/00000658-200204000-00005.
15. George EI, Brand TC, LaPorta A, Marescaux J, Satava RM. Origins of Robotic Surgery: From Skepticism to Standard of Care. JSLS. 2018;22:e2018.00039. doi: 10.4293/JSLS.2018.00039.
16. Ji H, Park S, Yeo J, Kim Y, Lee J, Shim B. Ultra-Reliable and Low-Latency Communications in 5G Downlink: Physical Layer Aspects. [Internet]. IEEE Wirel Commun. 2018;25:124–30. Available at. <https://arxiv.org/pdf/1704.05565>. doi: 10.48550/arXiv.1704.05565.
17. Kim SSY, Dohler M, Dasgupta P. The Internet of Skills: use of fifth-generation telecommunications, haptics and artificial intelligence in robotic surgery. BJU Int. 2018;122:356-8. doi: 10.1111/bju.14388.
18. Dohler M. The Internet of Skills: How 5G-Synchronized Reality Is Transforming Robotic Surgery. In: Robotic Surgery. Cham: Springer International Publishing. 2021; pp. 207–15.
19. Pandav K, Te AG, Tomer N, Nair SS, Tewari AK. Leveraging 5G technology for robotic surgery and cancer care. Cancer Rep (Hoboken). 2022;5:e1595. doi: 10.1002/cnr2.1595.
20. Li J, Yang X, Chu G, Feng W, Ding X, Yin X, et al. Application of Improved Robot-assisted Laparoscopic Telesurgery with 5G Technology in Urology. Eur Urol. 2023;83:41-4. doi: 10.1016/j.eururo.2022.06.018.
21. Fan S, Xu W, Diao Y, Yang K, Dong J, Qin M, et al. Feasibility and Safety of Dual-console Telesurgery with the KangDuo Surgical Robot-01 System Using Fifth-generation and Wired Networks: An Animal Experiment and Clinical Study. Eur Urol Open Sci. 2023;49:6-9. doi: 10.1016/j.euros.2022.12.010.
22. Moschovas MC, Saikali S, Rogers T, Gamal A, Perera R, Reddy S, et al. Exploring the ethical implications in the telesurgery ERA. Int Braz J Urol. 2024;50:375-7. doi: 10.1590/S1677-5538.IBJU.2024.0133.
23. Alfano CG, Moschovas MC, Montagne V, Soto I, Porter J, Patel V, et al. Implementation and outcomes of Hugo(TM) RAS System in robotic-assisted radical prostatectomy. Int Braz J Urol. 2023;49:211-20. doi: 10.1590/S1677-5538.IBJU.2023.9902.
24. Covas Moschovas M, Bhat S, Rogers T, Onol F, Roof S, Mazzone E, et al. Technical Modifications Necessary to Implement the da Vinci Single-port Robotic System. Eur Urol. 2020;78:415-23. doi: 10.1016/j.eururo.2020.01.005.
25. Zhang Q, Liu J, Zhao G. Towards 5G Enabled Tactile Robotic Telesurgery. [Internet]. Arxiv. 2018. Available at. <https://arxiv.org/pdf/1803.03586> doi: https://doi.org/10.48550/arXiv.1803.03586
26. Nankaku A, Tokunaga M, Yonezawa H, Kanno T, Kawashima K, Hakamada K, et al. Maximum acceptable communication delay for the realization of telesurgery. PLoS One. 2022;17:e0274328. doi: 10.1371/journal.pone.0274328.
27. Pandav K, Te AG, Tomer N, Nair SS, Tewari AK. Leveraging 5G technology for robotic surgery and cancer care. Cancer Rep (Hoboken). 2022;5:e1595. doi: 10.1002/cnr2.1595.
28. Gamal A, Moschovas MC, Jaber AR, Saikali S, Perera R, Headley C, et al. Clinical applications of robotic surgery platforms: a comprehensive review. J Robot Surg. 2024;18:29. doi: 10.1007/s11701-023-01815-4.
29. Moschovas MC, Patel V. Nerve-sparing robotic-assisted radical prostatectomy: how I do it after 15.000 cases. Int Braz J Urol. 2022;48:369-70. doi: 10.1590/S1677-5538.IBJU.2022.99.03.
30. Moschovas MC, Patel V. Neurovascular bundle preservation in robotic-assisted radical prostatectomy: How I do it after 15.000 cases. Int Braz J Urol. 2022;48:212-9. doi: 10.1590/S1677-5538.IBJU.2022.99.04.
31. Covas Moschovas M, Bhat S, Onol FF, Rogers T, Roof S, Mazzone E, et al. Modified Apical Dissection and Lateral Prostatic Fascia Preservation Improves Early Postoperative Functional Recovery in Robotic-assisted Laparoscopic Radical Prostatectomy: Results from a Propensity Score-matched Analysis. Eur Urol. 2020;78:875-84. doi: 10.1016/j.eururo.2020.05.041.
32. Moschovas MC, Menon M, Noël J, Patel V. Techniques and Potency Outcomes for Nerve-Sparing RARP. In: Robotic Urologic Surgery. Cham: Springer International Publishing; 2022; pp. 165–70.
33. Martini A, Falagario UG, Villers A, Dell'Oglio P, Mazzone E, Autorino R, et al. Contemporary Techniques of Prostate Dissection for Robot-assisted Prostatectomy. Eur Urol. 2020;78:583-91. doi: 10.1016/j.eururo.2020.07.017.

34. Bhat KRS, Moschovas MC, Onol FF, Rogers T, Reddy SS, Corder C, et al. Evidence-based evolution of our robot-assisted laparoscopic prostatectomy (RALP) technique through 13,000 cases. J Robot Surg. 2021;15:651-60. doi: 10.1007/s11701-020-01157-5.
35. Patel V, Marescaux J, Covas Moschovas M. The Humanitarian Impact of Telesurgery and Remote Surgery in Global Medicine. Eur Urol. 2024;86:88-9. doi: 10.1016/j.eururo.2024.04.029.
36. Morohashi H, Hakamada K, Kanno T, Tadano K, Kawashima K, Takahashi Y, et al. Construction of redundant communications to enhance safety against communication interruptions during robotic remote surgery. Sci Rep. 2023;13:10831. doi: 10.1038/s41598-023-37730-9.
37. Patel V, Moschovas MC, Marescaux J, Satava R, Dasgupta P, Dohler M. Telesurgery collaborative community working group: insights about the current telesurgery scenario. J Robot Surg. 2024;18:232. doi: 10.1007/s11701-024-01995-7.
38. Moschovas MC, Saikali S, Rogers T, Gamal A, Perera R, Reddy S, et al. Exploring the ethical implications in the telesurgery ERA. Int Braz J Urol. 2024;50:375-7. doi: 10.1590/S1677-5538.IBJU.2024.0133.
39. Patel V, Saikali S, Moschovas MC, Patel E, Satava R, Dasgupta P, et al. Technical and ethical considerations in telesurgery. J Robot Surg. 2024;18:40. doi: 10.1007/s11701-023-01797-3.

Correspondence address:
Marcio Covas Moschovas, MD
AdventHealth Global Robotics Institute, USA
380 Celebration Pl Suite 401,
Celebration, FL 34747, USA
E-mail: marcio.doc@hotmail.com

ORIGINAL ARTICLE

Vol. 50 (6): 764-771, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.9916

Development of nerves and vessels in the penis during the human fetal period

Carla B. M. Gallo [1], Waldemar S. Costa [1], Luciano A. Favorito [1], Francisco J. B. Sampaio [1]

[1] *Unidade de Pesquisa Urogenital, Universidade do Estado do Rio de Janeiro - UERJ, Rio de Janeiro, RJ, Brasil*

ABSTRACT

Introduction: Although nerves and vessels of the penis play important role in erection, there are few studies on their development in human fetus. Therefore, the objective of the present study is to analyze, quantitatively, in the corpora cavernosa and corpus spongiosum, the development of the nerves and vessels in the fetal penis at different gestational ages.

Material and Methods: Fifty-six fresh, macroscopically normal human fetuses aged from 13 to 36 weeks post-conception (WPC) were used. Gestational age was determined by the foot length criterion. Penises were immediately fixed in 10% formalin, and routinely processed for paraffin embedding, after which tissue sections from the mid-shaft were obtained. We used immunohistochemical staining to analyze the nerves and vessels in the corpus cavernous and in the corpus spongiosum. These elements were identified and quantified as percentage by using the Image-J software.

Results: The quantitative analysis showed that the percentage of nerves varied from 3.03% to 20.35% in the corpora cavernosa and from 1.89% to 23.88% in the corpus spongiosum. The linear regression analysis indicated that nerves growth (incidence) in the corpora cavernosa and corpus spongiosum correlated significantly and positively with fetal age (r2=0.9421, p<0.0001) and (r2=0.9312, p<0.0001), respectively, during the whole fetal period studied. Also, the quantitative analysis showed that the percentage of vessels varies from 2.96% to 12.86% in the corpora cavernosa and from 3.62% to 14.85% in the corpus spongiosum. The linear regression analysis indicated that vessels growth (appearance) in the corpora cavernosa and corpus spongiosum correlated significantly and positively with fetal age (r^2=0.8722, p<0.0001) and (r^2=0.8218, p<0.0001), respectively, during the whole fetal period studied. In addition, the linear regression analysis demonstrated a more intense growth rate of nerves in the corpus spongiosum during the 2nd trimester of gestation, when compared with nerves in the corpora cavernosa. In addition, the linear regression analysis demonstrated a more intense growth rate of vessels in the corpus spongiosum when compared with the corpora cavernosa, during the whole fetal period studied.

Conclusions: In the fetal period, the human penis undergoes major developmental changes, notably in the content and distribution of nerves and vessels. We found strong correlation between nerves and vessels growth (amount) with fetal age, both in the corpora cavernosa and corpus spongiosum. There is significant greater proportional number of nerves than vessels during the whole fetal period studied. Also, nerves and vessels grow in a more intense rate than that of the corpora cavernosa and corpus spongiosum areas.

ARTICLE INFO

Carla B. M. Gallo
https://orcid.org/0000-0001-8233-1476

Keywords:
Blood Vessels; Penis; Fetus; Humans

Int Braz J Urol. 2024; 50: 764-71

Submitted for publication:
July 10, 2024

Accepted after revision:
July 30, 2024

Published as Ahead of Print:
August 10, 2024

INTRODUCTION

The urinary and genital systems have the same embryological origin and are derived from the intermediate mesoderm. The general plan of vertebrate development is very similar and well known since the 19th century, however, little is known about human fetal development, especially in relation to the penis and its components.

The erectile tissue of the human penis is composed of elastic fibers, collagen fibers, smooth muscles, arteries and veins, and has important functions in the mechanism of penile erection (1-5).

Some works from our group have shown the characterization of morphological components of the penis during embryonic and fetal development (6-11). Histochemical and immunohistochemical analyses, of which some were associated with morphometry, have characterized structural components in the erectile tissue of adult penis (3, 4, 12), and, in preliminary works, these techniques have been used to investigate erectile tissue in the human fetal penis (4, 6). The knowledge of such structures is necessary for understanding the normal physiology of the adult penis, commonly altered in different clinical or experimental situations (12, 13, 15). Therefore, it is important to know the changes of these penile structures during the human fetal development.

Recently, it has been demonstrated the development of the penile, the corpora cavernosa and the corpus spongiosum areas, during the human fetal period (10). Also recently, it has been studied the morphology, development, modifications and distribution of the erectile tissue in the fetal penis (11). Nevertheless, despite nerves and vessels present an essential role in erection, there are few or even no studies on its development in the penis of human fetuses.

Therefore, the objective of the present work is to analyze, qualitative and quantitatively, in the corpora cavernosa and corpus spongiosum, the development of nerves and blood vessels during the whole fetal period (13 to 36 weeks post-conception – WPC), providing normative patterns of growth.

MATERIAL AND METHODS

The study protocol was approved by the ethical committee on human research at our institution.

Our analysis was done every 15 days, during the 2nd and 3rd trimesters of pregnancy. The analysis began from the 13th week, when the characteristics of the main elements of the corpora cavernosa and corpus spongiosum were already present.

We studied 56 penises from fresh normal human fetuses. All fetuses had died of causes unrelated to the urogenital tract. The fetuses were well preserved, and none had any detectable congenital malformation. Gestational age ranged from 13 to 36 weeks post-conception (corresponding to 15 to 38 menstrual weeks) and was estimated by the foot length criterion (16-19). The fetuses were dissected with a magnification glass, and the urogenital bloc containing kidneys, ureters, bladder, prostate, testes and penis was removed. We used 1 to 5 fetuses of each gestational age.

After dissection, the penis was incised at the pubic symphysis, around 2 mm from it, cross-sectioned at its mid shaft and fixed in 10% formalin, prepared in PBS for 24 hours and routinely processed for paraffin embedding and sectioned at 5-μm with intervals of 200-μm between each section.

We used immunohistochemistry methods to analyze the nerves and vessels in the corpora cavernosa and in the corpus spongiosum. Endothelial cells were detected by using a primary antibody anti-CD31 (Abcam, Cambridge, MA, USA) at a dilution of 1:30. An anti-tubulin (Zymed Lab, Carlsbad, California) with Histostain-Plus Kit secondary antibody (Invitrogen Immunodetection, Camarillo, California) was used for characterization and quantification of nerves. Histological images were captured on a digital camera (DP71, Olympus, Tokyo, Japan) coupled to a light microscope (BX51, Olympus). These elements were identified and quantified as percentage by using the Image-J software.

Statistical Analysis - With the aid of GraphPad Prism® 5.0 software, by using the mean values for each

fetus, we performed the statistical analysis by simple linear regression, assessing the association between the variables analyzed with fetal age and other variables. Also, the correlation coefficient (r^2) and p-value were obtained for each regression analysis, with $p \leq 0.05$ considered significant.

RESULTS

The quantitative analysis showed that the percentage of nerves varied from 3.03% to 20.35% in the corpora cavernosa and from 1.89% to 23.88% in the corpus spongiosum. The linear regression analysis indicated that nerves growth (incidence) in the corpora cavernosa and corpus spongiosum correlated significantly and positively with fetal age (r^2=0.9421, p<0.0001) and (r^2=0.9312, p<0.0001), respectively, during the whole fetal period studied (Figures 1 and 2).

Also, the quantitative analysis showed that the percentage of vessels varies from 2.96% to 12.86% in the corpora cavernosa and from 3.62% to 14.85% in the corpus spongiosum. The linear regression analysis indicated that vessels growth (incidence) in the corpora cavernosa and corpus spongiosum correlated significantly and positively with fetal age (r^2=0.8722, p<0.0001) and (r^2=0.8218, p<0.0003), respectively, during the whole fetal period studied (Figures 3 and 4).

The linear regression analysis demonstrated a more intense growth rate of nerves in the corpus spongiosum during the 2nd trimester of gestation, when compared with the nerves in the corpora cavernosa. Also, the linear regression analysis demonstrated a more intense growth rate of vessels in the corpus spongiosum when compared with the corpora cavernosa, during the whole fetal period studied.

Figure 1 - Photomicrographs showing: A and C: Nerves in the corpora cavernosa (arrows). A) Fetus with 14 weeks post-conception (WPC) and C) Fetus with 22 WPC. B and D: Nerves in the corpus spongiosum (arrows). B) Fetus with 14 WPC and D) fetus with 22 WPC. Immunohistochemistry for anti-tubulin-β3, X200.

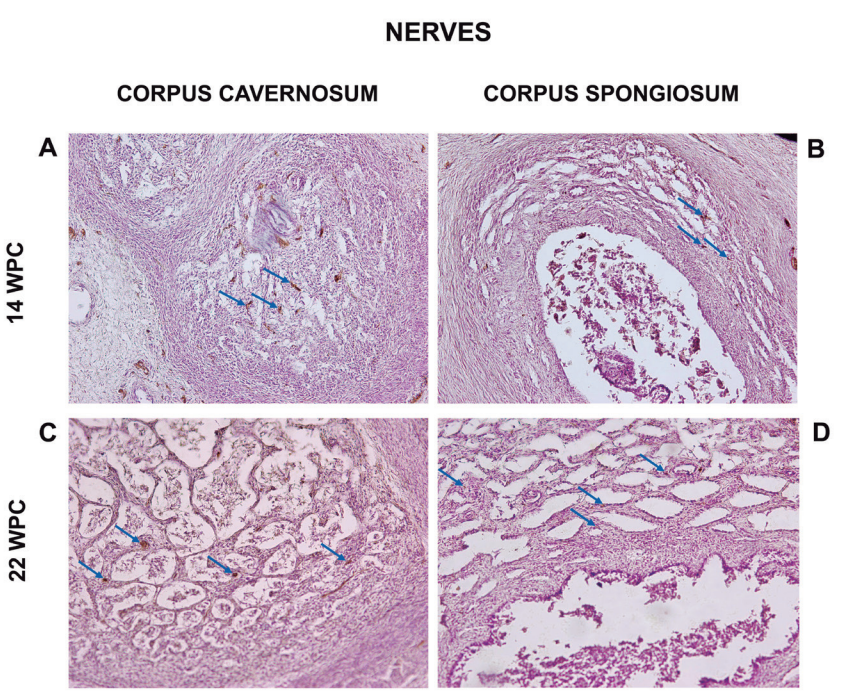


Figure 2 - Linear regression analysis showing the percentage of nerves in the corpora cavernosa (CC) and corpus spongiosum (CS), according to the fetal age in weeks post-conception (WPC).

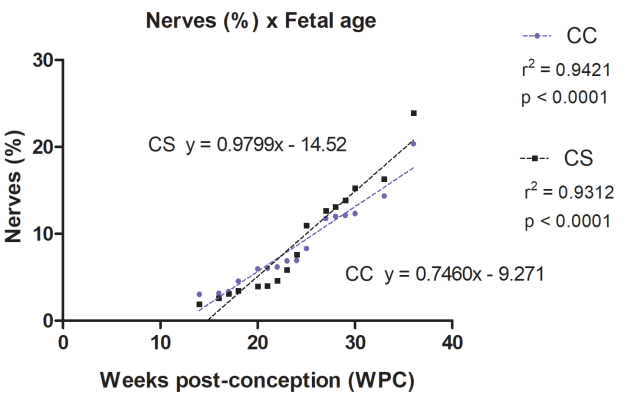


Figure 4 - Linear regression analysis showing the percentage of vessels in in the corpora cavernosa (CC) and corpus spongiosum (CS), according to fetal age in weeks post-conception (WPC).

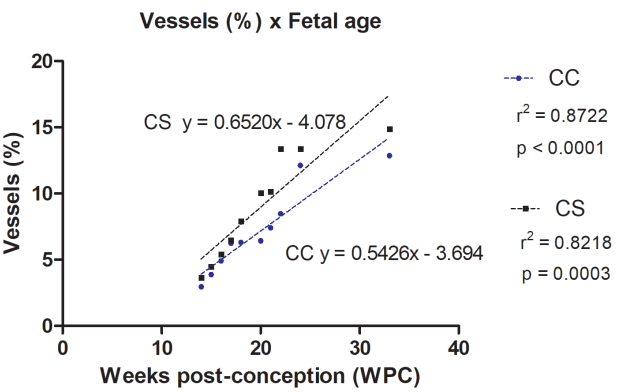
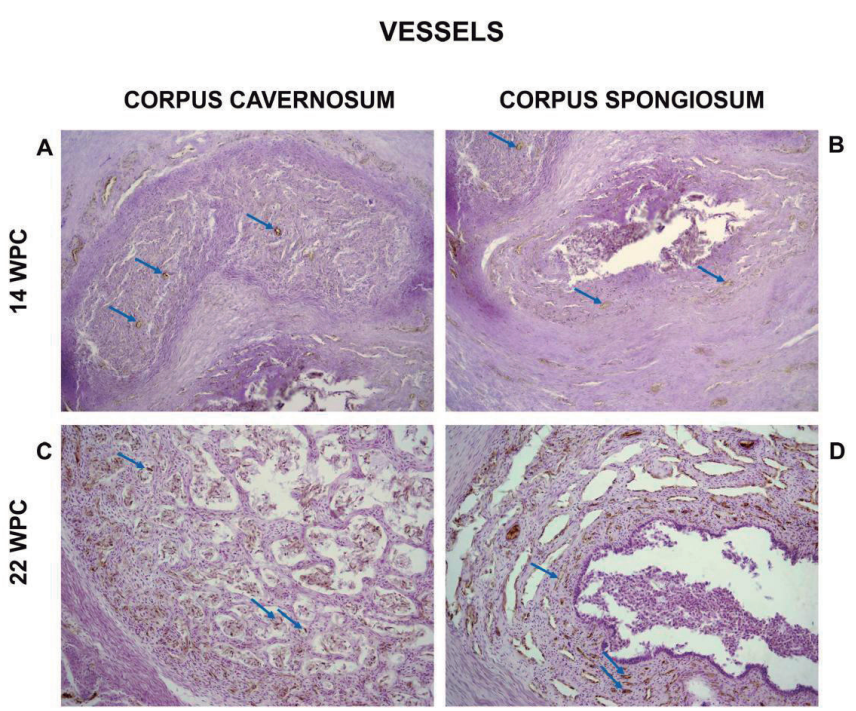


Figure 3 - Photomicrographs showing: A and C: Vessels in the corpora cavernosa (arrows). A) Fetus with 14 weeks post-conception (WPC) and C) Fetus with 22 WPC. B and D: Vessels in the corpus spongiosum (arrows). B) Fetus with 14 WPC and D) fetus with 22 WPC. Immunohistochemical for anti-alpha-actin of smooth muscle, X200.



In addition, the linear regression analysis demonstrated that the nerves grow in a more intense rate than the growth of the area of the penis, both of the corpora cavernosa and corpus spongiosum, during the whole fetal period studied (Figure-5).

Also, the linear regression analysis demonstrated that the vessels grow in a more intense rate than the growth of the area of the penis, both of the corpora cavernosa and the corpus spongiosum, during the whole fetal period studied (Figure-6).

Figure 5A - Linear regression analysis showing the correlation of number of Nerves versus Area Growth in the Corpora Cavernosa. Nerves presented a significant and positive correlation with the area of the corpora cavernosa. The rate of nerves growth in the corpora cavernosa was 2.5 times greater, on average, during the entire period studied, when compared to the growth of the area of the corpora cavernosa.

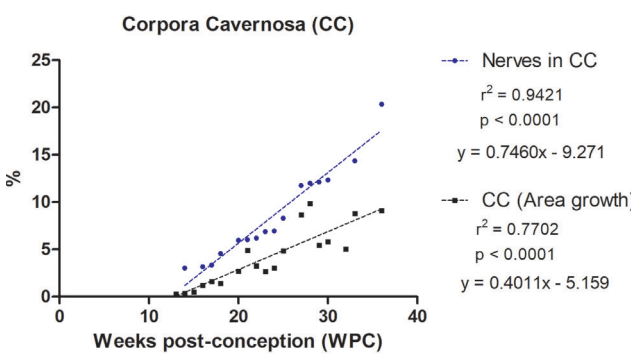


Figure 6A - Linear regression analysis showing the correlation of number of Vessels versus Area Growth in the Corpora Cavernosa. Vessels presented a significant and positive correlation with the area of the corpora cavernosa. The rate of vessels growth in the corpora cavernosa was 4.1 times greater, on average, during the entire period studied, when compared to the growth of the area of the corpora cavernosa.

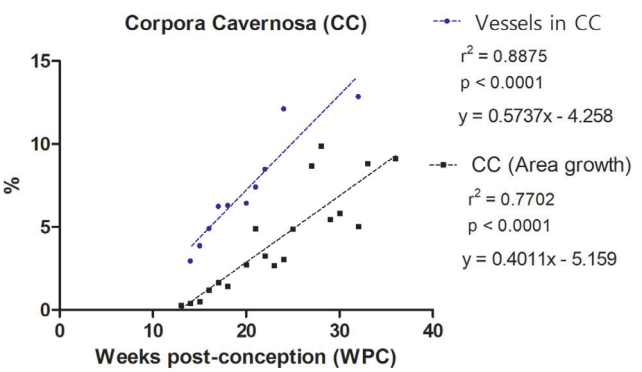


Figure 5B - Linear regression analysis showing the correlation of number of Nerves versus Area Growth in the Corpus Spongiosum. Nerves presented a significant and positive correlation with the area of the corpus spongiosum. The rate of nerves growth in the corpus spongiosum was 4.5 times greater, on average, during the entire period studied, when compared to the growth of the area of the corpus spongiosum.

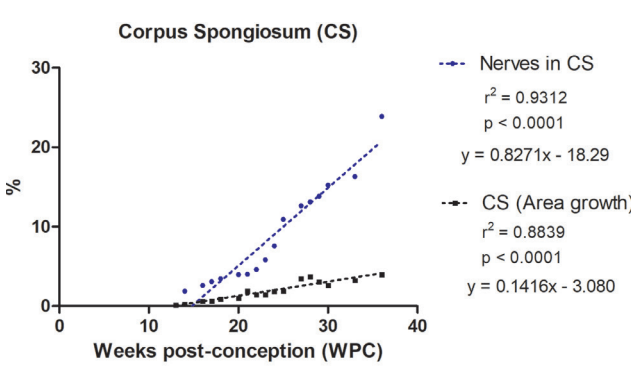
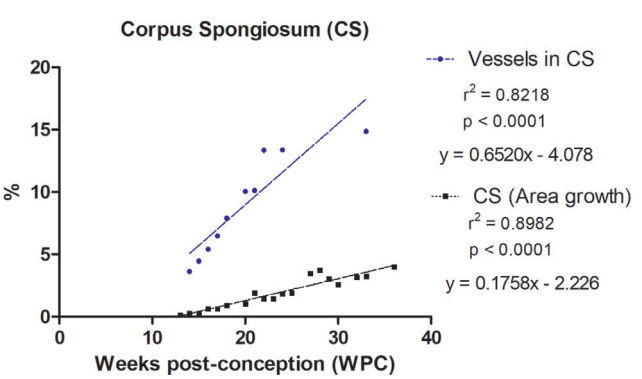


Figure 6B - Linear regression analysis showing the correlation of amount of Vessels versus Area Growth in the Corpus Spongiosum. Vessels presented a significant and positive correlation with the area of the corpus spongiosum. The rate of vessels growth in the corpus spongiosum was 9.4 times greater, on average, during the entire period studied, when compared to the growth of the area of the corpus spongiosum.



DISCUSSION

The identification of alterations in the development of the genitalia during embryonic and fetal period, can lead to an early characterization of other various abnormalities such as genetic diseases and endocrine disorders (20). Furthermore, the surgical correction of penile anomalies is based on knowledge of the anatomy of the penis (21).

Gallo et al. 2014 (11) showed that at 13 weeks post-conception the corpora cavernosa, the corpus spongiosum and the intracavernous septa are already present as well individualized anatomical structures, and, therefore, could be characterized and quantified in the human fetal penis.

The autonomic innervation of the penis derives from the bladder and prostatic plexus, which is composed of the sympathetic nerves L1 and L2, and parasympathetic nerves S2 to S4 (22). In the 13th WPC, the innervation of the corpora cavernosa occupies 14% of the total area, and in the 36th WPC occupies 20% of the total area. In the corpus spongiosum, also in the 13th WPC, the area occupied by the nerves is 8%, and in the 36th WPC is 23%. Therefore, at the end of the third trimester of gestation, the nerves are more numerous in the corpus spongiosum than in the corpora cavernosa. One should take into account that the area of the corpora cavernosa is 9.12mm^2 in the 36th WPC, while the area of the corpus spongiosum is 3.99mm^2 (10). This result showed a more intense innervation in the corpus spongiosum than that in the corpora cavernosa at the end of the human gestational period.

Regarding the blood vessels, the absolute area occupied by them is always greater in the corpus spongiosum (3.62% at the 13th WPC and 14.85% at the 36th WPC) than that in the corpora cavernosa (2.2% at the 13th WPC and 12.86% at the 36th WPC) during the whole fetal period.

The results also showed that nerves and vessels, both in the corpora cavernosa and in the corpus spongiosum, have a higher growth rate during the 2nd trimester, when compared with the third trimester. Also, nerves and vessels, grow in a more intense rate than that of the growth of the penile area, during the whole fetal period studied.

The use of ultrasound to determine the patterns of the external genitalia has been used as a tool to determine the sex of the embryo and to characterize the normal patterns of development (23). The different patterns obtained by morphometric analysis of images such as CT, MRI and other methods could be perfectly complemented with structural analysis characterizing microscopically the different structures of the human fetal penis.

Morphological studies showing the embryological development of the tissue components of different organs, and specifically the penis, are few and incomplete. Furthermore, studies using human embryos clearly demonstrated the differences between humans and other animals used as experimental models (24). Rat and mice are often used as laboratory animals for the study of the penis; however, these animals have some disadvantages because the penile structures are different from the human pattern (25). For example, the presence of penile bone, as well as erectile tissue with different structure and distribution. The bone is absent in man and the erectile tissue is predominantly fibrous in rat and mouse, whereas in humans is primarily muscle (25).

This study, therefore, aimed to contribute a line of research that shows the peculiar characteristics of the penis in human fetuses. Also, the study helps to characterize the abnormalities that occur during human development, since it presents a normative pattern of development.

CONCLUSIONS

In the fetal period, the human penis undergoes major developmental changes, notably in the content and distribution of nerves and vessels. We found strong correlation between nerves and vessels growth with the fetal age, both in the corpora cavernosa and in the corpus spongiosum. There is significant greater proportional number of nerves than vessels during the whole fetal period studied. Nerves and vessels, both in corpora cavernosa and in corpus spongiosum, grow in a more intense rate than that of the growth of the penile area, during the whole fetal period studied.

ACKNOWLEDGEMENTS

Supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and from the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Goldstein AM, Meehan JP, Morrow JW, Buckley PA, Rogers FA. The fibrous skeleton of the corpora cavernosa and its probable function in the mechanism of erection. Br J Urol. 1985;57:574-8. doi: 10.1111/j.1464-410x.1985.tb05869.x.
2. Wespes E, Goes PM, Schiffmann S, Depierreux M, Vanderhaeghen JJ, Schulman CC. Computerized analysis of smooth muscle fibers in potent and impotent patients. J Urol. 1991;146:1015-7. doi: 10.1016/s0022-5347(17)37990-9.
3. Raviv G, Kiss R, Vanegas JP, Petein M, Danguy A, Schulman C, et al. Objective measurement of the different collagen types in the corpus cavernosum of potent and impotent men: an immunohistochemical staining with computerized-image analysis. World J Urol. 1997;15:50-5. doi: 10.1007/BF01275157.
4. Sampaio FJ, Pinto JL, Silva-Costa W, Pereira MJ. Quantitative analysis of smooth muscle fibers in corpus cavernosum of human fetuses. J Urol. 1998;159:2226-8. doi: 10.1016/S0022-5347(01)63310-X.
5. Yiee JH, Baskin LS. Penile embryology and anatomy. ScientificWorldJournal. 2010;10:1174-9. doi: 10.1100/tsw.2010.112.
6. Bastos AL, Costa WS, Cardoso LE, Sampaio FJ. Collagen and elastic fibers in the penis of human fetuses at 28 weeks postconception. Eur Urol. 1999;36:158-63. doi: 10.1159/000067988.
7. Favorito LA, Cardinot TM, Morais AR, Sampaio FJ. Urogenital anomalies in human male fetuses. Early Hum Dev. 2004;79:41-7. doi: 10.1016/j.earlhumdev.2004.02.004.
8. de Carvalho JP, Costa WS, Sampaio FJ, Favorito LA. Anencephaly does not cause structural alterations in the fetal penis. J Sex Med. 2012;9:735-42. doi: 10.1111/j.1743-6109.2011.02589.x.
9. Favorito LA, Balassiano CM, Costa WS, Sampaio FJ. Development of the human foreskin during the fetal period. Histol Histopathol. 2012;27:1041-5. doi: 10.14670/HH-27.1041.
10. Gallo CB, Costa WS, Furriel A, Bastos AL, Sampaio FJ. Development of the penis during the human fetal period (13 to 36 weeks after conception). J Urol. 2013;190:1876-83. doi: 10.1016/j.juro.2013.05.050.
11. Gallo CB, Costa WS, Furriel A, Bastos AL, Sampaio FJ. Modifications of erectile tissue components in the penis during the fetal period. PLoS One. 2014;9:e106409. doi: 10.1371/journal.pone.0106409.
12. Costa WS, Carrerete FB, Horta WG, Sampaio FJ. Comparative analysis of the penis corpora cavernosa in controls and patients with erectile dysfunction. BJU Int. 2006;97:567-9. doi: 10.1111/j.1464-410X.2005.05917.x.
13. Costa WS, Rebello SB, Cardoso LE, Cavalcanti AG, Sampaio FJ. Stereological and biochemical analysis of muscular and connective tissue components in the penile corpus cavernosum adjacent to the fibrous plaque of Peyronie's disease. BJU Int. 2009;103:212-6. doi: 10.1111/j.1464-410X.2008.08023.x.
14. Costa WS, Felix B, Cavalcanti AG, Medeiros J Jr, Sampaio FJ. Structural analysis of the corpora cavernosa in patients with ischaemic priapism. BJU Int. 2010;105:838-41; discussion 841. doi: 10.1111/j.1464-410X.2009.08871.x.
15. Miranda AF, Gallo CB, De Souza DB, Costa WS, Sampaio FJ. Effects of castration and late hormonal replacement in the structure of rat corpora cavernosa. J Androl. 2012;33:1224-32. doi: 10.2164/jandrol.112.017012.
16. Streeter GL. Weight, sitting height, head size, foot length and menstrual age of the human embryo. Contrib Embryol. 1920; 11: 143.
17. Hern WM. Correlation of fetal age and measurements between 10 and 26 weeks of gestation. Obstet Gynecol. 1984;63:26-32.
18. Mercer BM, Sklar S, Shariatmadar A, Gillieson MS, D'Alton ME. Fetal foot length as a predictor of gestational age. Am J Obstet Gynecol. 1987;156:350-5. doi: 10.1016/0002-9378(87)90282-1.
19. Platt LD, Medearis AL, DeVore GR, Horenstein JM, Carlson DE, Brar HS. Fetal foot length: relationship to menstrual age and fetal measurements in the second trimester. Obstet Gynecol. 1988;71:526-31.

20. Zalel Y, Pinhas-Hamiel O, Lipitz S, Mashiach S, Achiron R. The development of the fetal penis--an in utero sonographic evaluation. Ultrasound Obstet Gynecol. 2001;17:129-31. doi: 10.1046/j.1469-0705.2001.00216.x.
21. Baskin LS, Lee YT, Cunha GR. Neuroanatomical ontogeny of the human fetal penis. Br J Urol. 1997;79:628-40. doi: 10.1046/j.1464-410x.1997.00119.x.
22. Yucel S, Baskin LS. Neuroanatomy of the male urethra and perineum. BJU Int. 2003;92:624-30. doi: 10.1046/j.1464-410x.2003.04435.x.
23. Nemec SF, Kasprian G, Brugger PC, Bettelheim D, Nemec U, Krestan CR, et al. Abnormalities of the penis in utero--hypospadias on fetal MRI. J Perinat Med. 2011;39:451-6. doi: 10.1515/jpm.2011.042.
24. Ostrer H, Wilson DI, Hanley NA. Human embryo and early fetus research. Clin Genet. 2006;70:98-107. doi: 10.1111/j.1399-0004.2006.00640.x.
25. Pinheiro AC, Costa WS, Cardoso LE, Sampaio FJ. Organization and relative content of smooth muscle cells, collagen and elastic fibers in the corpus cavernosum of rat penis. J Urol. 2000;164:1802-6.

Correspondence address:
Francisco J. B. Sampaio, MD, PhD
Unidade de Pesquisa Urogenital, Universidade do Estado do Rio de Janeiro - UERJ
Av 28 de Setembro, 87, Fundos, Vila Isabel
Rio de Janeiro, RJ, 20551-030, Brasil
E-mail: sampaio.uerj@gmail.com

EXPERT OPINION

Vol. 50 (6): 772-775, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0470

Robotic versus open radical Prostatectomy: comparing automobiles and carriages in 2024

Tomás Bernardo Costa Moretti [1], Leonardo Oliveira Reis [2,3]

[1] Departamento de Urologia, Pontifícia Universidade Católica de São Paulo, PUC-São Paulo, São Pailo, SP, Brasil; [2] UroScience, Universidade de Campinas, UNICAMP, Campinas, SP, Brasil; [2] ImunOncologia, Pontifícia Universidade Católica de Campinas, PUC-Campinas, Campinas, SP, Brasil

COMMENT

The second Randomized Clinical Trial (RCT) to date comparing robotic (RARP) versus open (RRP) radical prostatectomy, the São Paulo trial (1) highlights the challenges of randomization in a period where technological access is widespread in the US and Europe. The Brisbane Trial, published 8 years ago, stands as the first and only comparator in this context (2).

As new scientific insights emerge from centers adopting robotic surgery, RARP is increasingly viewed as the gold standard in current technology. However, open surgery can provide comparable oncological control and late quality of life and remains prevalent in developing countries due to limited resources. While robotic surgery may offer slightly better early sexual and urinary function, these remain secondary outcomes in both RCTs conducted so far.

In the hierarchy of evidence, systematic reviews and RCTs are deemed the most robust. To delineate the natural history of Radical Prostatectomy (RP), the Reverse Systematic Review (RSR) method, recently described by Moretti TBC and Reis LO, compiled a population-based database named EVIDENCE. This database amalgamates data from 910 studies across 80 Systematic Reviews (SR) on RRP, laparoscopic, and RARP, encompassing 1,353,485 patients (3-8). The clinical heterogeneity generated by RSR allows EVIDENCE to provide central tendency values for population samples with a narrow standard error of the mean, enhancing the precision of mean values relative to the population. This heterogeneity also increases the generalization and representativeness, serving as a practical reference for urologists in real-world settings, and enabling comparisons across the available RCT.

Table-1 summarizes key outcomes comparing the EVIDENCE database (3-6), São Paulo Trial [1], and the Brisbane Trial [2] and presents a didactic graphic representation for the pentafecta results between open and robotic radical prostatectomy by different assays. Values are color-coded (significant difference - red for above, green for below - and yellow for non-significant difference). While it is noted that the EVIDENCE was able to predict the results of the RTC's, acting as a weighting factor for the averages through its representative heterogeneity of scenarios, the São Paulo Trial [1] tends to report higher values, while the Brisbane Trial [2] reports lower values compared to EVIDENCE, illustrating how different randomized studies can depict diverse scenarios that require careful comparison.

Surgeon related variabilities might play a significant role in the disagreements illustrated in Table-1, even between São Paulo and Brisbane randomized controlled trials, considering the wide variability among surgeons

Table 1 - Summarizes key outcomes comparing the EVIDENCE database.

	Moretti TBC et al. (3-7) (EVIDENCE Database)				Nahas W et al. (1) (São Paulo RTC)		Coughlin GD et al. (2) (Brisbane RTC)	
Surgery period	Jan, 1962 to Apr, 2018				Feb, 2014 to Jul, 2018		Aug, 2010 to Nov, 2014	
Total n	RRP		RARP		RRP	RARP	RRP	RARP
	881,719		366,006		156	171	151	157
Preoperative	**Mean**	**SE**	**Mean**	**SE**	**CTM**	**CTM**	**CTM**	**CTM**
Age (years)	**62.8**	0.16	**61.4**	0.1	**64.0**	**64.0**	**60.4**	**59.6**
BMI (m\kg/m2)	**26.2**	0.17	**27.0**	0.1	**27.1**	**27.3**	NA	NA
iPSA (ng/ml)	**8.9**	0.26	**7.7**	0.2	**7.9**	**7.2**	**7.6**	**7.4**
cT (%)								
cT1	**58.7**	1.36	**68.7**	1.0	**49.4**	**48.5**	NA	NA
cT2	**38.7**	1.28	**31.7**	1.0	**46.2**	**45.0**	NA	NA
cT3	**8.0**	1.24	**5.9**	0.7	**4.5**	**6.4**	NA	NA
cISUP (%)								
1	**55.9**	1.5	**53.2**	1.1	**50.0**	**46.2**	**15.0**	**18.0**
2	**34.2**	1,2	**35.6**	0.8	**30.1**	**33.3**	**50.0**	**45.0**
3					**9.6**	**10.5**	**18.0**	**22.0**
4	**11.1**	0.9	**12.6**	0.8	**7.7**	**6.4**	**7.0**	**9.0**
5					**2.6**	**3.5**	**10.0**	**6.0**
Surgical	**Mean**	**SE**	**Mean**	**SE**	**CTM**	**CTM**	**CTM**	**CTM**
Operative Time (min)	**169.5**	3.9	**199.8**	3.0	**120.0**	**212.0**	**234.3**	**202.0**
EBL (mL)	**852.1**	29.9	**228.2**	6.2	**719.5**	**250.0**	**1338.1**	**443.7**
Blood Transfusion (%)	**19.8**	1.5	**2.8**	0.3	**1.3**	**0.0**	**2.0**	**1.0**
Complication (%)	**20.2**	1.4	**12.3**	0.5	**17.3**	**11.1**	**9.0**	**4.0**
Oncological	**Mean**	**SE**	**Mean**	**SE**	**CTM**	**CTM**	**CTM**	**CTM**
pT (%)								
pT2	**66.9**	1.0	**73.6**	0.7	**60.9**	**50.9**	**68.0**	**65.0**
pT3	**31.6**	1.0	**25.9**	0.8	**39.1**	**49.1**	**31.0**	**35.0**
pT3a	**22.3**	0.9	**18.6**	0.7	**29.5**	**39.1**	**28.0**	**29.0**
pT3b	**10.3**	0.8	**7.2**	0.5	**9.6**	**10.0**	**5.0**	**6.0**
pISUP (%)								
1	**44.3**	1.6	**36.3**	1.0	**13.5**	**13.5**	**3.0**	**4.0**
2	**45.1**	1.3	**52.4**	0.9	**62.8**	**56.7**	**48.0**	**46.0**
3					**15.4**	**17.5**	**38.0**	**40.0**
4	**13.2**	1.0	**10.8**	0.6	**2.6**	**4.1**	**0.0**	**1.0**
5					**5.8**	**8.2**	**11.0**	**9.0**
PSM (%)								
Total	**23.6**	0.7	**19.7**	0.5	**29.5**	**36.3**	**10.0**	**15.0**
pT2	**13.3**	0.9	**11.7**	0.6	**22.1**	**25.3**	**2.0**	**3.0**
pT3	**44.3**	2.2	**40.5**	1.3	**41.0**	**47.6**	**8.0**	**11.0**
Biochemical Reccurence (%)	5 years				3 years		2 years	
	20.4	13.3	**23.4**	12.0	**16.0**	**24.0**	**9.0**	**3.0**
Functional	**Mean**	**SE**	**Mean**	**SE**	**CTM**	**CTM**	**CTM**	**CTM**
Continence (%)	0-1 PAD				0-1 PAD		0-1 PAD	
3 months	**63.8**	0.7	**74.7**	0.1	**64.7**	**80.5**	NA	NA
6 months	**78.7**	0.5	**84.8**	0.1	**81.6**	**90.1**	**87.0**	**87.0**
12 months	**91.0**	0.1	**91.0**	0.1	**83.8**	**90.4**	**93.0**	**90.0**
18 months	**93.0**	0.1	**93.0**	0.1	**78.8**	**95.4**	NA	NA
Potency (%)	SHIM ≥ 17				SHIM ≥ 17		ESI ≥ 50%	
3 months	**30.0**	0.4	**23.8**	1.4	**5.3**	**23.9**	NA	NA
6 months	**43.5**	0.5	**51.1**	1.2	**6.9**	**30.6**	**22.0**	**22.0**
12 months	**24.8**	0.4	**35.0**	0.3	**24.0**	**37.8**	**30.0**	**35.0**
18 months	NA	NA	**59.0**	0.1	29.6	**39.8**	NA	NA

Legend: RRP = Retropubic Radical Prostatectomy; RARP = Robot-assisted Radical Prostatectomy; n = number of patients; CTM = Central Tendency Measure (mean or median); SE = Standard Error; BMI = Body Mass Index; iPSA = initial Prostate Specific Antigen; cT = clinical T Stage; cISUP = clinical ISUP Grade group; EBL = Estimated Blood Loss; pT = pathological T Stage; pISUP = pathological ISUP Grade group; PSM = Positive Surgical Margins; SHIM = Sexual Health Inventory for Men; ESI = Erections Sufficient for Intercourse more than 50% of the time; NA = Not available. Values in bold: Black = EVIDENCE reference (95% Confidence interval +- 2 x SE); Green - below 95% IC; Red - above 95%IC; Yellow - inside 95% CI.

performing radical prostatectomy. The higher variability of the results in the São Paulo study might be related to the participation of more surgeons, compared to smaller differences between the results in the Brisbane study, carried out by only one surgeon in each technique.

Most surgical trials represent, in a great measure, the comparison of surgeons' performances, with limited generalizability, also diverse robotic platform systems might implicate in different performance, to be compared in the future (9). Compared to pharmacological trials that utilize identical drugs and doses, surgical randomized trials are unique regarding the inherent diversities related to the human surgeons and the surgical theater. The relevance and accuracy of an RCT's findings depend heavily on the rigor of its design, execution, and analysis. This rigorous process, while essential, might limit the study's reproducibility compared to the representativeness of the RSR (4), mainly regarding the surgical performance due to disparities in skill and experience between surgeons and centers. Advances of generative AI will soon transform surgery in a more predictable science, as technical, ethical and regulatory evolution rapidly evolves to progressive surgical platform autonomy (10), making surgical trials less surgeon dependent, reaching the drug consistency of pharmacological trials.

Considering the existing evidence, the scientific consensus may not support substantial changes regarding the advantages of RARP over RRP. The diversity of scenarios makes the comparison inherently biased, with RRP predominating in developing countries with focus on short term cost-effectiveness, versus RARP concentrated in centers that hold cutting-edge technologies and are responsible for scientific and technological development.

Ultimately, this debate is more about access in public health than declaring a definitive winner, as the truth in this field remains dynamic, subjective, and sometimes contradictory over time. From a pragmatic point of view, much beyond the difficulty of carrying out adequate and representative controlled studies, the scientific community has progressively lost interest in reconciling these two scenarios, which emulate the challenges of comparing automobiles and carriages, different journeys that lead to the same destination.

While studies on cost-effectiveness and quality of life can still influence decisions, particularly in resource-constrained healthcare settings, including those in developing countries, the debate on functional outcomes, mainly in the short and midterm might question the randomization of patients between the two techniques. As advances in surgical techniques, imaging and robotic systems continue to evolve, it is crucial to further refine outcomes and broaden accessibility. Future studies may address disparities across diverse healthcare settings, with efforts focused on expanding access and enhancing habilitation in advanced surgical technologies in a rapidly transforming scenario.

For those less attached to immediateness, intriguingly the RSR identified a lack of RARP data on intermediate and long follow-up (4), compromising the EVIDENCE, and the available RCT are so far limited to 12 months. RARP long term oncological control needs more robust evidence. As technology evolves, the "new" surgical negative margins might not guarantee the results of wider margins of open dissection. If there is an oncological price to be paid for the functional short-term gains is still an open question for the long-term robust evidence.

After over 20 years of scientific debate, thousands of under-analyzed studies, hundreds of them summarized in 80 systematic reviews (EVIDENCE) and two RTC's highlight the complexity of the subject at a global healthcare level. In the new era of big data, perhaps it is time for the scientific community to explore new ways of exploring data, through connecting real-life data in a multicentric and real-time way with the implementation of data-driven culture and business intelligence tools, capable of showing the beauty of a realistic heterogeneity.

FUNDING STATEMENT

National Council for Scientific and Technological Development – CNPq, Research Productivity: 304747/2018-1 and 310135/2022-2 (Reis LO). The funder was not involved in study design, data collection, data analysis, manuscript preparation, and/or publication decisions.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Nahas WC, Rodrigues GJ, Rodrigues Gonçalves FA, Sawczyn GV, Barros GG, et al. Perioperative, Oncological, and Functional Outcomes Between Robot-Assisted Laparoscopic Prostatectomy and Open Radical Retropubic Prostatectomy: A Randomized Clinical Trial. J Urol. 2024;212:32-40. doi: 10.1097/JU.0000000000003967..
2. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol. 2018;19:1051-60. doi: 10.1016/S1470-2045(18)30357-7.
3. Moretti TBC, Magna LA, Reis LO. Surgical Results and Complications for Open, Laparoscopic, and Robot-assisted Radical Prostatectomy: A Reverse Systematic Review. Eur Urol Open Sci. 2022;44:150-61. doi: 10.1016/j.euros.2022.08.015.
4. Moretti TBC, Magna LA, Reis LO. Open, Laparoscopic, and Robot-Assisted Radical Prostatectomy Oncological Results: A Reverse Systematic Review. J Endourol. 2023;37:521-30. doi: 10.1089/end.2022.0819.
5. Moretti TBC, Magna LA, Reis LO. Continence criteria of 193 618 patients after open, laparoscopic, and robot-assisted radical prostatectomy. BJU Int. 2024;134:13-21. doi: 10.1111/bju.16180.
6. Moretti TBC, Magna LA, Reis LO. Erectile dysfunction criteria of 131,350 patients after open, laparoscopic, and robotic radical prostatectomy. Andrology. 2024;20. doi: 10.1111/andr.13634. Epub ahead of print.
7. Moretti TBC, Reis LO. The paradox of erectile dysfunction data after radical prostatectomy. Int Braz J Urol. 2022;48:880-2. doi: 10.1590/S1677-5538.IBJU.2022.0289.
8. Azal W Neto, Capibaribe DM, Dal Col LSB, Andrade DL, Moretti TBC, Reis LO. Incontinence after laparoscopic radical prostatectomy: a reverse systematic review. Int Braz J Urol. 2022;48:389-96. doi: 10.1590/S1677-5538.IBJU.2021.0632.
9. Alfano CG, Moschovas MC, Montagne V, Soto I, Porter J, Patel V, et al. Implementation and outcomes of Hugo(TM) RAS System in robotic-assisted radical prostatectomy. Int Braz J Urol. 2023;49:211-20. doi: 10.1590/S1677-5538.IBJU.2023.9902.
10. Liu Y, Wu X, Sang Y, Zhao C, Wang Y, Shi B, et al. Evolution of Surgical Robot Systems Enhanced by Artificial Intelligence: A Review. [Internet]. Adv. Intell. Syst., 2024; 6: 2300268. Available at. <https://onlinelibrary.wiley.com/doi/10.1002/aisy.202300268>

ARTICLE INFO

Leonardo Oliveira Reis
https://orcid.org/0000-0003-2092-414X

Int Braz J Urol. 2024; 50: 772-5

Submitted for publication:
August 12, 2024

Accepted:
August 15, 2024

Published as Ahead of Print:
August 25, 2024

Correspondence address:
Leonardo Oliveira Reis, MD, PhD
UroScience, Universidade de Campinas, UNICAMP,
Campinas, SP, Brasil
+55 19 35217481
E-mail: reisleo.l@gmail.com

RADIOLOGY PAGE

Vol. 50 (6): 776-778, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.9919

Tomographic aspect of a giant stone in a bricker urinary diversion

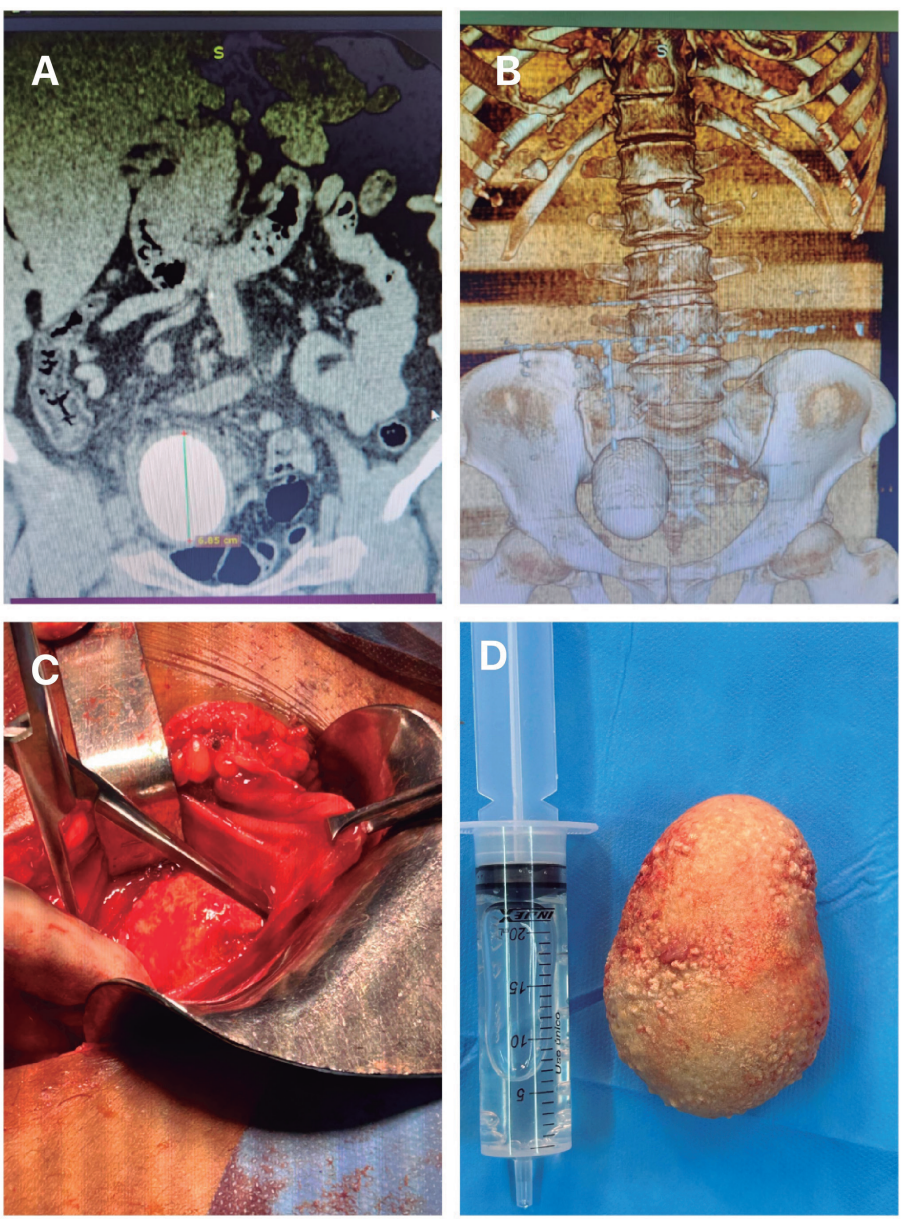
Luciano A. Favorito [1, 2], Arthur Valdier [1], André L. Diniz [1], Ana Raquel M. Morais [2], José A. de Resende Júnior [1]

[1] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil; [2] Unidade de Pesquisa Urogenital, Universidade do Estado do Rio de Janeiro - UERJ, Rio de Janeiro, RJ, Brasil

COMMENT

Robotic cystectomy has become increasingly popular for the treatment of muscle invasive bladder cancer, but open cystectomy is the gold standard treatment for this disease (1, 2). The ileum is used as a conduit to drain urine to the abdominal wall as a urinary stoma after radical cystectomy usually (Bricker urinary diversion) (1, 2). There are some complications after the radical cystectomy with Bricker reconstruction and the urolithiasis is one of the most common (3-5). Many factors contribute to stone formation, being urinary stasis, mucus production and bacteriuria the most important (3, 4). One of the techniques to treat urolithiasis in Bricker diversion is the open surgical removal, mainly in large stones (3-5). In this paper we present a 65-year-old patient with a large stone inside of Bricker, 5 years after radical cystectomy for the treatment of muscle invasive bladder cancer. The patient had pain and urinary infection with fever. The CT shows a stone inside the Bricker measuring 6.5cm (Figure-1). The patient was submitted to open laparotomy to remove the stone inside the Bricker. The stone weighted 670g (Figure-1). The patient had excellent evolution after the procedure.

Figure 1 - A) The figure shows the CT with the measurement of the stone inside the urinary diversion; B) In this figure we can observe a CT reconstruction showing the aspects of the Bricker stone; C) The figure shows the access to the Bricker to remove the stone and D) The figure shows the stone with 6.6cm removed after the open surgery.



CONFLICT OF INTEREST

None declared.

REFERENCES

1. Rocco B, Assumma S, Calcagnile T, Sangalli M, Turri F, Micali S, et al. Reproducibility of a modified posterior reconstruction during robotic intracorporeal neobladder reconfiguration. Int Braz J Urol. 2022;49:136-42. doi: 10.1590/S1677-5538.IBJU.2022.0417.
2. McNicholas DP, El-Taji O, Siddiqui Z, Hanchanale V. Systematic review comparing uretero-enteric stricture rates between open cystectomy with ileal conduit, robotic cystectomy with extra-corporeal ileal conduit and robotic cystectomy with intra corporeal ileal conduit formation. J Robot Surg. 2024;18:100. doi: 10.1007/s11701-024-01850-9.
3. Gómez Pascual JA, del Rosal Samaniego JM, García Galisteo E, Bonilla Parrilla R, Ramos Titos J, Alvarado Rodríguez A, et al. Litiasis gigante en derivación urinaria tipo Bricker. Uropatía obstructiva como forma de presentación [Giant stone in a Bricker urinary diversion. Obstruction uropathy as the presenting form]. Actas Urol Esp. 2003;27:240-3. Spanish. doi: 10.1016/s0210-4806(03)72912-x.
4. Espinheira Santos V, Costa Borges EV, de Oliveira Carneiro J, Rodrigues de Araújo JL, Araújo Andrade J. Giant Stone in Ileal Conduit. Urol Int. 2020;104:163-6. doi: 10.1159/000499091.
5. Okhunov Z, Duty B, Smith AD, Okeke Z. Management of urolithiasis in patients after urinary diversions. BJU Int. 2011;108:330-6. doi: 10.1111/j.1464-410X.2011.10194.x.

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

Int Braz J Urol. 2024; 50: 776-8

Submitted for publication:
July 10, 2024

Accepted after revision:
July 30, 2024

Published as Ahead of Print:
August 10, 2024

Correspondence address:
Luciano Alves Favorito, MD, PhD
Unidade de Pesquisa Urogenital
Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

VIDEO SECTION

Vol. 50 (6): 779-780, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0333

Single-Port Transvesical Robotic Radical Prostatectomy in a Patient with Hostile Abdomen

Sij Hemal [1], **Sina Sobhani** [1]

[1] *Institute of Urology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA*

ABSTRACT

Introduction: Robotic Radical Prostatectomy using the Da-Vinci Single-Port (SP) robot can provide comparable functional and oncological outcomes with potential advantages pertaining to peri-operative morbidity, especially in patients with an extensive history of prior abdominal surgeries (1, 2).

Materials and Methods: Our case is a 74-year-old male with a history of diabetes, cardiac bypass, hypertension, and hyperlipidemia, presenting with a PSA of 7.2. His MRI showed a PIRADS-5 lesion in the left apex and mid-gland peripheral zone, and he was diagnosed with unfavorable intermediate-risk prostate cancer after MRI guided fusion biopsy. His BMI was 31, and past surgical history was pertinent for two exploratory laparotomies due to gunshot wounds and a colostomy creation followed by reversal. The standardized steps of robotic radical prostatectomy were carried out using SP robotic platform performed by author SH (3, 4).

Results: Total operative time and estimated blood loss were 210 minutes and 150mL respectively. The patient was discharged on postoperative day one and final pathology showed adenocarcinoma of the prostate Gleason score 4+3=7, pT2NxR0 and negative surgical margins. The patient was continent four weeks after surgery and the PSA continues to be undetectable after three months.

Conclusion: Transvesical Radical prostatectomy using the single port platform provides acceptable oncological and functional outcomes and quicker recovery given decreased risk of ileus and peritoneal irritation. Given that the abdominal cavity is not violated, the risk of bowel or vascular injury is mitigated, especially in patients with a hostile abdomen.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ferguson EL, Ramos-Carpinteyro R, Soputro N, Chavali JS, Geskin A, Kaouk JH. Single-Port Robotic Radical Prostatectomy Using Transvesical and Transperineal Access in Patients with a Hostile Abdomen. J Endourol. 2024;38:150-8. doi: 10.1089/end.2023.0128.
2. Pettenuzzo G, Ditonno F, Cannoletta D, Morgantini L, Sauer RC, Torres-Anguiano JR, et al. Single Port Radical Prostatectomy as a Viable Option for Highly Complex Patients: A Single Center Experience. Urology. 2024;189:55-63. doi: 10.1016/j.urology.2024.04.051.
3. Menon M, Tewari A, Peabody JO, Shrivastava A, Kaul S, Bhandari A, et al. Vattikuti Institute prostatectomy, a technique of robotic radical prostatectomy for management of localized carcinoma of the prostate: experience of over 1100 cases. Urol Clin North Am. 2004;31:701-17. doi: 10.1016/j.ucl.2004.06.011.
4. Soputro NA, Kaouk J. Single-port robot-assisted radical prostatectomy. World J Urol. 2024;42:245. doi: 10.1007/s00345-024-04914-5.

Submitted for publication:
June 11, 2024

Accepted after revision:
July 30, 2024

Published as Ahead of Print:
August 25, 2024

Correspondence address:
Sij Hemal, MD
Institute of Urology,
Norris Comprehensive Cancer Center,
University of Southern California
1441 Eastlake Avenue, Suite 7416
Los Angeles, CA 90089, USA
Telephone: + 1 323 865-3700
E-mail: kshitij.hemal@med.usc.edu

ARTICLE INFO

Sina Sobhani
https://orcid.org/0000-0001-9089-4148

Available at: http://www.intbrazjurol.com.br/video-section/202403333_Hemal_et_al
Int Braz J Urol. 2024; 50 (Video #11): 779-80

VIDEO SECTION

Vol. 50 (6): 781-782, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0360

Totally Intracorporeal Robot-Assisted Bilateral Ileal Ureter Replacement for the Treatment of Ureteral Strictures using Kangduo Surgical Robot 2000 Plus

Shubo Fan [1], Silu Chen [1], Xinfei Li [1], Zhihua Li [1], Kunlin Yang [1], Han Hao [1], Liqun Zhou [1], Xuesong Li [1]

[1] Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, National Urological Cancer Center, Beijing, China

ABSTRACT

Purpose: Ureteroplasty using buccal or lingual mucosa graft Is feasible for complex proximal ureteral stricture (1, 2). Ileal ureter replacement is considered as the last resort for ureteral reconstruction. Totally intracorporeal robot-assisted ileal ureter replacement can be performed safely and effectively (3). In China, the KangDuo Surgical Robot 2000 Plus (KD-SR-2000 Plus) has been developed featuring two surgeon consoles and five robotic arms. This study aims to share our experience with totally intracorporeal robot-assisted bilateral ileal ureter replacement using KD-SR-2000 Plus.

Materials and Methods: A 59-year-old female patient underwent a complete intracorporeal robot-assisted bilateral ileal ureter replacement for the treatment of ureteral strictures using KD-SR-2000 Plus. The surgical procedure involved dissecting the proximal ends of the bilateral ureteral strictures, harvesting the ileal ureter, restoring intestinal continuity, and performing an anastomosis between the ileum and the ureteral end as well as the bladder. The data were prospectively collected and analyzed.

Results: The surgery was successfully completed with single docking without open conversion. The length of the harvested ileal ureter was 25 cm. The docking time, operation time and console time were 3.4 min., 271 min and 231 min respectively. The estimated blood loss was 50 mL. The postoperative hospitalization was 6 days. No perioperative complications occurred.

Conclusions: It is technically feasible to perform totally intracorporeal robot-assisted bilateral ileal ureter replacement for the treatment of ureteral strictures using KD-SR-2000 Plus. A longer follow-up and a larger sample size are required to evaluate its safety and effectiveness.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Guliev BG, Komyakov B, Avazkhanov Z, Shevnin M, Talyshinskii A. Laparoscopic ventral onlay ureteroplasty with buccal mucosa graft for complex proximal ureteral stricture. Int Braz J Urol. 2023;49:619-27. doi: 10.1590/S1677-5538.IBJU.2023.0170.
2. Yang K, Fan S, Wang J, Yin L, Li Z, Xiong S, et al. Robotic-assisted Lingual Mucosal Graft Ureteroplasty for the Repair of Complex Ureteral Strictures: Technique Description and the Medium-term Outcome. Eur Urol. 2022;81:533-40. doi: 10.1016/j.eururo.2022.01.007.
3. Yang K, Wang X, Xu C, Li Z, Han G, Fan S, et al. Totally Intracorporeal Robot-assisted Unilateral or Bilateral Ileal Ureter Replacement for the Treatment of Ureteral Strictures: Technique and Outcomes from a Single Center. Eur Urol. 2023;84:561-70. doi: 10.1016/j.eururo.2023.04.022.

Submitted for publication:
June 23, 2024

Accepted after revision:
July 09, 2024

Published as Ahead of Print:
August 25, 2024

Correspondence address:
Xuesong Li, MD
Department of Urology,
Peking University First Hospital,
Institute of Urology, Peking University,
National Urological Cancer Center.
No. 8 Xishiku St, Xicheng District,
Beijing 100034, China
Fax: + 86 10 6655-1726
E-mail: pineneedle@sina.com

ARTICLE INFO

Shubo Fan
https://orcid.org/0000-0002-3510-5799

Available at: http://www.intbrazjurol.com.br/video-section/20240360_Xuesong_et_al
Int Braz J Urol. 2024; 50 (Video #12): 781-2

VIDEO SECTION

Vol. 50 (6): 783-784, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0400

The atlas of supine single port extraperitoneal access

Luca Lambertini [1, 2], Matteo Pacini [1, 3], Luca Morgantini [1], Jhon Smith [1], Juan Ramon Torres-Anguiano [1], Simone Crivellaro [1]

[1] Department of Urology, University of Illinois at Chicago, Chicago, Illinois, USA; [2] Department of Experimental and Clinical Medicine, University of Florence - Unit of Oncologic Minimally-Invasive Urology and Andrology, Careggi Hospital, Florence, Italy; [3] Urology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

ABSTRACT

Introduction: The introduction of Single-Port (SP) platform opened the field to new surgical options, allowing to perform major urological robot-assisted procedures extraperitoneally and with a supine patient positioning (1-3). Nevertheless, a comprehensive description of different supine access options is still lacking (4–6). In this light, we provided a step-by-step guide of SP extraperitoneal supine access options also exploring preliminary surgical outcomes.

Materials and methods: Transvesical access was performed by a transversal incision 3cm above the pubic bone, after the anterior abdominal sheet incision, the bladder was insufflated with a flexible cystoscope and the detrusor muscle was incised at the level of the bladder dome. Similarly, the extraperitoneal access was carried out with a 4cm incision above the pubic bone, once visualized the preperitoneal space the prevesical fat was gently spread. The Low Anterior Access was performed with a 3cm incision at the McBurney point, the abdominal muscles were then spread. A gentle dissection was used laterally to develop the retroperitoneal space.

Results: Overall, sixteen different procedures were performed with supine extraperitoneal access on 623 consecutive patients. No intraoperative conversions occurred. The median access time was 16 (IQR 12-21), 11 (IQR 7-14) and 14 (IQR 10-18) minutes in case of transvesical, extraperitoneal and low anterior access, respectively. Notably, 81.5 % of patients were discharged on the same day with a postoperative opioid free rate of 73%.

Conclusion: The Atlas provides a comprehensive step-by-step guide to successfully perform all major urological SP procedures extraperitoneally and with supine patient positioning.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Soputro NA, Kaouk J. Single-port robot-assisted radical prostatectomy. World J Urol. 2024;42:245. doi: 10.1007/s00345-024-04914-5.
2. Cannoletta D, Pellegrino A, Pettenuzzo G, Pacini M, Sauer RC, Torres-Anguiano JR, et al. Single-Port Transvesical Vesico-Vaginal Fistula Repair: An Initial Experience. Int Braz J Urol. 2024;50:502-3. doi: 10.1590/S1677-5538.IBJU.2024.0146.
3. Pellegrino AA, Chen G, Morgantini L, Calvo RS, Crivellaro S. Simplifying Retroperitoneal Robotic Single-port Surgery: Novel Supine Anterior Retroperitoneal Access. Eur Urol. 2023;84:223-8. doi: 10.1016/j.eururo.2023.05.006.
4. Moschovas MC, Brady I, Noel J, Zeinab MA, Kaviani A, Kaouk J, et al. Contemporary techniques of da Vinci SP radical prostatectomy: multicentric collaboration and expert opinion. Int Braz J Urol. 2022;48:696-705. doi: 10.1590/S1677-5538.IBJU.2022.99.16.
5. Flammia RS, Anceschi U, Tuderti G, Di Maida F, Grosso AA, Lambertini L, et al. Development and internal validation of a nomogram predicting 3-year chronic kidney disease upstaging following robot-assisted partial nephrectomy. Int Urol Nephrol. 2024;56:913-21. doi: 10.1007/s11255-023-03832-6.
6. Ditonno F, Franco A, Licari LC, Bologna E, Manfredi C, Katz DO, et al. Implementation of single-port robotic urologic surgery: experience at a large academic center. J Robot Surg. 2024;18:119. doi: 10.1007/s11701-024-01884-z.

Submitted for publication:
July 17, 2024

Accepted after revision:
July 18, 2024

Published as Ahead of Print:
August 15, 2024

Correspondence address:
Luca Lambertini, MD
Department of Urology,
University of Illinois Hospital & Health Sciences System,
820 S Wood St, Chicago, IL 60612
Telephone: +1 773 257-6701
E-mail: l.lambertini7@gmail.com

ARTICLE INFO

Luca Lambertini
https://orcid.org/0000-0002-5917-019X

Available at: http://www.intbrazjurol.com.br/video-section/20240400_Lambertini_et_al
Int Braz J Urol. 2024; 50 (Video #13): 783-4

VIDEO SECTION

Vol. 50 (6): 785-786, November - December, 2024
doi: 10.1590/S1677-5538.IBJU.2024.0420

Single Port Robotic Nephrectomy via lower anterior retroperitoneal approach: feasible, safe and effective option in surgically complex patients

Angelo Orsini [1, 2], Francesco Lasorsa [1, 3], Gabriele Bignante [1, 4], Jamie Yoon [1], Kyle Anna Dymanus [1], Edward E. Cherullo [1], Riccardo Autorino [1]

[1] Department of Urology, Rush University, Chicago, IL, USA; [2] Department of Urology, D'Annunzio University of Chieti-Pescara, Chieti, Italy; [3] Division of Urology, Department of Precision and Regenerative Medicine and Ionian Area-Urology, Andrology and Kidney Transplantation Unit, University of Bari "Aldo Moro", Bari, Italy; [4] Division of Urology, Department of Oncology, University of Turin, San Luigi Gonzaga Hospital,Turin, Italy

ABSTRACT

Purpose: Minimally invasive radical nephrectomy is often preferred for larger renal tumours not suitable for partial nephrectomy (1). When performed with a multiport robot, the procedure is routinely performed with a transperitoneal approach, with recent studies highlighting important factors for surgical outcomes, including predictive factors (2), segmental artery unclamping techniques (3), and comparisons of robotic techniques (4).

This video shows that SP Robot-Assisted Radical Nephrectomy (RARN) via a lower anterior approach is valuable in challenging cases.

Materials and Methods: We performed SP-RARN on two complex patients using a retroperitoneal lower anterior approach. The first patient, a 54-year-old female with a BMI of 36.8 kg/m^2, had a ventral hernia and bowel obstruction history, with a 9 cm right middle kidney mass. The second patient, a 58-year-old male with a BMI of 31.19 kg/m^2, had ESRD and was on peritoneal dialysis for 8 years, with a 3.4x3.7 cm mass in the right superior pole, suspected to be RCC. The surgical technique is detailed in the video.

Results: Both procedures were successful, with operative times of 173 and 203 minutes and blood loss of 150 mL. No complications occurred. Patients were discharged after 31 and 38 hours, respectively. Histopathology confirmed RCC. At the 3-month follow-up, no complications or readmissions were reported. Second patient continued peritoneal dialysis without issues.

Conclusion: Retroperitoneal SP-RARN via the lower anterior approach avoids the peritoneal cavity, making it suitable for certain patients. In these patients, more so than in others, this procedure is feasible, safe, and less morbid than the standard multiport approach.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ljungberg B, Bex A, Albiges L, Bedke J, Capitanio U, Dabestani S, et al. EAU Guidelines on Renal Cell Carcinoma - Disease management - Uroweb. Uroweb - [Internet]. European Association of Urology. 2023. Available at. <https://uroweb.org/guidelines/renal-cell-carcinoma/chapter/disease-management>
2. Bai N, Qi M, Shan D, Liu S, Na T, Chen L. Trifecta achievement in patients undergoing partial nephrectomy: a systematic review and meta-analysis of predictive factors. Int Braz J Urol. 2022;48:625-36. doi: 10.1590/S1677-5538.IBJU.2021.0095.
3. Huang Y, Cen J, Tang Y, Yao H, Chen X, Chen W, et al. Robot-assisted partial nephrectomy for large complex renal cancer: step-by-step segmental artery unclamping. Int Braz J Urol. 2023;49:393-4. doi: 10.1590/S1677-5538.IBJU.2022.0572.
4. Schulze L, Dubeux VT, Milfont JCA, Peçanha G, Ferrer P, Cavalcanti AG. Analysis of surgical and histopathological results of robot-assisted partial nephrectomy with use of three or four robotic arms: an early series results. Int Braz J Urol. 2022;48:493-500. doi: 10.1590/S1677-5538.IBJU.2021.0495.

Submitted for publication:
July 19, 2024

Accepted after revision:
July 22, 2024

Published as Ahead of Print:
August 15, 2024

Correspondence address:
Riccardo Autorino, MD
Department of Urology,
Rush University,
1725 W Harrison St Ste 970
Chicago Illinois 60612-3801, USA
E-mail: ricautor@gmail.com

ARTICLE INFO

Riccardo Autorino
https://orcid.org/0000-0001-7045-7725

Available at: http://www.intbrazjurol.com.br/video-section/20240420_Autorino_et_al
Int Braz J Urol. 2024; 50 (Video #14): 785-6

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Luciano A. Favorito, MD, PhD
Editor, International Braz J Urol

Submit your article here:
https://www.intbrazjurol.com.br

Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Ur**ol.

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: **www.icmje.org.**

In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The International Braz J Urol contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology**

Page and Video Section. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine (**http://www.nlm.nih.gov/mesh/meshhome.html**). One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases.
Structure of the articles

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario**: Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
4) IMPORTANT - Avoid - Do Not

a) **DO NOT** embed the images in the text; save them as a separate file
b) **DO NOT** supply artwork as a native file. Most illustration packages now give the option to "save as" or export as EPS, TIFF or JPG.
c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of all authors must be included; when exist more than six authors, list the first six authors followed by et al. The initial and the final pages of the reference should be provided:

Papers published in periodicals:

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

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

Books:

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

Chapters in Books:

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

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

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

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

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the International Braz J Urol

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- Check that each figure is cited in the text. The illustrations are not merged in the text.
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
- A list of abbreviations is provided.