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CZŁONKOWIE WSPIERAJĄCY 2025

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W MIEJSCOWO ZAAWANSOWANYM LUB PRZERZUTOWYM RAKU UROTELIALNYM

WYBIERZ KURS NA **DŁUŻSZE ŻYCIE**

Z LEKIEM PADCEV W PORÓWNANIU ZE STANDARDOWĄ CHEMIOTERAPIĄ WYBRANĄ ZGODNIE Z DECYZJĄ BADACZA

PADCEV to innowacyjne leczenie ukierunkowane na nektynę-4, wydłużające mOS do 12,9 miesięcy u pacjentów, którzy otrzymali wcześniej chemioterapię zawierającą platynę i inhibitor PD-1 lub PD-L1 w porównaniu ze standardową chemioterapią wybraną przez badacza (mOS, 12,9 vs 9 miesięcy; HR = 0,70, 95% CI: 0,56–0,89; p = 0,001)[1,2].

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Produkt leczniczy PADCEV w skojarzeniu z pembrolizumabem jest wskazany w pierwszej linii leczenia raka urotelialnego nieresekcyjnego lub z przerzutami u dorosłych pacjentów, którzy kwalifikują się do chemioterapii opartej na pochodnych platyny[1].
Produkt leczniczy PADCEV jest wskazany w monoterapii raka urotelialnego miejscowo zaawansowanego lub z przerzutami u dorosłych pacjentów, którzy otrzymali wcześniej chemioterapię opartą na pochodnych platyny i inhibitor receptora programowanej śmierci komórki 1 lub inhibitor ligandu programowanej śmierci komórki 1[1].

CI – przedział ufności; HR – współczynnik ryzyka; mOS – mediana przeżycia całkowitego; PD-1 – inhibitor receptora programowanej śmierci komórki 1; PD-L1 – inhibitor ligandu programowanej śmierci komórki 1.

Referencje: 1. Charakterystyka Produktu Leczniczego Padcev. 2. Powles T et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021; 384(12): 1125-1135.

Charakterystyka Produktu Leczniczego dostępna po zeskanowaniu kodu QR.

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Prosimy o poinformowanie przedstawiciela medycznego, jeśli preferują Państwo otrzymać ChPL w formie papierowej.

Pozwolenie na dopuszczenie do obrotu wydane przez Komisję Europejską.
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MAT-PL-PAD-2025-00022 | Marzec 2025

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REFUNDACJA
W PL B.56.[2]

nmHSPC*
EMBARK
hormonowrażliwy rak gruczołu krokowego bez przerzutów

mHSPC*
ARCHES
hormonowrażliwy rak gruczołu krokowego z przerzutami

nmCRPC*
PROSPER
oporny na kastrację rak gruczołu krokowego bez przerzutów

mCRPC*
AFFIRM
oporny na kastrację rak gruczołu krokowego z przerzutami, progresja choroby (post-chemo)

mCRPC*
PREVAIL
oporny na kastrację rak gruczołu krokowego z przerzutami (pre-chemo)

*** Szczegółowy zakres wskazań**
Produkt leczniczy Xtandi jest wskazany[1]:

- w monoterapii lub w połączeniu z leczeniem deprywacją androgenów w leczeniu biochemicznie nawracającego (ang. *biochemical recurrent,* BCR) hormonowrażliwego raka gruczołu krokowego wysokiego ryzyka (ang. *non-metastatic hormone-sensitive prostate cancer,* nmHSPC) bez przerzutów u dorosłych mężczyzn, którzy nie klasyfikują się do radioterapii ratunkowej;
- w połączeniu z leczeniem deprywacją androgenów w leczeniu hormonowrażliwego raka gruczołu krokowego z przerzutami (ang. *metastatic hormone-sensitive prostate cancer,* mHSPC) u dorosłych mężczyzn;
- w leczeniu opornego na kastrację raka gruczołu krokowego wysokiego ryzyka (ang. *castration- resistant prostate cancer,* CRPC) bez przerzutów u dorosłych mężczyzn;
- w leczeniu CRPC z przerzutami u dorosłych mężczyzn, u których nie występują objawy lub występują łagodne objawy po niepowodzeniu leczenia deprywacją androgenów, i u których chemioterapia nie jest jeszcze klinicznie wskazana;
- w leczeniu CRPC z przerzutami u dorosłych mężczyzn, u których podczas lub po zakończeniu leczenia docetakselem nastąpiła progresja choroby.

1. Charakterystyka Produktu Leczniczego Xtandi.
2. Obwieszczenie Ministra Zdrowia z dnia 19 marca 2025 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 kwietnia 2025 r.

MAT-PL-XTD-2025-00044 | Marzec 2025

Charakterystyka Produktu Leczniczego dostępna po zeskanowaniu kodu QR.

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3) kliknąć w link, który pojawi się na ekranie

Prosimy o poinformowanie przedstawiciela medycznego, jeśli preferują Państwo otrzymać ChPL w formie papierowej.

Pozwolenie na dopuszczenie do obrotu wydane przez Komisję Europejską.
Produkt leczniczy wydawany na receptę.

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ZWRÓĆ SWOIM PACJENTOM WOLNOŚĆ

ROZWAŻ MIRABEGRON U PACJENTÓW Z OAB, ABY ZWIĘKSZYĆ ZADOWOLENIE Z LECZENIA[1]

OAB – zespół pęcherza nadreaktywnego (ang. *overactive bladder*)

1. Charakterystyka Produktu Leczniczego Betmiga.

MAT-PL-BET-2024-00001 | Kwiecień 2024

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Informacja o leku

Nazwa produktu leczniczego: Betmiga 25 mg, Betmiga 50 mg; tabletki o przedłużonym uwalnianiu. **Skład jakościowy i ilościowy:** Każda tabletka zawiera 25 mg lub 50 mg mirabegronu. Pełny wykaz substancji pomocniczych, patrz punkt 6.1 Charakterystyki Produktu Leczniczego (ChPL). **Postać farmaceutyczna:** Tabletka o przedłużonym uwalnianiu. **Wskazania do stosowania:** Objawowe leczenie naglącego parcia na mocz, częstomoczu i (lub) nietrzymania moczu spowodowanego naglącymi parciami, które mogą wystąpić u dorosłych pacjentów z zespołem pęcherza nadreaktywnego (ang. *overactive bladder*, OAB). **Dawkowanie i sposób podawania:** Dawkowanie: *Dorośli (w tym pacjenci w podeszłym wieku):* Zalecana dawka to 50 mg raz na dobę. *Szczególne grupy pacjentów: Zaburzenia czynności nerek i wątroby:* Produktu leczniczego Betmiga nie badano u pacjentów z krańcowym stadium niewydolności nerek (GFR < 15 ml/min/1,73 m^2 pc. lub pacjenci wymagający hemodializy) czy u pacjentów z ciężkimi zaburzeniami czynności wątroby (klasa C wg skali Child-Pugh), z tego względu nie zaleca się jego stosowania w tej grupie pacjentów (patrz punkt 4.4 i 5.2 ChPL). Zalecenia dotyczące dawki dobowej u pacjentów z zaburzeniami czynności nerek lub wątroby, gdy stosuje się silne inhibitory CYP3A i gdy się ich nie stosuje. Gdy nie stosuje się silnych inhibitorów CYP3A: Łagodne i umiarkowane zaburzenia czynności nerek* oraz łagodne zaburzenia czynności wątroby**: 50 mg. Ciężkie zaburzenia czynności nerek* oraz umiarkowane zaburzenia czynności wątroby**: 25 mg. Gdy stosuje się silne inhibitory CYP3A: Łagodne i umiarkowane zaburzenia czynności nerek* oraz łagodne zaburzenia czynności wątroby**: 25 mg. Ciężkie zaburzenia czynności nerek* oraz umiarkowane zaburzenia czynności wątroby**: nie zaleca się stosowania produktu. *(* Zaburzenia czynności nerek: łagodne: GFR od 60 ml/min/1,73 m^2 pc. do 89 ml/min/1,73 m^2 pc.; umiarkowane: GFR od 30 ml/min/1,73 m^2 pc. do 59 ml/min/1,73 m^2 pc.; ciężkie: GFR od 15 ml/min/1,73 m^2 pc. do 29 ml/min/1,73 m^2 pc. ** Zaburzenia czynności wątroby: łagodne: klasa A wg skali Child-Pugh; umiarkowane: klasa B wg skali Child-Pugh. Silne inhibitory CYP3A: patrz pkt 4.5 ChPL).* Płeć: Nie ma konieczności dostosowania dawki w zależności od płci. Dzieci i młodzież: Nie określono dotychczas bezpieczeństwa stosowania i skuteczności mirabegronu u dzieci w wieku do 18 lat. Dane nie są dostępne. Sposób podawania: Tabletkę należy połknąć w całości, popijając płynami, nie należy jej żuć, dzielić ani kruszyć. Można ją przyjąć z posiłkiem lub bez posiłku. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1 ChPL. Ciężkie niekontrolowane nadciśnienie tętnicze [ciśnienie skurczowe ≥ 180 mmHg i (lub) ciśnienie rozkurczowe ≥ 110 mmHg]. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Zaburzenia czynności nerek: Nie przeprowadzono badań produktu Betmiga u pacjentów z krańcowym stadium niewydolności nerek (GFR < 15 ml/min/1,73 m^2 pc. lub pacjenci wymagający hemodializy), z tego względu nie zaleca się jego stosowania w tej grupie pacjentów. Dane dotyczące pacjentów z ciężkimi zaburzeniami czynności nerek (GFR od 15 ml/min/1,73 m^2 pc. do 29 ml/min/1,73 m^2 pc.) są ograniczone; na podstawie badań farmakokinetycznych (patrz punkt 5.2 ChPL) zaleca się zmniejszenie dawki do 25 mg w tej grupie pacjentów. Nie zaleca się stosowania tego produktu leczniczego u pacjentów z ciężką niewydolnością nerek (GFR od 15 ml/min/1,73 m^2 pc. do 29 ml/min/1,73 m^2 pc.), przyjmujących jednocześnie silne inhibitory CYP3A (patrz punkt 4.5 ChPL). Zaburzenia czynności wątroby: Nie przeprowadzono badań produktu Betmiga u pacjentów z ciężkimi zaburzeniami czynności wątroby (klasa C wg skali Child-Pugh), z tego względu nie zaleca się jego stosowania w tej grupie pacjentów. Nie zaleca się stosowania tego produktu leczniczego u pacjentów z umiarkowanymi zaburzeniami czynności wątroby (klasa B wg skali Child-Pugh) przyjmujących jednocześnie silne inhibitory CYP3A (patrz punkt 4.5 ChPL). Nadciśnienie tętnicze: Mirabegron może zwiększać ciśnienie tętnicze krwi. Należy zmierzyć ciśnienie krwi przed rozpoczęciem stosowania mirabegronu i monitorować je okresowo w trakcie leczenia, szczególnie u pacjentów z nadciśnieniem tętniczym. Istnieją ograniczone dane dotyczące pacjentów z nadciśnieniem 2. stopnia [ciśnienie skurczowe ≥ 160 mmHg i (lub) ciśnienie rozkurczowe ≥ 100 mmHg]. Pacjenci z wrodzonym lub nabytym wydłużeniem odstępu QT: W badaniach klinicznych produkt leczniczy Betmiga, w dawkach terapeutycznych, nie powodował znaczącego klinicznie wydłużenia odstępu QT (patrz punkt 5.1 ChPL). Jednakże, ze względu na to, że pacjenci z wydłużeniem odstępu QT w wywiadzie lub pacjenci przyjmujący produkty lecznicze, o których wiadomo, że wydłużają odstęp QT, nie byli włączeni do tych badań, działanie mirabegronu u tych pacjentów nie jest znane. Należy zachować ostrożność, stosując mirabegron u tych pacjentów. Pacjenci ze zwężeniem drogi odpływu moczu z pęcherza moczowego i pacjenci przyjmujący antymuskarynowe produkty lecznicze w leczeniu OAB: Po wprowadzeniu produktu leczniczego do obrotu, u pacjentów przyjmujących mirabegron, w grupie pacjentów ze zwężeniem drogi odpływu moczu z pęcherza moczowego (ang. *bladder outlet obstruction*, BOO) i u pacjentów przyjmujących antymuskarynowe produkty lecznicze w leczeniu OAB, zgłaszano zatrzymanie moczu. Kontrolowane badanie kliniczne dotyczące bezpieczeństwa stosowania przeprowadzone u pacjentów z BOO nie wykazało zwiększenia występowania zatrzymania moczu u pacjentów przyjmujących produkt leczniczy Betmiga. Tym niemniej należy zachować ostrożność, stosując produkt leczniczy Betmiga u pacjentów z istotnym klinicznie BOO. Należy również zachować ostrożność, stosując produkt leczniczy Betmiga u pacjentów przyjmujących antymuskarynowe produkty lecznicze w leczeniu OAB. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Bezpieczeństwo stosowania produktu leczniczego Betmiga oceniano u 8433 pacjentów z OAB, z których 5648 otrzymało co najmniej jedną dawkę mirabegronu w ramach programu klinicznego II/III fazy, a 622 pacjentów otrzymywało produkt leczniczy Betmiga przez co najmniej 1 rok (365 dni). W trzech, trwających 12 tygodni, badaniach klinicznych III fazy, przeprowadzonych metodą podwójnie ślepej próby, kontrolowanych placebo, 88% pacjentów ukończyło leczenie tym produktem leczniczym, a 4% pacjentów przerwało leczenie ze względu na zdarzenia niepożądane. Większość działań niepożądanych wykazywało nasilenie łagodne do umiarkowanego. Najczęstszymi działaniami niepożądanymi zgłaszanymi przez pacjentów, którym podawano produkt leczniczy Betmiga w dawce 50 mg, w trzech, trwających 12 tygodni, badaniach klinicznych III fazy, przeprowadzonych metodą podwójnie ślepej próby, kontrolowanych placebo, były tachykardia i zakażenia układu moczowego. Tachykardia występowała z częstością 1,2% u pacjentów otrzymujących produkt leczniczy Betmiga w dawce 50 mg. Tachykardia prowadziła do zaprzestania leczenia u 0,1% pacjentów otrzymujących produkt leczniczy Betmiga w dawce 50 mg. Zakażenia układu moczowego występowały z częstością 2,9% u pacjentów otrzymujących produkt leczniczy Betmiga w dawce 50 mg. Zakażenia układu moczowego nie prowadziły do zaprzestania leczenia u żadnego z pacjentów otrzymujących produkt leczniczy Betmiga w dawce 50 mg. Ciężkie działania niepożądane obejmowały migotanie przedsionków (0,2%). Działania niepożądane obserwowane w trakcie trwającego rok (długotrwałego) badania klinicznego kontrolowanego substancją czynną (antagonista receptorów muskarynowych) były podobnego rodzaju i o podobnym nasileniu, jak działania niepożądane zgłaszane w trzech, trwających 12 tygodni, badaniach klinicznych III fazy, przeprowadzonych metodą podwójnie ślepej próby, kontrolowanych placebo. Poniżej przedstawiono działania niepożądane obserwowane w trakcie stosowania mirabegronu w trzech, trwających 12 tygodni, badaniach klinicznych III fazy, przeprowadzonych metodą podwójnie ślepej próby, kontrolowanych placebo. Częstość działań niepożądanych zdefiniowano w następujący sposób: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1000); bardzo rzadko (< 1/10 000) i częstość nieznana (nie może być określona na podstawie dostępnych danych). W obrębie każdej grupy o określonej częstości występowania działania niepożądane wymieniono zgodnie ze zmniejszającym się nasileniem. Zakażenia i zarażenia pasożytnicze: często: zakażenie układu moczowego; niezbyt często: zakażenie pochwy, zapalenie pęcherza moczowego. Zaburzenia psychiczne: częstość nieznana: bezsenność*, stan splątania*. Zaburzenia układu nerwowego: często: ból głowy*, zawroty głowy*. Zaburzenia oka: rzadko: obrzęk powiek. Zaburzenia serca: często: tachykardia; niezbyt często: kołatanie serca, migotanie przedsionków. Zaburzenia naczyniowe: bardzo rzadko: przełom nadciśnieniowy*. Zaburzenia żołądka i jelit: często: nudności*, zaparcia*, biegunka*; niezbyt często: niestrawność, zapalenie żołądka; rzadko: obrzęk warg. Zaburzenia skóry i tkanki podskórnej: niezbyt często: pokrzywka, wysypka; wysypka plamista, wysypka grudkowa, świąd; rzadko: alergiczne zapalenie naczyń, plamica, obrzęk naczynioruchowy*. Zaburzenia mięśniowo-szkieletowe i tkanki łącznej: niezbyt często: obrzęk stawów. Zaburzenia nerek i dróg moczowych: rzadko: zatrzymanie moczu*. Zaburzenia układu rozrodczego i piersi: niezbyt często: świąd pochwy i sromu. Badania diagnostyczne: niezbyt często: wzrost ciśnienia tętniczego, wzrost GGT, wzrost AspAT, wzrost AlAT. (*) Obserwowane po wprowadzeniu produktu leczniczego do obrotu. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: Al. Jerozolimskie 181C, PL-02 222 Warszawa, tel.: +48 22 49 21 301, faks: +48 22 49 21 309, strona internetowa: https://smz.ezdrowie.gov.pl. **Podmiot odpowiedzialny:** Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE Leiden, Holandia. **Numery pozwoleń na dopuszczenie do obrotu:** EU/1/12/809/001-006, EU/1/12/809/008-013, EU/1/12/809/015-018 wydane przez Komisję Europejską. **Kategoria dostępności:** Produkty lecznicze wydawane z przepisu lekarza – Rp.

Charakterystyka Produktu Leczniczego dostępna na stronie internetowej Europejskiej Agencji Leków http://www.ema.europa.eu/ lub na stronie www.astellas.com/pl/product-introductions/charakterystyki-produktow-leczniczych.

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T – testosteron; OS – czas całkowitego przeżycia
* W retrospektywnej analizie zbiorczej danych z trzech prospektywnych badań fazy III udowodniono, że nadir stężenia testosteronu <10 ng/dl osiągnięty podczas leczenia tryptoreliną wpływa na poprawę OS i DSS u pacjentów z zaawansowanym rakiem gruczołu krokowego[1]
Odsetek liczby pacjentów leczonych tryptorelinią 11,25 mg, u których nadir stężenia testosteronu wynosił <10 ng/dl[1]
Ultra-niskie stężenia T - znacznie poniżej rekomendowanego poziomu kastracyjnego; dolna granica oznaczalności stężenia testosteronu w badaniu klinicznym wynosiła 0,2 nmol/l (6 ng/dl)[1]
** Badanie przeprowadzone na tryptorelinie, brak szczegółowych danych dla pozostałych substancji czynnych z grupy analogów GnRH

1. Klotz L et al. 2023, BJUI Compass, 1-11

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DIP-PL-000726

Diphereline® SR 11,25 mg (Triptorelinum); Skład jakościowy i ilościowy: 1 fiolka zawiera 11,25 mg tryptoreliny (Triptorelinum) w postaci tryptoreliny pamoinianu. **Postać farmaceutyczna:** Proszek i rozpuszczalnik do sporządzania zawiesiny o przedłużonym uwalnianiu do wstrzykiwań (*im.* lub *sc.*) **Wskazania do stosowania:** Rak gruczołu krokowego Leczenie raka gruczołu krokowego kiedy wymagane jest obniżenie stężenia testosteronu do stężenia charakterystycznego dla braku czynności gruczołów płciowych (stężenia kastracyjnego). Pacjenci, którzy uprzednio nie byli poddawani terapii hormonalnej, lepiej reagują na leczenie tryptoreliną. **Dawkowanie i sposób podawania:** Jedno wstrzyknięcie domięśniowe lub podskórne preparatu o przedłużonym uwalnianiu co 3 miesiące. U pacjentów z rakiem gruczołu krokowego z przerzutami opornym na kastrację, niepoddającym się leczeniu operacyjnemu, otrzymujących tryptorelinę oraz kwalifikujących się do leczenia inhibitorami biosyntezy androgenów, leczenie tryptoreliną powinno być kontynuowane. **Przeciwwskazania:** Nadwrażliwość na GnRH, jej analogi lub na którąkolwiek substancję pomocniczą. Stosowanie tryptoreliny jest przeciwwskazane w okresie ciąży i karmienia piersią. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Stosowanie analogów GnRH może zmniejszać gęstość mineralną kości. U mężczyzn wstępne dane wskazują, że stosowanie bisfosfonianów w skojarzeniu z analogami GnRH może zmniejszyć utratę gęstości kości. Zachowanie szczególnej ostrożności jest konieczne u pacjentów z dodatkowymi czynnikami ryzyka osteoporozy (np. przewlekłe nadużywanie alkoholu, palenie papierosów, długoterminowa terapia lekami zmniejszającymi gęstość mineralną kości, np. leki przeciwdrgawkowe lub kortykosteroidy, dodatni wywiad rodzinny w kierunku osteoporozy, niedożywienie). W rzadkich przypadkach stosowanie analogów GnRH może ujawnić obecność wcześniej nierozpoznanego gruczolaka wywodzącego się z komórek gonadotropowych przysadki. U pacjentów tych może wystąpić udar przysadki, objawiający się nagłym bólem głowy, wymiotami, zaburzeniami widzenia i porażeniem mięśni oka. Istnieje zwiększone ryzyko wystąpienia epizodu depresyjnego (z możliwymi przypadkami ciężkiej depresji) u pacjentów będących w trakcie leczenia agonistami hormonu uwalniającego gonadotropinę, takich jak tryptorelina. Pacjentów należy odpowiednio poinformować i leczyć w zależności od występujących objawów. Pacjenci z depresją powinni być ściśle kontrolowani podczas terapii. Na początku leczenia tryptorelina, podobnie jak inne analogi GnRH, powoduje przemijający wzrost stężenia testosteronu w surowicy. W rezultacie, sporadycznie, w pierwszych tygodniach leczenia w pojedynczych przypadkach rozwijało się przemijające nasilenie przedmiotowych i podmiotowych objawów raka gruczołu krokowego. W początkowej fazie leczenia należy rozważyć dodatkowe podanie odpowiedniego antyandrogenu, aby przełamać początkowy wzrost stężenia testosteronu w surowicy i nasilenie objawów klinicznych. U niewielkiej liczby pacjentów może dojść do przejściowego nasilenia podmiotowych i przedmiotowych objawów raka gruczołu krokowego (przejściowe zaostrzenie objawów nowotworu) i przejściowego nasilenia bólu związanego z chorobą nowotworową (ból związany z przerzutami), które można leczyć objawowo. Podobnie jak w przypadku innych analogów GnRH obserwowano izolowane przypadki ucisku (kompresji) rdzenia kręgowego lub niedrożności cewki moczowej. Jeżeli rozwinie się ucisk (kompresja) rdzenia kręgowego lub niewydolność nerek, należy wdrożyć standardowe leczenie, a w ekstremalnych przypadkach należy rozważyć wykonanie pilnej orchidektomii (usunięcie jądra). W pierwszych tygodniach leczenia wskazane jest staranne monitorowanie terapii, szczególnie u pacjentów z przerzutami do kręgosłupa, narażonych na ryzyko ucisku rdzenia kręgowego oraz u pacjentów z niedrożnością układu moczowego. Po kastracji chirurgicznej tryptorelina nie indukuje dalszego zmniejszenia stężenia testosteronu w surowicy. Długotrwała deprywacja androgenu, zarówno po obustronnej orchidektomii (usunięcie jądra), jak i po podaniu analogów GnRH, związana jest ze zwiększonym ryzykiem utraty masy kostnej i może prowadzić do osteoporozy oraz wzrostu ryzyka złamań kości. Deprywacja androgenowa może wydłużać odstęp QT. U pacjentów z występującym w wywiadzie wydłużeniem odstępu QT lub z czynnikami ryzyka jego wystąpienia, jak również u pacjentów otrzymujących leczenie towarzyszące, które może powodować wydłużenie odstępu QT lekarz powinien oszacować stosunek korzyści do ryzyka, w tym możliwość wystąpienia zaburzeń rytmu serca typu torsade de pointes, przed włączeniem produktu leczniczego Diphereline SR 11,25 mg. Ponadto, w badaniach epidemiologicznych obserwowano, że u pacjentów może dojść do zmian metabolicznych (np. nietolerancja glukozy, stłuszczenie wątroby) lub może zwiększać się ryzyko choroby układu krążenia w czasie terapii z deprywacją androgenu. Jednakże prospektywne dane nie potwierdziły związku pomiędzy analogami GnRH i wzrostem śmiertelności z przyczyn sercowych. Pacjentów z dużym ryzykiem chorób metabolicznych i chorób układu krążenia należy starannie ocenić przed włączeniem leczenia i w odpowiedni sposób kontrolować w czasie terapii z deprywacją androgenu. Podawanie tryptoreliny w dawkach terapeutycznych powoduje supresję osi przysadkowo-gonadalnej. Normalna funkcja powraca zwykle po zaprzestaniu leczenia. Dlatego testy diagnostyczne gonadalnej funkcji przysadki w czasie leczenia i po zaprzestaniu terapii za pomocą analogów mogą być mylące. Na początku leczenia stwierdza się przemijające zwiększenie aktywności fosfatazy kwaśnej. W czasie leczenia zaleca się przeprowadzać ocenę reakcji układu kostnego za pomocą scyntygrafii i (lub) tomografii komputerowej, natomiast ocenę reakcji gruczołu krokowego na leczenie przeprowadza się za pomocą USG i (lub) tomografii komputerowej oraz badania klinicznego i *per rectum*. Skuteczność leczenia może być monitorowana poprzez oznaczanie stężenia testosteronu i antygenu specyficznego dla prostaty w surowicy krwi. Ten produkt leczniczy zawiera mniej niż 1 mmol (23 mg) sodu na dawkę, to znaczy produkt leczniczy uznaje się za „wolny od sodu". **Działania niepożądane:** Ponieważ pacjenci z miejscowo zaawansowanym lub przerzutowym zależnym od hormonów rakiem gruczołu krokowego są zazwyczaj osobami w starszym wieku i występują u nich inne choroby typowe dla wieku podeszłego, działania niepożądane leku zgłosiło ponad 90% pacjentów uczestniczących w badaniach klinicznych, ocena istnienia związku przyczynowego między stosowanym lekiem a występującym objawem jest trudna. Podobnie jak w przypadku leczenia z udziałem innych agonistów GnRH lub po kastracji chirurgicznej, najczęściej obserwowane działania niepożądane związane z leczeniem tryptoreliną spowodowane były przewidywanym działaniem farmakologicznym. Działania te obejmowały uderzenia gorąca i spadek libido. Wszystkie zdarzenia niepożądane z wyjątkiem reakcji immuno-alergicznych (rzadko) oraz odczynów w miejscu podania wstrzyknięcia (<5%), są związane ze zmianą stężenia testosteronu. Uznano, że zgłoszone następujące działania niepożądane były prawdopodobnie związane ze stosowaniem tryptoreliny. O większości z nich wiadomo, że są związane z biochemiczną lub chirurgiczną kastracją. Częstość występowania działań niepożądanych została sklasyfikowana w następujący sposób: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100.); rzadko (≥ 1/10 000 do < 1/1000).*Bardzo często:* osłabienie, ból pleców, parestezje w kończynach dolnych, zmniejszenie libido, zaburzenia erekcji (w tym brak wytrysku, zaburzenia wytrysku), nadmierna potliwość, uderzenia gorąca; *Często:* uczucie suchości w jamie ustnej, nudności, odczyn w miejscu wstrzyknięcia (w tym rumień, zapalenie i ból), obrzęk, nadwrażliwość, zwiększenie masy ciała, ból mięśniowo-szkieletowy, ból kończyn, zawroty głowy, ból głowy, depresja*, utrata libido, zaburzenia nastroju*, ból miednicy, nadciśnienie tętnicze; *Niezbyt często:* trombocytoza, kołatanie serca, szum w uszach, zawroty głowy, upośledzenie widzenia, ból brzucha, zaparcie, biegunka, wymioty, letarg, obrzęki obwodowe, ból, dreszcze, senność, zwiększona aktywność aminotransferazy alaninowej, zwiększona aktywność aminotransferazy asparginowej, zwiększone stężenie kreatyniny we krwi, wzrost ciśnienia tętniczego krwi, zwiększone stężenie mocznika we krwi, zwiększona aktywność gamma-glutamylotransferazy, spadek masy ciała, jadłowstręt, cukrzyca, dna moczanowa, hiperlipidemia, zwiększenie apetytu, ból stawów, ból kości, skurcze mięśni, osłabienie mięśniowe, ból mięśniowy, parestezje, bezsenność, drażliwość, nokturia, zatrzymanie moczu, ginekomastia, ból sutków (gruczołów piersiowych), atrofia jąder, ból jąder, duszność, krwawienie z nosa, trądzik, łysienie, rumień, świąd, wysypka, pokrzywka; *Rzadko:* nieprawidłowe uczucie w obrębie oczu, zaburzenia widzenia, wzdęcia, zaburzenia smaku, wzdęcia z oddawaniem wiatrów, ból w klatce piersiowej, trudność w utrzymaniu pozycji stojącej, objawy grypopodobne, gorączka, reakcja anafilaktyczna, zapalenie jamy nosowej i gardła, zwiększona aktywność fosfatazy alkalicznej we krwi, sztywność stawów, obrzęk stawów, sztywność układu mięśniowo-szkieletowego, zapalenie kości i stawów, zaburzenia pamięci, stan splątania, zmniejszenie aktywności, euforyczny nastrój, duszność w pozycji leżącej, powstawanie pęcherzy, plamica, spadek ciśnienia; *Dodatkowe działania niepożądane stwierdzone w okresie po wprowadzeniu do obrotu - częstość występowania nieznana:* wydłużenie odstępu QT *(Częstość występowania podano na podstawie częstości występowania wspólnej dla całej klasy agonistów GnRH)*, udar przysadki *(Działanie niepożądane zgłaszane po pierwszym podaniu u pacjentów z gruczolakiem przysadki)*, złe samopoczucie, wstrząs anafilaktyczny, niepokój, nietrzymanie moczu, obrzęk naczynioruchowy. Tryptorelina powoduje przemijający wzrost stężenia krążącego testosteronu w ciągu pierwszego tygodnia po pierwszej iniekcji postaci o przedłużonym uwalnianiu. Przy takim początkowym wzroście stężenia krążącego testosteronu u niewielkiego odsetka pacjentów (≤ 5%) może dojść do przemijającego nasilenia podmiotowych i przedmiotowych objawów raka gruczołu krokowego (przejściowe zaostrzenie objawów nowotworu), które zwykle objawia się nasileniem objawów ze strony układu moczowego (< 2%) oraz bólu związanego z obecnością przerzutów (5%), które można leczyć objawowo. Objawy te są przemijające i zwykle ustępują w ciągu jednego do dwóch tygodni. W pojedynczych przypadkach wystąpiło zaostrzenie objawów choroby, objawiające się niedrożnością cewki moczowej lub uciskiem (kompresją) rdzenia kręgowego, związaną z obecnością przerzutów. Dlatego pacjentów z przerzutami do kręgosłupa i (lub) niedrożnością górnego lub dolnego odcinka dróg moczowych należy ściśle obserwować w pierwszych tygodniach terapii. Stosowanie analogów GnRH w terapii raka gruczołu krokowego może wiązać się ze zwiększoną utratą masy kostnej i może prowadzić do osteoporozy oraz zwiększonego ryzyka złamań kości. U pacjentów otrzymujących długotrwałe leczenie analogiem GnRH w połączeniu z radioterapią może wystąpić więcej działań niepożądanych, głównie żołądkowo-jelitowych i związanych z radioterapią. **Podmiot odpowiedzialny:** Ipsen Pharma, 65 Quai Georges Gorse, 92100, Boulogne Billancourt, Francja. **Informacji o leku udziela:** Ipsen Poland Sp. z o.o., ul. Chmielna 73, 00-801 Warszawa, tel.: (22) 653 68 00, fax: (22) 653 68 22. **Numer pozwolenia na dopuszczenie do obrotu wydanego przez MZ:** 8944. Kategoria dostępności: Produkt leczniczy wydawany z przepisu lekarza - Rp. 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Contents

Contents

TRAUMA AND RECONSTRUCTIVE UROLOGY

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Central European Journal of Urology

CASE REPORT

UROLOGICAL ONCOLOGY

Urinary incontinence as the first clinical symptom of urinary bladder leiomyosarcoma

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Urinary bladder leiomyosarcoma is an extremely rare malignancy of the urogenital system.
We present the case of a 59-year-old Caucasian male with a gigantic bladder leiomyosarcoma. The patient was subdued to the surgical excision of the urinary bladder – laparoscopic radical cystectomy with extended pelvic lymphadenectomy, with urinary diversion by bilateral ureterocutaneostomy. The excision was complete both macroscopically and microscopically. No additional adjuvant therapy was administered. In the 6-month follow-up, the patient remained in radiological remission.
Surgical excision with extended pelvic lymphadenectomy seems to be sufficient in the treatment of urinary bladder leiomyosarcoma.

Key Words: leiomyosarcoma ‹› urinary incontinence ‹› minimally invasive surgery

CASE REPORT

We present the case of a 59-year-old Caucasian male without any significant comorbidities, except benign prostate hyperplasia, who was admitted to the Department of Urology.
The patient experienced gradually worsening bladder outlet obstruction symptoms over 6 months. Last month, he experienced urinary incontinence, requiring the utilization of absorbent pads. Retrospectively, he also experienced abdominal fullness, regardless of food intake. He ascribed the symptoms to benign prostatic hyperplasia (BPH) and did seek help in the general practitioner's office.
Basic laboratory tests revealed microhematuria. Based on this sole finding, the patient was referred for an abdominal ultrasound, which showed a pathological mass in the urinary bladder, which at the time did not lead to obstructive uropathy.
Based on the mentioned findings above, he was referred for transurethral resection of bladder tumor (TURBT) performed in another hospital a month before admission to the Department of Urology. Due to the tumor size, complete resection was impossible. Multiple biopsies were collected.
The histopathological picture indicated leiomyosarcoma – low grade (LG). Differential diagnosis with Myofibroblastic inflammatory tumor was performed. The image was ambiguous and required clinical and radiological correlation. Immunohistochemistry is shown in Table 1.
A contrast-enhanced CT scan of the abdomen and pelvis performed a month before admission revealed a urinary bladder with heterogeneous masses,

probably filled with thrombi. In the lower part, the pathological mass of approx. 65 × 58 mm – approximate measurement due to poor secretion. The tumor appeared to grow beyond the walls, infiltrating the seminal vesicles and, in some cases, the prostate gland, including the ostium of the right ureter, with secondary dilatation of the pelvicalyceal system of the right kidney. There was no visible lymphadenopathy, except for a single left internal iliac lymph node up to 9 mm in the short axis (Figure 1). In the contrast-enhanced CT scan, there were no distant metastases.

If staged according to the abovementioned CT – the tumor would be classified as T2N0M0 (AJCC 8th).

After the diagnosis, the patient sought help in the tertiary referral center with experience with bladder tumor treatment with the use of minimally invasive methods and hence was referred to our Department. At admission, the patient had already developed bilateral stage I hydronephrosis with slightly elevated creatinine concentration (1.22 mg/dl) and macroscopic hematuria.

Abdominal ultrasound at admission revealed an extensive, heterogeneous, hyperechoic mass in the lower abdomen measuring 10 × 11 × 20 cm with visible marginal flows in the color Doppler option. However, vascularization was scarce in the central parts of the tumor. Also, in the center, there were homogenous, avascular areas with blurred borders, most probably necrosis-related areas.

After admission to the Department of Urology and reassessment in ultrasound and laboratory tests, the patient was qualified for bilateral percutaneous nephrostomies to prevent acute kidney injury due to obstructive uropathy. A urinary catheter was also placed. A multidisciplinary team consisting of urologists, radiologists, and oncologists qualified the patient for a radical surgical treatment – cystectomy.

After a month, the patient was admitted to the tertiary care center and, after necessary laboratory tests, qualified for surgery. According to the center's experience, the laparoscopic approach was utilized. The patient was placed on the operative table in a supine manner in Trendelenburg position, and the tumor was visible and palpable through the abdominal wall (Figure 2). Due to the tumor size, the higher placement of trocars was necessary in comparison to standard cystectomy. The 11 mm trocar was used for the 30° angular camera, and three 5 mm trocars for the surgical tools. A pneumoperitoneum of 15 mmHg was sufficient for proper visualization of the operative field. The surgery proceeded in the standard manner. The bilateral extended pelvic lymphadenectomy was performed. Due to the risk of bowel involvement, we decided to perform non-continent urinary diversion – ureterocutaneostomies. The procedure was finished with a laparoscopic technique alone. We did not find any macroscopic infiltration of the surrounding tissues.

Table 1. *Immunohistochemistry*

Parameter	Value
Ki67	3%
Atypia	Slight
SMA	+
EMA	–
PAX8	+
Caldesmon	+
CD34	–
S100	+/–
CK	–
Desmin	+
ALK1	–

ALK1 – anaplastic lymphoma kinase 1; CK – cytokeratin; EMA – epithelial membrane antigen; SMA – smooth muscle actin

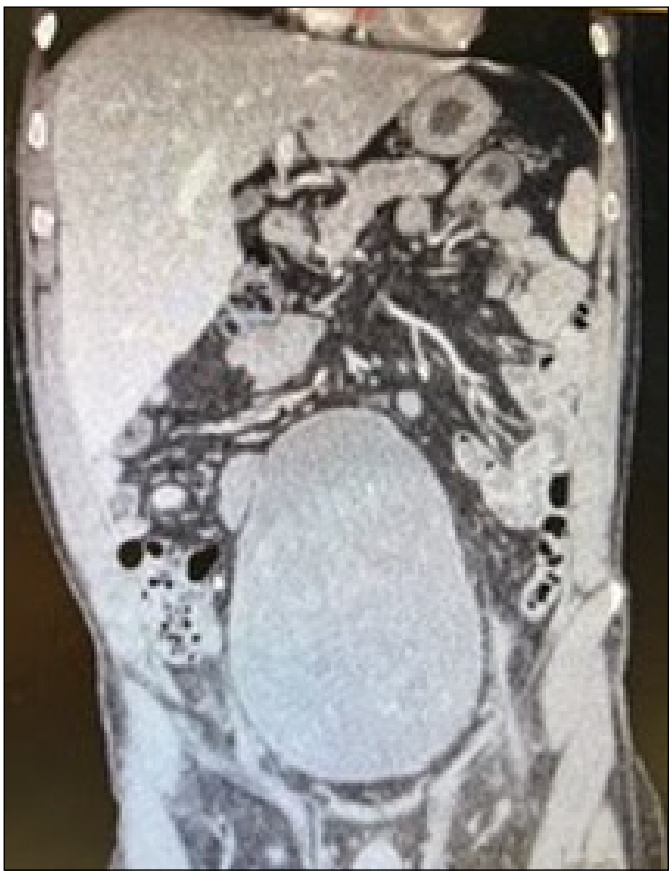

Figure 1. *CT scan of bladder tumor – coronal plane.*

Total blood loss was 300 ml. Due to the bladder's size, we performed Pfannenstiel's incision of approximately 20 cm for the removal of the bladder. The organ was entirely removed (Figures 3, 4) and subdued to histopathological assessment.

Table 2. *Immunohistochemistry*

Parameter	Value
Ki67	5%
Desmin	–
SMA	+
S100	+
EMA	+
Myogenin	–
Calponin	+
ALK1	–
SOX10	–
TFE3	–
HMB45	–
MelanA	–
Mucicarmine	–

ALK1 – anaplastic lymphoma kinase 1; EMA – epithelial membrane antigen; HMB45 – human melanin black 45; SMA – smooth muscle actin

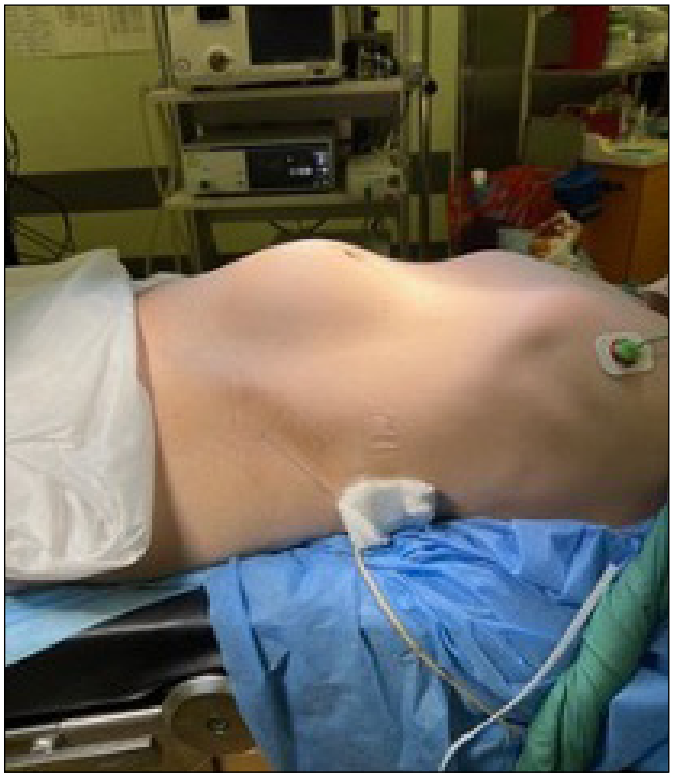

Figure 2. *Patient on the operative table. The tumor's impression on the soft tissues allows for easy identification.*

The sarcoma invaded the entire thickness of the muscularis propria (pT1). The urothelial epithelium over the tumor was normal, without any features of dysplasia. Perivesical fat tissue without cancer infiltration. Minimum tumor distance from the serosal surface – 0.1 cm. No features of angio- or neuroinvasion were visible. Number of mitoses per 10HPF: 4. Necrosis present – less than 50% of cells. Surgical margins were free from tumor infiltration. Immunohistochemistry (Table 2). Surgical specimen was 20 × 10 × 20 cm, including, among others, urinary bladder – 20 × 16 × 5 cm and tumor 15 × 17 × 8 cm, growing on the stem of 5 cm.

The tumor had a smooth surface with ecchymoses and areas of necrosis, comprising 15% of the tumor volume. It was limited to the bladder wall, infiltrating the tunica muscularis with focal infiltration of serosa. The surgical margin on the urethra was 3.5 cm.

The strict follow-up regimen was scheduled. The patient was to be tested every 3 months during the first year after the treatment. At present, the patient remains in follow-up for 6 months. At the 3-month follow-up visit, the patient had no deviations in physical examination and no signs of disease recurrence in contrast-enhanced chest, abdominal, and pelvic CT. Six months after surgery, the patient remains free of the disease's recurrence, as assessed by contrast-enhanced computed tomography. In the 6 months post-surgery, the patient remains content with the treatment and declares a satisfied quality of life.

DISCUSSION

Leiomyosarcoma (LMS) is a malignant tumor belonging to soft tissue sarcomas originating from smooth muscle tissue. It is the most common subtype among malignant mesenchymal tumors, accounting for approximately 10–20% of newly diagnosed soft tissue sarcomas [1].

In the immunohistochemical panel verifying the diagnosis, the LMS sample should express smooth muscle actin (SMA), desmin, and h-caldesmon with negative markers CD117, CD34, and DOG1, which distinguish LMS from GIST [2, 3].

LMS can develop within any smooth muscle tissue in proximity to blood vessels. In 35% of cases, this type of neoplasm is located in the retroperitoneal space and the intra-abdominal area; 30% of the locations are the uterus, followed by the limbs and trunk [4].

Leiomyosarcoma of the urinary bladder is very rare and accounts for approximately 0.1% of bladder malignancies, and is associated with an unfavorable prognosis [5].

In the early stages of the disease, the 5-year overall survival may reach 50% [6]. However, that data is extrapolated from uterine Leiomyosarcoma, a more common disease than bladder leiomyosarcoma. Considering the prognosis and treatment, we have only data from case reports and case series, which contain heterogeneous presentations of the diseases and often differ in immunohistochemical markers. Hence, the exact prognosis is hard to estimate [7].

However, all the available case reports indicate the best therapeutic option remains complete surgical excision with extended pelvic lymphadenectomy [8, 9].

Due to limited data, bladder LMS's 5-year overall survival (OS) rate is difficult to estimate. In the case of uterine LMS, the OS is over 50% when the diagnosis is made at an early stage. However, in FIGO stages III and IV with generated resistance to treatment, the survival rate decreases and ranges between 35% and 29% [6].

Due to the rare occurrence of this disease, there are several difficulties in determining its etiology and distinguishing a strictly defined therapeutic protocol [7].

Due to the significant malignancy of LMS, surgical treatment was preferred over systemic therapy. Surgery is the standard of treatment in patients with LMS of a known location. The method of choice is complete, radical surgical excision of the urinary bladder with extended pelvic lymphadenectomy. In the case of R1 or R2 margin invasion, reoperation is recommended in highly experienced tertiary referral centers [8, 9].

Systemic therapy and radiotherapy have been most often described based on data on uterine LMS. Adjuvant systemic therapy is only used in clinical trials. Based on historical data, it can be concluded

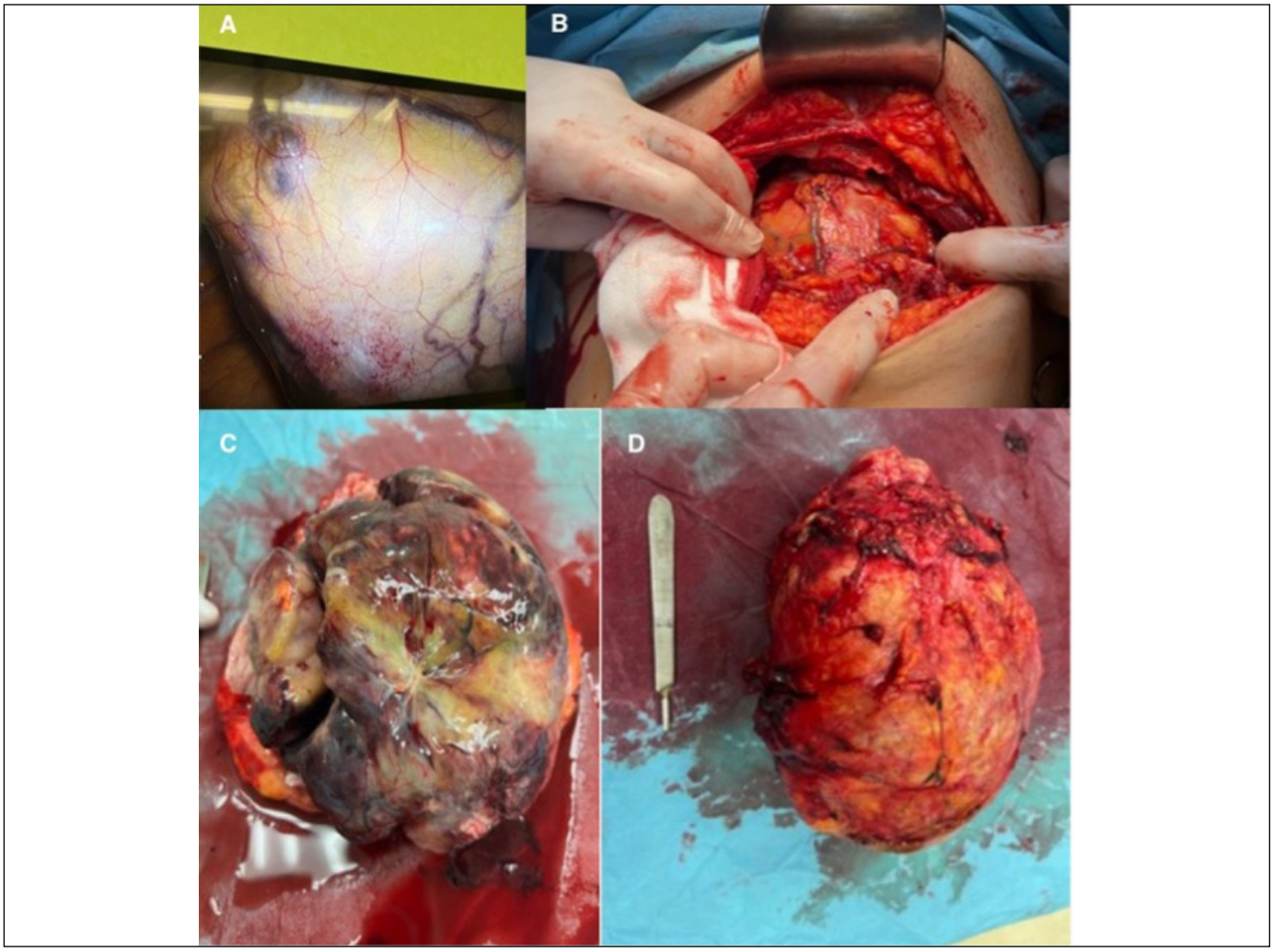

Figure 3. A) *Intraoperative, laparoscopic view of the bladder dome with widened, thrombotic vessels.* **B)** *Intraoperative view of the bladder before organ excision.* **C)** *Bladder tumor after opening the bladder.* **D)** *Bladder size in comparison to the scalpel handle.*

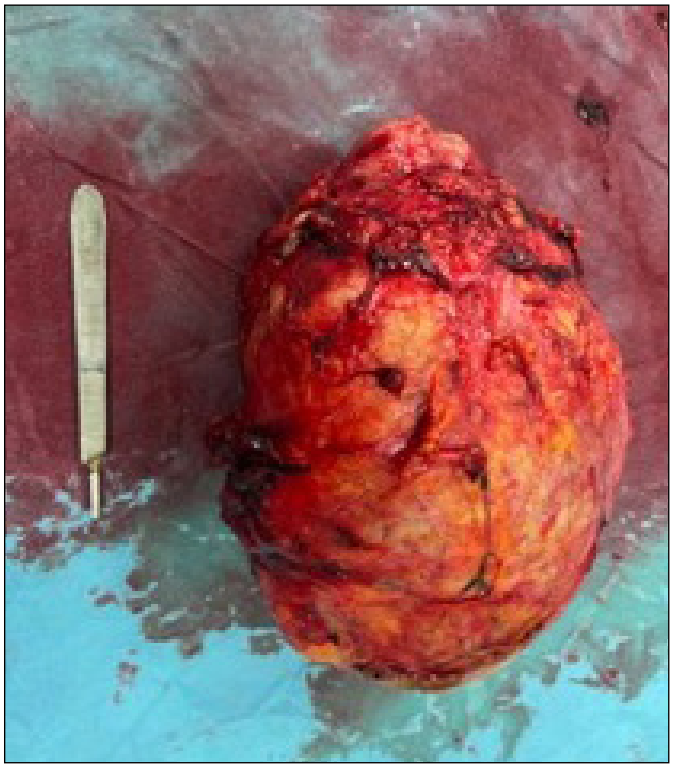

Figure 4. *The removed organ, the urinary bladder, contained the tumor. For comparison, the 13 cm scalpel handle. The size of the bladder was 20 × 16 × 5 cm. The lumen was filled with tumor mass (15 × 17 × 8 cm).*

that the use of combined treatment with docetaxel/gemcitabine followed by doxorubicin increases survival in LMS limited to the uterus alone compared to monotherapy or without chemotherapy. There are reasons to claim that the use of radiochemotherapy also increases 3-year progression-free survival while increasing the toxicity of the therapy [10].

In our case, discrepancies in the tumor size cannot be unequivocally ascribed to rapid tumor growth since the radiologist's CT description clearly states that the measurement is only an approximation due to poor contrast secretion. Moreover, abdominal CT and ultrasound are different imaging modalities.

Adjuvant treatment remains a subject of debate due to the high rate of relapse and progression despite the therapy used and the side effects resulting from the treatment. There are also opinions recommending active surveillance after complete resection without adjuvant therapy due to questionable reports about its effectiveness [11].

Epidemiological data are also conflicting.

Some sources claim that the average age of patients diagnosed with the tumor is approximately 65 years, and there is no clear predominance of the incidence of urinary bladder leiomyosarcoma in relation to gender [12].

Other data show that this cancer occurs with an increased frequency in men, and the median age is approximately 52 years. Probably the most common symptoms reported by patients with this cancer are mainly painless hematuria. Less common symptoms include painful urination, symptoms of constipation, nocturia, increased frequency of urination with abdominal and pelvic pain, etc. [13].

In short-term follow-up, radical cystectomy with extended pelvic lymphadenectomy has proven effective treatment for Leiomyosarcoma of the urinary bladder. Due to conflicting data, systemic therapy, especially without surgical excision, should not be attempted. Strict follow-up is necessary. Minimally invasive techniques, such as laparoscopy and robot-assisted laparoscopic surgery, should be considered when applicable.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Differential prognostic impact of favourable prostate cancer pathology risk score patterns predicted by Briganti's 2012 nomogram across EAU risk groups: Analysis of 757 cases treated with robotic surgery

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Introduction The aim of this study was to evaluate the prognostic impact of favourable prostate cancer (PCa) pathology patterns through Briganti's 2012 nomogram and beyond EAU risk classes in patients treated with robotic surgery.

Material and methods We analysed 757 patients from January 2013 to December 2021 with favourable pathology features (ISUP 1-3, pT2/pT3a, and pN0/x) and available follow-up. Pathologic features were scored from zero (ISUP 1 + pT2) to three (ISUP 3 + pT3a). Associations with Briganti's 2012 nomogram by EAU risk class were evaluated to determine the prognostic impact on PCa progression, defined as biochemical persistence/recurrence or loco-regional/metastatic recurrence.

Results Favourable pathology risk scores were most commonly grades one (49%) and two (30.95%), followed by zero (15.2%) and three (4.9%). After adjusting for EAU prognostic groups, higher nomogram scores were associated with increased risk scores of two and three. PCa progression occurred in 12.7% of cases after a mean follow-up of 92.1 months. Patients with recurrence had a worse prognosis as risk scores increased from one to three, even after adjustment for Briganti's 2012 nomogram by EAU class.

Conclusions Favourable pathology risk scores, grouped by Briganti's 2012 and EAU nomograms, impact prognosis. As scores increase, the likelihood of disease progression rises, potentially influencing treatment strategies.

Key Words: prostate cancer ‹› EAU risk classes ‹› prostate cancer nomograms ‹› robot assisted radical prostatectomy ‹› favorable prostate cancer pathology ‹› prostate cancer progression

INTRODUCTION

The increasing incidence of clinical prostate cancer (PCa) has prompted the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) to update guidelines to reduce overtreatment and prevent treatment-related patient regret. Treatment options include monitoring strategies like active surveillance (AS) and watchful waiting (WW), surgery (robotic-assisted radical prostatectomy [RARP] with or without extended pelvic lymph node dissection [ePLND]), radiation therapy, and combination therapies tailored to prognostic risk categories (low to high).

Prognostic risk classes differ between classification systems and remain heterogeneous due to a mix of favourable and unfavourable pathology features. Reliable predictors are lacking, as molecular biology is not yet part of routine practice and multiparametric magnetic resonance imaging (MRI) is not consistently reproducible in multicentre studies.
Preoperative nomograms, such as Briganti's 2012 model, estimate the risk of pelvic lymph node invasion (PLNI) by integrating multiple clinical variables. Among these tools, Briganti's 2012 nomogram is one of the most effective and widely used. This study aimed to evaluate the impact of favourable pathology patterns on PCa progression after assessing associations with the Briganti's 2012 nomogram using EAU risk stratification in patients treated with robotic surgery.

MATERIAL AND METHODS

Evaluation of parameters in the investigated prostate cancer patient population

We analysed 757 patients (January 2013–December 2021) with no prior PCa treatment, including androgen blockade. Robotic surgery, with or without ePLND, was performed by five experienced surgeons following a standardised template. Data were collected prospectively and analysed retrospectively. Clinical factors included age, body mass index (BMI), physical status, prostate-specific antigen (PSA), prostate volume (PV), biopsy positive cores percentage (BPC), and tumour grade and stage. Surgical specimens included the resected prostate and any sampled lymph nodes. Tumours were graded according to the International Society of Urological Pathology (ISUP) system and staged according to the TNM system. The samples were evaluated according to the pathological guidelines in force at the time of surgery. Patient follow-up adhered to guidelines, and a multidisciplinary team reviewed decisions regarding disease progression to optimise and personalise recommendations.

Model assumptions with evaluation of endpoints

The study focused on identifying favourable pathological features in surgical specimens, such as ISUP 1/3, pT2/3a, and pN0/x. These features were categorised into grades (0–3) based on different combinations. The study then assessed the relationship between these grades, Briganti's 2012 nomogram, and EAU classes. The goal was to determine the impact of these combined patterns on PCa progression, including biochemical recurrence, local recurrence, or metastases. Individual cancer factor scores were not calculated for Briganti's 2012 nomogram and EAU prognostic classes.

Statistical methods

Continuous variables were evaluated as medians with interquartile ranges (IQR), and categorical variables were evaluated as frequencies (percentages). Associations of risk score patterns were tested using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. The multinomial logistic regression model evaluated the associations between Briganti's 2012 nomogram, EAU classes, and the risk of combined patterns. Time to event occurrence was censored as the time between surgery and PCa progression or the last follow-up. Cox's proportional model was used to evaluate the risk of disease progression by examined patterns adjusted for Briganti's 2012 nomogram beyond EAU classes. Unadjusted Kaplan-Meier related curves were also generated. IBM-SPSS version 26 was used for the analysis. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Bioethical standards

The Institutional Review Board of Univeristy of Verona approved the study, and all patients provided informed consent.

RESULTS

Associations of favourable pathology risk score patterns

Grades one and two were the most frequent favourable pathologic risk score patterns (49% and 30.95%, respectively), followed by grades zero (15.2%) and three (4.9%). Increasing risk score patterns were associated with older age, unfavourable cancer features, higher nomogram scores, and unfavourable EAU prognostic classes. Extended pelvic lymph node dissection (ePLND) was performed in 54.8% of cases, with a median of 26 lymph nodes counted (Table 1).

Favourable pathology risk score patterns predicted by Briganti's 2012 nomogram through EAU risk classes

As the nomogram score increased, patients were more likely to have less favourable patterns. This included risk scores two (OR = 1.088; 95% CI: 1.010–1.171; p = 0.025) and three (1.096; 95% CI: 1.096; 1.010–1.189; p = 0.028) compared to pattern zero. It also included risk scores two (OR = 1.075;

95% CI: 1.038–1.114; p <0.0001) and three (OR = 1.084; 95% CI: 1.032–1.139; p = 0.001) compared to pattern one. Risk score one showed no significant association with pattern zero on multivariate analysis (Table 2).

Prognostic impact of favourable pathology risk score patterns

Prostate cancer (PCa) progression occurred in 12.7% (Table 3) of cases after a mean follow-up of 92.1 months. Patients with higher risk scores were more likely to have a worse prognosis. Compared to score zero, the hazard ratios were 2.478 for score one, 4.361 for score two, and 7.227 for score three, after adjusting for Briganti's 2012 and EAU classes. Kaplan-Meier survival risk curves for PCa progression are shown in Figure 1. There were 19 (2.5%) patient deaths, of which 4 (0.5%) were related to PCa. Androgen deprivation therapy was administered in 9.2% of patients and radiation therapy in 10.6%, with 4.9% receiving salvage therapy.

Table 1. *Associations of factors with favorable pathology risk cores patterns in 757 patients treated with robotic surgery*

	Favorable pathology risk score pattern in the surgical specimen				p
	Zero	One	Two	Three	
Cases, n (%)	15 (15.2)	371 (49.0)	234 (30.9)	37 (4.9)	
Physical features					
Age (years)	63 (58–68)	64 (58–69)	65 (61–71)	66 (60.5–70.5)	0.005
BMI [kg/m^2]	25.6 (23.7–28.0)	25.8 (24.0–27.8)	26.0 (23.9–28.1)	26.1 (22.8–28.5)	0.729
ASA score 1	13 (4.3)	36 (9.7)	17 (7.3)	5 (13.5)	0.266
ASA score 2	96 (83.5)	304 (81.9)	189 (80.8)	27 (73.0)	
ASA score 3	6 (5.2)	31 (8.4)	28 (12.0)	5 (13.5)	
PV [ml]	42 (32–53)	40 (30–50)	36.7 (28.7–47.2)	34 (30–47)	0.054
Clinical cancer features					
PSA [ng/ml]	6.1 (4.6–7.9)	6.2 (4.7–8.1)	6.4 (5.0–8.6)	8.1 (5.6–10.1)	0.007
BPC (%)	21.4 (14.2–35.7)	28.5 (16.6–42.8)	30 (20–50)	30 (21.8–51.6)	<0.0001
ISUP 1	96 (83.5)	156 (42.0)	62 (26.5)	7 (18.9)	<0.0001
ISUP 2/3	19 (16.5)	209 (56.3)	160 (68.4)	30 (81.1)	
ISUP 4/5	0 (0.0)	6 (1.6)	12 (5.1)	0 (0.0)	
cT1	90 (78.3)	232 (62.5)	138 (59.0)	16 (43.2)	<0.0001
cT2/3	25 (21.7)	139 (37.5)	96 (41.0)	21 (56.8)	
EAU risk class					
Low-risk	92 (80)	122 (32.9)	51 (21.8)	4 (10.8)	<0.0001
Intermediate-risk	19 (16.5)	219 (59.0)	149 (63.7)	25 (67.6)	
High-risk	4 (3.5)	30 (8.1)	34 (14.5)	8 (21.6)	
Nomogram for PLNI					
Briganti 2012 (%)	2 (1–3)	2 (1–4)	4 (2–8)	4 (2.5–8.5)	<0.0001
PLND	32 (27.8)	199 (53.6)	157 (67.1)	27 (73.0)	<0.0001
Pathology features					
ISUP 1	115 (100)	1 (0.3)			<0.0001
ISUP 2		370 (99.7)	20 (8.5)		
ISUP 3		214 (91.5)	37 (100)		
pT2	115 (100)	370 (99.7)	214 (91.5)		<0.0001
pT3a		1 (0.3)	20 (8.5)	37 (100)	
R1	12 (10.4)	74 (19.9)	42 (17.9)	20 (54.1)	<0.0001

Continuous variables are reported as medians (interquartile ranges) while categorical factors as frequencies (percentages); and methods; for further details see sections relative to material

ASA – American Society of Anesthesiologists; BMI – body mass index; EAU – European Association of Urology

DISCUSSION

Managing PCa is challenging due to the heterogeneity of prognostic risk groups, which differ between the two main systems [1, 2, 9–12]. Treated PCa can become life-threatening, with progression occurring in about 35% of cases and mortality affecting about 16% of patients [1, 2, 9–12].

Table 2. *Impact of Briganti's 2012 nomogram through EAU risk classes for predicting favourable pathology risk score patterns*

	Univariate analysis		Multivariate analysis	
Statistics	OR (95% CI)	p	OR (95% CI)	p
a) Risk score one vs zero				
Briganti 2012 nomogram	1.119 (1.030–1.217)	0.008	1.011 (0.939–1.089)	0.768
EAU intermediate vs low risk	8.692 (5.059–14.934)	<0.0001	8.524 (4.890–14.860)	<0.001
EAU high vs low risk	5.656 (1.925–16.618)	0.002	5.435 (1.795–15.458)	0.003
b) Risk score two vs zero				
Briganti 2012 nomogram	1.216 (1.119–1.322)	<0.0001	1.088 (1.010–1.171)	0.025
EAU Intermediate vs low risk	14.147 (7.862–25.454)	<0.0001	11.733 (6.428–21.417)	<0.0001
EAU high vs low risk	15.333 (5.150–45.654)	<0.0001	10.042 (3.244–31.086)	<0.0001
c) Risk score three vs zero				
Briganti 2012 nomogram	1.236 (1.131–1.352)	<0.0001	1.096 (1.010–1.189)	0.028
EAU Intermediate vs low risk	30.263 (9.437–97.052)	<0.0001	24.478 (7.532–79.544)	<0.0001
EAU high vs low risk	46.000 (9.638–219.542)	<0.0001	28.264 (5.603–142.579)	<0.0001
d) Risk score two vs one				
Briganti 2012 nomogram	1.086 (1.050–1.124)	<0.0001	1.075 (1.038–1.114)	<0.0001
EAU Intermediate vs low risk	1.628 (1.105–2.398)	0.014	1.376 (0.925–2.049)	0.115
EAU high vs low risk	2.711 (1.503–4.890)	0.001	1.848 (0.990–3.451)	0.054
e) Risk score three vs one				
Briganti 2012 nomogram	1.104 (1.050–1.124)	<0.0001	1.084 (1.032–1.139)	0.001
EAU Intermediate vs low risk	3.482 (1.184–10.237)	0.023	2.872 (0.967–8.531)	0.058
EAU high vs low risk	8.133 (2.296–28.816)	0.001	5.201 (1.395–19.389)	0.014

CI – confidence interval; EAU – European Associan of Urology risk classes; see also materials, methods and results for further details; OR – odds ratio

Table 3. *Impact of favourable pathology risk score patterns on prostate cancer progression through EAU risk classes and by Briganti's 2012 nomogram in 757 cases treated with robotic surgery*

	Total cases	Cases progressing	Univariate analysis		Multivariate analysis	
Statistics	757	96 (12.7)	HR (95% CI)	P	HR (95% CI)	P
Briganti's 2012 nomogram						
one-two	385	37 (9.6)	Ref.		Ref.	0.03
> two	372	59 (15.9)	2.455 (1.616–3.693)	<0.0001	1.595 (1.030–2.470)	
EAU prognostic risk class						
Low risk	269	25 (9.3)	Ref.		Ref.	
Intermediate risk	412	59 (14.3)	3.152 (1.962–5.063)	<0.0001	2.035 (1.234–3.355)	0.005
High risk	76	12 (15.8)	3.997 (1.990–8.030)	<0.0001	2.050 (0.971–4.330)	0.06
Favourable pathology pattern						
Risk score zero	115	6 (5.2)	Ref.		Ref.	
Risk score one	371	37 (10.0)	3.307 (1.393–7.850)	0.007	2.478 (1.027–5.981)	0.044
Risk score two	234	42 (17.9)	6.901 (2.925–16.283)	<0.0001	4.361 (1.793–10.612)	0.001
Risk score three	37	11 (2.97)	13.063 (4.803–35.526)	<0.0001	7.227 (2.520–20.724)	<0.0001

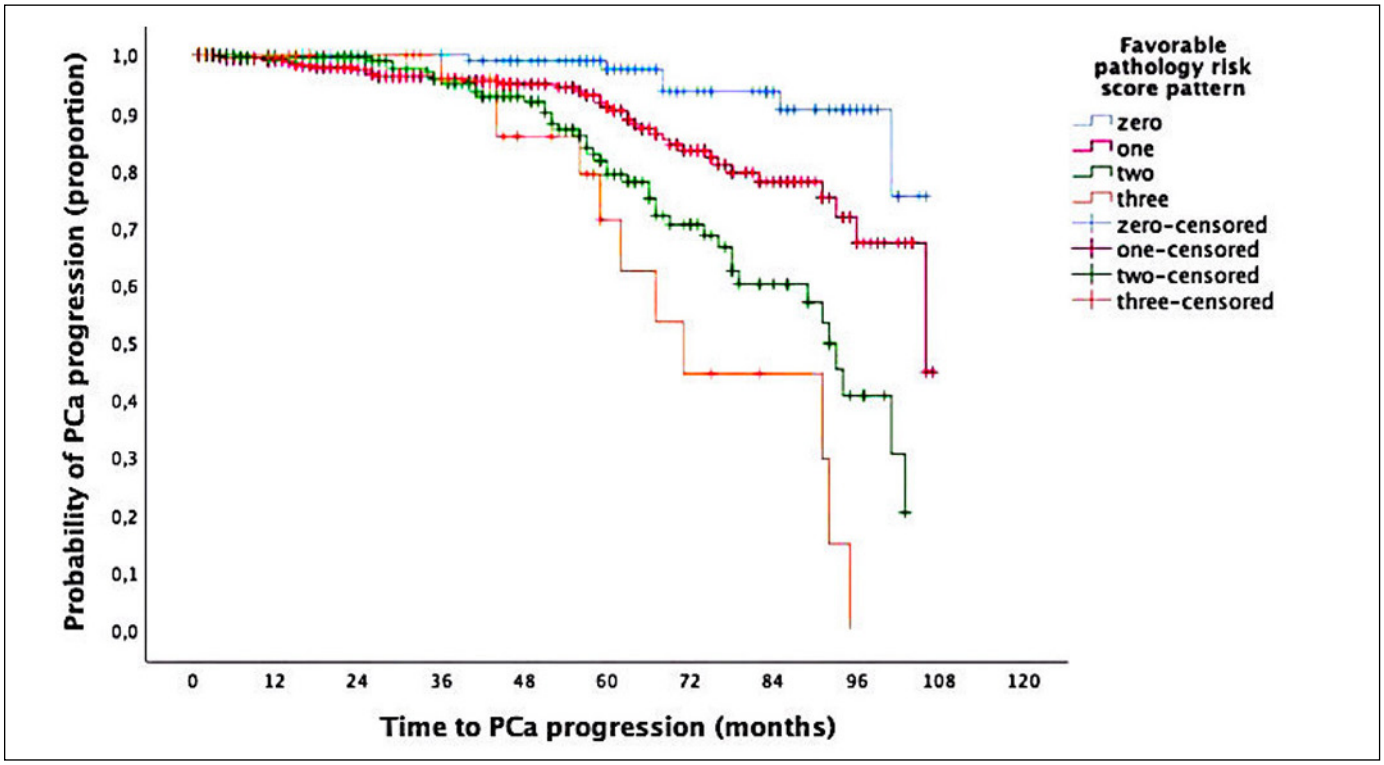

Figure 1. *Kaplan-Meyer survival risk curves of prostate cancer (PCa) progression in 757 patients treated with robotic surgery and stratified through favourable pathology risk score patterns in the surgical specimen. Accordingly, mean survival time of PCa progression decreased from favourable pathology pattern risk score zero (101.7 months; 95% CI: 98.6–104.9 months), one (94.5 months, 95% CI: 90.9–98.1 months), two (83.3 months; 95% CI: 78.6–87.9 months), and three (73.4 months; 95% CI: 63.3–83.5 months) with the difference being significant (Mantel-Cox log rank test: p <0.0001).*

The Cambridge Prognostic Group Classification reports mortality rates between 1.2% and 13.7% [1, 2, 9–12]. Surgically treated PCa may present with various pathological features, categorised as unfavourable (e.g. high-grade tumours with seminal vesicle invasion or lymph node invasion) or favourable [13–20]. Molecular biology and mpMRI are not yet reliable tools for resolving this issue in daily practice [1, 2, 5, 6, 9–20].

This study highlights new considerations for evaluating surgically treated PCa patients with favourable pathological features.

Higher pathology risk scores were associated with increased disease progression, regardless of EAU risk classes or Briganti's 2012 nomogram [21–24]. These findings require further confirmation.

Given these results, it is crucial to consider whether patients with favourable pathology should undergo more intensive follow-up or alternative management strategies. While current protocols primarily focus on high-risk features, our findings suggest that patients with intermediate favourable pathology risk scores may benefit from a more tailored surveillance approach. For example, patients with a pathology risk score of 2 or 3 could undergo closer PSA monitoring, earlier imaging assessment, or discussions about adjuvant therapy options, particularly in those with additional risk factors such as high PSA levels or adverse molecular markers. However, prospective studies are needed to validate these recommendations before modifying current standard protocols.

Grouping favourable pathology features into risk scores, as predicted by Briganti's 2012 nomogram and EAU classifications, may help improve patient counselling [1, 2, 21–24]. This study shows that patients with favourable features may have different prognostic risk patterns predictable preoperatively.

Although Briganti's 2012 nomogram independently predicted prognosis, it did not significantly differentiate between risk scores zero and one in multivariate analysis. This suggests that, for very low-risk patients, additional factors may be required to refine prognostic accuracy.

Briganti's 2012 nomogram is associated with the risk of several favourable pathologic prognostic patterns and disease progression. This may be because it combines several clinical variables into a risk score associated with an aggressive cancer biology phenotype.

However, the role of preoperative nomograms in risk stratification is evolving, particularly with the widespread use of mpMRI and targeted biopsies. These modern imaging techniques improve tumour localisation and risk assessment, potentially reducing the reliance on traditional nomograms. Despite this, our study demonstrates that Briganti's 2012 nomogram retains prognostic value, particularly in settings where mpMRI access remains variable or where additional risk stratification is needed beyond imaging findings.

Managing PCa is complex because EAU prognostic groups are not homogeneous [1, 2, 9–12]. Unrecognised aggressive cancers classified as indolent and vice-versa can lead to undertreatment or overtreatment [1, 2, 9–12].

The natural history of PCa is influenced by a combination of favourable and adverse pathology features that combine into patterns with varying prognostic impacts. This study showed that favourable pathology risk score zero had the best prognosis, while pattern risk score three (ISUP grade group 3 with extracapsular extension) had the worst. Briganti's 2012 nomogram predicted this outcome through EAU risk classes. These results have implications for clinical practice. These findings suggest that integrating pathology risk scores with existing nomograms may refine risk stratification and potentially influence postoperative management strategies.

This study has limitations, as it was retrospective, included several surgeons, and did not evaluate the extent of cancer invasion in each biopsy core or mpMRI findings. However, its strengths include the cohort size, the adequate number of lymph nodes counted when ePLND was performed, and its reflection of daily practice in urologic units.

CONCLUSIONS

Favourable pathology risk score characteristics clustered into risk score groups predicted by Briganti's 2012 nomogram by EAU risk classes showed prognostic impact. As the favourable pathology risk score increased, patients were more likely to progress, regardless of Briganti's 2012 nomogram and/or EAU risk class. Different patterns of favourable pathology risk scores impact prognosis and may alter treatment paradigms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROV AL STATEMENT

The Institutional Review Board of Univeristy of Verona approved the study.

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REVIEW PAPER

UROLOGICAL ONCOLOGY

Simulation-based training in minimally invasive partial nephrectomy

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Introduction Minimally-invasive partial nephrectomy (MIPN) is the standard treatment for kidney tumors with a diameter smaller than 4 cm. It is also performed in selected cases of tumors reaching 7 cm, but it may lead to potential complications. We investigated the current literature for simulators that could be used to teach urologists alone or within the boundaries of a course or a curriculum.

Material and methods We performed a literature search using PubMed (Ovid Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE [R] Daily, and Ovid MEDLINE [R]). Search terms included: simulation, simulation training, education, curricul*, partial nephrectomy, and nephron-sparing surgery. The primary endpoints were the efficacy of different simulators and the impact of different devices, curricula, or courses in training and trainee learning curves.

Results We identified 16 studies evaluating simulation with 3D reconstruction, *ex vivo*, *in vivo*, synthetic models, and virtual reality simulators. Additionally, we identified one study presenting a training curriculum. The results appeared promising, although currently available studies are scarce. Regardless of the type of simulator, participants stated that, to some degree, their skills were improved and their confidence was elevated.

Conclusions Simulation-based training can help novice surgeons familiarize themselves with complex procedure steps and reduce learning curves. A specific validated curriculum for this operation still needs to be included. Validating simulators or curricula for MIPN could be essential to enable more urologists to treat patients safely and effectively.

Key Words: simulation ‹› simulation training ‹› education ‹› curricula ‹› partial nephrectomy ‹› nephron-sparing surgery

INTRODUCTION

Renal cell carcinoma (RCC) is the 6th most frequently diagnosed cancer in men and the 10th in women, accounting for 5.0% and 3.0% of all oncological diagnoses worldwide in men and women, respectively [1]. The increase in early diagnosis has been attributed mainly to the widespread availability of computed tomography (CT) and magnetic resonance imaging (MRI) [2]. For localized RCC, surgery remains the gold standard treatment.

The European Association of Urology (EAU) guidelines suggest minimally-invasive partial nephrectomy (MIPN) as the first treatment option for localized T1 cancer [3]. This procedure is considered more complex than radical nephrectomy, especially the laparoscopic approach, which has a steep learning curve [4] and relatively high rates of potential complications [4, 5]. The robotic-assisted approach also has a steep learning curve, with up to 150 cases needed for excellence [6]. Training with a simulation modality is one way to face these difficulties and improve the outcomes.

This work presents a descriptive overview of currently available simulation modalities and curricula in MIPN.

MATERIAL AND METHODS

We searched using the following terms: simulation, simulation training, education, curricul*, partial nephrectomy, nephron-sparing surgery. We carried out a comprehensive electronic search using MEDLINE (Ovid Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE [R] Daily, and Ovid MEDLINE [R]). The study search strategy was conducted without limitation on publication year until December 2023. Additionally, we reviewed cited references from published systematic reviews/meta-analyses and the included studies.

The study is registered on the OSF platform with registration number (https://doi.org/10.17605/OSF.IO/Z7FYU). After excluding duplicate records, citations in abstract form, and non-English citations from the final literature search, the titles and abstracts of full papers were screened for relevance and defined as original research. A narrative synthesis was conducted due to the nonstandardized quality appraisal and the heterogeneity of the studies. Consideration is given to the drawbacks of utilizing a single database for assessment [7].

RESULTS

We included 17 studies suitable for qualitative synthesis. Five studies presented simulation models with 3D reconstruction [8–12], 5 presented simulation *ex vivo* models [13–17], 2 studied virtual reality (VR) simulation modalities [18, 19], 2 studied *in vivo* models [20, 21], and 2 presented synthetic models [22, 23].

Simulation with 3D reconstruction

In a prospective feasibility study, one surgeon had rehearsals using the daVinci™ Sirobotic surgical system (Intuitive Surgical, Sunnyvale, CA, USA) on 10 kidney models with complex renal masses (R.E.N.A.L. nephrometry score ≥7). The models were based on pre-operative CT or MRI and made of silicone and thinner. The rehearsals took place in a laparoscopic box trainer. The results were promising in surgical planning, pre-surgical rehearsal, and robotic-assisted laparoscopic MIPN training, showing successful construct validity. No differences were detected in volume, shape, negative margins, or time to resection between the model and the tumor [12].

Another prospective study for laparoscopic MIPN on 3 patients used 3 silicone models for pre-operative rehearsals. Resection and renorrhaphy were performed on the model before the actual operation. The average training and operation time of removal was similar in all cases. The study failed to present face, content, or construct validity [9].

Soft tissue physical individual models from selectively deposited photopolymer material filled with agarose were used in another prospective study for robotic-assisted MIPN, including 6 patients with 7 tumors. Investigators prospectively resected tumors on the models using the da Vinci Si surgical robot platform (Intuitive Surgical, Sunnyvale, CA, USA), followed by renorrhaphy the week before the surgery. The average R.E.N.A.L. nephrometry score was 8. The results of the operations were compared to the prospectively maintained robotic-assisted MIPN database. No significant differences were detected except the overall blood loss in favor of the study group. Although a larger cohort is needed to evaluate face and content validity, the authors considered this novel modality a potentially helpful training tool [10].

Another prospective study included 24 individuals: 4 medical students, 14 residents, 3 fellows, and 3 attending surgeons. A representative kidney with a single tumor was selected from the hospital's database. R.E.N.A.L. nephrometry score was 8. Models with and without tumors were printed and filled with 9 : 4 silicone to deadener, initially in the tumor mold. Then, in the tumor mold, the cavity was filled with silicone. Four trials, 2 on two different days, were executed from each participant. All had the same script, and the process was performed on a da Vinci robot system. One blinded researcher evaluated the 3 operation-specific metrics (renal artery clamp time, preserved renal parenchyma, and surgical margins). Metrics were significantly improved from trials 1 to 4. Face and content validity were assessed at the end of the trial (questionnaire 0–100/realistic–unrealistic, useful–useless for training) with mean responses of 79.2 and 90.7 for realism and usefulness, respectively. The trainee self-assessed operative demand was surveyed using the NASA Task Load Index (NASA TLX), significantly improving specific metrics from trials 1 to 4. The standardized and validated Global Evaluative Assessment of Robotic Surgeons (GEARS) was used for surgical performance by blinded experts, and significant improvement was observed in several metrics from trials 1 to 4. The results suggested that training could benefit from such a model, especially for naïve trainees to robotic-assisted MIPN, but can also help experienced trainees improve their skills [11].

Lastly, a prospective multi-institutional study validated a perfused robot-assisted MIPN simulation 3D platform. Face, content, and construct validity were assessed. A CT of a tumor with a nephrometry score of 7 and polyvinyl alcohol (PVA) as material were used for the model. Water-tight hilar structures were 3D-printed with an inner lumen to mimic bleeding and urine leakage functionality. Finally, other anatomical structures to replicate the anatomy were assembled. Artificial blood was perfused to simulate bleeding, and a pad allowed diathermy. From the 5 participating institutes, a total of 43 patients were recruited. Twenty-seven surgeons, novices (1–30 upper tract robotic cases), and 16 experts (>150 cases) participated in the study. Si or Xi da Vinci robotic platforms were used. Experts completed non-validated surveys assessing educational impact, realism, and comparison with other platforms. The validated GEARS was used for third-party validation of 30 participants (10 experts, 20 novices). Clinically Relevant Objective Metrics of Simulators (CROMS) were used for validation. Experts had significantly better results in all aspects of CROMS than novices. The same applied to GEARS.
Finally, experts rated the model higher than porcine or cadaveric models in terms of replication of the steps of the procedure. The experts believed the model's perfused nature benefited trainees [8].
The different simulations with 3D reconstruction are presented in Table 1.

Simulation *ex vivo* models

One study used a fresh porcine kidney in a metallic box for the laparoscopic MIPN training [16]. Red-dyed water was used to simulate the blood of renal vessels. Key steps used in *in vivo*.
MIPN were reproduced. Five experienced residents participated in the study. Two experts mindlessly evaluated them after completing 1 simulation every 2 days for a total of 10 in 20 days regarding the improvement of the quality of the operation. The evaluation was done through a video of the operations. Significant progress was found in all review aspects from the first to the last trial, with the mean quality score steadily increasing from 2.02 to 4.50 on a scale from 1 to 5.
Finally, the participants completed a questionnaire and characterized the model as valuable and helpful regarding their skills in laparoscopic MIPN, intracorporeal suturing and knotting techniques, and instrument manipulation of the renal parenchyma. However, no face, content, or construct validity was assessed.
Another prospective validation study for robotic MIPN used a porcine kidney, in which a Styrofoam ball was built to replicate a tumor [14]. Forty-six participants were categorized as novices (24 completed no robotic console cases), intermediate (9, at least one robotic console case but <100 console cases), or experts (13, ≥100 robotic cases).

Table 1. *Simulation with 3D reconstruction*

			3D reconstruction					
Author, year of publication	Participants	Design and structures	Evaluation	Face validity	Content validity	Construct validity	Important findings	MERSQI score
Ghazi et al. 2021 [8]	n = 43 (27 novices,16 experts)	Multi-institutional prospective	1. CROMS 2. GEARS	✓	✓	✓	Experts significantly outperformed novices Model useful as a training tool (93.8%) and assessment simulation platform (87.5%)	14.5
Golab et al. 2017 [9]	Expert/s 3 patients	Prospective	–	–	–	–	No complications No positive margins	7
Maddox et al. 2018 [10]	Expert/s 6 patients	Prospective	–	–	–	–	Simulation: significantly lower blood loss	9.5
Monda et al. 2018 [11]	n = 24 (4 medical students, 14 residents, 3 fellows, 3 experts)	Prospective	1. GEARS 2. NASA TLX	✓	✓	✓	Mean responses: 79.2 on realism, 90.2 for usefulness as a training tool GEARS scores: significantly better in experts Scores: improved across trials	13.5
von Rundstedt et al. 2017 [12]	Expert/s 10 patients	Feasibility prospective study	–	–	–	✓	Resection time, resected tumor volume, and margins: similar between rehearsals and operations	9.5

CROMS – Clinically Relevant Objective Metrics of Simulators; GEARS – Global Evaluative Assessment of Robotic Surgeons; MERSQI – The Medical Education Research Study Quality Instrument score; NASA TLX – the NASA Task Load Index

The first task was to remove the Styrofoam ball with clear margins without damaging the parenchyma.
After completion, the experts completed a questionnaire concerning realism and its utility as a training tool on a scale of 1–10 (face and content validity). The model was characterized as very realistic (7/10) and valuable as a training tool (9/10) for residents and fellows but not for experts (5/10). Furthermore, 3 experts (>300 robotic cases) blindly validated objective parameters from video recordings prospectively of all the participants (construct validity), such as time to task completion, number of robotic instrument collisions, tumor margin status, and closest tumor margin if the margin was negative. Performance scoring was based on the Global Operative Assessment of Laparoscopic Skills (GOALS). Overall, the experts outperformed the intermediates and the novices. Lastly, 2 novel metrics, "precision, instrument, and camera awareness", were correlated with the GOALS results.
The results showed that such a model could be an essential tool for training, especially for residents and fellows.
In another *ex vivo* porcine model for robot-assisted MIPN simulation, 12 participants (residents, postgraduate years 2 to 6) participated [13]. Four surgical simulations were conducted in a year. Each surgery was performed with a da Vinci SI surgical system with a three-arm setup, and each tumor area was marked on the anterior side of the porcine kidney. Excision of the tumor with clear borders and depth to the collecting system plus renorrhaphy were performed. The participants completed a questionnaire from 1 to 5 before and after the sessions to evaluate content validity, concluding that the model improved skills and confidence. Furthermore, 5 fellowship-trained robotic surgery faculty members blindly assessed the participants using GEARS. Mean excision, renorrhaphy, and total times decreased significantly throughout the simulations. Significant improvement to the overall GEARS scores was also found for each subsequent session from 1 to 4 for residents in postgraduate year 4.
In another study, testing a hemorrhaging laparoscopic MIPN simulation scenario, 7 residents participated in testing the non-technical skills with the Non-Technical Skills for Surgeons (NOTSS) framework [15]. They completed a self-assessment NOTSS after the scenario, and it was compared with NOTSS recorded videos from the staff.
Each simulation used a porcine kidney with a Styrofoam ball in the renal parenchyma as the renal tumor. A foley catheter connected to a bag with dyed water was punctured into the renal hilum to simulate the bleeding. The four-step scenario started with the excision of the tumor, continued with minor bleeding after half unclamping the tube to cause minor bleeding, and then major bleeding with a whole opening of the tube. The scenario finished with at least one round of chest compressions and the alleged success in converting to open surgery to stop the bleeding.
The residents stated that the simulation's usefulness lay in decision-making and communication with anesthesia. This feasibility study found that urology residents needed more experience practicing non-technical surgical skills in simulation and cited interdisciplinary communication as the most critical aspect of the study. The study failed to present face content or construct validity.
Finally, an randomized controlled trial (RCT) evaluated a continuously perfused laparoscopic MIPN model using porcine kidneys [17]. A plastic bag containing 1,000 ml of red gelatin and glycerol was placed above the porcine kidney to simulate blood perfusion with a specially designed glass syringe and rubber catheter connected to the plastic bag and renal artery. Six experts (more than 100 cases), 5 intermediate (some experience), and 18 novices (little exposure) were recruited. Before the training, novices were asked to attend lectures, pre-training sessions, and examinations. Finally, they were examined on picking up beans, suturing silicone models, and having basic knowledge of laparoscopic MIPN. Those who passed the test were eligible to participate. They were then randomly assigned to 2 groups completing 15 rounds of training, a single-model training group (SMTG) training only on a continuously perfused model (CPTM) or a mixed-model training group (MMTG) training first half on a low-fidelity dry-box training models (DBTMs) and the second half on (CPTM). The experts completed a laparoscopic MIPN on a CPTM. The validity was based on the Messick frame, which has 3 parts: content, relationships with other variables, and consequences elements.
Experts assessed content validity and intermediates on a 5-point scale regarding the realism, anatomy, surgical feedback, and sensation during the model's cutting, stitching, and bleeding. All experts and intermediates gave positive questionnaire scores. Significant differences were detected among experts and intermediates compared to the novices. Significant intergroup differences were detected regarding tear length and postoperative bleeding volume within 5 minutes between the SMTG and MMTG in the 8th round in favor of SMTG, with the same results plus fixation rate in the 15th round. The learning curve in the SMTG also showed significant progression of skills, with a plateau in the

11th round. The study showed positive results and suggested that CTPM is a valuable tool for laparoscopic training for novices.
The simulation *ex vivo* models are presented in Table 2.

Virtual reality simulation modalities

The application of virtual reality (VR) in everyday practice is becoming increasingly imminent (Table 3). Although some verified VR simulations exist for robotic surgeries, none are specific to MIPN. A novel platform based on the dV-Trainer (Mimic, Seattle, WA, USA) that features augmented reality (AR) and VR content was validated in a prospective study with 42 participants (15 experts with at least 100 procedures,13 intermediate with less than 100 procedures, and 15 novices without experience) [18].
A recorded operation was shown, and questions and tasks regarding the anatomy and steps of the operation were given. In the end, a full VR renorrhaphy exercise was embedded. Experts found the platform very realistic and helpful as a training tool for residents and fellows, with a median of 9/10 and 8/10 on a scale from 1 to 10, respectively (face and content validity). However, the platform seemed inferior compared to an *in vivo* porcine model. Experts outperformed novices in all tasks of the AR platform. Finally, for the renorrhaphy task, GEARS was as-

Table 2. *Simulation ex vivo models*

Ex vivo models								
Author, year of publication	Participants	Design and structures	Evaluation	Face validity	Content validity	Construct validity	Study result	MERSQI score
Chow et al. 2021 [13]	n = 12 (resident PGY 2–5)	Prospective	Questionnaire GEARS	✓	✓	–	GEARS improves in all residents, statistically significant only in PG4 Confidence and skills improved in all participants	12.5
Hung 2012 [14]	n = 46 (24 novices, nine intermediates, 13 experts)	Prospective	Questionnaire GOALS	✓	✓	✓	Model: cited as realistic (9/10) and helpful (9/10) Experts outperformed novices	14
Lusty 2022 [15]	n = 7 (resident PGY 3–5)	Prospective	Questionnaire NOTSS	–	–	–	Interdisciplinary communication: the most important component of simulation	7.5
Yang et al. 2009 [16]	n = 5 (trainees)	Prospective	Questionnaire and quality evaluation from 2 supervisors	–	–	–	Model: helpful in increasing confidence Quality scores: increased through trials	12.5
Zhang et al. 2023 [17]	n = 29 (6 experts, 6 intermediates,18 novices)	RCT	Questionnaire	✓	✓	✓	Model: better results than the dry-box training	14.5

GEARS – Global Evaluative Assessment of Robotic Surgeons; GOALS – Global Operative Assessment of Laparoscopic Skills; MERSQI score – The Medical Education Research Study Quality Instrument score; NOTSS – Non-Technical Skills for Surgeons; PGY – postgraduate year; RCT – randomized controlled trial

Table 3. *Virtual reality simulation modalities*

VR simulations								
Author, year of publication	Participants	Design and structures	Evaluation	Face validity	Content validity	Construct validity	Study result	MERSQI score
Hung et al. 2015 [18]	n = 42 (14 experts, 13 intermediates, 15 novices)	Prospective	Questionnaire GEARS	✓	✓	✓	Experts found the model very realistic (8/10) and a good training tool (8/10) Experts outperformed novices	13.5
Rasheed 2023 [19]	n = 12 (7 final year residents, 5 interns)	Prospective	Questionnaires	✓	✓	–	Precision and interactivity: Metrics with the highest scores (6/9) Model: helpful for novices to improve cutting skills (7/9)	7.5

MERSQI score – The Medical Education Research Study Quality Instrument score; VR – virtual reality

signed as a validation score by computer metrics and blinded expert video review. Experts outperformed intermediates, and the correlation between porcine and VR models was high. This study showed that specific VR simulations are possible and that further understanding tissue deformity will elevate the whole process.

Another prospective study with 12 participants (7 final-year residents and 5 interns) validated a novel VR laparoscopic MIPN modality [19]. The modality has an interactive interface with a physical and a 3D visualizing aspect. The trainees needed a CT scan to identify the mass and then identify the mass on the kidney being displayed. Trainees could mark and cut with precision along the malignant structure with the aid of 2 laser-emitting controllers while minimizing harm to the nearby tissues. After completing the task, participants answered questionnaires with a scale of 0–9 for face and content validity. The platform was found easy to use with precision and interactivity as the metrics with the highest scores (6/9). The simulation could have been more helpful for advanced surgeons but was useful for novices to enhance their cutting tissue skills (7/9).

In vivo models

Porcine models are standard *in vivo* models for laparoscopic training. Specific models for laparoscopic MIPN are scarce (Table 4).

In one study, investigators used liquid plastic and placed it in the kidneys of 5 pigs under anesthesia to simulate exophytic tumors [21]. The study assessed content validity. The model was evaluated in 2 phases. The first 5 experienced surgeons performed unilateral laparoscopic MIPN. The tumors were easily detected with ultrasound; visually, the margins were negative, and the mean operational time was 32 minutes. In the second phase of evaluation, 28 urologists attended the course, and one week after, a questionnaire with a scale of 1 to 10 was completed. The response rate was 86.0%, 96.0% considered the tumor model to have enhanced their learning experience, 63.0% thought the tumors to be easily resectable. Seventeen participants used ultrasound to locate the tumor, and 4 had difficulties with hemostasis. This novel model with liquid plastic resembles features of actual tumors and can be used as a training model for laparoscopic MIPN.

Another study using *in vivo* swine models evaluated the time required to complete different steps in laparoscopic radical nephrectomy and MIPN, with 12 residents participating [20]. The curriculum lasted 2 weeks, including didactic instruction, inanimate simulation, and live-tissue models. After the didactic instructions and laparoscopic training box skills, on the 14th day, participants participated in live tissue surgery. Senior residents were randomly assigned to junior residents for the live tissue operations. Ten laparoscopic MIPNs were performed, 6 of which were from seniors and 4 of which were junior residents. The mean times were 152 and 173 minutes, respectively. The senior residents required half the time to achieve hilar control, taking 23 minutes vs 42 minutes for junior residents. Additionally, seniors outperformed junior residents during the excision of the simulated lesion.

The results showed that the only significant difference in time to complete a step was found in hilar control, and thus, focusing on this area in the training process should be necessary. No face, content, or construct validity was assessed.

Synthetic models

In this category, the simulation training is done on a kidney made of an artificial material (Table 5). In one study, a kidney model made of polyvinyl alcohol with two threaded tumors was used. Five residents participated, completing 10 identifications, each with laparoscopic ultrasound and 10 laparoscopic MIPN. From the 50 identification processes, the tumor was not visible in only one case, and the same applied in the MIPN with 49 successful procedures. Thirteen cases had positive margins. In the questionnaire (scale 1 to 5), residents found that the tumor was eas-

Table 4. *In vivo models stimulations*

In vivo models								
Author, year of publication	Participants	Design and structures	Evaluation	Face validity	Content validity	Construct validity	Study result	MERSQI score
Eber et al. 2022 [20]	n = 12 (residents PGY 3–6)	Prospective	NA	–	–	–	Junior residents: longer time for hilar control	14
Hidalgo et al. 2005 [21]	n = 28 (experts)	Prospective	Questionnaire	–	✓	–	Model: enhanced laparoscopic skills (96.0%)	8.5

MERSQI score – The Medical Education Research Study Quality Instrument score; PGY – postgraduate year

ily identified in the model with good realism. The texture was found realistic except for one student who considered it moderate (face validity).
Residents found conducting laparoscopic MIPN on the model strenuous and moderate, respectively. All residents found the model helpful for training and would recommend it for teaching. However, because of the small sample of participants, content validity was not evaluated. Polyvinyl alcohol, a material resembling actual tissue in US CT and MRI, showed promising results as a simulation modality for partial nephrectomy [23].
Another study for laparoscopic MIPN simulation also used a polyvinyl alcohol kidney model with a 3-cm exophytic tumor affixed to a silicone slab. Anesthesia urology residents and the nursing staff participated in the study. The number of urology residents was 9. The NOTSS assessment tool was used to evaluate non-technical skills, which was the study's primary goal. Technical skills involved in MIPN were also assessed as the second goal.
The study involved a scenario with phases, control of the right tools, the patient's anaphylaxis during the tumor's excision, and wrong reports from the pathologist during the renorrhaphy. After the scenario, a debriefing session followed. Residents in postgraduate years 4–5 were considered seniors, and those in postgraduate years 2–3 were considered juniors. As far as the results of the technical skills, seniors outperformed the juniors. Non-technical skills were assessed blindly by 2 raters based on recorded videos. The overall Network Time Protocol (NTP) score was significantly higher for the seniors. Residents thought the debriefing was essential and gave them insight into what is necessary for communication. The residents agreed that simulation-based training improves technical and communication skills [22].

Curricula

There are no validated curricula for laparoscopic or robotic MIPN. EAU's Robotic Urology Section (ERUS) developed a curriculum for robot-assisted MIPN and made a pilot clinical validation [24]. Using the Delphi modified method and through surveys based on robotic-assisted MIPN and robotic-assisted training programs literature, opinions from 30 experts were collected. The clinical validation was done with one trainee in an ERUS operational center under mentorship for 18 months.
Robot-assisted MIPN was divided into 10 steps, each with a 1 to 5 degree of difficulty. In the first phase, the trainee observed cases and received theoretical material. In the second phase, the trainee practiced robotic skills using various types of simulators, from VR to *in vivo* porcine models. The third phase was clinical training with a console, and the fourth consisted of a blind evaluation of recorded video of robotic-assisted MIPN. During the curriculum, 40 patients were treated while the trainee took part in the operation and 160 by an expert. No significant differences were found regarding outcome or complications except the duration of the operation (longer for the patients treated involving the trainee).
The curriculum from ERUS seemed very effective; it successfully transitioned a beginner surgeon to be able to complete an entire case and ensured patients were treated safely during the learning curve period of a surgeon. The most significant cohort of trainees and patients is needed to establish the program.
The results of this review of MIPN simulation models and curricula are promising, although currently available studies are scarce. Each study was assessed for quality using the MERSQI score as a tool [25]. The mean score for all the studies was 11.2. The *ex vivo* studies achieved the highest score, with 12.2, while the lowest score was shared between phantom models and VR simulators, with 10.5. The average score of studies that are published is above 10.7. Those getting rejected have a score below 9 [26].
This assessment shows that the quality of the published studies trying to create a model for partial nephrectomy needs significant improvement. Even though the mean was above 10.7, some studies had

Table 5. *Synthetic models stimulations*

Phantoms/Materials models								
Author, year of publication	Participants	Design and structures	Evaluation	Face validity	Content validity	Construct validity	Study result	MERSQI score
Abdelshehid et al. 2013 [22]	n = 9 (residents)	Prospective	Questionnaire NOTSS	–	✓	–	Model: helpful in developing communication skills (100.0%), and developing technical skills (88.0%)	12.5
Fernandez et al. 2012 [23]	n = 5 (residents)	Prospective	Questionnaire	✓	–	–	Model: realistic and helpful for training	8.5

MERSQI – The Medical Education Research Study Quality Instrument score; NOTSS – Non-Technical Skills for Surgeons

a mean below 9, and the mean score of the 2 categories in this review was below 10.7. Regardless of the different types of modalities used as a simulation model, participants stated that, to some degree, their skills were improved, and their confidence was elevated. Simulations can help novice surgeons familiarize themselves with complex procedures and reduce learning curves. These aspects are essential in clinical practice, considering that robotic and laparoscopic operations tend to replace open surgeries completely. Nevertheless, the laparoscopic and robotic MIPN approach is highly demanding, and a validated simulator/curriculum, especially for this operation, is absent.

That leads to a wide heterogeneity between the studies and renders it impossible to compare the different models and their efficiency. One critical heterogeneity factor is the non-uniformly defined surgeon experience through the studies. External validation is also lacking in most studies, and the results are based on participants' opinions or non-validated questionnaires. Another limitation is the non-randomized design of most of the included studies and the lack of comparison between the model and a control group. Furthermore, some studies did not have MIPN training as the main objective, and the sample of participants was too small to make conclusions about the model's usefulness safely. Finally, only a few studies included face, content, and constructed validity, while 5 studies did not conduct any validation.

CONCLUSIONS

Through simulation-based training, inexperienced surgeons can shorten their learning curves and become more comfortable with intricate procedural processes like MIPN. However, a specialized, verified curriculum for this procedure remains necessary. Validating MIPN simulators or curricula might empower more urologists to provide safe and efficient patient care.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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REVIEW PAPER

UROLOGICAL ONCOLOGY

Reclassification of prostate cancer on first confirmatory prostate biopsy in men under active surveillance: A systematic review and meta-analysis

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Introduction Prostate cancer is typically diagnosed following prostate biopsy. In low-risk and selected favourable intermediate-risk disease, active surveillance is the treatment strategy of choice. In these men, a confirmatory biopsy performed. We report on the rates of risk upgrading at biopsy confirmatory that may represent a need to pursue further treatment in lieu of active surveillance.

Material and methods We performed a systematic review and meta-analysis of pooled reclassification rates of men on active surveillance at first confirmatory biopsy, in line with PRISMA recommendations. PubMed, EMBASE, and Cochrane central registry for clinical trials were searched until June 2024. Stata was used to pool reclassification rates at first confirmatory biopsy.

Results Seventeen studies from 9 countries comprising 6,039 patients were included. Transrectal biopsy was the most common biopsy method for confirmatory biopsy. Weighted pooled rates of upgrading on first confirmatory biopsy were 20% with a 95% confidence interval of 19–21%.

Conclusions Approximately 20% of men undergoing active surveillance were upgraded at confirmatory biopsy. This may alter the management of these patients, and it highlights the importance of a confirmatory biopsy.

Key Words: prostate cancer ‹› prostate biopsy ‹› active surveillance ‹› Gleason score

INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed cancer in men and is the sixth most common cause of cancer mortality. It has been reported that 359,000 men died as a result of PC in 2018 [1]. Worldwide PC diagnoses are expected to increase from 1.5 million to 2.9 million per year by 2040 [2].

A relevant clinical history, an abnormal digital rectal examination (DRE), or elevated prostate-specific antigen (PSA) levels may raise clinical suspicion of PC. Multiparametric magnetic resonance imaging (MRI) of the prostate is commonly used to further stratify patients who warrant a biopsy. If MRI is not available, nomogram based risk calculators can be used to

help select patients who require further stratification [3]. Pre-biopsy MRI increases the likelihood of diagnosing significant PC and decreases the likelihood of diagnosing clinically insignificant PC [4, 5]. It has also been shown to be beneficial prior to performing a confirmatory biopsy in MRI-naïve patients [6, 7].

The adoption of active surveillance (AS) aims to identify patients who can avoid or defer intervention and reduce the risk of overtreatment in men with low-risk or favourable intermediate-risk disease [8]. It consists of monitoring patients at pre-determined timepoints with a combination of clinical examination, PSA testing, MRI, and biopsy. Curative treatment may be prompted if there is an indication of clinical progression [3].

Men deemed appropriate for AS will typically undergo a confirmatory biopsy at a per protocol determined timepoint to reduce the risk of missing clinically significant disease [9]. Despite being recommended by the EAU, AUA, and NICE, there is no clear consensus on inclusion criteria or follow-up protocol for patients undergoing AS with discrepancies between guidelines [10–12].

Patients selected for AS typically undergo confirmatory prostate biopsies within 18 months of initial diagnosis. This is to evaluate the appropriateness of AS and the potential need for intervention. The purpose of this review is to summarise the findings of repeat/confirmatory biopsies reported in the literature, with particular attention to a change in Gleason score/ISUP grade. We aim to evaluate the rate of disease reclassification at confirmatory biopsy and review it's role in PC surveillance.

MATERIAL AND METHODS

Registration and search strategy

Our search was conducted in line with the most recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [13]. The study was registered on PROSPERO under CRD42024551202. An electronic search was conducted of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases utilising the search algorithms provided below. The search was completed on June 5, 2024: ("gleason score" OR "gleason grade") AND (change OR increase OR decrease OR reclassification) AND ("active surveillance") AND ("repeat biopsy" OR "confirmatory biopsy" OR "confirm* biopsy" OR "rebiopsy" OR "re biopsy" OR "re-biopsy" OR "subsequent biopsy").

A complete breakdown of the analysed studies can be viewed in the PRISMA diagram (Figure 1). The bibliographies of included publications were also searched for any relevant studies.

Inclusion criteria

- Reports the rates of upgrade on confirmatory biopsy in men undergoing AS for PC.
- English language or translation available.
- Prospective studies or prospectively maintained database studies.
- Full text available.
- Studies reporting upgrading based on pathological diagnosis and not radiology were included.
- Must include Gleason score as a criterion for reclassification.

Exclusion criteria

- Studies that utilised datasets of patients from studies previously included were excluded so as not to include the same data twice.
- Case reports, conference abstracts, retrospective studies.
- Not fulfilling inclusion criteria.
- MRI or PSA prompt to re-biopsy outside of a predefined confirmatory biopsy timepoint.
- If histopathological reclassification figures were not available.
- Not first confirmatory biopsy.
- Studies examining the effect of a medication on PC progression were excluded.
- Studies reporting targeted confirmatory biopsy only based on PIRADs score >3 or excluding some cohort of patients to be generalisable to patients in a non-targeted cohort.

Identification of studies and outcomes of interest

Studies that satisfied the inclusion and exclusion criteria were included. The following PICO elements were used as the basis for selecting studies [14]:

- Population: Patients under AS for PC.
- Intervention: Confirmatory prostate biopsy.
- Comparison: PC grade post confirmatory biopsy versus original diagnostic grade.
- Outcome: Rates of grade upgrading on reclassification post confirmatory biopsy.

Studies were independently reviewed by three separate authors (BMC, KD, HT) using Rayyan [15]. If there was any disagreement between authors, an alternative author (GC) was used to mediate the discussion, and consensus was reached.

The primary outcome of interest was the rate of Gleason score reclassifications post first confirmatory prostate biopsy.

Secondary outcomes of interest were biopsy method, targeted or systematic biopsy, primary and confirmatory biopsy Gleason score/histology, and confirmatory biopsy timing.

Data extraction

Study demographics and biopsy variables of interest were transcribed using Google Sheets (Mountain View, California, United States). Five independent authors (WQ, AD, BMC, AOM, RMC) were involved in the data extraction due to the large number of studies included.

Study selection

Prospective studies including randomised trials were included in this systematic review and meta-analysis. Both the rates and definition of reclassification were used as the primary criterion for inclusion, and the rates provided the metric of interest in our meta-analysis. Secondary outcomes of interest as reported above were included in our systematic review, as were study demographics.

Risk of bias assessment

Assessment of potential biases for non-randomised studies was assessed using a modified Newcastle-Ottawa scale risk of bias tool [16], with the results tabulated in Suppl. Table 1. This assessment tool grades each study as being "satisfactory" or "unsatisfactory" across various categories. We assigned stars to evaluate study quality: 7 stars – "very good", 5–6 stars "good", 3–4 stars "satisfactory", and 0–2 stars "unsatisfactory". The critical appraisal was completed by 2 reviewers independently (EC and AOM), where once again a third reviewer (HCT) was asked to arbitrate in cases of discrepancies in opinion.

Statistical analysis

We performed a proportional meta-analysis as part of this review [17]. Statistical analysis was run using Stata 17 (StataCorp., 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Proportions were pooled using the "metaprop" function within Stata [18]. 95% confidence intervals were employed, and p ≤0.05 was considered statistically significant. Heterogeneity was reported using I^2 [18]. It has been put forward that I^2 values of 25%, 50%, and 75% can be used to assess the degree of heterogeneity [19]. We considered there to be a notable degree of heterogeneity if I^2 was greater than 50%. A random effects model was used due to evidence of significant statistical heterogeneity as well as evidence of study design heterogeneity [20]. Qualitative bias assessment was conducted as proposed by Barker et al. [17] because this was a proportional meta-analysis.

RESULTS

Study and patient demographics

Included studies and patient characteristics are outlined in Table 1. Overall, 783 studies were identified in the database search. After 129 duplicates and non-English texts were removed, 654 articles remained. Titles, abstracts, and full texts were then reviewed, and 637 were excluded. Exclusion criteria are summarised in the PRISMA flow diagram (Figure 1).
In total, data was collected from 17 studies (n = 6,039) for the systematic review [21–37]. The mean age of patients at initial diagnosis was 65 years.

Confirmatory biopsy disease reclassification rate

Biopsy and reclassification details are presented in Table 2. Twelve studies detailed the original biopsy type used, with 10 studies utilising TRUS-guided biopsy [21–27, 29, 35, 36], one study utilising TP bi-

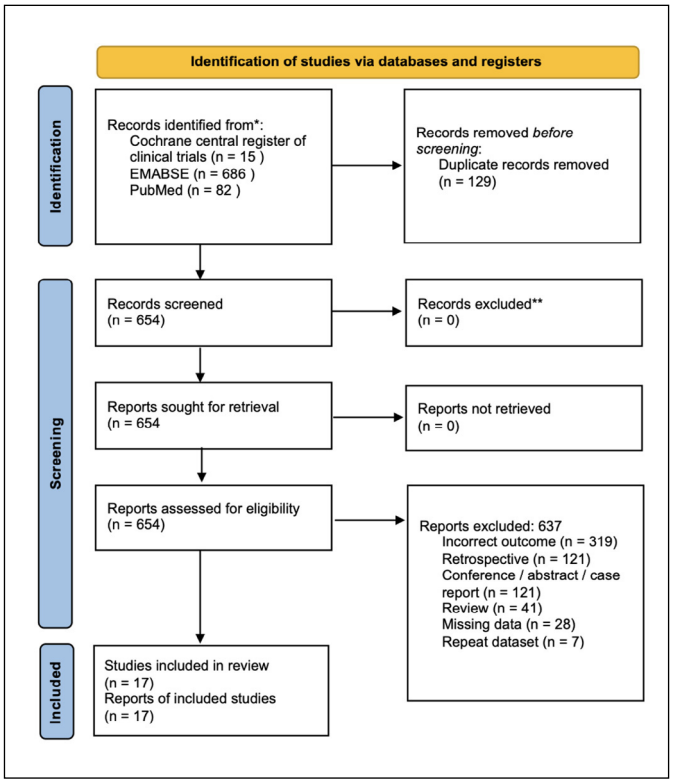


Figure 1. *PRISMA Flowchart.*

opsy [30], and one study utilising TRUS and TP biopsies [37]. Choo et al. [36] also included TURP samples. Five studies did not outline the biopsy method [28, 31–34].

For confirmatory biopsy, 7 studies utilised transrectal biopsy alone [21–23, 25, 26, 29, 36] and 3 utilised TP biopsy alone [24, 27, 30]. One study utilised both TRUS and TP biopsy [37]. One study used a combination of systematic TRUS and MRI assisted targeted biopsy [35]. The 5 remaining studies did not outline the method of confirmatory biopsy [28, 31–34].

Five studies specifically reported patients undergoing MRI pre biopsy, as seen in Table 2 [26, 27, 29, 30, 32].

The primary outcome examined was disease reclassification after confirmatory biopsy. Disease reclassification included cases of upgrade or downgrade. Studies differed in their definition of upgrade; with Kato et al. [37] we used Gleason upgrade alone due to lack of data granularity.

Confirmatory biopsies were performed at various time intervals across the included studies, ranging from 4 to 24 months. From the 6039 patient cases included across all studies, 1454 patients (24.1%) had diagnosis reclassification based on their initial confirmatory biopsy. When examining the rate of upgrading, a total of 1,115 patients had an upgrade after confirmatory biopsy. The pooled rate of upgrade at confirmatory biopsy was 20% (95% CI: 19–21%). The Forest plot displaying this pooled reclassification rate is demonstrated in Figure 2.

Gleason score change was then analysed based on the score itself and not the overall rate of change. Of note, in the study by Venkitaraman et al. [21] and Barnett et al. [33], grouped Gleason scores into categories of no cancer, 6 or less, 3 + 4, 4 + 3, 4 + 4 or greater, and as such the 6 or less group were included in the 3 + 3 forest plot, and the 4 + 4 or greater were included in the 4 + 4 forest plot. Choo et al. [36] and Voss et al. [27] reported Gleason 7 changes and did not report 3 + 4 or 4 + 3 individually. This study was excluded from the meta-analysis regarding Gleason 7 changes as seen in Suppl. Figures 1 and 2 [27, 36]. Because data were included in the 4 + 4 cohort as 4 + 4 or greater, Voss et al.'s [27] patients who were Gleason 9 or 10 were also included in this plot. Pessoa et al. [35] also grouped patients into 4 + 4 or greater.

Overall, there was no cancer observed in 32% (95% CI: 30–34%) of patients who were enrolled in AS, as observed in Figure 3. At confirmatory biopsy, 44% (95% CI: 42–46%) were found to have Gleason 3 + 3 disease (Figure 4). Suppl. Figure 1 shows Gleason 3 + 4 rates of 6% (95% CI: 5–7%) at confirmatory biopsy. Suppl. Figure 2 shows Gleason 4 + 3 rates of 3% (95% CI: 2–3%) at confirmatory biopsy, and Suppl. Figure 3 shows rates of change on confirmatory biopsy of Gleason 4 + 4 or higher of 2% (95% CI: 1–2%). These are the pooled proportions of all studies that reported Gleason score on confirmatory biopsy. It does not imply that all these results were upgrades,

Table 1. *Study demographics*

Study	Journal	Country	Study type	Number of patients	Age
Venkitaraman et al. 2007 [21]	The Journal of Urology	UK	Prospective	119	66 (median)
Choo et al. 2007 [36]	The Prostate	Canada	Prospective	105	70 (median)
Porten et al. 2011 [22]	Journal of Clinical Oncology	USA	Prospective	377	61 (mean)
Whitson et al. 2011 [23]	The Journal of Urology	USA	Prospective	241	61 (mean)
Ayres et al. 2012 [24]	BJU International	Denmark	Prospective	95	68 (median)
Selkirk et al. 2015 [25]	Urology	USA	Prospective	200	66 ±6.9
Pessoa et al. 2017 [35]	BJU International	Brazil	Prospective	105	65 ±24
Elkjaer et al. 2018 [26]	Scandinavian Journal of Urology	Denmark	Prospective	50	65.6 ±5.3
Voss et al. 2018 [27]	BJU International	UK	Prospective	208	63.5 (mean)
Kearns et al. 2018 [28]	European Urology	USA	Prospective	657	63 (median)
Kortenbach et al. 2021 [29]	Scandinavian Journal of Urology	Denmark	Prospective	127	65 (mean)
Kato et al. 2021 [37]	Prostate Cancer and Prostatic Diseases	Japan	Prospective	135	68 (median)
Pepe et al. 2024 [30]	In vivo	Italy	Prospective	30	63 (median)
Bul et al. 2013 [31]	European Urology	Netherlands	Prospective	1,480	65.8 (median)
Jung et al. 2023 [32]	The World Journal of Men's Health	Korea	Prospective	148	68.7 (mean)
Barnett et al. 2018 [33]	Cancer	USA	Prospective	1,370	66 (mean)
Jain et al. 2015 [34]	The Journal of Urology	Canada	Prospective	592	66 ±13

Table 2. *Biopsy details and upgrading rates.*

Study	Original biopsy type	MRI?	Targeted or systematic	Original Gleason score/Benign	Timing of confirmatory biopsy	Confirmatory biopsy mode	Targeted or systematic	Reclassified Gleason score/Benign	Number upgraded	Definition of upgrade utilised
Venkitaraman et al. 2007 [21]	TRUS	No	–	GS ≤6: 104 (87%), GS 3 + 4: 15 (13%)	18–24 months	TRUS	–	No cancer: 25 (21%), GS 3 or less + 3: 68 (57.1%), GS 3 + 4: 18 (15.1%), GS 4 + 3: 6 (5%), GS 4 or greater + 4: 2 (1.7%)	33 (28%) upgraded	Increase in Gleason score, Increase in number of involved cores
Choo et al. 2007 [36]	98 TRUS, 7 TURP	No	–	Gx: 1 (1%), GS 4: 2 (1.9%), GS 5: 14 (13.3%), GS 6: 67 (63.8%), GS 7: 21 (20%)	12–18 months	TRUS		No cancer: 27 (25.7%), GS 5: 4 (3.8%), GS 6: 29 (27.6%), GS 7: 37 (35.2%), GS 8: 8 (7.6%)	37 (35%) upgraded, 34 (32%) downgraded, 33 (31%) unchanged	Increase in Gleason Score only
Porten et al. 2011 [22]	TRUS	No	–	GS 2-6: 356 (94%), GS 7 (3 + 4): 17 (5%), GS 7 (4 + 3): 3 (1%), GS 8-10: 1 (<1%)	12–24 months	TRUS	–	–	81 (21%) upgraded	Increase in Gleason Score only
Whitson et al. 2011 [23]	TRUS	No	–	–	10 months (median)	TRUS	–	–	55 (23%) upgraded	Increase in Gleason Score, Increase In number of involved cores and % core involvement
Ayres et al. 2012 [24]	TRUS	No	Systematic	GS 3 + 3: 101	12 months	TP	Systematic	GS 3 + 4: 20%, GS 4 + 3: 4%, GS >7: 2%, increase vol: 5%, stable 3 + 3: 51%, No cancer: 18%	29 (31%) upgraded	Increase in Gleason score and Increased % core involvement
Selkirk et al. 2015 [25]	TRUS	No		GS ≤6: 200	6 months	TRUS	–	3 + 3 31 (48.4%) 3 + 4 19 (29.7%) 4 + 3 8 (12.5%) 4 + 4 4 (6.3%) Unknown 2 (3.1%)	64 (32%) upgraded	Increase in Gleason Score, Increase In number of involved cores and increased % core involvement
Pessoa et al. 2017 [35]	TRUS	MRI before confirmatory biopsy.	Systematic	GS ≤6: 105	4 to 6 months	Combination of systematic TRUS and MRI assisted targeted biopsy	Both	Gleason 3 + 4 34 (32.38%) Gleason 4 + 3 11 (10.47%) Gleason ≥8 2	58 (total) (55%) upgraded	Increase in Gleason Score, Increase In number of involved cores and increased % core involvement
Elkjaer et al. 2018 [26]	TRUS	MRI at baseline and pre confirmatory biopsy	Systematic	GS ≤6: 25	12 months	TRUS		GS 6 = 20, GS 7 = GS 8 =1	7 (total) (14%) upgraded	Increase in Gleason Score, Increase In number of involved cores
Voss et al. 2018 [27]	TRUS	MRI before confirmatory biopsy	Systematic	GS 3 + 3 (196) GS 3 + 4 (12)	9.9 months	TP	Systematic	Benign = 23 GS 6 = 99 GS 7 = 77 GS 8 = 6 GS 9 = 3	83 (39.9%) upgraded	Increase in Gleason Score, does not state if other metrics used or not.

Table 2. *Continued*

Study	Original biopsy type	MRI?	Targeted or systematic	Original Gleason score/Benign	Timing of confirmatory biopsy	Confirmatory biopsy mode	Targeted or systematic	Reclassified Gleason score/Benign	Number upgraded	Definition of upgrade utilised
Kearns et al. 2018 [28]	–	Variable – data not given	–	GS 3 + 4: 657	11.58 ±4.4 months 1st biopsy	–	–	–	165 (25%) at 1 year	Increase in Gleason score and Increased % core involvement
Kortenbach et al. 2021 [29]	TRUS	50% of patients had a pre initial biopsy MRI	Systematic	–	12 months	TRUS	50% targeted, 50% non-targeted	–	7 (6%) upgraded (targeted) 25 (20%) non targeted and no pre MRI	Increase in Gleason Score Only
Kato et al. 2021 [37]	TP and TRUS	Variable – data not given.	–	G3 + 2 = 1 (0.7%), 3 + 3 = 129 (95.6%), 3 + 4 = 5 (3.7%)	12 months	Both	–	3 + 2 = 0 (0%), 3 + 3 96 (97%), 3 + 4 3(3%)	30 Gleason only (83.3% of reclassified) upgraded	Increase in Gleason Score Only
Pepe et al. 2024 [30]	TP	All men pre confirmatory biopsy	Targeted	G3 + 4: 30	12 months	TP	Targeted	4 + 3 3	3 (10%) upgraded	Gleason Score, Increase In number of involved cores and increased % core involvement
Bul et al. 2013 [31]	–	No	–	–	12 months	Systematic (volume based)	-	-	415 (28%) upgraded – 89 demonstrated GS upgrading, 212 reclassified based on # of positive cores, 114 combination of both	Increase in Gleason Score, Increase In number of involved cores
Jung et al. 2023 [32]	–	96% of patients had MRI with 33% of these being pre initial biopsy and 66% post initial biopsy	–	G3 + 3 = 268 (94.4%), G3 + 4 = 16 (5.6%)	9.5 months mean	–	–	Upgrading of ISUP grade 20 (13.5%), but GG not specified	41 upgraded	Increased % positive cores or ISUP grade
Barnett et al. 2018 [33]	–	No	–	GS ≤6: 1488 (99.7%), NA: 5 (0.3%)	13 months (mean)	–	–	No cancer: 568 (41.5%), GS ≤6: 670 (48.9%), GS 7: (3 + 4) 78 (5.7%), GS 7: (4 + 3): 30 (2.2%), GS ≥8: 18 (1.3%), NA: 6 (0.4%)	126 (9.2%) upgraded	Increase in Gleason Score only
Jain et al. 2015 [34]	–	No	–	–	16 months (median)	–	–	–	136 upgraded (22.9%), 242 (40.8%) no change, 19 downgrade (3.2%), 198 (33.3%) negative	Increase in Gleason Score only

TRUS – transrectal ultrasound; TP – transperineal; TURP – transurethral resection of the prostate; GS – Gleason score

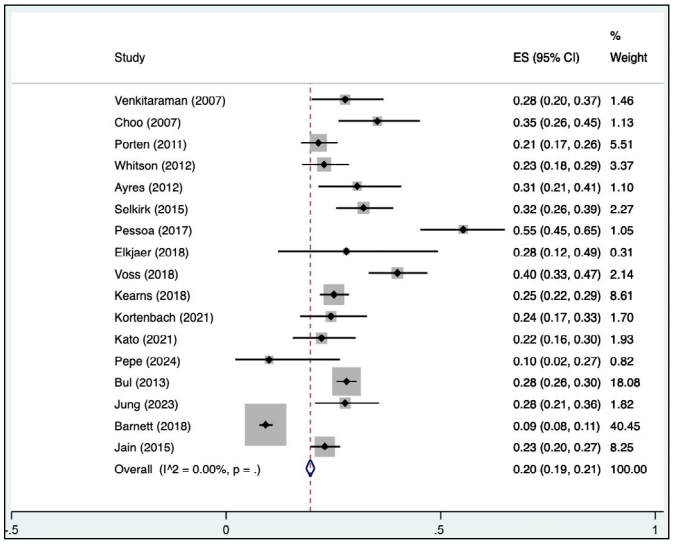


Figure 2. *Pooled rates of prostate cancer upgrade at confirmatory biopsy.*

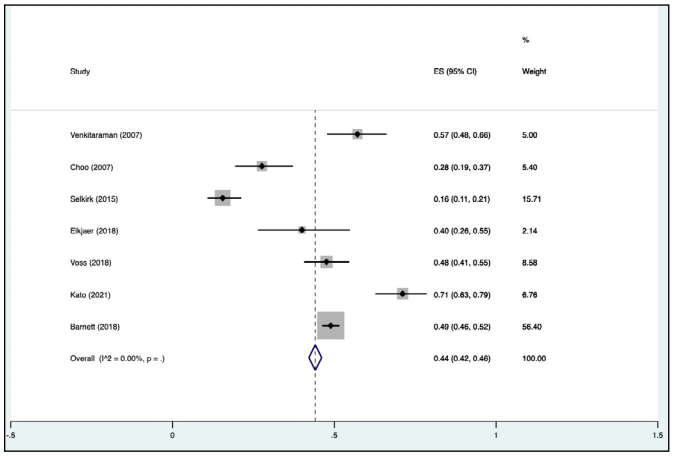


Figure 3. *Proportion of no cancer at confirmatory biopsy.*

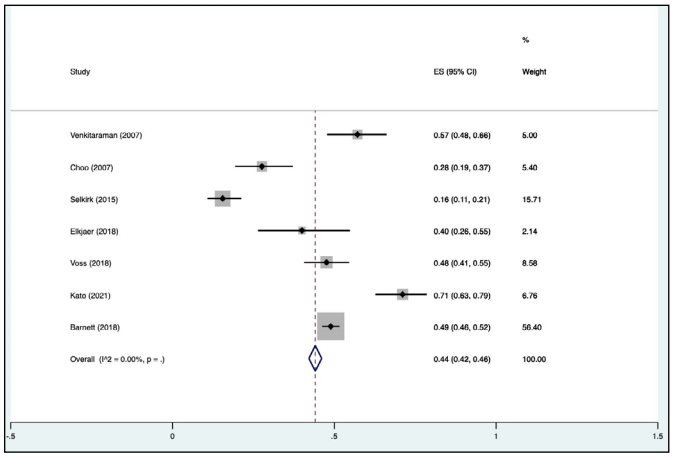


Figure 4. *Proportion of Gleason 3 + 3 at confirmatory biopsy.*

and of course, because no cancer was found in some samples, some were downgrades.

Risk of bias assessment

Fourteen studies received a score of 9 [21–34], while 2 received an 8 [35, 36] and one a 7 [37].

DISCUSSION

In this systematic review and meta-analysis, we have synthesised evidence in relation to AS of PC and the rate of reclassification at confirmatory biopsy. We report on the pooled rate of upgrade reclassification at first confirmatory biopsy.

Our calculated rate of 20% is in line with other previous individual studies on the topic, which interestingly found that the timing of first confirmatory biopsy did not influence the rates of upgrading observed [38]. Furthermore, immediate repeat biopsy has shown similar rates of upgrading [39]. This may imply that the sampling as well as disease progression may account for disease reclassification typically associated with repeat biopsies. This may alter our approach and care when taking initial prostate biopsies. Overall, we observed a considerable amount of initial confirmatory re-biopsy to be clinically insignificant. While this study does not take into account disease volume, 32% of repeat biopsies were observed to show no cancer and 44% were Gleason 3 + 3 disease or less. Of course, Gleason 7 and above disease was picked up on confirmatory biopsy, which may have ultimately prompted further management. Also, some patients with Gleason 3 + 3 disease on initial confirmatory biopsy may have ultimately opted for further management if they had a higher volume disease.

We observed that just one study, by Pepe et al. [30], included only transperineal prostate biopsy. All other studies either did not report on the biopsy type used or used TRUS. One study reported using a mix of TRUS and TP [37].

One such way to ensure adequate sampling is perhaps to employ a targeted as well as a systematic approach [40]. The use of targeted biopsy alone has also been seen to eliminate the risk of finding clinically insignificant disease, which must be weighed against the risk of undersampling [41]. A previous meta-analysis has demonstrated the value of prebiopsy MRI in improving diagnostic accuracy [42]. Previous studies have suggested that MRI use may defer the need for confirmatory biopsy [43]; however, our results, including some studies from the MRI era, indicate that there is still utility in confirmatory biopsy demonstrated by the significant rate of PC

reclassification [44]. We acknowledge that this was not the main aim of this study, however, we excluded studies with targets solely on MRI prior to confirmatory biopsy. This was done to examine the rate of upgrade in our patient cohorts in which they may or may not have had an MRI, or there was no target on MRI, for example in a PIRADS 2 MRI with a PSA density >0.2. There is a paucity of data detailing if the biopsies were targeted or systematic; however, Kortenbach et al. [45] reported an upgrade rate of 6% for targeted and 20% for systematic. This may support the use of targeted biopsy alone in low-risk men as per the latest EAU guidelines; however, with the significant upgrade rate we report it also supports the use of systematic biopsy prior to very low-risk disease being included in AS protocols.

With the advent of improved diagnostic techniques, including pre-biopsy MRI and trans-perineal biopsy, the role of routine confirmatory biopsy has been brought into question [46].

There remains a significant rate (20%) of Gleason score reclassification at confirmatory biopsy. This suggests that undersampling remains a consideration even with modern diagnostic techniques; however, this should again be taken with the consideration that not all upgrades prompt treatment. The EAU defines confirmatory biopsy as taking place usually between 6 and 12 months post initial diagnosis, suggesting that if an MRI-targeted and systematic biopsy is performed, then a confirmatory biopsy can be omitted; however, they state that should a confirmatory biopsy be performed, then it should be MRI targeted and systematic [45].

There is significant heterogeneity regarding active surveillance protocols. Mean first confirmatory biopsy times of 6 months have been described in the literature [47]. However, as can be observed from our results, a wide range of timelines are followed in practice. Included in this review are studies from Europe, North America, South America, and Asia, and as such, a broad timing of biopsy protocols may be expected. Taking this into account, these figures should represent global practise.

Further implications are the impact of subsequent benign or unchanged biopsy results, which identify patients with an excellent prognosis [48]. The extra prognostic information provided by confirmatory biopsy must be weighed against the risk of complications of a biopsy and use of resources. Additionally, some men opt for radical treatment without evidence of progression, which illustrates the mental toll AS may have on some men [49].

This meta-analysis demonstrates a significant rate of reclassification to a higher Gleason score. While this may not necessitate treatment, histological grade is one of the mainstays of prognostication, and therefore accuracy is paramount. While this study is important and novel, several limitations are present. There is significant heterogeneity between studies in relation to the use of MRI, biopsy technique, and timing of confirmatory biopsy. These data also include significant data weighting towards the Johns Hopkin's data set, which included favourable-risk PC and older men with low-risk disease [33]. Percentage core volume involvement and core involvement amongst other metrics would be used in conjunction with a Gleason score upgrade in clinical practice, and as such some of these figures do not represent an entire decision-making tool, but they do represent a possible illustration of the usefulness of confirmatory biopsy. Porten et al. [22] also included a Gleason 8 or above disease cohort, illustrating the patient selection heterogeneity.

Based on this review, we conclude that confirmatory biopsy plays an important role in patients managed with AS who do not undergo pre-biopsy MRI or, who have no target on MRI and undergo systematic biopsy. This may represent patients with no lesion on 2 MRI with a high PSA density, for example. This is also in agreement with current EAU guidelines for low-risk men who undergo targeted and perilesional biopsy alone, i.e. that they require a repeat systematic biopsy prior to being enrolled in AS. This data change to "supports this" recommendation because the risk of upgrading may be as high as 20%; however, a limitation of this data is that targeted cohorts are lacking. The role of MRI to replace confirmatory biopsy remains unproven but warrants further evaluation. Further studies may be prudent to evaluate the effect of per protocol vs for cause biopsy in confirmatory biopsy, as well as the impact of initial MRI and biopsy targeting status on reclassification rates, which may inform further EAU guidelines.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

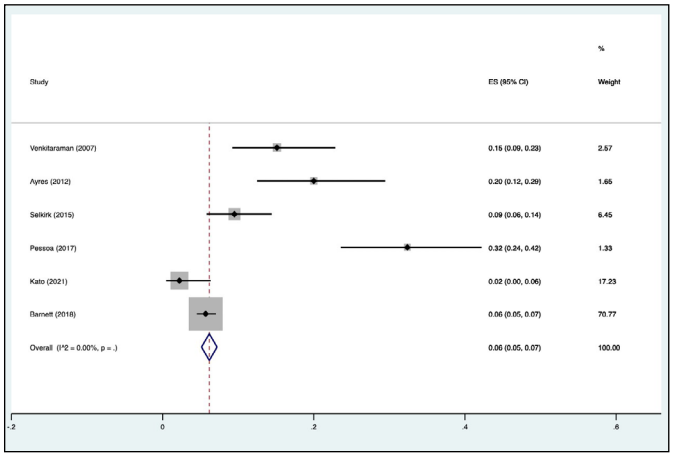
FUNDING

This research received no external funding.

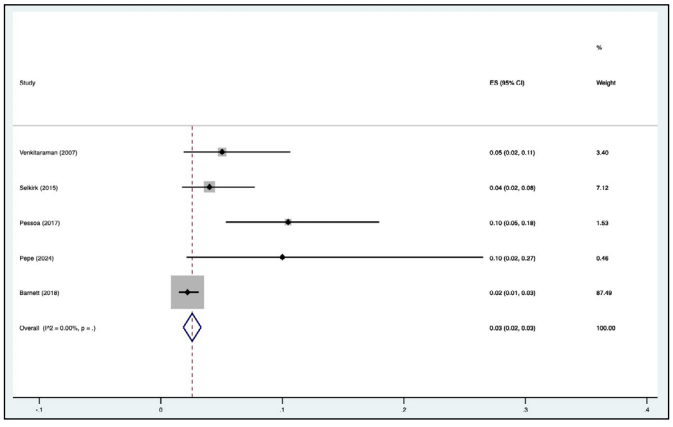
ETHICS APPROVAL STATEMENT

The ethical approval was not required.

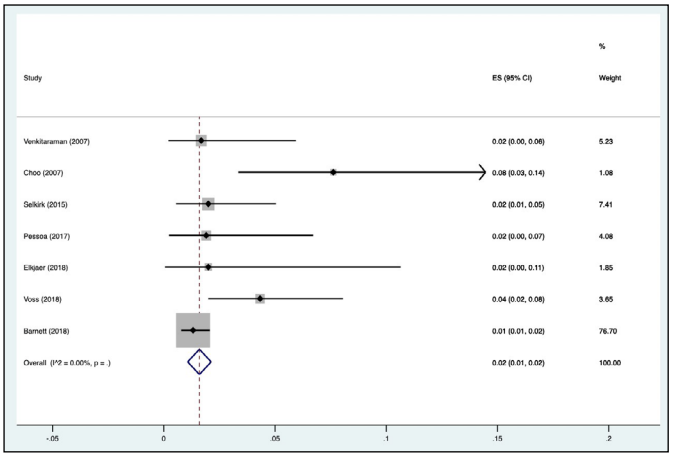
SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *Proportion of Gleason 3 + 4 change at confirmatory biopsy.*



Suppl. Figure 2. *Proportion of Gleason 4 + 3 change at first confirmatory biopsy.*



Suppl. Figure 3. *Proportion of Gleason 4 + 4 or greater change at first confirmatory biopsy.*

Suppl. Table 1. *Risk of bias assessment*

Author	Selection				Comparability of cohorts on the basis of the design or analysis		Outcome			Total score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that this outcome was not present at the start	Main factor	Additional factor	Assessment of outcome	Sufficient follow-up time for outcomes to occur (≥6 months)	Adequacy of follow-up	
Venkitaraman et al. 2007 [21]	*	*	*	*	*	*	*	*	*	9
Choo et al. 2007 [36]	*	*	*	*	*	*	*	*	/	8
Porten et al. 2011 [22]	*	*	*	*	*	*	*	*	*	9
Whitson et al. 2011 [23]	*	*	*	*	*	*	*	*	*	9
Ayres et al. 2012 [24]	*	*	*	*	*	*	*	*	*	9
Selkirk et al. 2015 [25]	*	*	*	*	*	*	*	*	*	9
Pessoa et al. 2017 [35]	*	*	*	*	*	*	*	*	/	8
Elkjaer et al. 2018 [26]	*	*	*	*	*	*	*	*	*	9
Voss et al. 2018 [27]	*	*	*	*	*	*	*	*	*	9
Kearns et al. 2018 [28]	*	*	*	*	*	*	*	*	*	9
Kortenbach et al. 2021 [29]	*	*	*	*	*	*	*	*	*	9
Kato et al. 2021 [37]	*	*	*	*	*	/	*	*	/	7
Pepe et al. 2024 [30]	*	*	*	*	*	*	*	*	*	9
Bul et al. 2013 [31]	*	*	*	*	*	*	*	*	*	9
Jung et al. 2023 [32]	*	*	*	*	*	*	*	*	*	9
Barnett et al. 2018 [33]	*	*	*	*	*	*	*	*	*	9
Jain et al. 2015 [34]	*	*	*	*	*	*	*	*	*	9

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ORIGINAL PAPER

FUNCTIONAL UROLOGY

Complications of anatomical endoscopic enucleation of the prostate in real-life practice: What we learnt from the 6,193 patients from the Refinement in Endoscopic Anatomical enucleation of Prostate registry

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Introduction Anatomical endoscopic enucleation of the prostate (AEEP) is a guideline-recommended treatment for benign prostatic hyperplasia (BPH). We aimed to analyze postoperative complications and outcomes within a large real-world database.

Material and methods The Refinement in Endoscopic Anatomical enucleation of Prostate (REAP) registry includes patients who received AEEP for BPH in 8 centers worldwide from January 2020 to January 2022. Exclusion criteria included previous prostate/urethral surgery, prostate cancer, pelvic radiotherapy, and concomitant lower urinary tract surgery (internal urethrotomy, cystolithotripsy, or transurethral resection of bladder tumor). The primary outcome was postoperative incontinence; secondary outcomes included early complications (<30 days) and late complications (>30 days).

Results We analyzed 6,193 patients; the mean age was 68 years. Thulium laser was used in 37% and high-power holmium laser in 32%. Median operation time was 67 min [IQR 50–95 min]. The 2-lobe enucleation technique was utilized in 49%, and en-bloc resection was utilized in 39%. Early postoperative complications included urinary tract infection (4.7%), acute urinary retention (4.1%), post-operative bleeding requiring additional intervention (0.9%), and sepsis requiring intensive care admission (0.1%).

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The incidence of postoperative incontinence was 14.8%, of which 54% were stress incontinence; 84% cases resolved by 3 months. On univariate and multivariate analysis, prostate volume >100 ml was a significant predictor of postoperative incontinence. Late complications such as bulbar urethral stricture, bladder neck sclerosis, and need for redo BPH surgery each occurred in <1% of patients.
Conclusions Analysis of the real-world REAP database shows favorable safety outcomes for AEEP, with a low incidence of serious complications and postoperative incontinence beyond 3 months.

Key Words: benign prostate hyperplasia ‹› anatomical endoscopic enucleation of the prostate ‹› prostate

INTRODUCTION

Anatomical endoscopic enucleation of the prostate (AEEP) is recommended by international guidelines [1, 2] for the surgical management of clinical benign prostate hyperplasia (BPH). When counseling patients on operative outcomes, it is imperative to highlight the pros and cons of any surgery, as AEEP is not devoid of complications even in experienced hands [3, 4]. To optimize laser AEEP procedures, a Delphi consensus statement on a standardized practices has been published, with the aim to improved outcomes and patient satisfaction [5]. Although considered safe, complications still occur and can be attributed to patient selection, instrument, intra-operative technical difficulties [6], surgeons' experience and learning curve [4]. The Refinement in Endoscopic Anatomical enucleation of Prostate (REAP) database [7] was established with the aim of analyzing outcomes from a multicenter real-world experience. Our primary aim is to report and analyze complications from the REAP database, where AEEP is practiced and adapted via various techniques and energy sources according to local expertise and resources.

MATERIAL AND METHODS

Registry design and enrolment protocol

The REAP registry is a retrospective multicenter anonymised database aimed at understanding how enucleation is performed in different parts of the world. Data from this registry is hoped to strengthen results known in the literature, reveal unknown issues and ultimately help to improve the real-world practice of AEEP. 6,193 patients were enrolled in the registry from 12 surgeons, from 8 centers, with at least 200 cases of enucleation experience for each surgeon. This study included adult patients who underwent AEEP for clinical BPH between January 2020 and January 2022. Patients with previous prostate/urethral surgery, prostate cancer, and pelvic radiotherapy were excluded. Patients who underwent concomitant lower urinary tract surgery were also excluded (i.e., internal urethrotomy, cystolithotripsy, or transurethral resection of bladder tumor). If there was a suspicion of prostate cancer, it was ruled out with prostate biopsy before enucleation. Oral anticoagulant agents were switched to low-weight molecular heparin in preparation for surgery and resumed as per each center's discretion. Antibiotic prophylaxis was administered to all patients according to local protocols. Intraoperative, immediate postoperative (within 24 hours), intermediate (within 3 months), and late, more than 3 months and within a year, were also recorded.

Patient follow-up and secondary treatment

Patients were assessed post-surgery according to the local standard of care. Follow-up time intervals were at 1, 3, and up to 6 months. Enucleation time was calculated from the start of enucleation to the start of morcellation. Surgical time was considered from cystoscopy to catheter placement. Incontinence was defined as any urine leakage as reported by the patients. Details for histopathology were also obtained. Information on functional outcomes at 3-month or 6-month follow-up and up to 1 year, as available, was requested. The follow-up reflected each participant's center's protocols.

Statistical analysis

All statistical analyses were performed using R Statistical language, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with $p < 0.05$ indicating statistical significance. Continuous variables are reported using medians and interquartile ranges (IQR), while categorical variables as absolute numbers and percentages. Univariable logistic regression analysis (UVA) was performed

to evaluate factors associated with complications and postoperative urinary incontinence. Relevant potentially prognostic variables in UVA were entered into a multivariable model (MVA) to assess their significance as independent predictors. Predictors were described using odds ratios (OR), 95% confidence intervals (CI), and p-values.

Bioethical standards

Institutional review board approval was obtained by the Asian Institute of Nephrology and Urology (AINU 11/2022), and the remaining centers received approval from their respective institutional boards.

RESULTS

6,193 patients, who met the inclusion criteria were included in the final analysis. Table 1 shows patients' baseline characteristics. Median age was 68 years, with 8% of the cohort being >80 years. The majority (40.5%) of patients were ASA 2 score. Preoperative PSA was reported in 5,232 patients with a median value of 4.30 ng/dl [2.40, 7.15]. Only 21.95% of patients were on a preoperative indwelling catheter for acute urinary retention. AEEP was performed in 2,326 (37.8%) patients with a prostate volume larger than >80 ml. Table 2 shows the operative characteristics of the cohort. The most popular energy source was the holmium laser. Both low-power (2.7%) and high-power holmium lasers (HLs) (31.6%) were used. Thulium fiber laser (TFL) was used in 36.5% of cases. Monopolar electrocautery devices were used in 1.1% of patients.

The most common technique used for enucleation across all gland sizes was the 2-lobe technique in 48.8% of cases with the en-bloc technique being the next preferred approach in 38.6% of patients. 86.2% of the procedures were performed under spinal anesthesia with a median operation time, [IQR] of 67 min [50, 95]. The most used morcellator was Piranha (Richard-Wolf, Germany) (81.4%). Median postoperative catheter time was 2 [1, 3] days. Table 3 shows the postoperative outcomes. The early postoperative complication rate was very low with urinary tract infections as the most commonly reported (4.7%) followed by acute urinary retention within 24 hours of post-operative catheter removal (4.1%). Postoperative bleeding needing additional intervention was only reported in 57 patients (0.9%) and sepsis needing intensive care admission in 9 patients only

Table 1. *Patient baseline characteristics and demographics (n = 6,193)*

Parameter	
Age, median [IQR]	68 [62, 74]
Age categories, n (%)	
<50	47 (0.76)
50–60	882 (14.3)
60–70	2,676 (43.3)
70–80	2,084 (33.6)
>80	498 (8.0)
Prostate volume (cc), median [IQR]	73 [55, 95]
<30 cc, n (%)	145 (2.4)
30–80 cc, n (%)	3,686 (59.9)
>80 cc, n (%)	2,326 (37.8)
Preoperative IDC for urinary retention, n (%)	1,355 (21.9)
ASA score, n (%)	
1	1,249 (33.8)
2	1,497 (40.5)
3	940 (25.4)
4	14 (0.4)
Preoperative IPSS, median [IQR]	23 [21, 26]
Preoperative QoL, median [IQR]	5.0 [4.0, 5.0]
Preoperative Q_{max}, median [IQR]	8.0 [6.0, 10.5]
Preoperative PVR, median [IQR]	70 [50, 100]
Preoperative PSA, median [IQR]	4.30 [2.40, 7.15]

ASA – American Society of Anesthesiologists; IDC – indwelling catheter; IQR – interquartile range; IPSS – International Prostate Symptom Score; Q_{max} – maximum flow rate; QoL – quality of life; LWMH – low-weight molecular heparin; PSA – prostate-specific antigen; PVR – post-voiding residual urine

Table 2. *Operative characteristics*

Parameter	
Energy source for enucleation, n (%)	
Low power holmium (up to 30 W)	166 (2.7)
High power holmium (>30 W)	1,954 (31.6)
Holmium laser with MOSES technology	176 (2.8)
Thulium fiber laser	2,262 (36.5)
Thulium-YAG laser	676 (10.9)
Bipolar electrocautery	391 (6.3)
Monopolar electrocautery	70 (1.1)
Holmium laser with virtual basket	498 (8.0)
Enucleation type, n (%)	
3 lobes	775 (12.5)
2 lobes	3,021 (48.8)
En bloc	2,390 (38.6)
Early apical release, n (%)	2,898 (46.8)
Spinal anesthesia, n (%)	5340 (86.2)
Operation time, median [IQR]	67 [50, 95]
Enucleation time, median [IQR]	50 [35, 77]
Morcellation time, median [IQR]	20 [10, 40]
Morcellator events, n (%)	
Malfunction	10 (0.16)
Minor bladder injury	40 (0.65)
Major bladder injury	1 (0.02)
Fragment retrieval issues	1 (0.02)
Day surgery, n (%)	49 (0.8)
Postoperative catheter time (days), median [IQR]	2.0 [1.0, 3.0]

BPH – benign prostatic hyperplasia; IQR – interquartile range

(0.1%). 3-month follow-up visit showed decreased IPSS, with improvement in micturition parameters and QoL. These improvements were sustained one year after surgery (Table 3). Stress urinary incontinence was the most frequently reported type, affecting 53.9% of patients with incontinence. After three months, it persisted in 16.2% of the cohort. 25.5% of the patients were put on postoperative Kegel exercises to cope with postoperative urinary incontinence. The all-cause 30-day readmission rate was only seen in 3% of the cohort. Over the 1-year follow-up, only 8 patients (1.4%) had a surgical re-intervention for management of residual adenoma. Table 4 shows that when analyzed for prostate size, the incidence of post-operative incontinence was more significant if the prostate volume was larger than 100mls, with no statistical difference in duration of incontinence or delayed complications such as urethral stricture or redo BPH surgery within a year. On further subgroup analysis (Table 5), enucleation type did not have any impact on the incidence of postoperative incontinence but rather the duration of incontinence and need for Kegel exercise.

Table 3. *Early and late post-operative complications, and symptoms and micturition parameters at follow-up*

Early complications, n (%) (24 hours to 30 days)	
Acute urinary retention within 24 hours (Clavien 2)	252 (4.1)
Postoperative bleeding needing surgical control or additional hemostasis (Clavien 3)	57 (0.9)
Urinary tract infection (Clavien 2)	289 (4.7)
Sepsis needing ICU (Clavien 4)	9 (0.1)
Postoperative incontinence, n (%) within 3 months	916 (14.8)
Urge	296 (29.5)
Stress	541 (53.9)
Mixed	167 (16.6)
Postoperative incontinence	916 (14.8)
Duration <1 month	407 (44.4)
Urge	179
Stress/mixed	228
Duration 1–3 months	252 (27.5)
Urge	69
Stress/mixed	166
Duration >3 months	127 (13.8)
Urge	48
Stress/mixed	78
Kegel exercise needed, n (%)	609 (25.5)
30-day readmission, n (%) (any cause)	138 (3.0)
Late complications, n (%)	61 (11.0)
Bulbar urethral stricture requiring dilatation alone as an outpatient:	
Urethral stricture requiring urethrotomy under anesthesia	20 (3.6)
Bladder neck sclerosis requiring transurethral incision	45 (8.1)
Redo BPH surgery within 1 year	8 (1.4)
3-month follow-up	
IPSS, median [IQR]	6.0 [4.0, 8.0]
QoL, median [IQR]	2.0 [1.0, 2.0]
Q_{max}, median [IQR]	21.3 [18.0, 25.2]
PVR, median [IQR]	16 [10, 30]
12-month follow-up	
IPSS, median [IQR]	5.0 [3.0, 7.0]
QoL, median [IQR]	1.0 [1.0, 2.0]
Q_{max}, median [IQR]	22.0 [18.0, 27.0]
PVR, median [IQR]	15 [0, 31]

BPH – benign prostatic hyperplasia; ICU – intensive care unit; IPSS – International Prostate Symptom Score; Q_{max} – maximum flow rate; QoL – quality of life; PVR – post-voiding residual urine

DISCUSSION

Primarily, AEEP can be described in two main steps: 1) enucleation of prostatic adenoma (any energy modality) and 2) intravesical morcellation [8]. When first described in 1998 by Gilling and Fraundorfer, holmium laser resection of the prostate (HoLRP) was reported to be inferior to transurethral resection of the prostate (TURP) with respect to operative time, as there were limitations with morcellation, thereby limiting widespread acceptance [9]. Despite the advent of the electromechanical/power

Table 4. *Analysis of post-operative complications grouped by prostate volume*

	All	Prostate volume <100 (n = 4,753)	Prostate volume >100 (n = 1,404)	p
Postoperative incontinence, n (%)	916 (14.8)	682 (14.3)	232 (16.5)	0.049
Urge	296 (29.5)	216 (28.9)	80 (31.4)	
Stress	541 (53.9)	418 (56.0)	123 (48.2)	
Mixed	167 (16.6)	113 (15.1)	52 (20.4)	
Duration of incontinence for those affected, n (%)				0.148
1–3 months	252 (32.1)	193 (33.9)	59 (27.4)	
>3 months	127 (16.2)	93 (16.3)	33 (15.3)	
Kegel exercise needed, n (%)	609 (25.5)	443 (23.0)	165 (36.1)	<0.001
30-day readmission, n (%)	138 (3.0)	113 (3.2)	24 (2.4)	0.254
Delayed complications, n (%)				
Bulbar urethral stricture requiring dilatation alone as outpatient	61 (11.0)	45 (0.9)	16 (1.1)	0.626
Urethral stricture requiring urethrotomy under anesthesia:	20 (3.6)	17 (0.4)	3 (0.2)	0.571
Bladder neck sclerosis requiring transurethral incision	45 (8.1)	30 (0.6)	13 (0.9)	0.326
Redo BPH surgery within 1 year:	8 (1.4)	6 (0.1)	2 (0.1)	>0.99

BPH – benign prostatic hyperplasia

morcellator in 1993 being utilized in other surgical domains, it still remained unsuitable for transurethral surgery [10, 11]. Only with the innovation of the first enucleation morcellator design [8, 12] and its use in prostate surgery did AEEP catalyze a paradigm shift. Henceforth, several morcellators have been developed with improvements in their efficacy and efficiency but with their own drawbacks too [13].

In our series, minor bladder injury, which was classified as Clavien-Dindo 1 (CD1), defined as injury that does not preclude further morcellation or requiring further intervention, was only seen in 40 cases (0.65%). Perhaps this can be attributed to the experience of the surgeons who are well-versed with issues pertaining to improper morcellation. One patient (0.02%) with a gland more than 80 ml had a CD3 bladder injury at morcellation, necessitating a suprapubic catheter placement and prolonged catheterization when using the drill-cut morcellator. Ibrahim et al also reported a similar complication [13]. A need to utilize different devices (e.g., monopolar loop, cystoscopic forceps, grasper) to retrieve small fragments of adenoma can occur commonly [13]. We had only 1 reported case where there was a significant challenge in removing the enucleation tissue at morcellation, necessitating open removal via the suprapubic route. The retrospective design of this study could have a bias of many cases performed at these centers, where morcellation-specific complications were either underreported or not recorded.

Often, urinary incontinence is interchangeably reported as a complication or a measure of functional outcome when patients are counselled, and it depends on several factors. Continence in men depends on a complex mechanism where the external (striated) sphincter's activity is not the sole factor responsible. Indeed, urinary continence can still be preserved even when the striated sphincter is paralyzed [14]. It is proposed that the muscular and elastic tissue located in the distal third of the prostatic urethra might have a crucial role in sustaining continence [15]. Damage to this specific segment of the urethra could potentially contribute to SUI following surgery for BPH. Consequently, the preservation of the distal prostatic urethra seems to play an important role in maintaining continence after EEP, as demonstrated by the application of the early apical release technique [16].

In our study, larger prostates of >100 cc was significantly associated with postoperative incontinence (Table 4). A possible hypothesis could be due to the common finding of a wide prostatic fossa after EEP, due to the more complete adenoma removal compared with transurethral resection of the prostate. Indeed, transition zone prostate volume was found to be associated with a 5-fold of persistent SUI after holmium laser enucleation of the prostate [17]. Moreover, a large prostatic fossa can lead to the entrapping of urine and leakage not only with stress maneuvers but also after detrusor contractions correlated to the change in bladder response to filling as a result of distorted feedback from the prostatic fossa itself [18]. This could also explain why there was a proportion of patients who complained of mixed urinary incontinence (MUI) and a higher number who needed Kegel exercises for a longer duration (Table 4).

Press et al. [19] showed no differences in continence rates at 3 months, 6 months, and 1 year after surgery in a series of 95 men undergoing either en-bloc holmium

Table 5. *Analysis of post-operative complications grouped by enucleation technique*

	All	2 lobe (n = 3,021)	3 lobe (n = 775)	En-bloc (n = 2,390)	p
Postoperative incontinence, n (%)	916 (14.8)	468 (15.5)	93 (12.0)	355 (14.9)	0.051
Urge	296 (29.5)	110 (21.6)	37 (24.2)	149 (44.5)	
Stress	541 (53.9)	327 (64.2)	104 (68.0)	103 (30.7)	
Mixed	167 (16.6)	72 (14.1)	12 (7.8)	83 (24.8)	
Duration of incontinence for those affected, n (%)					<0.001
1–3 months	252 (32.1)	146 (39.4)	17 (18.9)	89 (27.4)	
>3 months	127 (16.2)	67 (18.1)	16 (17.8)	44 (13.5)	
Kegel exercise needed, n (%)	609 (25.5)	378 (22.3)	37 (71.2)	194 (30.3)	<0.001
30-day readmission, n (%)	138 (3.0)	67 (2.4)	15 (2.8)	56 (4.5)	0.001
Delayed complications, n (%)					
Bulbar urethral stricture requiring dilatation alone as an outpatient	61 (11.0)	39 (1.3)	7 (0.9)	15 (0.6)	0.048
Urethral stricture requiring urethrotomy under anesthesia	20 (3.6)	5 (0.2)	3 (0.4)	12 (0.5)	0.091
Bladder neck sclerosis requiring transurethral incision	45 (8.1)	21 (0.7)	10 (1.3)	14 (0.6)	0.128
Redo BPH surgery within 1 year	8 (1.4)	4 (0.1)	2 (0.3)	2 (0.1)	0.501

BPH – benign prostatic hyperplasia

laser enucleation of the prostate with early apical release (EAR) or standard approach. In our study, the type of enucleation technique did not affect the incidence of postoperative incontinence but rather the duration of incontinence and need for Kegel exercise (Table 5). To our knowledge, the use of EAR is for the first time being reported alongside the 2- and 3-lobe techniques. Understandably, this is done to try and minimize post-op incontinence, a simple reflection of how evidence-based practice is adopted in experience-based practice in real-life settings.

This is also why perhaps the heterogeneity of our data from surgeons' own preferences compounds the analysis to make resolute conclusions. In a recent meta-analysis, Castellani et al. [20] reported that the incidence of transient MUI is often multifactorial and significantly higher after enucleation vis-à-vis other transurethral interventions (OR 3.26, 95% CI: 1.51–7.05, p = 0.003). We reported a cumulative 16.6% incidence (Table 1), and this was significantly associated with prostate volume >100 ml (Table 4) and en bloc enucleation (Table 5). We could not ascertain any other factors that might be related to energy used for AEEP.

Kuo et al. [21] reported in their series of 206 patients following HoLEP, a 2.4% incidence of urethral strictures and 3.9% for bladder neck contracture. Shat et al. [22] documented an incidence of urethral stricture at 4.3% and bladder neck contracture of 0.28%, with a higher rate of stricture in prostate of large volumes. In a meta-analysis [23], the pooled incidence of bladder neck stenosis was highest at 1.3% after TURP, 0.66% after enucleation and 1.2% after ablation.

In a systematic review and meta-analysis of RCTs of AEEP utilizing various lasers, Pang et al. [24] did not identify any significant differences with regards to the incidence of urinary retention, urinary incontinence, bladder neck contracture, and urethral stricture. Based on prostate size and technique, we found that the incidence of urethral strictures that could be easily managed by simple dilation was marginally higher in those who had the two-lobe technique, with no correlation to large size. Perhaps miniaturization as described in the Minimally invasive Laser Enucleation of the Prostate (MiLEP) using Slim (22Ch) and Ultra Slim (18.5Ch) HoLEP technique might indeed prevent these in future [25]. This is the largest and only multicenter global registry created by contributions from highly experienced surgeons that attempts to understand in depth the nuances of performing AEEP in real-world practice, including complications. Our study has several limitations, including its retrospective design and the absence of long-term follow-up on incontinence rates. Additionally, we did not have data on any subsequent surgical treatments for incontinence. We acknowledge that postoperative patient management was not standardized, but we realized from data received that in real-world practice outside of a clinical trial, there is no uniformity in follow-up AEEP, and perhaps this is an area of focus for future studies. We feel that a standardized reporting of complications is needed for a structured follow-up, and this may perhaps help in training as well. By having a large database, we were able to reflect on almost all complications reported in literature in single or smaller series, and indeed, EEP seems to be very safe irrespective of energy and technique. We hypothesize that complications may occur by virtue of technical inexperience or depending on the dynamic interaction relative to gland size. Finally, the findings of our study, being based on data from high-volume centers, may have limitations when it comes to generalizing the results to centers with less experience or lower patient volumes. It is indeed well established that experience is an important variable in minimizing complications of AEEP [26].

CONCLUSIONS

Analysis of complications from the REAP database shows that AEEP is indeed a safe procedure with a low incidence of serious complications irrespective of the type of technique or energy used. Urinary incontinence, which depends on enucleation proper and bladder injury, a sequela of improper morcellation, are the two main concerns. While the risk of complications may increase with enucleation of glands larger than 100 ml, this is observed even among highly experienced surgeons, all of whom had completed at least 200 cases prior to inclusion in the study. Patients must be appropriately counseled as these complications can negatively impact quality of life in the immediate postoperative period.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The study was approved by the Institutional Review Board of the Asian Institute of Nephrology and Urology (approval number: AINU 11/2022), and the remaining centers received approval from their respective institutional boards.

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ORIGINAL PAPER

FUNCTIONAL UROLOGY

Outcomes of Rezum water vapor therapy for benign prostate obstruction with 1-year follow-up: Largest real-world data from Turkey

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Introduction The study aimed to retrospectively assess the safety and efficacy of Rezum, a promising minimally invasive treatment method for BPH, in patients treated at our clinic.

Material and methods From January 1, 2022, to December 31, 2022, a cohort of 71 patients presenting with moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) were enrolled in the study. These individuals opted for Rezum therapy as their treatment approach. Primary outcome measures included the International Prostate Symptom Score (IPSS), maximum flow rate (Q_{max}), post-void residual volume (PVR), Quality of Life (QoL), prostate volume (PV), prostate-specific antigen (PSA), and the International Index of Erectile Function (IIEF) questionnaire.

Results The median age of the 71 patients was 62.1 ±9.3 years, with a median PV of 60.4 ±16.6 ml. Preoperatively, IPSS was 21.9 ±5.2, Q_{max} was 9.67 ±3.2, QoL was 3.35 ±0.61, IIEF-5 was 23.9 ±5.4, total PSA was 2.43 ±1.27 ng/ml, and PVR was 177.4 ±216.5 ml. At the 3-month follow-up, IPSS improved to 10.1 ±5.6, Q_{max} to 24.5 ±3.7, QoL to 1.2±0.51, IIEF-5 to 24.5 ±5.4, total PSA to 1.8 ±0.9 ng/ml, and PVR remained at 177.4 ±216.5 ml. At the 12-month follow-up, IPSS was 6.0 ±3.1, Q_{max} was 18.12 ±3.7, QoL was 1.2 ±0.51, IIEF-5 was 24.5 ±5.4, total PSA was 1.8 ±0.9 ng/ml, and PVR was 24.9 ±25.2 ml.

Conclusions Rezum therapy is a safe, effective, and minimally invasive option for the treatment of men with moderate to severe lower urinary tract symptoms (LUTS).

Key Words: BPH ‹› minimally invasive ‹› prostate ‹› surgery ‹› Rezum

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent condition in older men, significantly impairing urinary function and quality of life [1]. The primary treatment objective for symptomatic BPH is to alleviate bladder outlet obstruction (BOO) caused by prostate enlargement, which can be achieved through surgical interventions or medical therapies targeting symptom relief. Traditionally, transurethral resection of the prostate (TUR-P) has been regarded as the gold standard for BPH surgery, although its use has sparked some debate [2].

Despite its efficacy, TUR-P is associated with considerable perioperative and postoperative complications, reported at approximately 20%. These include anejaculation (65%), erectile dysfunction (10%), urethral strictures (7%), and urinary incontinence (3%) [3, 4]. These challenges have spurred interest in minimally invasive surgical treatments (MIST) as alternative approaches for BPH/LUTS therapy. MIST options are especially appealing because they often require minimal anesthesia and can be performed in outpatient settings, offering a more patient-friendly approach [5]. The Rezum System is a novel MIST that utilizes water vapor thermal therapy to ablate obstructive

prostatic tissue [6]. This system delivers convective water vapor energy (WAVE), providing a unique mechanism to effectively and continuously relieve lower urinary tract symptoms (LUTS) associated with BPH. Studies have demonstrated its safety and efficacy, positioning Rezum as a promising alternative to traditional surgical interventions [7].

In recent years, numerous studies have explored various aspects of the Rezum System; however, comparative randomized trials remain scarce. Two studies published in 2024 compared Rezum therapy with TUR-P. The first, conducted by Tayeb et al. [8], assessed the efficacy of Rezum therapy in catheter-dependent patients over a one-year follow-up. Using propensity score matching, Rezum patients were compared with TUR-P patients. Both groups achieved high rates of successful postoperative voiding (90.2% for Rezum vs 92.7% for TUR-P). Although TUR-P showed superior voiding outcomes at one and three months, LUTS reduction in the Rezum group became comparable at 6 and 12 months in terms of International Prostate Symptom Score (IPSS), Quality of Life (QoL) indices, and maximum urinary flow rate (Q_{max}) [8].

In contrast, a randomized trial with a two-year follow-up demonstrated greater effectiveness and durability for bipolar TUR-P compared to Rezum therapy. The re-treatment rate for Rezum therapy was reported as 8%, primarily among patients with larger prostates (91.5 ±24.61 ml) or catheter dependency. Nonetheless, the study highlighted Rezum's advantages for sexually active men seeking to preserve erectile and ejaculatory functions while achieving symptom relief [9].

This study retrospectively evaluates the safety and efficacy of Rezum therapy, a promising minimally invasive treatment for BPH, in a real-world clinical setting at our institution.

MATERIAL AND METODS

Study design and patients

Between January 1, 2022, and December 31, 2022, a cohort of 71 patients presenting with moderate to severe LUTS associated with BPH was enrolled in the study. The study was recorded on the website ClinicalTrials.gov (NCT06257654). These individuals opted for Rezum therapy as their selected treatment approach. Primary outcome measures employed for BPH diagnosis and follow-up included the IPSS, Q_{max}, post-void residual volume (PVR), QoL, prostate volume (PV), prostate-specific antigen (PSA), and the International Index of Erectile Function (IIEF) questionnaire.

Outcome measures

The IPSS, which is scored between 0 and 35, with higher scores indicating more frequent BPH symptoms, served as a key diagnostic and follow-up tool [10]. Additionally, parameters such as PV, PSA values, postoperative complications (Clavien-Dindo classification), anesthesia types, anesthesia durations, and catheter durations were assessed.

Thermal treatment procedure

The thermal treatment procedure utilized the previously described Rezum System for lower urinary tract symptoms/benign prostatic hyperplasia, as outlined in detail by Mynderse et al. [11]. In brief, thermal energy in the form of water vapor was generated using radiofrequency current against an inductive coil heater in the device handle. The system delivered water vapor (at 103°C) through a retractable needle, accompanied by saline flush irrigation to enhance visualization and cool the urethral surface. The vapor needle was deployed, and a 9-second delivery of water vapor was administered.

The radiofrequency (RF) thermal therapy employed the Rezum System, comprising an RF power supply, a generator, and a single-use transurethral delivery device with a standard 4 mm, 30-degree endoscopic cystoscopy lens. The instrument delivered RF water vapor thermal energy into the prostate through a retractable needle, with saline flush irrigation used to enhance visualization and cool the urethra. The needle tip was positioned and inserted starting approximately 1 cm distal to the bladder neck into the transition and central prostate adenoma. The total number of treatments in each lobe of the prostate was determined by the length of the prostatic urethra and could be customized to the gland's configuration, including the median lobe.

For blinding purposes, a surgical drape prevented subjects from visualizing the device and the treating physician. Outcome assessments were conducted by an assessor blinded to the procedures, as detailed by Dixon et al. [12] and McVary et al. [13].

Patient follow-up

After catheter removal, all patients were administered alpha-blockers for approximately one month, and antiplatelet therapies were continued. For one week postoperatively, patients were provided with antibiotics and anti-inflammatory therapy. Patients were reevaluated at 3 and 12 months during follow-up assessments. Inclusion criteria included the following: age ≥45 years; IPSS ≥14; Q_{max} ≥15 ml/s;

and PV ≥30–≤120 ml. Exclusion criteria included the following: prostate cancer, Parkinson's disease, neurogenic bladder, overactive bladder, bladder stones, bladder tumor, urinary infection, and Alzheimer's disease.

Bioethical standards

The study was approved by the Hisar Intercontinental Hospital Local Ethics Committee according to the ethical principles of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (approval number 24-2).
For surviving patients who had routine visits to the study site, evidence of a personally signed and dated informed consent document was obtained. Evidence of oral or written informed consent was obtained for surviving patients who had been transferred to another hospital. Deceased patients fulfilling the above inclusion criteria were also included in this study unless patients' families opted out of inclusion.

RESULTS

Baseline characteristics

Out of the 71 patients included in the study, the median age was 62.1 ±9.3 years, with a median PV of 60.4 ±16.6 ml. Among these, 52 patients had PV ≤80 ml, and 13 had volumes >80 ml.
The average operative time was 15.6 ±3.2 minutes. General anesthesia was utilized in 77.47% (55/71) of the procedures, while 22.53% (16/71) were performed under intravenous sedation due to comorbidities.
Preoperative baseline parameters included:
- IPSS: 21.9 ±5.2,
- Q_{max}: 9.67 ±3.2 ml/s,
- QoL: 3.35 ±0.61,
- IIEF-5: 23.9 ±5.4,
- total PSA: 2.43 ±1.27 ng/ml,
- PVR: 177.4 ±216.5 ml.

Patients; comorbidities were assessed using the American Society of Anesthesiologists (ASA) classification: 13 patients were classified as ASA 2, 6 as ASA 3, and 1 as ASA 4. The cohort included 34 patients (47.8%) with middle lobe enlargement, and the average prostate length was 3.7 ±1.1 cm (Table 1).
Anticoagulation protocol: Twenty patients were on aspirin (100 mg) and clopidogrel (75 mg). These medications were discontinued five days before surgery and replaced with low molecular weight heparin, which was continued for one week postoperatively. Afterward, patients resumed their regular anticoagulant regimen.
Catheterization details: Patients were discharged on the same day as the procedure, with an average catheter duration of 4.8 ±1.9 days. Five patients (7%) experienced initial catheter removal failure:
- 2 patients: catheters were removed after one week,
- 3 patients: catheters were removed after ten days.

All 5 patients achieved spontaneous urination following catheter removal.

Table 1. *Descriptive data of benign prostate hyperplasia cases*

	BPH (before treatment)
Age (year)	62.1 ±9.3
PV (cc)	60.4 ±16.6
30–80 cc	52
>80 cc	13
Prostate length (cm)	3.7 ±1.1
Prostate Middle Lobe	47.8% (34/71)
ASA classification	
ASA 2	13
ASA 3	6
ASA 4	1
General anesthesia	55
Intravenous sedation	16
Number of injections	6.5 ±2.0
Catheter duration (day)	4.8 ±1.9

ASA – American Society of Anesthesiologists; BPH – benign prostate hyperplasia; PV – prostate volume

Follow-up results

At the 3-month follow-up, significant improvements were observed across several parameters:
- IPSS: decreased to 10.1 ±5.6,
- Q_{max}: increased to 24.5 ±3.7 ml/s,
- QoL: improved to 1.2 ±0.51,
- IIEF-5: increased to 24.5 ±5.4,
- total PSA: reduced to 1.8 ±0.9 ng/ml,
- PVR: unchanged at 177.4 ±216.5 ml.

At the 12-month follow-up, the most substantial improvements included:
- IPSS: reduced further to 6.0 ±3.1,
- Q_{max}: stabilized at 18.12 ±3.7 ml/s,
- QoL: maintained at 1.2 ±0.51,
- PVR: significantly decreased to 24.9 ±25.2 ml ($p < 0.05$).

These outcomes confirm the sustained efficacy of Rezum therapy over 12 months in alleviating symptoms associated with BPH (Table 2, Figure 1).

Complications

Clavien-Dindo grade I/II complications were reported in 37% of patients, with a higher incidence (45%) among those with PVs >80 ml. Table 3 provides a detailed summary of these complications, including dysuria (14%), hematuria (10%), and urinary tract infections (UTIs; 7%).

The most common complications observed were dysuria, urgency, hematuria, and UTIs:

- dysuria: reported in 10 patients, with 8 resolving by 6 weeks post-operation; the remaining

Table 2. *Third and twelfth month data after Rezum treatment in benign prostate hyperplasia cases*

	Before treatment	After treatment		p1	p2	p3
		3 months later	12 months later			
QoL	3.35 ±0.61	1.22 ±0.51	1.08 ±0.44	0.000	0.000	0.058
IEFF	23.9 ±5.4	24.5 ±5.3	24.8 ±5.4	0.000	0.001	0.481
Q_{max}	9.67 ±3.2	18.12 ±3.7	22.84 ±20.3	0.000	0.000	0.065
PVR	177.4 ±216.5	52.6 ±61.5	24.9 ±25.2	0.000	0.000	0.000
IPSS	21.9 ±5.2	10.1 ±5.6	6.0 ±3.1	0.000	0.000	0.000
PV [ml]	60.4 ±16.6	–	42.9 ±11.8	–	0.000	–
PSA [ng/ml]	2.43 ±1.27	–	1.8 ±0.9	–	0.000	–

Paired Samples Tests: significance p ≤0.05
p1: difference between before treatment and 3 months after treatment
p2: difference between before treatment and 12 months after treatment
p3: difference between 3 months and 12 months after treatment
IIEF – International Index of Erectile Function; IPSS – International Prostate Symptom Score; Q_{max} – maximum flow rate; QoL – Quality of Life; PSA – prostate-specific antigen; PV – prostate volume; PVR – post-void residual volume

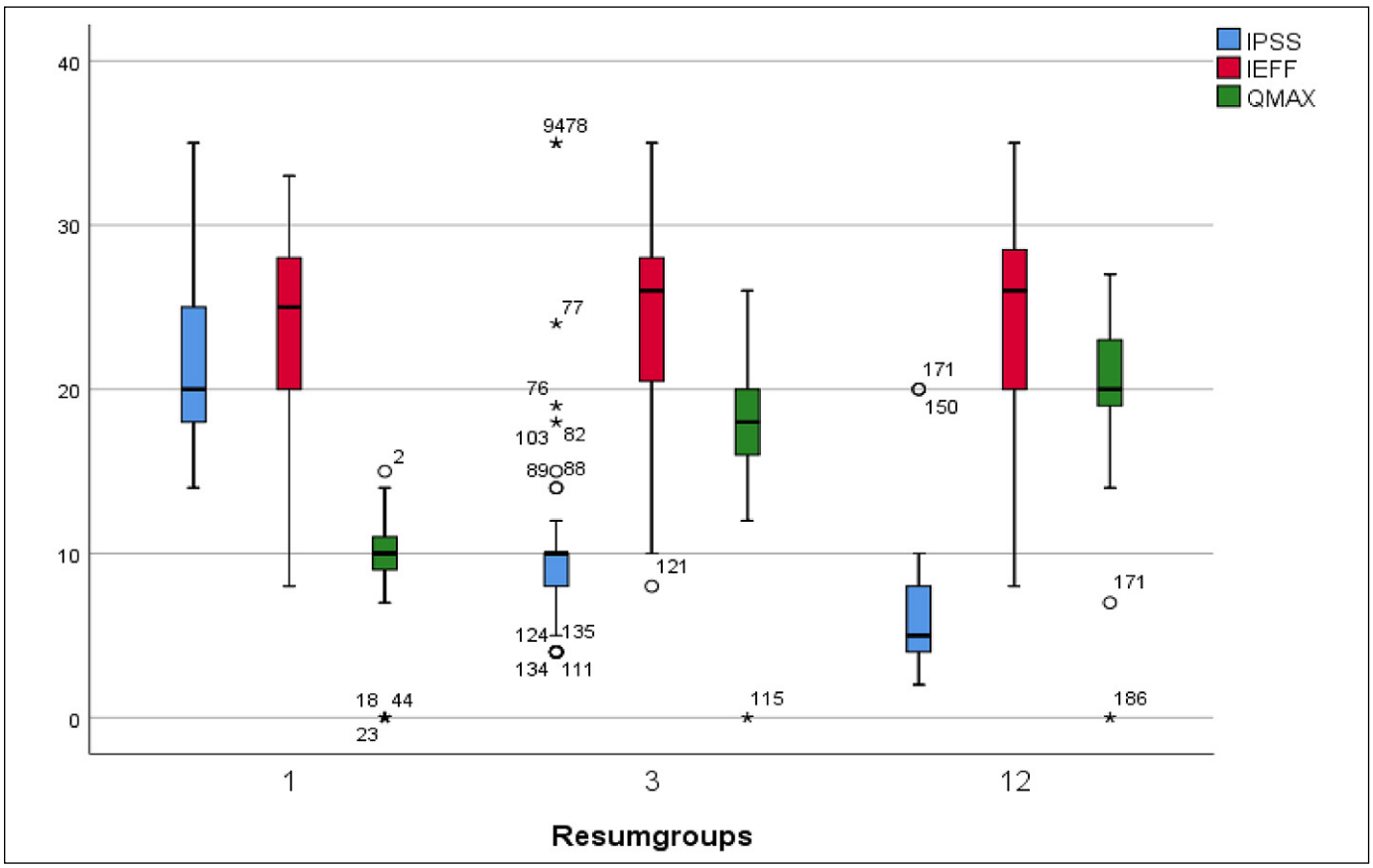

Figure 1. *Box plots of the data of BPH cases before Rezum treatment and at the 3rd and 12th months after treatment.*

2 patients experienced persistent dysuria for up to three months before eventual resolution;
- urgency: it was reported in 4 patients, all of whom experienced symptom resolution within the first 2 weeks post-treatment;
- hematuria: occurred in 7 patients, resolving spontaneously within the first week without additional intervention;
- UTIs: 5 patients developed UTIs, with *Escherichia coli* identified as the causative organism in all cases; these infections were effectively managed with outpatient antibiotic therapy.

Notably, no cases of urinary incontinence were observed in the cohort.

Postoperative 30-day complications are further detailed in Table 3, highlighting the safety profile of Rezum therapy even in patients with larger PVs.

DISCUSSION

This study represents the first report on the Turkish experience with the Rezum® system for the treatment of benign prostatic hyperplasia (BPH). Rezum utilizes convective thermal energy to ablate obstructive prostatic tissue by disrupting the cell membrane, leading to cell death and necrosis [14]. Mynderse et al. [11] demonstrated that magnetic resonance imaging (MRI) revealed a 91.5% reduction in ablation volume at three months and a 95.1% reduction at 6 months post-treatment. Additionally, there was a 28.9% reduction in total prostatic volume and a 38% reduction in transition zone volume at 6 months [11].

In long-term follow-up studies, Dixon et al. [15] reported a reduction in post-void residual (PVR) volume from 78.5 ml to 62.8 ml at 24 months [15]. In our cohort, ultrasound follow-up at 12 months showed a comparable 29% reduction in prostatic volume, demonstrating significant tissue ablation.

Wong et al. demonstrated that all 10 patients requiring catheterization due to urinary retention became catheter-free following Rezum therapy, with a significant reduction in PVR [4]. Similarly, McVary et al. [16], in their analysis of 38 catheter-dependent patients, showed that 70.3% achieved spontaneous urination after two unsuccessful voiding attempts and remained catheter-free post-treatment. Our findings align with these studies, as all three patients with indwelling catheters in our cohort became catheter-free after Rezum therapy.

Rezum therapy is FDA-approved for prostates ≤80 ml; however, its efficacy in larger prostates has also been explored. Bole et al. [18] analyzed 182 patients, including 47 with prostates >80 ml, reporting significant improvements in AUASS, peak flow rate, and PVR post-treatment. Similarly, Martinelli et al. [19] demonstrated significant reductions in bladder outlet obstruction index and prostate size (approx. 40%) in patients with larger prostates, underscoring the potential of Rezum therapy as a robust surgical alternative [18]. In our study, 11 patients with PVs >80 ml showed significant improvements in IPSS, QoL, Q_{max}, and PVR.

The re-treatment rate is a critical measure of the effectiveness of surgical interventions. Our study reports a re-treatment rate of 2.1% at one year, consistent with rates reported in the literature, including 2% by Darson et al. [20] and 3.7% by Roehrborn et al. at two years [21]. Two patients in our study required TUR-P due to persistently elevated residual urine volumes and impaired voiding.

Preservation of sexual function is a notable advantage of Rezum therapy. McVary et al. [7] reported no erectile dysfunction at two years post-treatment, while other studies observed improvements in IIEF scores ranging from 7.6% to 30.5% [12, 18, 22–26]. In our cohort, two patients experienced retrograde ejaculation or reduced ejaculation volume, but most patients showed a statistically significant improvement in IIEF-5 scores. This suggests that Rezum effectively preserves sexual function while providing symptomatic relief.

The safety profile of Rezum therapy is well-documented. Clavien-Dindo grade I/II complications such as dysuria, hematuria, urgency, and UTIs are reported in 3–33.8% of patients with prostates <80 ml [12, 27]. In our study, the overall complication rate was 37%, with higher rates observed in patients with PVs >80 ml.

The minimally invasive nature of Rezum therapy is another key advantage. Most patients tolerate the procedure well under oral sedation or local anesthesia, with only a minority requiring intravenous sedation [7]. In our cohort, 77.47% of patients underwent the procedure under general anesthesia for enhanced comfort, while 22.53% received intravenous sedation due to comorbidities.

Table 3. *Clavien-Dindo grade*

Safety outcomes of Rezum	Rezum patients (n = 71)
I	21
II	5
IIIa	0
IIIb	0
IVa	0
IVb	0
V	0

Recent studies have also highlighted the importance of understanding Rezum outcomes across different ethnicities. Obinata et al. reported on 25 Japanese patients, showing significant improvements in Q_{max} and PVR at three months, although 8% remained catheterized [28]. To our knowledge, this is the first and largest cohort study evaluating Rezum outcomes in the Turkish population.

While our study provides valuable insights into the effectiveness and safety of Rezum therapy in a Turkish population, its retrospective design limits the ability to establish causal relationships [29, 30]. The absence of a control group and the relatively small sample size may reduce the generalizability of our findings. Larger, prospective studies with long-term follow-up are needed to confirm these results.

CONCLUSIONS

Rezum therapy is regarded as a safe, effective, and minimally invasive option for treating lower urinary tract symptoms in men with benign prostatic hyperplasia. However, future research should focus on further understanding the efficacy and reliability of this treatment.

For surviving patients who had routine visits to the study site, evidence of a personally signed and dated informed consent document was obtained. Evidence of oral or written informed consent was obtained for surviving patients who had been transferred to another hospital. Deceased patients fulfilling the above inclusion criteria were also included in this study unless patients' families opted out of inclusion.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

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ETHICS APPROVAL STATEMENT

The study was approved by the Hisar Intercontinental Hospital Local Ethics Committee (approval number 24-2).

REGISTRY AND THE REGISTRATION NUMBER OF THE STUDY

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REVIEW PAPER

FUNCTIONAL UROLOGY

Does miniaturisation improve holmium laser enucleation of prostate outcomes? A meta-analysis of comparative studies

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Introduction Holmium laser enucleation of the prostate (HoLEP) is a versatile treatment for benign prostatic hyperplasia (BPH), serving as an alternative to transurethral resection of the prostate (TURP) and open/robotic-assisted prostatectomy. Recent advancements have focused on evaluating the impact of smaller (22–24 Fr) vs larger (26–28 Fr) resectoscope sheaths on procedural outcomes.
The aim of this study was to assess and compare the safety, efficiency, and complication rates associated with smaller and larger resectoscope sheaths in HoLEP procedures through a meta-analysis.
Material and methods A systematic review was conducted following PRISMA guidelines. Four studies (one RCT and three retrospective) comprising 633 patients (277 with small sheaths [SR] and 356 with large sheaths [LR]) met inclusion criteria. Outcomes assessed included operative time, enucleation/morcellation efficiency, complications (urethral strictures, transient incontinence), and recovery parameters.
Results In terms of efficiency, no significant differences were observed in operative time, enucleation time, or enucleation efficiency. LR showed faster morcellation time (p = 0.03). As for complications, SR had significantly lower urethral dilation rates (8.0% vs 39.5%, p = 0.01). No significant differences in urethral stricture rates, catheterisation duration, complication rates or transfusion rates. In terms of recovery, similar hospital stay durations and incontinence rates were seen at 3 months postoperatively between groups, and SR might decrease incontinence rates at 1 month postoperatively.
Conclusions Using smaller resectoscope sheaths in HoLEP reduces urethral dilation rates without compromising procedural efficiency or safety. Larger sheaths had shorter morcellation times. The choice of sheath size should be guided by patient anatomy, surgeon expertise, and procedural requirements. Further large-scale RCTs are needed to confirm long-term outcomes.

Key Words: benign prostatic hyperplasia ‹› holmium laser enucleation of the prostate ‹› resectoscope

INTRODUCTION

Holmium laser enucleation of the prostate (HoLEP) is a size-independent treatment option for benign prostatic hyperplasia (BPH). It serves as an alternative to traditional transurethral resection of prostate (TURP) for small to medium-sized prostates and to open or robotic-assisted simple prostatectomies (RASP) for larger prostates [1, 2].
HoLEP has been found to be superior to TURP in post-operative functional outcomes during both short and long-term follow-ups [3–5]. Compared to RASP, HoLEP has similar functional outcomes but offers advantages such as earlier recovery and a better safety profile with lower blood transfusion and moderate to significant complication rates [6].
Multiple recent studies have compared outcomes of HoLEP with miniaturised smaller resectoscope sheaths compared to the traditional larger sheaths [7–10]. It was hypothesised that smaller resectoscopes may lead to lower stricture rates compared to larger scopes, which have a stricture rate

of 1.2–7.3%, due to decreased urethral trauma [11–15]. This was first hypothesised in an observational study comparing the outcomes of HoLEP with a 26 Fr vs 28 Fr resectoscope sheath, however, the rate of urethral strictures was not found to be statistically different at 3.5% vs 1.8% [16].

The objective of this meta-analysis is to consolidate current research comparing the operative outcomes of HoLEP with smaller and larger resectoscope sheaths, including the following: operative time, enucleation and morcellation efficiency, complications (urethral stricture, transient incontinence), and recovery parameters. This review aims to provide clarity regarding the impact of resectoscope size on procedural safety and efficiency, contributing to an informed choice of equipment and approach in clinical practice.

MATERIAL AND METHODS

In March 2024, with PROSPERO registration (CRD42024603851), a systematic search for a systematic review was performed following the PRISMA criteria (Figure 1). PubMed, EMBASE, and Cochrane library of systematic reviews were queried for the terms "(HoLEP) AND (resectoscope)". No restrictions on publication date were applied; only English language articles were considered. Two independent (MZUA, MH) reviewers screened returned results for inclusion and data extraction. Data conciliation was performed through consensus. This study was exempt from review by the institutional review board, and informed consent was not required because data were publicly available.

Inclusion criteria

Randomised controlled trials (RCTs) and observational studies comparing small resectoscope (SR) sheaths (22–24 Fr) to large resectoscope (LR) sheaths (26–28 Fr).

Exclusion criteria

Our exclusion criteria included conference abstracts and non-English articles.

Data extraction

Data were extracted independently by two reviewers. Data relevant to this meta-analysis besides authorship and year of publication were as follows: risk of bias assessment, cohort size, Anticholinergic use postoperatively, bladder neck contracture rates, catheterisation time, enucleation volume, enucleation time, hospitalisation duration, major complications (IIIb or higher as per Clavien Dindo classifi-

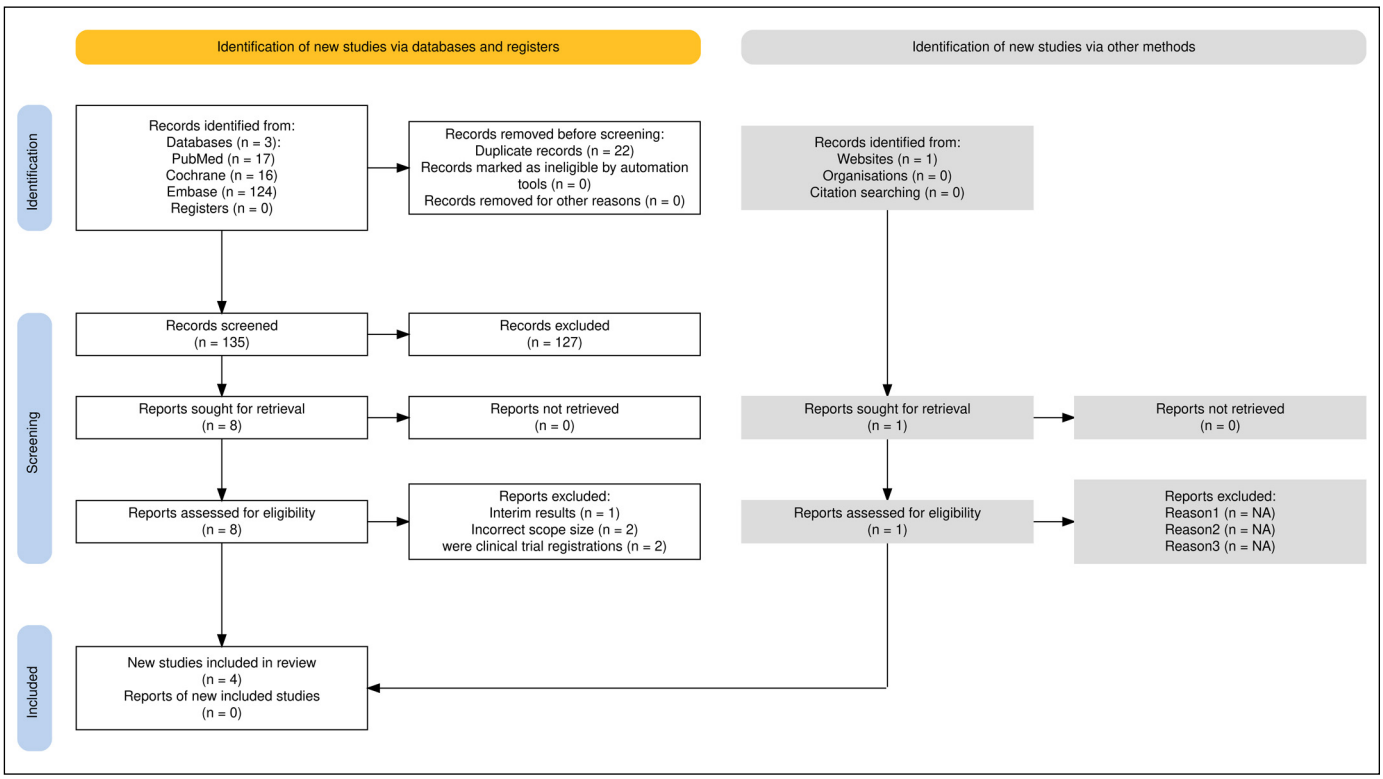


Figure 1. *PRISMA flowchart of article selection.*

cation system), morcellation efficiency, morcellation time, operative time, postoperative incontinence, total complications, transfusion rates, urethral dilation rates and urethral stenosis. Studies providing data in median and ranges were used to estimate mean and standard deviation using Wan's method [17]. Bias was assessed using Cochrane's Risk of Bias 2 tool for RCTs and the Newcastle-Ottawa Score, which is displayed in Tables 1 and 2.

Statistical analysis

Data analysis was performed in Review Manager V5.4 (Cochrane). Higgins' 12% test was employed to test heterogeneity, using 50% as a cutoff value. Random-effects models were used in place of fixed-effects for heterogeneous variables. Continuous data are reported as mean difference with 95% confidence intervals (CI). Dichotomous data, such as complications, were reported using odds ratios (OR) with 95% CI. The resulting values with associated p-values <0.05 were considered significant. Funnel plots were plotted to look for small study bias in dichotomous data.
The data analysis was rerun, excluding non-PubMed-indexed (Yildiz et al. 2022) studies in outcomes, with three studies remaining after exclusion [8].

Table 1. *Risk of bias 2 for Dean et al. 2023*

Domain	Risk of bias
1. Bias arising from the randomization process	Low
2. Bias due to deviations from intended interventions	Low
3. Bias due to missing outcome data	Low
4. Bias in measurement of the outcome	Some concerns
5. Bias in selection of the reported result	Low
Overall Bias Assessment	Some concerns

RESULTS

Four studies (one RCT and three retrospective studies) met the inclusion criteria and were analysed. This included 633 patients, 277 and 356 in the SR and LR groups, respectively. Overall characteristics of included studies are displayed in Table 3, baseline characteristics in Table 4, and outcomes analysed in each study in Table 5.

Operative time

Operative time was described in 3 studies, totalling 533 patients (237 and 296 in the SR and LR, respectively). Analysis revealed no differences between groups, with a mean difference of –0.5 minutes [–3.88, 2.87], p = 0.77, suggesting equivalent operative time with both methods. This finding is displayed in Figure 2.

Enucleation time

Enucleation time was described in 3 studies, totalling 553 patients (237 and 316 in the SR and LR, respectively). Analysis revealed no differences between groups, with a mean difference of –0.88 minutes [–3.53, 1.77], p = 0.52, suggesting equivalent enucleation time with both methods. This finding is displayed in Figure 3.

Enucleation efficiency

Enucleation efficiency was described in 3 studies, totalling 553 patients (237 and 316 in the SR and LR, respectively). Analysis revealed no differences between groups, with a mean difference of –0.07 g/min [–0.16, 0.02], p = 0.11, suggesting equivalent enucleation efficiency with both methods. This finding is displayed in Figure 4.

Table 2. *Newcastle Ottawa Score for non-randomised trials*

Study	Selection (Max 4)	Comparability (Max 2)	Outcome (Follow-up Adequacy Max 3)	Total Score (Max 9)	Limitations
Ibis et al. 2021 [10]	Representativeness: yes Non-exposed cohort: yes Exposure ascertainment: yes Baseline info: yes	Controls for BMI and prostate size: partial	Short-term follow-up (4, 12, 24 weeks)	7	Short (90-day) follow-up
Taha et al. 2023 [9]	Representativeness: yes Non-exposed cohort: yes Exposure ascertainment: yes Baseline info: yes	Propensity score matching: yes	Short-term follow-up (up to 3 months)	8	Short (24-week) follow-up and 26 Fr morcellator used following 22 Fr enucleation
Yildiz et al. 2022 [8]	Representativeness: yes Non-exposed cohort: yes Exposure ascertainment: no; Baseline info: no	Controls for age, BMI, IPSS: partial	Long-term follow--up (12 months)	6	Single surgeon performing with different endoscopes at different periods (introducing experience bias). Various sizes of instruments were used

Morcellation time

Morcellation time was described in 3 studies, totalling 553 patients (237 and 316 in the SR and LR, respectively). Analysis revealed statistically significant differences between groups with a mean difference of 0.97 minutes [0.11, 1.83], p = 0.03 in favour of LR. This suggests faster morcellation time with LR. This finding is displayed in Figure 5.

Morcellation efficiency

Morcellation efficiency was described in 3 studies, totalling 553 patients (237 and 316 in the SR and LR, respectively). Analysis revealed differences between groups with a mean difference of –0.71 g/min [–1.43, 0.02], p = 0.06, in favour of LR. However, this finding was not statistically significant. This finding is displayed in Figure 6.

Table 3. *Included studies characteristics*

Study	Study type	Journal (Impact factor)	HoLEP Technique	Resectoscope sheath sizes	Morcellator Used
Ibis et al. 2021 [10]	Observational (retrospective)	LUTS: Lower Urinary Tract Symptoms (1.5)	En-bloc HoLEP with early apical release	22F and 26F	26F nephroscope with VersaCut tissue morcellator (Lumenis)
Taha et al. 2023 [9]	Observational (prospective, propensity score-matched)	World Journal of Urology (2.8)	Mini-HoLEP (MiLEP) compared with standard HoLEP	22F (MiLEP) and 26F (HoLEP)	Wolf® Piranha
Yildiz et al. 2022 [8]	Observational (retrospective)	Haseki Medical Bulletin (0.2)	Standard three-lobe HoLEP	24F and 26F	Jena Surgical Multicut
Dean et al. 2023 [7]	Randomized controlled trial	Journal of Endourology (2.9)	Standard three-lobe/two-lobe HoLEP with early apical release	24F and 28F	24F and 28F morcellator

Table 4. *Baseline characteristics of the included studies*

Study	Baseline finding	Smaller resectoscope group	Larger resectoscope group	p
Ibis et al. 2022 [10]	Mean age [years]	66.3	67.1	0.575
	Prostate volume [ml]	63.9	66.0	0.213
	Preoperative IPSS	22.3	23.5	0.149
	Preoperative PSA	4.8	5.7	0.228
	BMI	29	30.7	0.195
Taha et al. 2023 [9]	Mean age [years]	74	74	0.200
	Prostate volume [ml]	100	100	0.940
	Chronic retention [%]	33	31	1.000
	ASA score	2	2	0.310
	Indwelling catheter use [%]	38	33	0.800
Yildiz et al. 2022 [8]	Mean age [years]	69.1	68.5	0.608
	Prostate volume [ml]	108.6	112.8	0.395
	Preoperative IPSS	26.5	27.3	0.102
	BMI	23.6	23.8	0.427
	Post void residual	151.1	150.9	0.983
Dean et al. 2023 [7]	Mean age [years]	68.6	70.1	0.218
	Prostate volume [cm³]	92.3	100.2	0.355
	Preoperative AUASS	20.6	20	0.732
	ASA score	2.3	2.3	0.288
	Indwelling catheter use [%]	22	26	0.574

ASA – American Society of Anesthesiologists; AUASS – American Urological Association symptom score; BMI – body mass index; IPSS – International Prostate Symptom Score; PSA – prostate-specific antigen

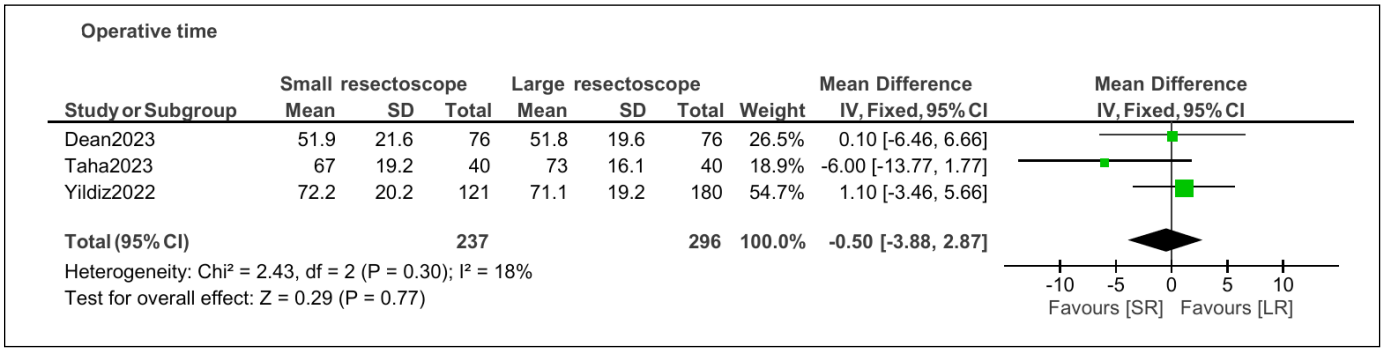


Figure 2. *Forest plot for operative time.*

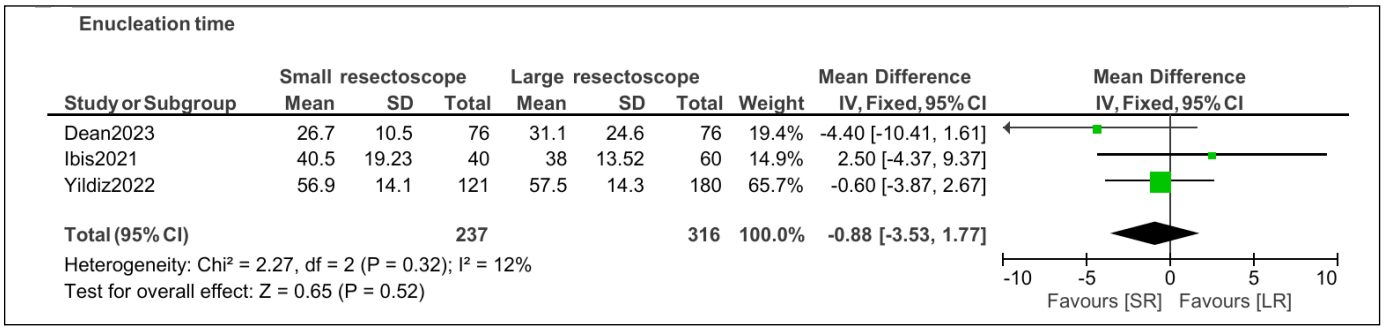


Figure 3. *Forest plot for enucleation time.*

Table 5. *Outcomes analysed*

Outcomes	Findings			
	Ibis et al. 2021 [10]	Taha et al. [9] 2023	Yildiz et al. 2022 [8]	Dean et al. 2023 [7]
Operative time	NR	NSD	NSD	NSD
Enucleation time	NSD	NR	NSD	NSD
Enucleation efficiency	NSD	NR	NSD	NSD
Morcellation time	NSD	NR	Lower in smaller resectoscope group	NSD
Morcellation efficiency	NSD	NR	Lower in smaller resectoscope group	NSD
Specimen weight	NSD	NR	NSD	NSD
Urethral dilation rates	NSD	Lower in smaller resectoscope group	Lower in smaller resectoscope group	NSD
Catheterisation duration	NSD	NR	NSD	NR, (Higher same day successful trial of void in larger resectoscope group)
Transfusion rates	NR	NR	NSD	NSD
Hospitalisation duration	NR	NSD	NSD	Lower in larger resectoscope group
Complication rates	NR	NSD	NSD	NSD
Urethral stricture rates	NR	NR	NSD	NSD
Bladder neck contracture	NR	NR	NSD	NSD
Urinary incontinence at one month	Lower incontinence in the smaller resectoscope group	Lower incontinence in the smaller resectoscope group	NSD	NSD
Urinary incontinence at three months	NSD	NSD	NR	NSD

NSD – no statistical difference; NR – not reported

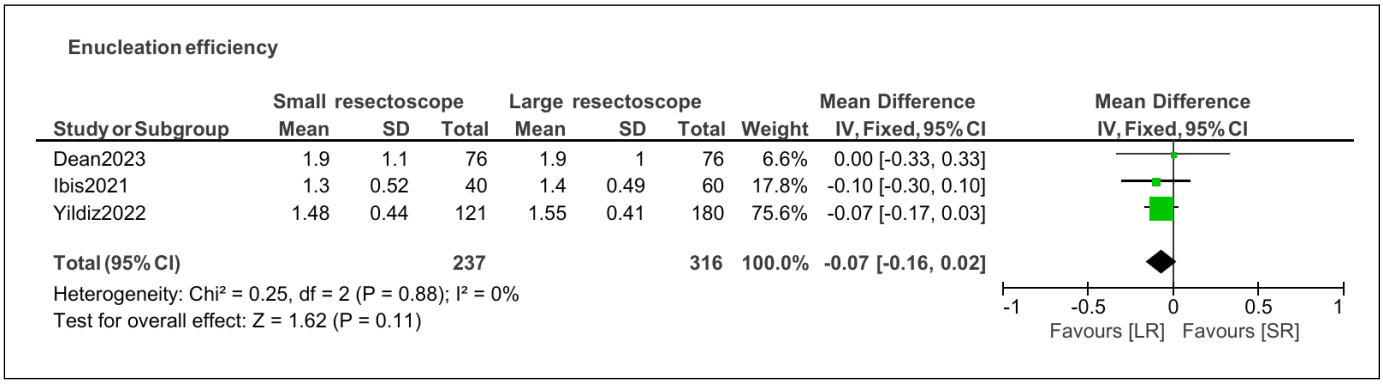


Figure 4. *Forest plot for enucleation efficiency.*

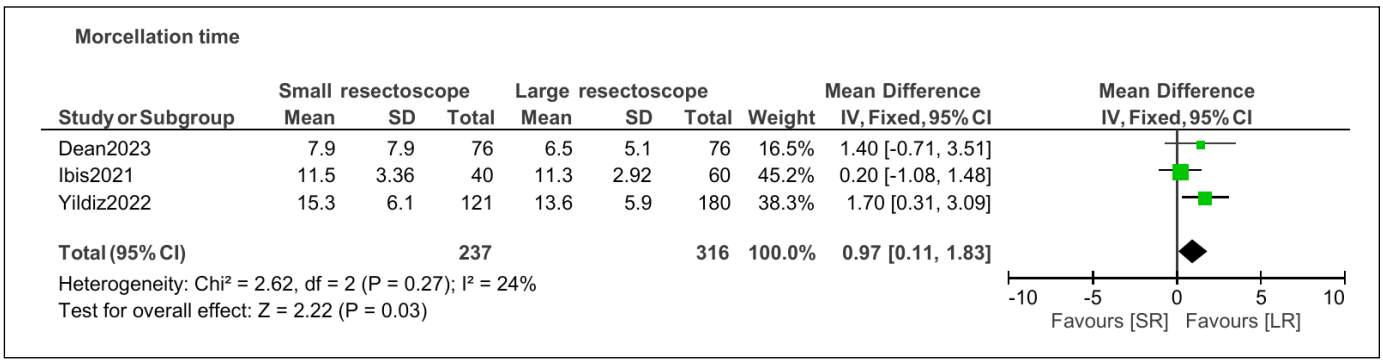


Figure 5. *Forest plot for morcellation time.*

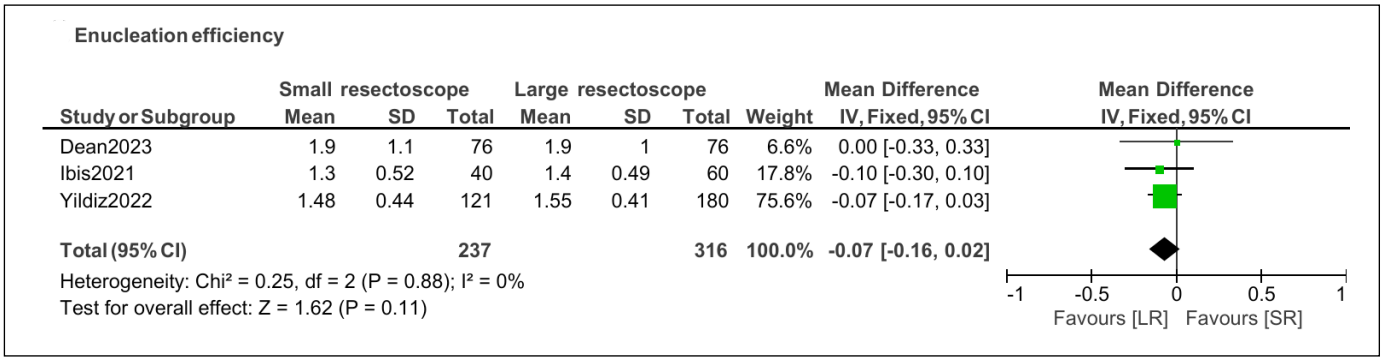


Figure 6. *Forest plot for morcellation efficiency.*

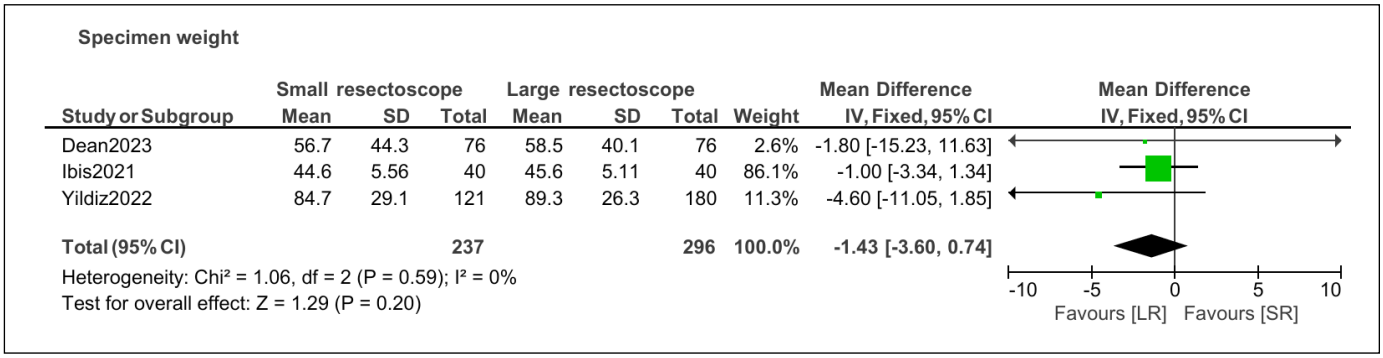


Figure 7. *Forest plot for specimen weight.*

Specimen weight

Specimen weight was described in 3 studies, totalling 533 patients (237 and 296 in the SR and LR, respectively). Analysis revealed no differences between groups with a mean difference of –1.43 g [–3.60, 0.74], p = 0.20, suggestive of equivalent enucleation volume with both methods. This finding is displayed in Figure 7.

Urethral dilation rates

Urethral dilation rates were described in 3 studies, totalling 533 patients (237 and 296 in the SR and LR groups, respectively). Urethral dilation rates for patients in the SR group were 8.0% as compared with 39.5% for LR. This finding was statistically significant with an associated OR of 0.17 [0.04, 0.69], p = 0.01. The funnel plot is included in the supplemental material. This finding is displayed in Figure 8.

Catheterisation duration

Catheterisation duration was described in 2 studies, totalling 401 patients (161 and 240 in the SR and LR, respectively). Analysis revealed no differences between groups, with a mean difference of 0.93 hours [–0.49, 2.35], p = 0.20, suggesting of equivalent catheterisation duration with both methods. This finding is displayed in Figure 9.

Transfusion rates

Transfusion rates were described in 2 studies, totalling 453 patients (197 and 256 patients in the SR and LR groups, respectively). Of these, SR reported 0 (0%) transfusions and LR 1 (0.4%) transfusion. This difference was not statistically significant OR = 0.49 [0.02, 12.19], p = 0.67. The funnel plot is included in the supplemental material. This finding is displayed in Figure 10.

Hospitalisation duration

Hospitalisation duration was described in 3 studies, totalling 533 patients (237 and 296 in the SR and LR, respectively). Analysis revealed no differences between groups with a mean difference of 1.35 hours [–2.88, 5.59], p = 0.53, suggestive of equivalent hospitalisation duration with both methods. This finding is displayed in Figure 11.

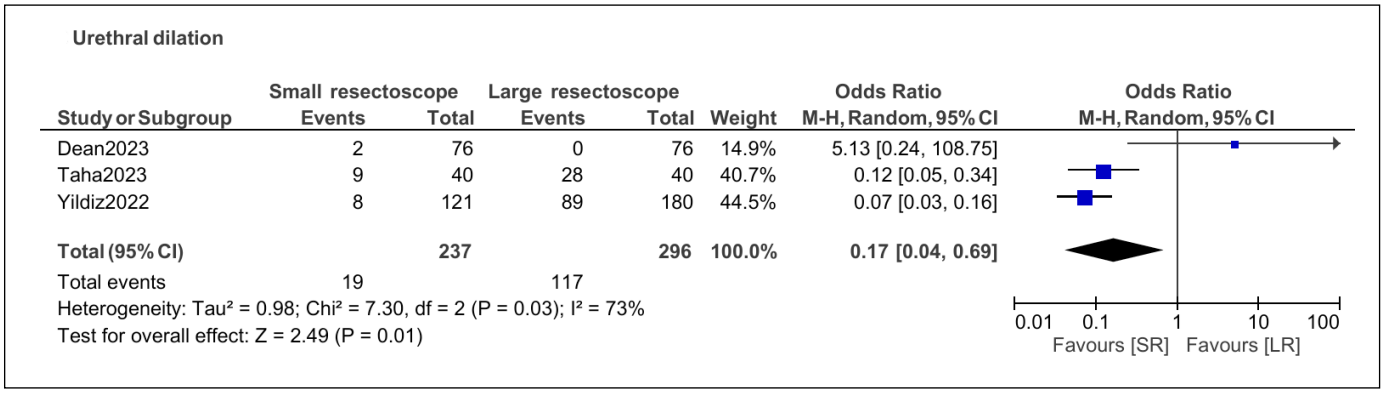


Figure 8. *Forest plot for urethral dilation rates.*

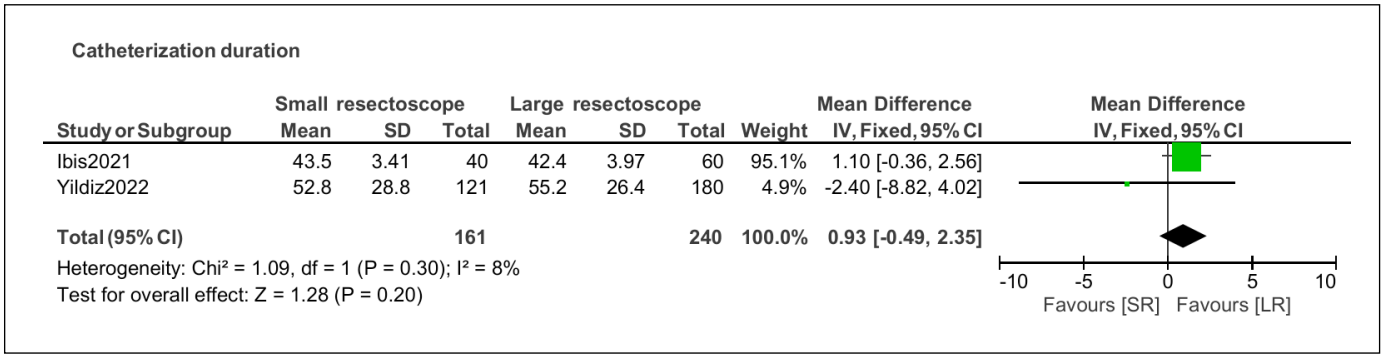


Figure 9. *Forest plot for catheterisation duration.*

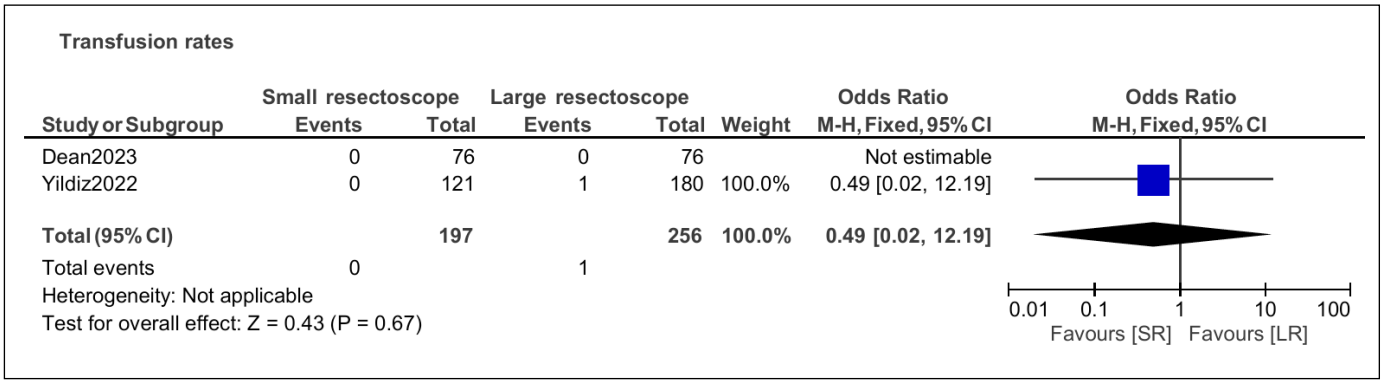


Figure 10. *Forest plot for transfusion rates.*

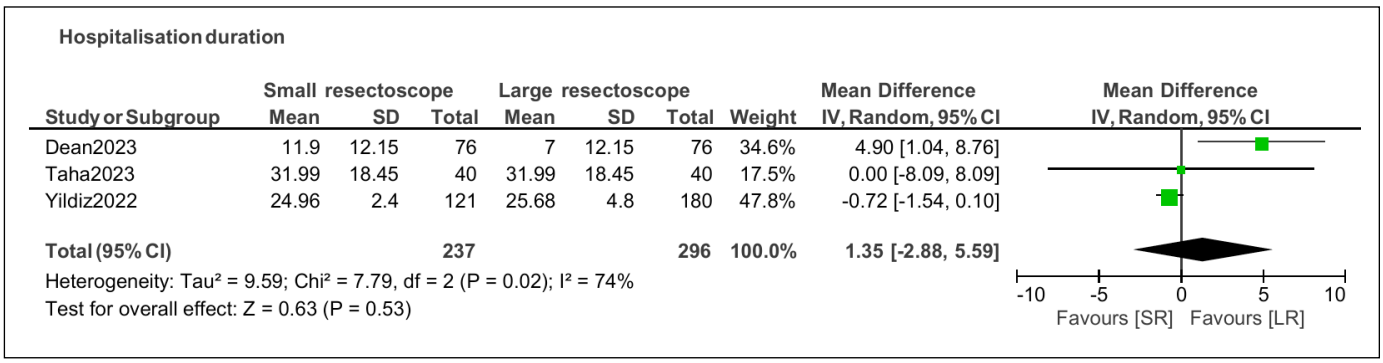


Figure 11. *Forest plot for hospitalisation duration.*

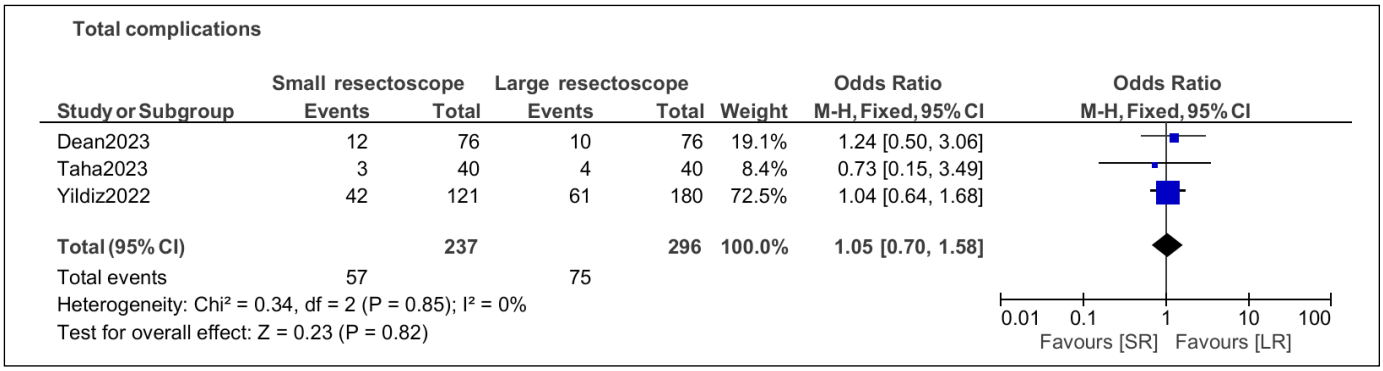


Figure 12. *Forest plot for total complications.*

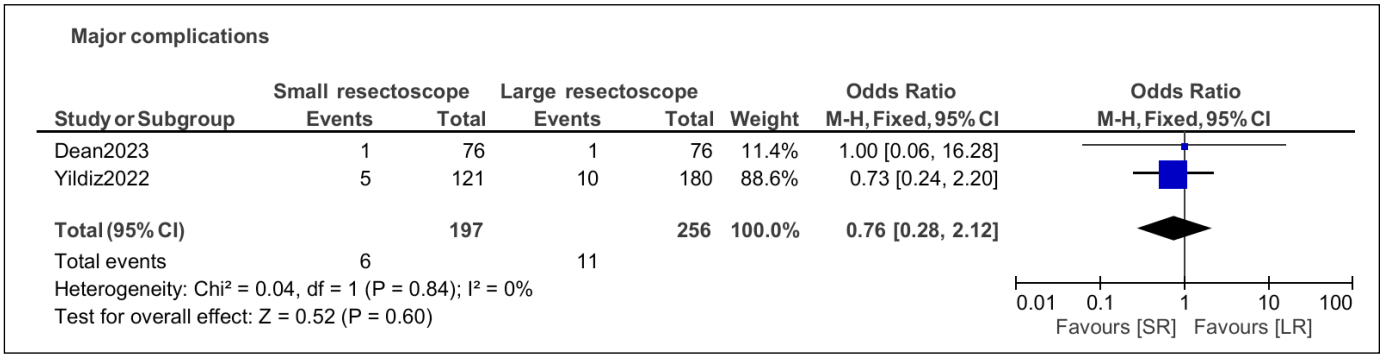


Figure 13. *Forest plot for major complications.*

Complication rates

Complication rates were described in 3 studies, totalling 237 patients in the SR group and 296 in the LR group. Significant complications were defined as complications of Clavien-Dindo classification grade ≥IIIb. The overall complication rates for SR and LR were 24.05% vs 25.34% (p = 0.82), with a moderate/severe complication rate of 3.05% vs 4.3% (p = 0.60), respectively. Odds of total complications between groups were OR = 1.05 [0.70, 1.58], p = 0.82; the odds of moderate to significant complications were OR = 0.76 [0.28, 2.12], p = 0.60. Funnel plots are included in the supplemental material. This finding is displayed in Figures 12 and 13.

Urethral stricture rates

Urethral stricture rates were described in 3 studies, totalling 545 patients (233 and 312 patients in the SR and LR groups, respectively). Of these, SR and LR reported a stricture rate of 4 (1.72%) and 10 (3.21%), respectively. This difference was not statistically significant OR = 0.59 [0.18, 1.90], p = 0.37. The funnel plot is included in the supplemental material. This finding is displayed in Figure 14.

Bladder neck contracture rates

Bladder neck contracture (BNC) rates were described in 2 studies, totalling 453 patients (197 and 256 patients in the SR and LR groups, respectively). Of these, SR reported 1 (0.51%) BNC and LR 2 (0.78%) BNC. This difference was not statistically significant, OR = 0.74 [0.07, 8.27], p = 0.81. The funnel plot is included in the supplemental material. This finding is displayed in Figure 15.

Urinary incontinence at one month

Urinary incontinence at one-month (UI@1) rates were described in 4 studies, totalling 633 patients (277 and 356 patients in the SR and LR groups, respectively). Of these, SR reported 27 (9.75%) UI@1 and LR 56 (15.73%) UI@1. This difference was not statistically significant (OR = 0.53 [0.25, 1.11], p = 0.09). The funnel plot is included in the supplemental material. This finding is displayed in Figure 16A.
On exclusion of Yildiz et al. [8], urinary incontinence at one-month (UI@1) rates were described in three

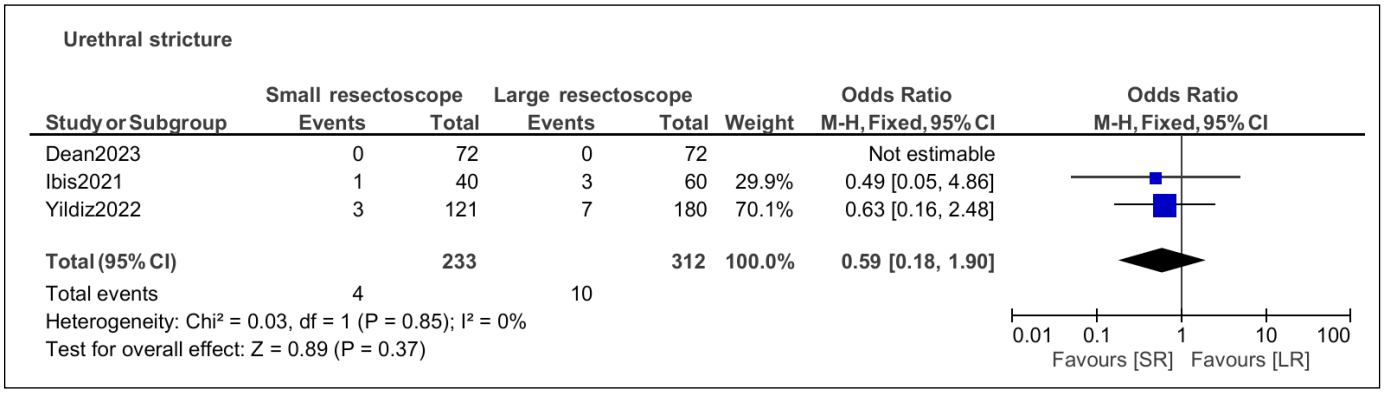


Figure 14. *Forest plot for urethral stricture.*

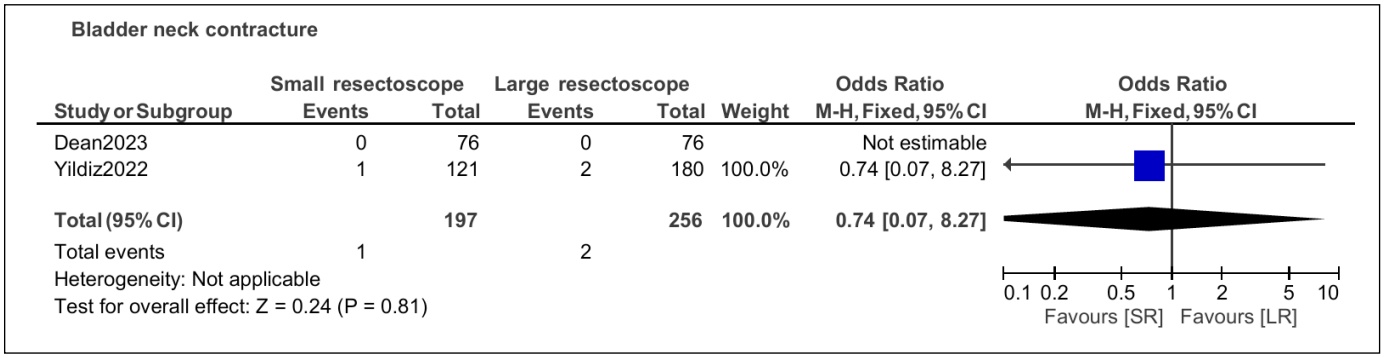


Figure 15. *Forest plot for bladder neck contracture.*

studies, totalling 332 patients (156 and 176 patients in the SR and LR groups, respectively). Of these, SR reported 19 (12.18%) UI@1 and LR 46 (26.14%) UI@1. This difference was statistically significant: OR = 0.40 [0.22, 0.72], p = 0.002. This is displayed in Figure 16B.

Urinary incontinence at three months

Urinary incontinence at 3-month (UI@3) rates were described in 3 studies, totalling 332 patients (156 and 176 patients in the SR and LR groups, respectively). Of these, SR reported 12 (7.69%) UI@3 and LR 18 (10.23%) UI@3. This difference was not statistically significant, OR = 0.75 [0.35, 1.62], p = 0.47. The funnel plot is included in the supplemental material. This finding is displayed in Figure 17.

DISCUSSION

The findings of this meta-analysis, which included one RCT and three retrospective studies encompassing 633 patients, shed light on key aspects

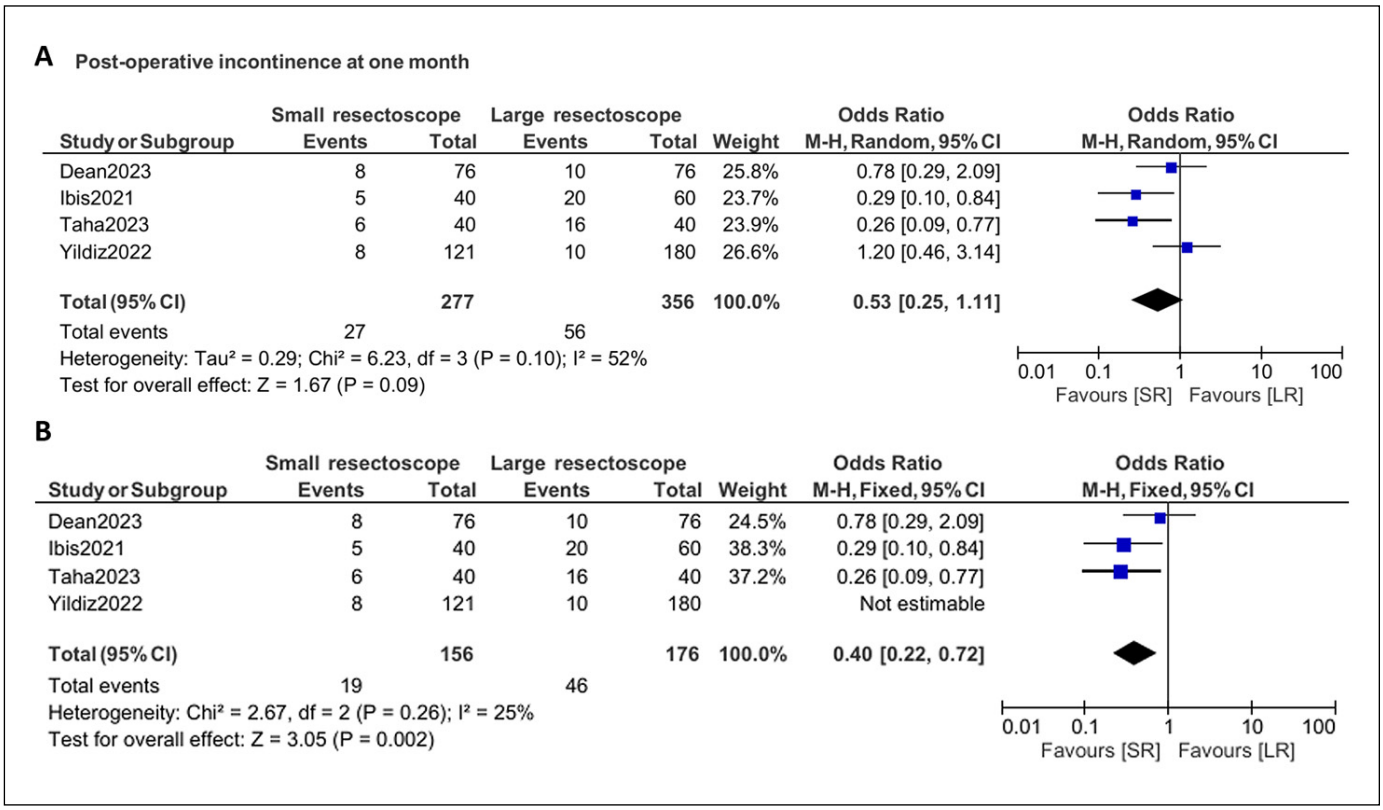


Figure 16. A) *Forest plot for urinary incontinence at one month.* **B)** *Forest plot for urinary incontinence at one month (excluding non-PubMed-indexed articles).*

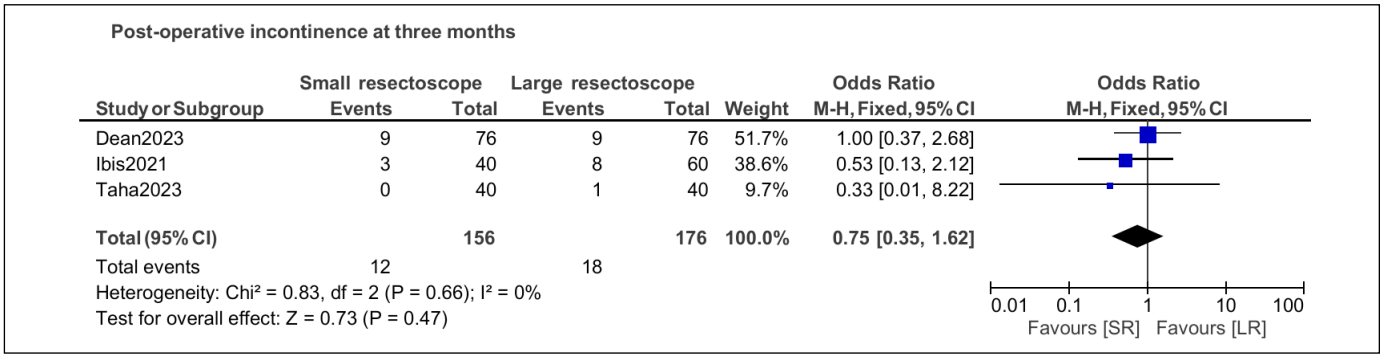


Figure 17. *Forest plot for urinary incontinence at three months.*

of using different resectoscope sheath sizes in HoLEP procedures and revealed several critical outcomes.

Both smaller (SR) and larger resectoscope sheath (LR) groups showed no significant differences in operative and enucleation times. This suggests that miniaturising the scope does not substantially impact the efficacy of the procedure, despite the reduced flow which is associated with a small scope. It could be argued that this might be due to relatively smaller prostate volume in included studies, as seen in Dean et al. [7], which excluded prostates above 200 ml. However, the average pre-operative prostate size was 90 ml or higher in three out of the four studies [7–10], which is similar to average pre-operative HoLEP prostate volumes as seen in the literature [14]. This indicates that surgeons can opt for either size based on comfort and institutional preference without compromising enucleation efficiency.

A significant finding was that the LR group demonstrated lower morcellation time. This may be attributed to the improved irrigation flow, which helps prevent bladder collapse and reduces the risk of bladder perforation requiring bladder repair. In a cohort of 1,476 patients, the rate of bladder injury during morcellation was 1.4% (20 patients), with 0.07% (1 patient) requiring open repair. Among the included studies, Dean et al. used 24 Fr and 28 Fr morcelloscopes. However, they switched the 24 Fr morcellator to a 28 Fr morcellator in 6 cases (8%) [7]. Alternatively, Yildiz et al. [8] and Ibis et al. [10] used a single-size Multicut morcellator system (Jena Surgical) and 26 F nephroscope with VersaCut tissue morcellator (Lumenis,) respectively, in all the cases. We believe this is currently the greatest challenge of miniaturised HoLEP. Using either a larger morcelloscope during morcellation or starting with a smaller scope but switching to the larger scope in cases of difficulties are acceptable strategies.

One of the most notable outcomes was the significantly lower urethral dilation rates observed in the SR group compared to LR (8.0% vs 39.5%, p = 0.01). This finding along with the hypothesis that smaller resectoscopes are associated with reduced urethral manipulation, potentially decreasing the risk of subsequent stricture formation might make SR HoLEP more attractive. However, in a RCT pre-operative dilation with Otis urethrotomy decreased the urethral stricture rates in patients undergoing HoLEP [11]. Thereby, it is possible to prevent the traditionally common complication associated with larger resectoscopes of urethral strictures by elective pre-operative dilation.

Although the rates of urethral strictures differed, it was not statistically significant at 1.7% with SR and 3.21% in LR, very similar rates were found in a retrospective cohort study of 502 patients undergoing HoLEP with urethral stricture rates of 1.8% vs 3.5% in 26 Fr and 28 Fr groups respectively (p = 0.405) [16]. Similarly, Gunes et al. [18], evaluating TURP resectoscope size, found a statistically significant increased urethral stricture rate with the larger resectoscope. Future adequately powered studies with a longer follow-up duration might show a statistically significant difference. This is likely the major advantage of miniaturised HoLEP.

The duration of catheterisation and hospitalization did not significantly differ between the SR and LR groups. Similarly, the total and significant complication rates, as well as transfusion rates, were comparable between the groups. These finding highlights that despite the reduced flow smaller sheath size had a similar safety profile as the large resectoscope. The improved urinary incontinence on exclusion of non-PubMed-indexed studies, suggest that SR HoLEP might lead to early sphincteric recovery. Notably, the similar rates of urinary incontinence at three months postoperatively suggest that both techniques have eventual improvement of sphincteric dysfunction in a majority of patients. It is possible that the true benefit might be greater with complete SR HoLEP as some studies used larger morcelloscope's during morcellation. Moreover, other techniques have been studied to decrease incontinence rates, including early apical release, pre-operative pelvic floor exercises and botulinum toxin administration during HoLEP, all of which have shown promising results [19–22].

The limitations of this study include the inclusion of non-randomised retrospective studies; however, they did not differ in pre-operative characteristics as seen in Table 4. The means of certain variables were estimated from the median and ranges via the Wans method [17]. Outcomes such as BNC and urethral stricture might be inadequately assessed due to the limited follow-up duration in the studies. Further large-scale RCTs are warranted to strengthen the evidence base, particularly regarding long-term outcomes such as stricture formation and functional recovery. Functional outcomes such as post-operative International Prostate Symptom Score (IPSS) and uroflowmetry were not analysed due to heterogeneous reporting, and it is unlikely to be different based on the resectoscope sheath size. Moreover, there was no difference in the post-operative American Urological Association symptom score (AUASS), IPSS and uroflowmetry between the groups in the included studies [7–10].

CONCLUSIONS

This meta-analysis indicates that using a smaller resectoscope sheath (22–24 Fr) during HoLEP lower urethral dilation rates and may decrease early incontinence rates without compromising operative time, enucleation efficiency, or complication rates. While larger sheaths (26–28 Fr) showed faster morcellation times. The choice of sheath size should be tailored to the surgeon's expertise, patient anatomy, and desired outcomes.

Overall, this review demonstrates that smaller resectoscopes are safe and efficacious in HoLEP.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

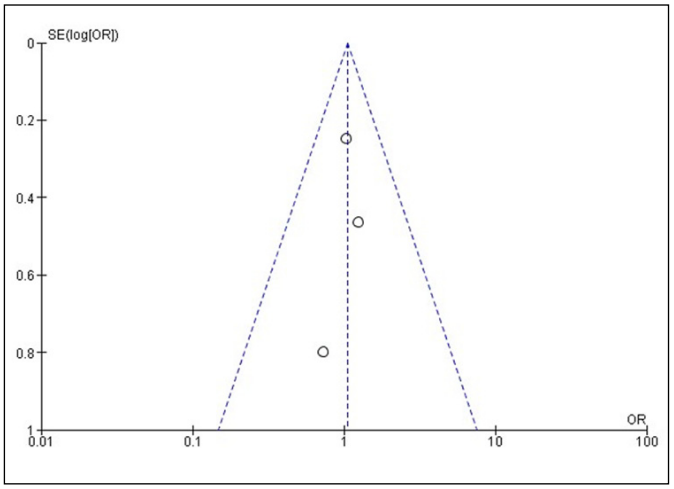
This research received no external funding.

ETHICS APPROVAL STATEMENT

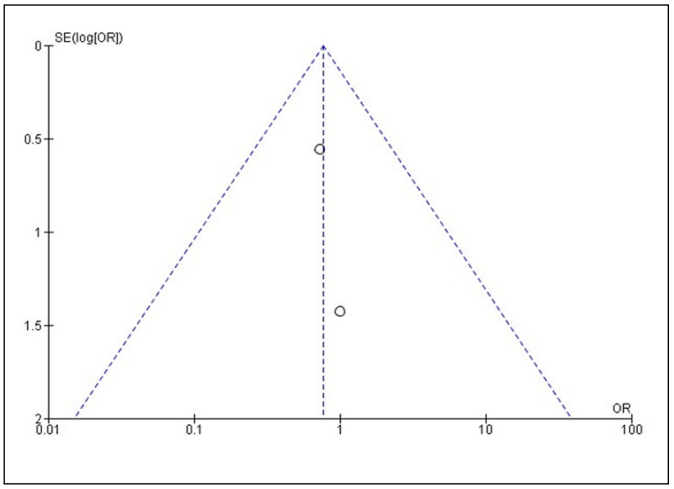
The ethical approval was not required.

SUPPLEMENTARY MATERIALS

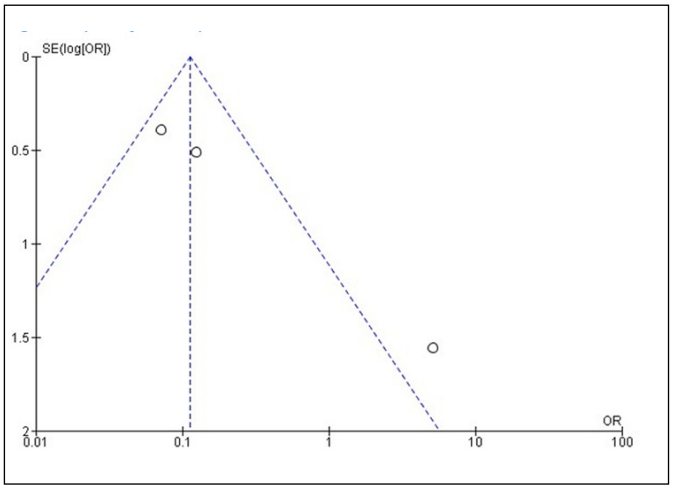
Funnel plots



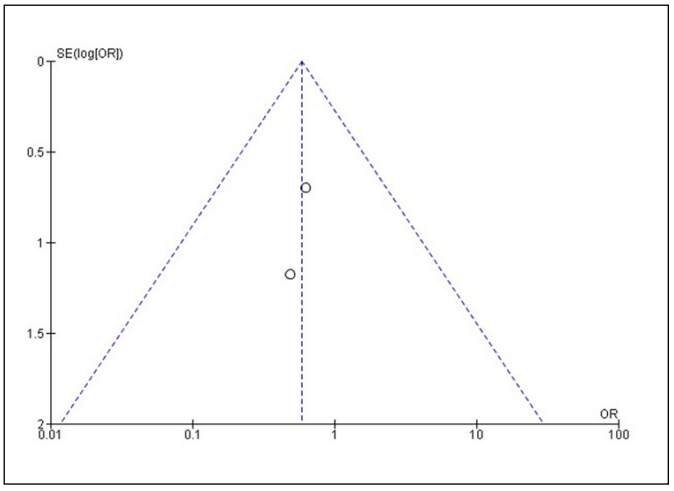
Suppl. Figure 1. *Total complications.*



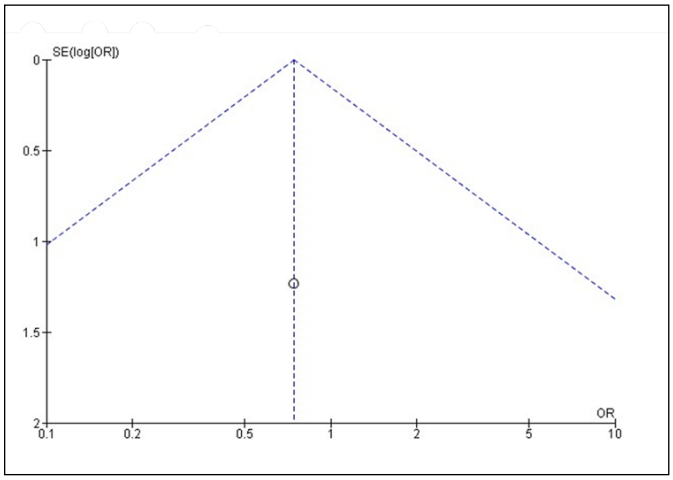
Suppl. Figure 2. *Major complications.*



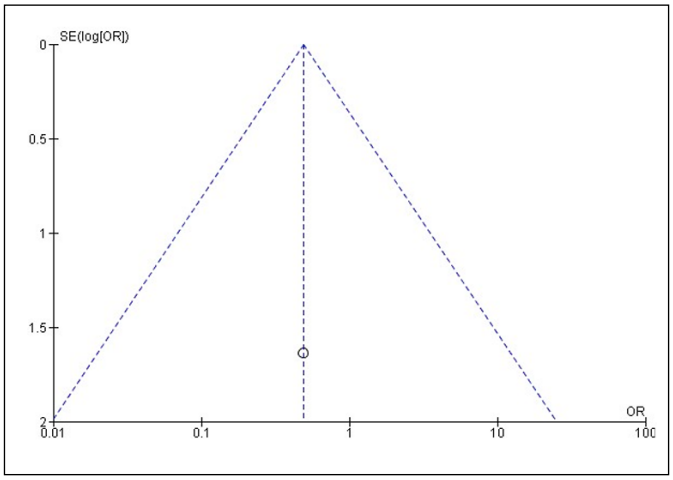
Suppl. Figure 3. *Urethral dilation.*



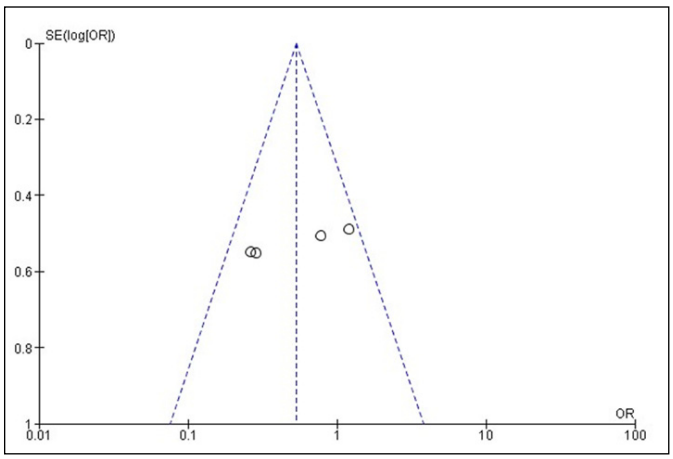
Suppl. Figure 4. *Urethral stricture.*



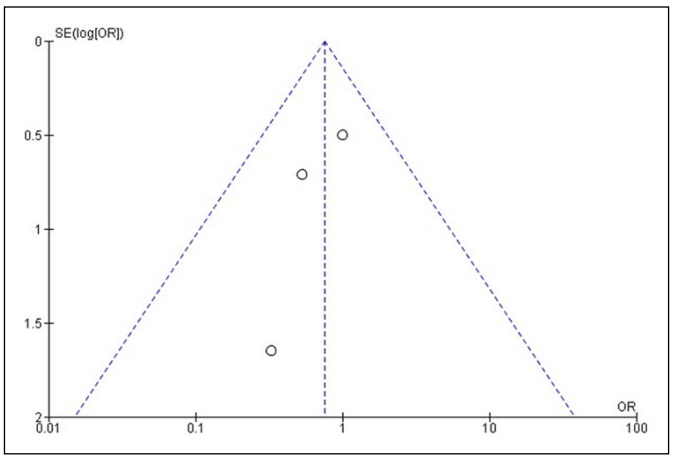
Suppl. Figure 5. *Bladder neck contracture.*



Suppl. Figure 6. *Transfusions.*



Suppl. Figure 7. *Post-operative incontinence at 1 month.*



Suppl. Figure 8. *Post-operative incontinence at 3 months.*

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REVIEW PAPER

FUNCTIONAL UROLOGY

Comparative efficacy and safety of silodosin and tadalafil combination or monotherapy for treating lower urinary tract symptoms due to benign prostatic obstruction: A systematic review and meta-analysis

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Introduction Over the last few years, trends in managing benign prostatic hyperplasia (BPH) have improved, advancing from reliance on surgery to satisfactory medical therapies. However, the efficacy and safety of combination therapies, including silodosin and tadalafil, are not well established compared to monotherapy for treating lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO).

Material and methods A systematic search was conducted in PubMed, ScienceDirect, Cochrane Library, and Scopus up to April 1, 2024. The quality of the studies was assessed using The Cochrane Risk of Bias (RoB) Tools 2 and Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E). Meta-analysis was conducted using RevMan 5.4.

Results A total of 1,300 records were screened, resulting in 7 final studies. Our meta-analyses showed that international prostate symptom score (IPSS), maximum urine flow rate (Q_{max}), and post-void residual volume (PVR) led to considerably greater improvements with the combination of silodosin and tadalafil compared to using either as monotherapy. However, combination therapy notably exhibited higher rates of adverse events (AE). On the other hand, as monotherapy, silodosin demonstrated a statistically significant improvement in Q_{max} ($p = 0.006$) and PVR ($p = 0.02$) over tadalafil but with higher rates of total AE, discontinuation, and risk of retrograde ejaculation.

Conclusions Silodosin and tadalafil are effective for treating LUTS in men due to BPO, especially when used in combination. However, with concerns about safety, tadalafil as monotherapy offers an advantage for patients with fertility desires due to its favorable side effect profile.

Key Words: benign prostatic obstruction ‹› lower urinary tract symptoms ‹› meta-analysis ‹› silodosin ‹› tadalafil

INTRODUCTION

Urology deals with both benign and malignant illnesses of the urinary tract and the genital system. With increasing age, men often experience dissatisfactory changes in their urinary system, particularly related to the continuous growth of the prostate gland. The majority of individuals with urological problems experience a decline in quality of life (QoL), which eventually results in a financial burden [1]. Benign prostatic hyperplasia (BPH), a disorder characterized by the enlargement

of the prostate gland, is a prevalent diagnosis in urology, affecting over 80% of men as they age. Over the last few years, trends in the management of BPH have improved, advancing from reliance on surgery to satisfactory medical therapies [2].

The utilisation of α-androgenic receptor blockers remains a fundamental therapeutic strategy for managing urological disorders, with silodosin being the preferred choice among α-blockers for treating lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) because of its strong α1A uroselectivity. A number of recent studies shows that silodosin is effective in treating a wide range of urological conditions [3].

On the other hand, tadalafil, a medication that inhibits the enzyme phosphodiesterase type 5 (PDE5i), has demonstrated its effectiveness in many controlled clinical trials involving LUTS due to BPO individuals with and without erectile dysfunction (ED) [4]. Given its demonstrated efficacy in treating both ED and BPH at the recommended dose of 5 mg per day, this medication offers significant therapeutic benefits for individuals seeking management for multiple urologic conditions [5]. The effectiveness of PDE5 inhibitors in combination with α-blockers for reducing LUTS has also been evaluated. Current research has demonstrated that this regimen offers advantageous additional benefits compared to a single therapy [6]. Therefore, the possibility of treating LUTS with or without ED using tadalafil alone or in combination with α-blockers may lead to the development of novel and more specific therapeutic approaches.

The effectiveness and safety of combined therapies like silodosin and tadalafil for treating LUTS due to BPO have yet to be widely recognized. To date, there is no published meta-analysis evaluating this combination treatment in BPH individuals. Thus, we aim to assess the effectiveness and safety of these combined therapies compared to monotherapy for managing LUTS associated with BPH.

MATERIAL AND METHODS

Search strategy

Two authors conducted a comprehensive search and analysis of all clinical studies (randomized controlled trials or observational studies) that examined the effectiveness and safety of combining silodosin and tadalafil, as well as their monotherapies. The search included databases such as PubMed, ScienceDirect, Scopus, and Cochrane Library, covering the period from the beginning until April 1st, 2024. The following keywords were employed by combining several terms including "Silodosin, Tadalafil, Benign Prostatic Hyperplasia (BPH) or Benign Prostatic Enlargement (BPE) or Benign Prostatic Obstruction (BPO) and LUTS". An additional database was utilized to conduct a comprehensive search for other studies. This study did not have any restrictions based on country or publication year. The protocol of this meta-analysis was registered in PROSPERO (CRD42024576429). This study also followed the guideline of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA 2020 guidelines) [7].

Eligibility criteria

This systematic review and meta-analysis included studies which met the following criteria: (1) the study either randomized or non-randomized controlled trials; (2) the study evaluated a comparison of combination therapy with silodosin and tadalafil vs silodosin monotherapy or tadalafil monotherapy for treatment of LUTS in men due to BPO; (3) the study provided precise information, mostly consisting of the quantity of subjects and the valuable outcomes of indicators; (4) full-text content and related data can be obtained; and (5) article available in English language. Studies presented as abstracts, review articles, and case reports were excluded from the analysis.

Selection process

Duplicate studies were identified and excluded after the initial search. The titles and abstracts of the remaining literature were screened by at two independent reviewers to determine eligibility. Studies meeting the criteria were included, while those which were not were excluded. Conflicts in study classification were resolved through group discussion.

Data extraction

Each study was reviewed by independent reviewers, and the following information was gathered for each study: (1) first author name; (2) publication date; (3) the type of study design; (4) patients description; (5) therapies received by patients, including dosage and treatment duration; (5) The number of individuals in all groups; (6) age, and (7) Furthermore, data related to the total International Prostate Symptom Score (IPSS), maximum urine flow rate (Q_{max}), postvoid residual volume (PVR), International Index of Erectile Function (IIEF), any adverse event (AE) and incidences of discontinuation that occurred as a result of AE.

Quality assessment

Two authors conducted an independent assessment of all the inclusion studies that were identified. In case of any disagreement between the authors, a third reviewer was included to resolve the issue. The Cochrane Risk of Bias (RoB) Tools 2 were used to evaluate the RCT study investigation. Risk Of Bias in Non-randomized Studies of Exposures (ROBINS-E) was used in the assessment of retrospective/observational study. Risk-of-bias VISualization (robvis) was used for the visualization of risk of bias graph [8].

Statistical analysis

The data obtained were processed using Review Manager 5.4 (Cochrane Collaboration, UK). We utilized the differences in data between the baseline and the end-point measure to assess changes in the outcomes. Mean difference (MD) was used to analyze continuous data, whereas the odds ratio (OR) was used for dichotomous outcomes with the corresponding 95% confidence interval (CI). The heterogeneity of the statistical analysis was seen in the I^2 value. The fixed-effects model is used if I^2 <50%, while the random-effects model is used if I^2 ≥50%. The results will be presented in a forest plot, and the overall effect is considered significant if $p < 0.05$. Asymmetry tests, including Egger's test for assessing potential publication bias via funnel plots, were not performed due to their restricted reliability in meta-analyses comprising less than 10 studies [9]. Furthermore, because of small number of studies, subgroup analysis and sensitivity analysis were also not conducted [10].

RESULTS

Literature search, screening results and characteristic of studies

From various databases, 1.300 studies were initially identified using keywords. Furthermore, we discovered two additional studies outside of the databases that were relevant to the topic, resulting in a final total of 1,302 studies. After removing 168 duplicates, two reviewers conducted independent assessments of the remaining 1,132 study titles and abstracts. Based on the inclusion and exclusion criteria, we removed 1,284 articles. Following a detailed examination of the full article, we excluded seven articles because of insufficient data or failure to match the study criteria. Finally, seven studies [11–17] were included in our analysis, consisting of five RCTs [11, 14–17] and two observational studies [12, 13], with a total of 1.208 patients. Full details of the search and selection process are presented in the PRISMA flow diagram (Figure 1) and the characteristics of these studies are presented in (Table 1).

Quality assessment result

The Cochrane RoBTools 2 was used to evaluate the RCT study investigation. ROBINS-E was used in the assessment of retrospective/observational study. The Cochrane RoBTools 2 was used to evaluate 5 RCT studies consist of 5 domains [18] and ROBINS-E evaluated 2 observational studies consist of 7 domains [19]. Overall risk-of-bias judgement of these instruments was classified into 3 groups which low bias risk (If the study is determined to have a minimal risk of bias in all areas), some concerns (if there is any apprehension in at least one area) and high bias risk (if the study is determined to have a significant risk of bias in at least one area). Out of the RCT studies, four [11, 14–16] raised some concern, primarily due to the lack of blinding among personnel to the intervention in domain D2, which refers to the risk of bias due to deviations from the intended interventions. All of the observational studies were classified as low risk of bias. The detailed assessment of the risk of bias was shown in supplementary materials.

Statistical analysis

Total IPSS

Total IPSS from two studies comparing the efficacy of the combination group vs silodosin showed that the combination revealed a marked decline in total IPSS (MD = –1.51; 95% CI: from –2.18 to –0.84; $p < 0.00001$) compared with the silodosin group (Figure 2A). Furthermore, three studies comparing combination group vs tadalafil also exhibited a significant decline in the combination group (MD = –2.76; 95% CI: from –3.66 to –1.86; $p < 0.00001$) relative to the tadalafil group (Figure 3A). Furthermore, an analysis of five studies comparing the effectiveness of silodosin and tadalafil found no statistically significant disparity in the total International Prostate Symptom Score (IPSS) between these monotherapies (MD = –0.89; 95% CI: from –1.85 to –0.06; $p = 0.07$; Figure 4A).

Q_{max}

Two trials comparing the combination group with silodosin monotherapy showed that the combination

Table 1. *Characteristics of included study*

No	Study (author, ref.)	Study design	Population	Intervention			Treatment duration	Mean age (years)	Total sample (each group)	Outcome assesments				Adverse event
				Combination	Silodosin monotherapy	Tadalafil monotherapy				IPSS Total	Q_{max} [ml/s]	PVR [ml]	IIEF Score	
1	Yoshida et al. 2017 [11]	RCT	Men ≥60 years old with LUTS due to BPO and IPSS ≥13	-	Silodoson 8 mg/day	Tadalafil 5 mg/day	8 weeks	70.1	Total sample: 181 (89 silodosin /92 tadalafil)	✓	✓	✓	–	Headache, orthostatic hypotension, retrograde ejaculation, etc.
2	Yoshida et al. 2017 [12]	Retrospective study	Men ≥50 years of age with a history of LUTS secondary to BPO and IPSS >8	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	-	8 weeks	76	Total sample: 101 (50 silodosin plus tadalafil /51 silodosin)	–	–	–	–	Headache, palpitation, dyspepsia, etc.
3	Singh et al. 2018 [13]	Prospective observational study	Men >45 years old with LUTS due to BPO	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	Tadalafil 5 mg/day	12 weeks	60.33	Total sample: 45 (15 combination /15 silodosin /15 tadalafil)	✓	✓	✓	–	Orthostatic hypotension
4	Vajpeyi and Chipde 2019 [14]	RCT	All men patients with LUTS due to BPO	-	Silodoson 8 mg/day	Tadalafil 5 mg/day	4 weeks	NR	Total sample: 100 (50 silodosin /50 tadalafil)	✓	–	–	–	NR
5	Abdelrazek et al. 2021 [15]	RCT	All men patients with LUTS due to BPO and ED	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	Tadalafil 5 mg/day	12 weeks	62.4	Total sample: 308 (105 combination /102 silodosin /101 tadalafil)	✓	✓	✓	✓	Headache, orthostatic hypotension, retrograde ejaculation, etc.
6	Abdallah et al. 2023 [16]	RCT	Men ≥45 years old with LUTS due to BPO with or without ED and IPSS ≥13	-	Silodosin 8 mg/day	Tadalafil 5 mg/day	12 weeks	58.7	Total sample: 97 (50 silodosin /47 tadalafil)	✓	✓	–	✓	Headache, orthostatic hypotension, retrograde ejaculation, back pain, etc.
7	Avinash et al. 2024 [17]	DBRCT	All men patients with LUTS due to BPO with IPSS ≥13 and ED with IIEF-EF ≤25	Silodosin 8 mg/day plus Tadalafil 5 mg/day	-	Tadalafil 5 mg/day	12 weeks	NR	Total sample: 376 (186 combination /196 tadalafil)	✓	–	–	–	NR

BPO – benign prostatic obstruction; CI – confidence interval; DBRCT – double blind randomized controlled study; ED – erectile dysfunction; IIEF-EF – International Index of Erectile Function-Erectile Function; IPSS – International Prostate Symptom Score; LUTS – lower urinary tract symptoms; NR – not reported; PVR – post-void residual urine; Qmax – maximum urine flow rate; RCT – randomized controlled trial

group had a significantly higher Q_{max} compared to silodosin used alone (MD = 0.68; 95% CI: 0.11–1.24; p = 0.02; Figure 3A). In the combination group vs tadalafil, two studies also exhibited that the combination group was superiorly related to tadalafil (MD = 1.50; 95% CI: 0.97–2.04; p <0.00001; Figure 3B). In addition, Q_{max} from three studies that compared monotherapy between silodosin vs tadalafil revealed that there was a significant difference in Q_{max} in the silodosin group in compare to tadalafil (MD = 1.40; 95% CI: 0.40–2.40; p = 0.006; Figure 4B).

Postvoid residual volume

Two studies revealed that patients who received combination intervention had a significantly reduced PVR compared to the silodosin (MD = –2.19; 95% CI: from –3.93 to –0.45; p = 0.01; Figure 2C), as well as two studies compared to the tadalafil (MD = –4.40; 95% CI: from –6.24 to –2.57; p <0.00001; Figure 3C). In addition, PVR from three studies that compared silodosin vs tadalafil revealed that silodosin is suggested to have more benefit at reducing PVR than tadalafil (MD = –2.14; 95% CI: from –3.97 to –0.31; p = 0.02; Figure 4C).

International Index of Erectile Function

There were only two studies that assessed the IIEF score and it is only in the silodosin vs tadalafil group. The random effects model showed that there was no significant difference in IIEF score changes between these monotherapy groups (MD = –0.04; 95% CI: from –1.38 to –1.30; p = 0.96; Figure 4D).

Safety: total adverse events, discontinuation due to adverse events and retrograde ejaculation

Three studies in the combination vs silodosin group, two studies in combination vs tadalafil group and four studies in silodosin vs tadalafil group assessed the number of total AE. Tadalafil monotherapy demonstrated a lower frequency of AE compared to the combination therapy (OR = 3.09, 95% CI: 1.57–6.09, p = 0.001; Figure 2D), but did not meet statistical significance compared to silodosin (OR = 1.22, 95% CI: 0.70, 2.10, p = 0.48; Figure 3D).

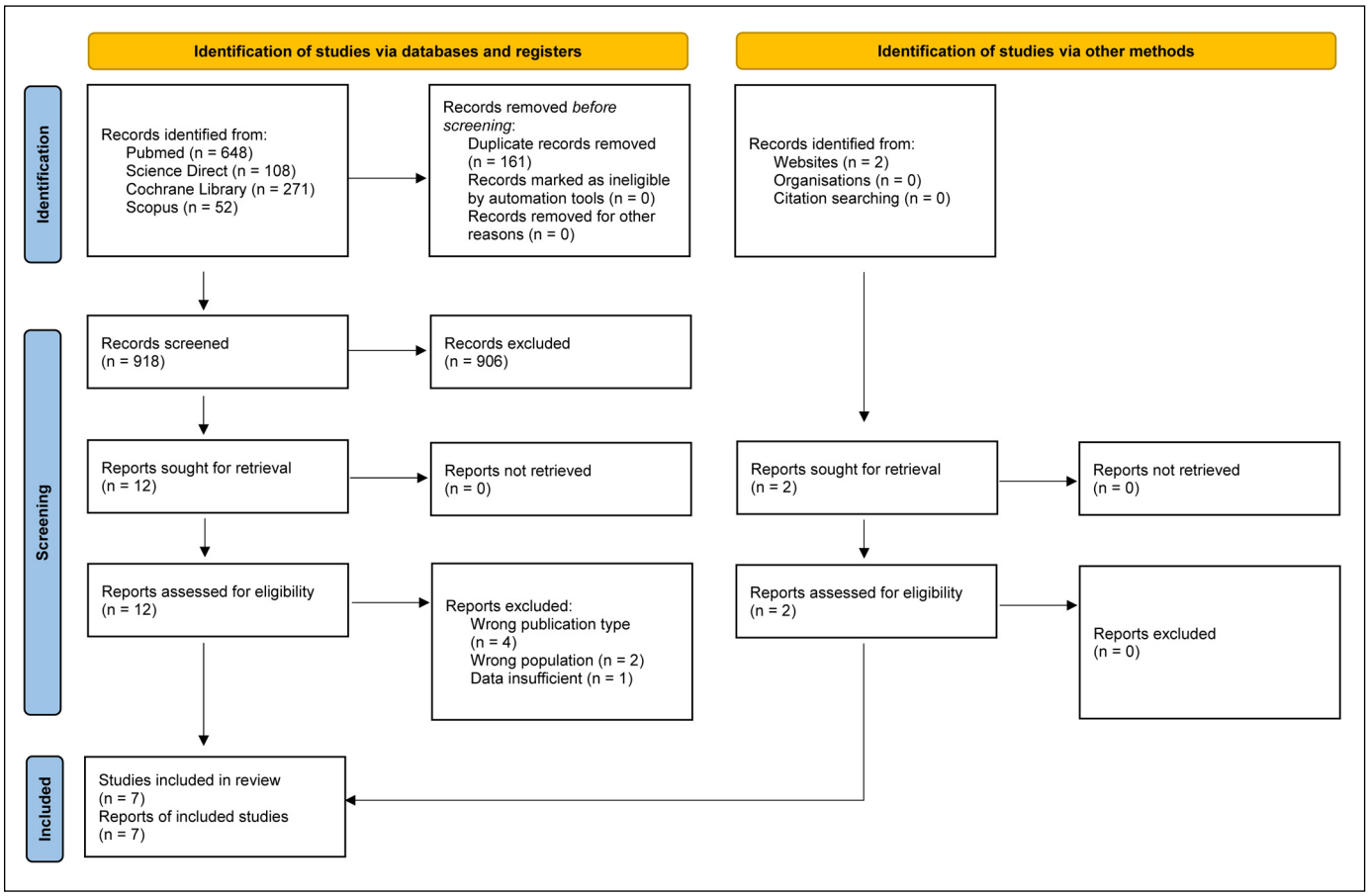

Figure 1. *Preferred reporting items for systematic reviews and meta-analyses flow chart.*

When comparing the monotherapy to total AEs, it was found that silodosin produced a higher incidence of AE compared to tadalafil (OR = 2.34, 95% CI: 1.49–3.68, p = 0.0002; Figure 4E). Regarding the events of discontinuation due to AE, all studies in combination vs silodosin (OR = 1.74,

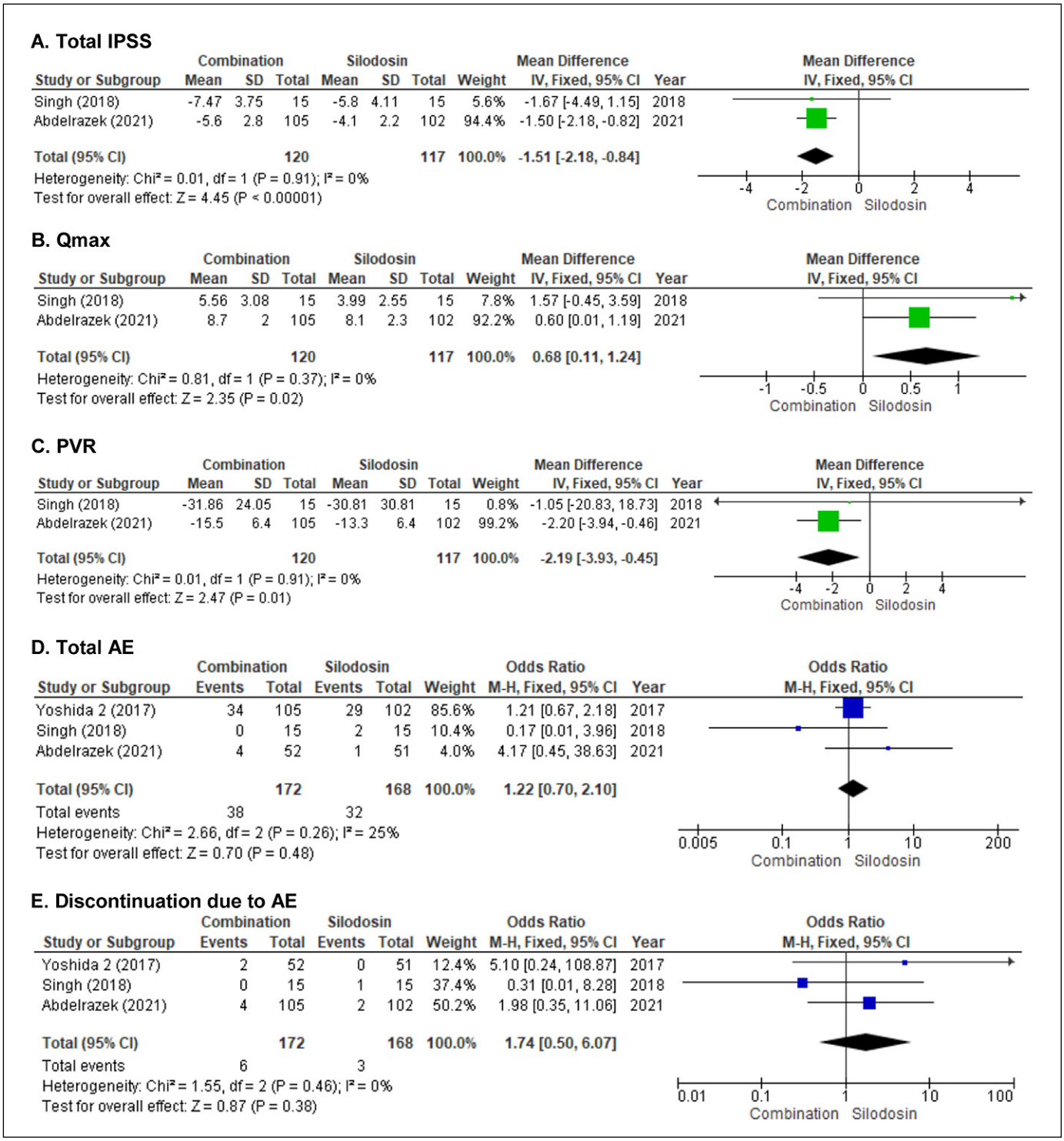

Figure 2. *Forest plot comparing the change between combination therapy versus silodosin monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR,* **D)** *total AE; and* **E)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

95% CI: 0.50–6.07, p = 0.38; Figure 2E), combination vs tadalafil (OR = 6.21, 95% CI: 0.72–53.28, p = 0.10; Figure 3E), and silodosin vs tadalafil (OR = 4.16, 95% CI: 0.45–38.46, p = 0.21; Figure 4G) did not meet statistical significance. In addition, we also assessed the rate of retrograde ejaculation

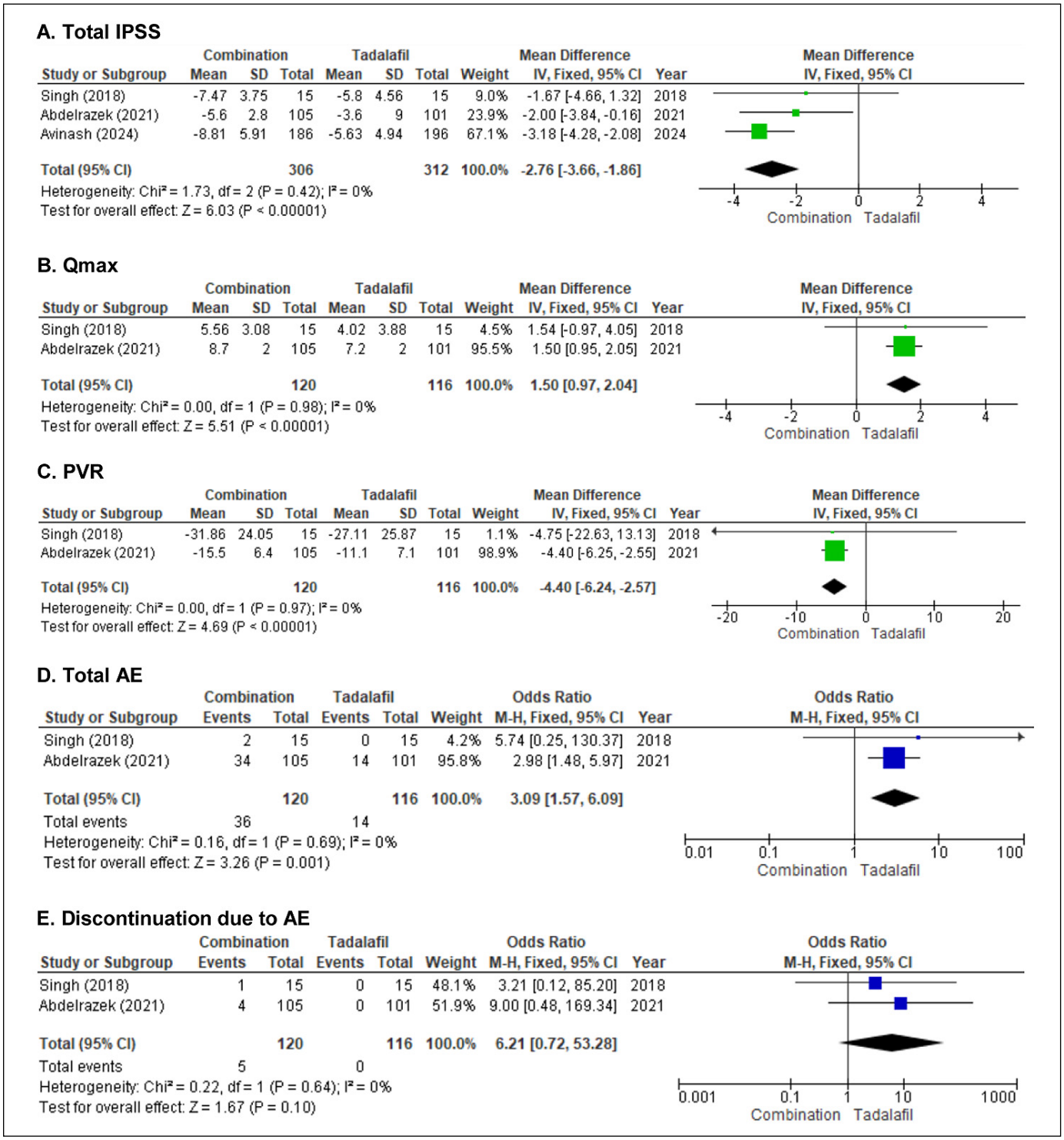

Figure 3. *Forest plot comparing the change between combination therapy versus tadalafil monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR;* **D)** *total AE; and* **E)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

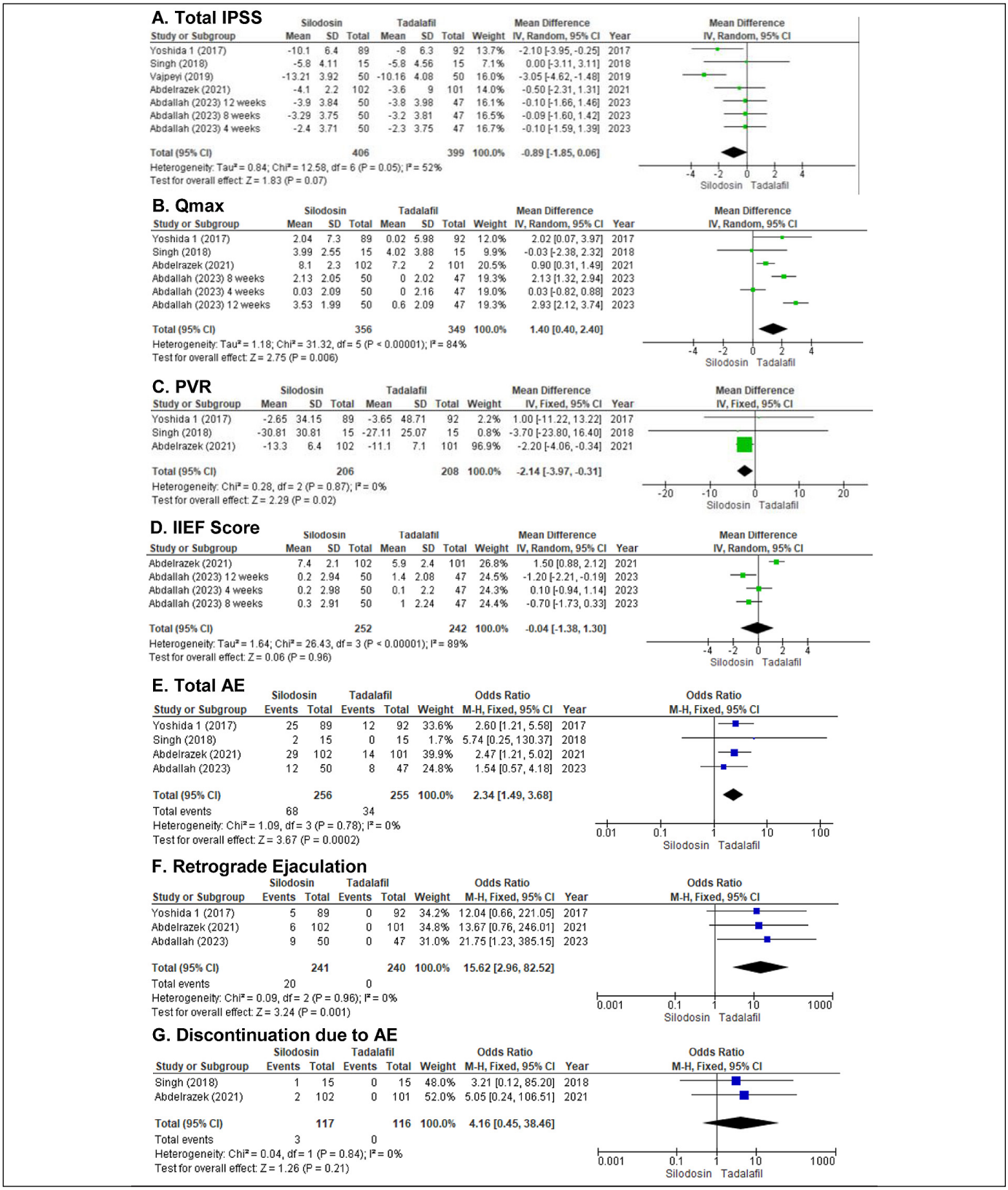

Figure 4. *Forest plot comparing the change between silodosin versus tadalafil monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR;* **D)** *IIEF score;* **E)** *total AE;* **F)** *retrograde ejaculation; and* **G)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IIEF – The International Index of Erectile Function; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

as a complication in the silodosin vs tadalafil group, which showed an absolutely higher incidence of retrograde ejaculation in the silodosin group compared to tadalafil (OR = 15.52, 95% CI: 2.96–82.52, p = 0.001; Figure 4F).

DISCUSSION

The results of this meta-analysis demonstrated that the combination therapy of silodosin and tadalafil provided greater improvement in LUTS due to BPO compared to either silodosin or tadalafil monotherapy as more significant reduction in both IPSS and PVR values as well as improvement in Q_{max} in the combination group. Generally, LUTS among patients are attributed to both static and dynamic components [20]. Static obstruction results from the direct effect of an enlarged prostate, causing periurethral compression and obstruction of the bladder outlet. The enlarged prostate distorts the bladder outlet causing urinary obstruction, while the periurethral compression result in increased pressure during urination to overcome the resistance to urine flow [21] Moreover, the dynamic component is caused by a decrease in elasticity and collagen in the prostatic urethra in BPH patients, which causes tension in the smooth muscles of the prostate and urethra. This explains the reason why the size of the prostate is not a constant indicator of BPH [22].

Silodosin is an α adrenoreceptor antagonist that is highly selective for α1A, which has a dominant effect in regulating smooth muscle tone in the prostate and prostatic urethra. A study reported that the affinity of silodosin for the α1A receptor is 593 times greater than for the α1B receptor and 57 times greater than for the α1D receptor. This shows that silodosin has high uroselective and is effective for the treatment of LUTS due to BPO [23]. In addition, Tadalafil is one of the PDE5-i groups which is able to inhibit the degradation of cGMP thereby increasing the activation of protein kinase, triggering the relaxation of smooth muscle in the prostatic urethra [24]. Previous studies reported that PDE5-I can enhance the action of α blockers by increasing NO mediated relaxant in penile smooth muscle, prostate, and bladder neck. *In vitro* studies by Angulo et al. on human prostate cells also showed that administration of tadalafil alone did not have any effect on nerve-mediated contraction of human prostate, whereas when combined with silodosin there was an inhibitory effect on nerve-mediated contraction, this demonstrates that the concurrent use of silodosin and tadalafil produces an additional effect on reducing muscle tone through inhibition of sympathetic tone [24, 25]. The results of this meta-analysis are supported by evidence from previous studies which reported that the combination of silodosin and tadalafil has a superior effect compared to silodosin or tadalafil monotherapy in the treatment of LUTS due to BPO.

Findings from this meta-analysis also indicated that there is no statistically significant difference in IIEF scores between the consumption of silodosin and tadalafil in combination therapy. However, only one study reported a comparison of the effectiveness of combination therapy with monotherapy on IIEF scores. The study indicated that the combination of silodosin and tadalafil yielded significantly superior results combination approach in comparison to using silodosin or tadalafil monotherapy [26]. Further research on a larger scale is still needed to learn more about the effects of this combination therapy on erectile function in men.

The relationship between IPSS, which reflects patient-perceived symptoms, and objective parameters like Q_{max} and PVR is essential in evaluating the effectiveness of therapy for BPH. Several studies have shown that although alpha blockers significantly reduce LUTS as measured by IPSS, improvements in Q_{max} and PVR are less consistent [27, 28]. For instance, a meta-analysis by Guo et al. involving 22 studies found that α-blockers reduced IPSS significantly compared to placebo but showed no significant difference in Q_{max} improvement when compared to PDE5-inhibitors like tadalafil (SMD: –0.59, 95% CI: from –1.73 to 0.54; p = 0.30) [28]. Another study also indicated that although the combination of α-blockers and PDE5 inhibitors gave better results in terms of IPSS reduction, the improvements in Qmax and PVR were not always in line with patients' perception of their symptoms [27]. The α-blockers appear to be more effective in alleviating subjective symptoms than in improving objective parameters. Therefore, evaluating both subjective and objective outcomes is essential for a comprehensive assessment of therapy effectiveness in managing LUTS due to BPO. Our analysis showed that combining silodosin with tadalafil was more effective in improving both subjective and objective parameters compared to using monotherapy. This suggests that while alpha blockers like silodosin effectively improve patients' conditions, adding tadalafil may provide additional benefits. Nonetheless, tadalafil remains a good option for patients prioritizing the preservation of sexual function due to its favorable side effect profile.

In terms of safety and side effects, the results of this meta-analysis showed that there was no sig-

nificant difference in the total incidence of adverse events between combination therapy and silodosin monotherapy. However, a significant difference was found between the total incidence of adverse events in the combination group compared to the tadalafil group alone. These results indicate that combination therapy has a slightly higher risk of adverse events compared to tadalafil monotherapy. The most common adverse events are headache, retrograde ejaculation, and orthostatic hypotension. The very high affinity of silodosin for α1A makes silodosin work very focused on smooth muscle in the bladder neck and proximal urethra, which has been shown to be able to reduce LUTS in the dynamic aspect. However, weakness in the bladder neck and proximal urethra muscles will increase the likelihood of retrograde ejaculation [29]. In addition, with spesific affinity of silodosin which focuses on α1A, the risk of orthostatic hypotension is significantly low [30]. However, when silodosin is combined with tadalafil, the risk of orthostatic hypotension tends to increase due to the effect of tadalafil which causes systemic vasodilation, thereby reducing peripheral systemic resistance [31]. Overall, there were no fatal and dangerous adverse events reported in all included studies, even the results of other meta-analyses in this study showed that there was no significant difference in the number of patients who discontinued due to AE between the combination group with silodosin or tadalafil monotherapy. Although the risk of adverse events remains, considering its effectiveness, we consider that the combination of silodosin and tadalafil has a very positive effect and safe on improving LUTS due to BPO and also well tolerated in BPH patients with or without ED. Patients with special conditions such as a history of hypotension or heart failure need to get special considerations before receiving the combination therapy of silodosin and tadalafil.

Medical therapy is widely accepted as the first-line treatment for LUTS due to BPO. However, when medication fails to provide adequate symptom relief, invasive and minimally invasive treatment options may be considered [32]. Furthermore, minimally invasive methods such as botulinum toxin injections have recently demonstrated efficacy in managing patients with BPH and neurogenic detrusor overactivity (NDO) [33, 34].

We acknowledge that this study still has several limitations, including the limited number of included studies and the variability of outcomes assessing LUTS in BPH patients. To minimize these limitations, we reviewed all reported outcomes to produce a comprehensive analysis. Based on the findings of this meta-analysis, we recommend using a combination of silodosin and tadalafil as a treatment for individuals with LUTS due to BPO, especially in cases where monotherapy is ineffective. The synergistic effect of silodosin and tadalafil is expected to improve LUTS and thus improve the quality of life of BPH patients. However, we do not recommend this combination therapy for patients who want to have children because of the risk of retrograde ejaculation due to the effects of silodosin.

CONCLUSIONS

The combined therapy shown greater effectiveness in treating LUTS due to BPO compared to the individual treatments of silodosin or tadalafil. While combination therapy resulted in a higher occurrence of AE compared to monotherapies, these effects were well tolerated. However, tadalafil monotherapy is preferred for patients who want to retain fertility due to its favorable side effect profile.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

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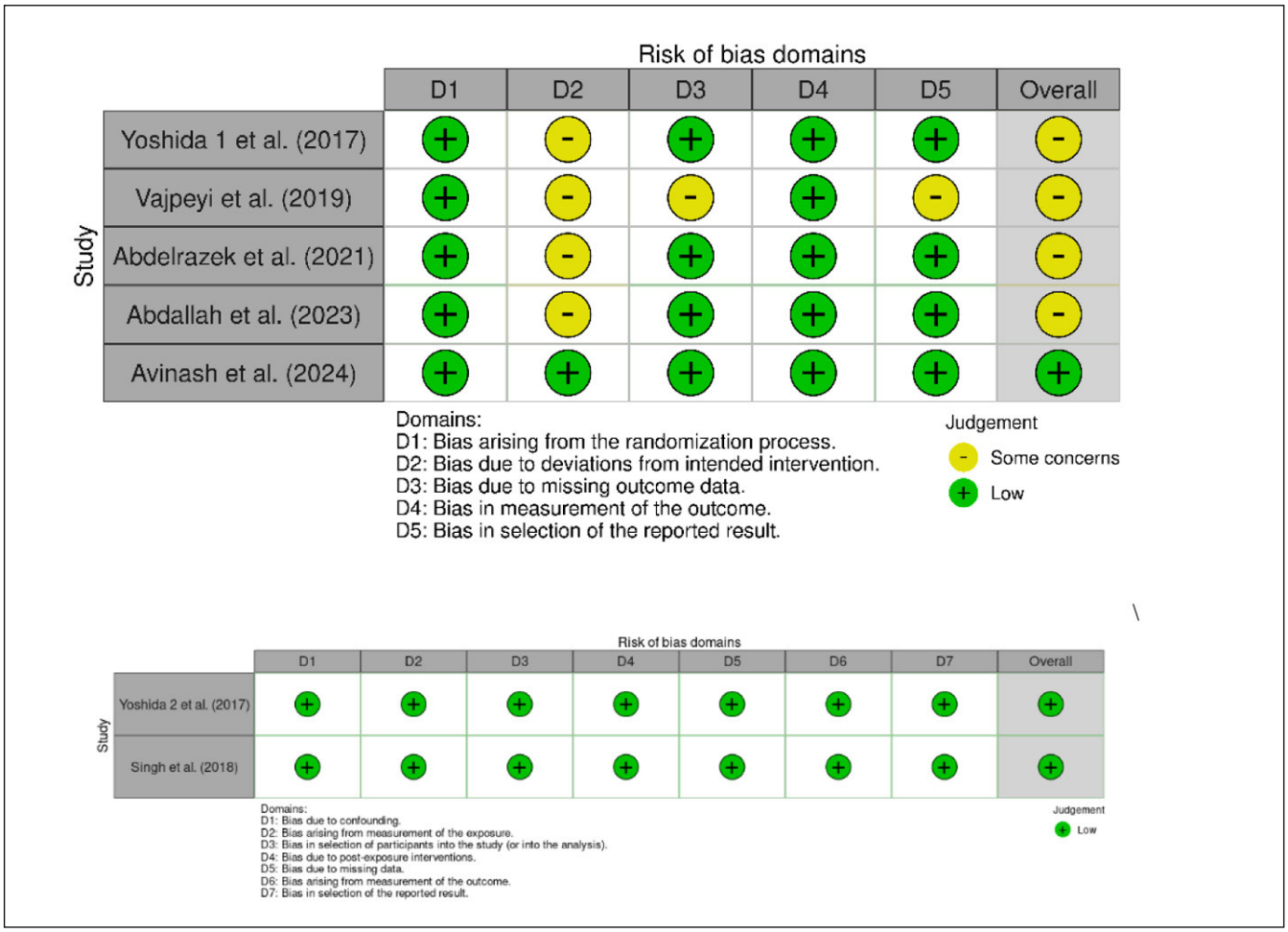
ETHICS APPROVAL STATEMENT

The ethical approval was not required.

SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *Risk of bias assessment using the Cochrane Risk of Bias (RoB) Tools-2 and the Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E).*

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SHORT COMMUNICATION

FUNCTIONAL UROLOGY

Holmium laser enucleation of the prostate vs single-port transvesical enucleation of the prostate: Single-center comparative surgical outcomes during early adoption

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Introduction To compare the surgical outcomes of holmium laser enucleation of the prostate (HoLEP) and robotic single-port transvesical enucleation of the prostate (STEP) for the treatment of benign prostatic hyperplasia (BPH) during early adoption at a single center.

Material and methods Data about consecutive BPH patients who underwent HoLEP and STEP at our Center from July 2023 to September 2024 were retrospectively analyzed. Both procedures were performed by surgeons at the beginning of their experience with the procedures.

Results Thirty HoLEP and 20 STEP cases were included in the analysis. STEP patients had larger prostate volume (median 101.5 vs 78.5 cc; p = 0.003). Median operative time was longer for STEP (286 vs 124 min, p <0.001). Median catheterization time was shorter for HoLEP (3 vs 7 days, p <0.001). Transient post-operative incontinence was higher for HoLEP (31% vs 5.3%, p = 0.032). There was no difference in median length of stay (30 hours for HoLEP and 31 hours for STEP; p = 0.108).

Conclusions Both HoLEP and STEP can be safely implemented for the minimally invasive treatment of BPH. Each of the procedures presents some appealing features that can be tailored to different subgroups of patients. HoLEP is appealing for higher surgical risk patients, while STEP allows to effectively manage larger glands even at the beginning of the surgeon's learning curve. As experience with SP robotic surgery matures, it is likely that STEP becomes a competitive alternative to the well-established HoLEP.

Key Words: STEP ‹› single port ‹› transvesical ‹› HoLEP ‹› benign prostatic hyperplasia ‹› surgical outcomes ‹› initial outcomes

INTRODUCTION

Bladder outlet obstruction (BOO) caused by benign prostatic hyperplasia (BPH) is a common and often debilitating condition in men causing lower urinary tract symptoms (LUTS) [1]. Surgical treatment is often required in patients with moderate to severe LUTS non-responsive to medical therapy, recurrent urinary tract infections, urinary retention, bladder stones, and risk of renal insufficiency secondary to BPH [1, 2].

Holmium laser enucleation of the prostate (HoLEP) is a well-established surgical technique with good perioperative, postoperative and functional outcomes, and it is recommend as first line treatment option by current guidelines [1, 3]. One of the concerns about HoLEP is the learning curve associated with the procedure [4].

Single-port transvesical enucleation of the prostate (STEP) has been recently described as a feasible surgical option and is gaining relevance in this space [5, 6]. Comparative studies of transurethral laser enucleation of the prostate vs STEP remain very limited [7, 8].

The aim of this study was to compare the surgical outcomes of HoLEP and STEP for the treatment

of benign prostatic hyperplasia (BPH) during early adoption at a single Center.

MATERIAL AND METHODS

This was a retrospective single-center analysis of HoLEP and STEP cases done at Rush University Medical Center (Chicago, IL, USA) from July 2023 to September 2024.

The STEP procedures were performed with da Vinci Single Port (SP) System (da Vinci SP®; Intuitive Surgical Inc.) by two fellowship trained robotic surgeons with extensive experience with Multi Port robotic surgery but at the beginning of their experience with the SP system. HoLEP procedures were performed with MOSES 2.0 holmium laser (Boston Scientific) and morcellation with Wolf Piranha Morcellation system (Richard Wolf), by a single fellowship trained surgeon also at the beginning of the experience with HoLEP.

Pre-operative data collected included age, body mass index (BMI), American Society of Anesthesiology (ASA) score, Charlson Comorbidity Index (CCI), anticoagulant therapy, BPH therapy, previous prostatic surgery, post-void residue (PVR), prostate-specific antigen (PSA), prostate volume and presence of median lobe or bladder stones.

Perioperative and early postoperative data (defined as 30-days after surgery) included total operative time, estimated blood loss (EBL), specimen weight, length of stay (in hours), intra-operative complications, foley catheter stay duration (in days), post-trial of void (TOV) PVR, post-TOV retention episodes, transient incontinence after Foley removal, 30-day postoperative complications, graded according to Clavien-Dindo, and readmissions.

Statistical analysis

Statistical analysis was performed using STATA (StataCorp LLC, 4905 Lakeway Drive, College Station, TX, USA), Version 18.0. Continuous variables were reported using median and interquartile range (IQR) while categorical variables were reported as frequencies and proportions. Comparison between surgery-groups was performed with MANN-Whitney U Test for continuous variables and with Fisher's Test for categorical variables. Statistical significance was set at $p < 0.05$.

Bioethical standards

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Rush University Medical Center.

RESULTS

A total of 30 HoLEP and 20 STEP patients were included in the analysis (Table 1). Patients treated with STEP had significantly larger prostate volume (median 101.5 cc vs 78.5 cc; $p = 0.003$), higher PSA (median 9.05 ng/ml vs 5.43 ng/ml, $p = 0.005$) and

Table 1. *Patients' characteristics, perioperative and early postoperative data*

Baseline characteristics	HoLEP (n = 30)	STEP (n = 20)	p
Age, median (IQR)	72.5 (68–77)	68 (63.5–76.5)	0.079
BMI, median (IQR)	27.56 (24.5–29.7)	26.85 (25.22–28.21)	0.699
Charlson Comorbidity Index (CCI)	4 (3–5)	3 (2–4)	**0.040**
Anticoagulant therapy	17 (56.7%)	1(5.0%)	**0.001**
Previous prostate surgery	5 (16.7%)	1 (5.0%)	0.219
PVR [ml] preoperative, median (IQR)	133 (70–250)	500 (300–784)	**0.014**
PSA [ng/ml], median (IQR)	5.43 (2.65–6.7)	9.05 (5.1–14.16)	**0.024**
Prostate volume (cc), median (IQR)	78.5 (55–105)	101.5 (91–155)	**0.004**
Bladder diverticula, n (%)	0 (0.0%)	1 (5.0%)	0.400
Bladder stones, n (%)	5 (16.7%)	1 (5.0%)	0.219
Outcomes			
Operative time [min], median (IQR)	124 (92–161)	286 (239.5–346.5)	**<0.001**
EBL [ml], median (IQR)	45 (20–50)	300 (150–500)	**<0.001**
Intra-operative complications, n (%)	0 (0.0%)	1 (5.0%)	0.400
Specimen weight [g], median (IQR)	41 (17–56)	56 (40–81)	0.069
Length of stay (hours), median (IQR)	30 (28–32)	31 (29–48)	0.252
Postoperative complications*, n (%) None Grade 2 Grade 3	 30 (100.0%) 0 (0.0%) 0 (0.0%)	 17 (85.0%) 2 (10.0%) 1 (5.0%)	 0.517
Catheterization time (days), median (IQR)	3 (1–5)	7 (6–11.5)	**<0.001**
Post-TOV PVR (ml), median (IQR)	37 (24–76)	39 (0–98)	0.873
Post-TOV retention, n (%)	3 (10%)	0 (0.0%)	0.148
Transient incontinence, n (%)	9 (30.0%)	1 (5.0%)	**0.032**
Readmission after surgery, n (%)	3 (10%)	1 (5.0%)	0.527

*According to Clavien-Dindo

BMI – body mass index; BPH – benign prostatic hyperplasia; PVR – post-void residual; PSA – prostate-specific antigen; EBL – estimated blod loss; TOV – trial of void

higher PVR (median 500 ml vs 133 ml, p = 0.028). A higher proportion of HoLEP patients were receiving anticoagulant therapy (56.7% vs 5% of STEP patients; p <0.001) and HoLEP patients had significantly higher CCI (median 4 vs 3, p = 0.040).
Median operative time was significantly longer for STEP (286 min [239.5–346.5] vs 124 min [92–161], p <0.001). EBL was also higher in STEP surgeries (median 300 ml vs 45 ml, p <0.001). Median catheterization time was shorter for HoLEP (3 days vs 7 days, p <0.001). Rate of transient post-operative incontinence was higher for HoLEP (31% vs 5.3%, p = 0.032). There was no difference in the median length of stay (30 hours for HoLEP and 31 hours for STEP (p = 0.108).

DISCUSSION

Our analysis offers several points worth discussing. In terms of surgical indication, HoLEP patients presented smaller glands at baseline and were more fragile, with a median higher CCI (4 vs 3, p = 0.040) and with about half of them receiving anticoagulant therapy. Balancing the risk of thromboembolism associated with cessation of anticoagulants vs the bleeding risk of continuing these agents around the time of surgery is challenging, but several investigations conclude that performing HoLEP on patients who require anticoagulant medication is feasible and safe although associated with increased length of catheterization and increased risk of requiring transfusion [9].
Those undergoing STEP had larger prostates and higher post-void residual volumes. The STEP procedure allowed us to tackle from the beginning larger prostate adenoma, which might suggest that the procedure might have a less steeper learning curve.
In terms of outcomes, longer operative time was observed in the STEP group. Indeed, as the prostatic volume increases, the operative time is expected to be longer as well [10]. However, while trainees were involved as console surgeons in the STEP procedure, all HoLEP procedures were entirely performed by the attending surgeon.
While hospitalization times were similar between the two procedures, both allowing the patient to be discharged the same or following day, the STEP required a longer catheter time. On the other hand, HoLEP patients reported a higher rate of transient urinary incontinence. This risk for transient incontinence is known and related, among other factors, to the surgeon's experience, as the procedure is characterized by a steep learning curve [11].
It needs to be mentioned that, in comparison with the multiport transvesical approach, for the SP robotic technique the impact of this factor is reduced, as the cystotomy is smaller. Moreover the SP robotic procedure is entirely extraperitoneal, without bowel manipulation, pneumo-peritoneum, and steep Trendelenburg positioning, which facilitates an early postoperative recovery [12]. This certainly represents a major step forwards compared to the the multiport transperitoneal robotic simple prostatectomy [13].
Our study findings are consistent with outcomes reported in the very limited literature on the comparison of transurethral vs SP robotic prostate enucleation. Talamini et al [8] studied a population of 103 patients (69 Thulep and 34 STEP) and found shorter postoperative catheter days (6 vs 3 days, p <0.0001) and decreased operative time (90 vs 180 min, p <0.0001) for laser technique and better continence rates for STEP (0 vs 13, p = 0.00). Accordingly, a recent comparative study between HoLEP and STEP [7] favored the SP approach in terms of transient incontinence at the expense of longer catheterization times. A total of 50 STEP and 90 HoLEP cases were analyzed, finding both techniques equally effective in terms of the amount of removal of obstructive prostatic adenoma. Notably, transient de novo incontinence was significantly higher in HoLEP cases (28%) compared to STEP cases (5%, p <0.01), whereas the robotic technique implied a longer catheterization time with a median of 6 days (IQR 3-7) compared to 1 day (IQR 1-1) for HoLEP (p <0.01).
Study limitations should be acknowledged. Our results reflect also our early experience with these types of BPH surgery at our Center. As the initial experience grows, we would expect improvements in post-operative outcomes using both techniques, particularly in terms of operative and catheterization times. Also, it is important to point out that supervised trainee's involvement in the cases might vary and influence the outcomes as well. Cases were performed at an academic teaching hospital and findings might vary in different hospital settings. Differences in baseline patient characteristics, such as the difference in prostate size between groups, certainly represent a selection bias. While we acknowledge that a propensity score-matched analysis would be ideal to address this bias, our cohort was not sufficient to support such methodology. Ultimately, we recognize as study limitations the small sample size of the population studied and the retrospective study design with intrinsic case selection.

CONCLUSIONS

Our findings suggest that both procedures can be safely introduced in a Center without previous

experience. Each of them presents some appealing features that can be tailored to different subgroups of patients, also considering their clinical characteristics and expectations. HoLEP is appealing for higher surgical risk patients, including those on anticoagulants. The STEP allows to effectively manage larger glands even at the beginning of the surgeon's learning curve with good overall outcomes. Patients might prefer one technique over the other after discussion about slightly longer catheter times for STEP and significantly higher risk of transient incontinence for HoLEP. In cases where a bladder diverticulectomy needs to be performed, a STEP should be preferred. Overall, the STEP procedure is emerging as a novel procedure that can be effectively included in the BPH surgical armamentarium.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Rush University Medical Center.

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EDITORIAL PAPER

UROLITHIASIS

Role of suction in revolutionising endourology: Is it the final frontier – an overview from EAU Endourology

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Key Words: kidney calculi ‹› suction ‹› ureteroscopy ‹› FANS ‹› DISS ‹› laser ‹› PCNL

Kidney stone disease (KSD) has been rising secondary to lifestyle and other dietary and environmental factors [1–3]. Consequently, there has been a technological revolution with newer lasers, smaller scopes, better patient pathways, use of artificial intelligence (AI), and finally the introduction of suction technology in endourology [4–8]. Suction is arguably the final piece of the puzzle in endourological stone management. While advances in energy sources have enabled effective stone fragmentation, the ability to efficiently clear fragments is what ultimately determines the success of the procedure. Suction facilitates superior stone clearance, improves stone-free rates, and enhances procedural safety by maintaining lower intrarenal pressures (IRP) and reducing the risk of sepsis. Without effective fragment evacuation, even a high-quality fragmentation can result in residual and recurrent stones, diminishing the overall efficacy of the intervention [9, 10].

This editorial looks at the role of suction in endourology, the clinical and physiological rationale for its integration, current clinical and technological advances, the challenges and controversies that remain with its use. Finally, looking at the shift towards suction-enabled endourology as a new standard of care.

While the concept of suction in endourology is not new with being used for percutaneous nephrolithotomy (PCNL) for past decades, its systematic application in flexible ureteroscopy (fURS) and miniaturized PCNL (mPCNL) has only recently gained serious traction. The rationale for its use includes but not limited to better IRP regulation, which is mediator for infectious complications. Continuous or intermittent suctioning during the procedure would negate this by mitigating pressure surges. There would also be better vision due to suction of debris, dust, and fragments during the procedure created by laser lithotripsy, possibly leading to a reduction in basketing and operative time. With high-power lasers there is a possibly of temperature rise and potentially damaging the urothelium, but suction would allow dissipation of this thermal buildup. And a better vision without worrying about temperature and pressure would lead to decreased cognitive burden on the surgeon with better efficiency.

Suction during fURS can be achieved through flexible and navigable suction sheath (FANS), direct in-scope suction (DISS), or via a paired pressure-controlled irrigation system. PCNL suction is via the suction probes or via a suction sheath [11–17]. Current evidence on their role suggests improved stone-free rate (SFR), lower infectious complications, reduced operative time and better ergonomics [18], whether it is a FANS or DISS system, although there is more evidence for its use with the former. Although studies still lack standardised outcomes and have a degree of heterogeneity with them. For its wider use and adoption, besides the evidence gap, we will also need to look at the cost and access, learning curve, standardised outcomes, and the effect on the environment with the single-use devices. Perhaps these could be addressed by integration into training curricula, value-based health care, and role of AI and automation of procedural aspects such as irrigation and suction settings [19].

In the future, we will need to consider the Quadrifecta in retrograde intrarenal surgery (RIRS) with suction, irrigation, IRP, and temperature, which are all interdependent variables [20]. Suction would therefore not just be an adjunct but a fundamental aspect of stone surgery by offering dynamic control over IRP, temperature, and visibility, enabling safer and more effective stone surgery. As we move into an era of precision endourology, integrating suction into both flexible and percutaneous procedures may become the rule, not the exception.

The question, therefore, is whether suction will become a new standard or remain just a technical add-on. The growing evidence and clinical experience point towards it becoming an essential part of endourological practice. As with many surgical innovations, its true value lies not just in what it does but in how it reshapes our approach. Embracing suction means committing to more complete stone clearance, improved outcomes, and ultimately, better care for our patients.

Table 1. *Suction in endourology – rationale, devices, evidence, limitations, and future directions*

SUCTION IN ENDOUROLOGY	
Rationale	Clearance of stone fragments and debris
	Intrarenal pressure regulation
	Enhanced visualisation and fragment clearance
	Temperature modulation
	Surgical ergonomics and efficiency
	Decrease operative times
Devices and systems	Flexible and navigable suction sheath (FANS)
	PCNL suction sheaths
	Direct in-scope suction (DISS)
	Pressure-controlled irrigation systems
Evidence and outcomes	Improved stone-free rates
	Reduced operative time
	Lower infectious complications
	Better ergonomics
Limitations and controversies	Cost and access
	Learning curve
	Environmental impact
	Evidence gap
Future directions	Standardized metrics
	Artificial intelligence and automation
	Integration into training curricula
	Value-based health care

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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ORIGINAL PAPER

UROLITHIASIS

Investigation of irrigation fluid temperature variations caused by thulium fiber laser with various settings and comparison with Ho:YAG laser: An *in vitro* experimental study

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Introduction Our experimental *in vitro* study aimed to evaluate the impact of four power settings with different energy and frequency combinations on the irrigation fluid temperature using the thulium fiber laser (TFL). In addition, we aimed to identify the differences between the Ho: YAG laser and TFL by direct comparison of the same power settings.

Material and methods All measurements were performed with a fluid volume fixed at 10 ml and an outflow rate at 10 ml/min. The laser was fired continuously for 30 seconds with total power settings of 10 W, 20 W, 40 W, and 60 W with different power settings (energy × frequency) and various pulse combinations using TFL and Ho: YAG laser (Quanta System, Samarate, Italy).

Results Higher temperatures were recorded when the power was increased from 10 W, 20 W, 40 W, to 60 W. The temperature exceeded the threshold of 43°C when power settings of ≥40 W were applied regardless of frequency (15–120 Hz) and energy (0.5–4 J). Similar temperature increase patterns were reported with different peak power settings. No major differences were found when the same power settings were applied using TFL and Ho: YAG lasers.

Conclusions Based on our results temperatures >43°C were recorded for power settings ≥40 W after continuous laser firing of 30 seconds using TFL. Modifying the frequency and energy settings, as well as firing with Ho:YAG laser under the same power setting did not affect the patterns of temperature increase. Generally, the TFL shows more regular thermal behavior in comparison with the Ho:YAG laser.

Key Words: urolithiasis ‹› thulium fiber laser ‹› temperature ‹› experimental study

INTRODUCTION

The recent evolution of management options for urolithiasis has presented a unique dilemma for modern urologists [1]. On one hand, the capability of applying higher powers for lithotripsy is very intriguing, and it is associated with shorter surgical time [2]. On the other hand, the high powers have been associated with an increased risk of complications due to intrarenal temperature rise [3, 4].

Since its first introduction, endoscopic nephrolithotripsy has gained wide popularity and nowadays constitutes the gold standard method for the treatment of upper tract urinary stones ≤2 cm [1]. The recent advances in laser technology, along with the established practices of retrograde

intra renal surgery (RIRS), have significantly contributed to the development and wider adoption of endoscopic combined intrarenal surgery (ECIRS), enabling the effective treatment of larger and more complex kidney stones [3, 4]. Among these advancements, the introduction of the thulium fiber laser (TFL) offers a wide variety of configurations of pulse energy, frequency and length [5, 6].

The gold standard for lithotripsy is the Holmium:YAG laser (Ho:YAG), which is the recommended treatment because of its demonstrated safety and efficacy [5]. The TFL has emerged as a promising alternative to the Ho:YAG laser. It offers a wide range of settings (from 0.025 to 6 J and from 5 to 2,400 Hz), providing greater flexibility during the lithotripsy procedure [3, 4].

With these benefits, the TFL is positioned as a strong and viable alternative to the conventional Ho:YAG laser lithotripsy, potentially revolutionizing the approach to treating urinary stones with enhanced precision and outcomes. Studies in TFL have advanced from preclinical trials into clinical practice, and there has been a notable decrease in retropulsion, or the backward movement of stones during fragmentation, which can complicate the process and lengthen the treatment time [6–8].

The use of TFL laser in lithotripsy is widely expanded and safety concerns were arisen due to pulse generation. In comparison to the Ho:YAG laser, the generation of the pulse is significantly different. A major difference is that with increasing energy the peak power stays the same as opposed to Ho:YAG [5]. Thus, it can be hypothesized that changing the energy within the same power settings may affect temperature generation. Further investigations may provide more detailed information regarding the safety and functional characteristics of this laser device. In this study, we evaluated the impact of four power settings with different energy and frequency combinations on the irrigation fluid temperature using the TFL. In addition, we aimed to identify the differences between the Ho:YAG laser and TFL by direct comparison of the same power settings.

MATERIAL AND METHODS

Experimental set-up

For the evaluation of the different power settings, an *in vitro* experimental study was conducted. The experimental setting was constructed in a 20 ml syringe immersed in the water bath (temperature ranging from 34–37°C degrees) using a dual lumen ureteral catheter (Cook Medical Cook Ireland Ltd., Limerick, Ireland) and a 12/14Fr ureteral access sheath (UAS) (Flexor® Ureteral Access Sheath with AQ® Hydrophilic Coating, COOK Medical, Cook Ireland Ltd., Limerick, Ireland). The irrigation inflow was connected to the side channel of the dual-lumen catheter, whereas the central channel was used to insert a laser fiber. For the lasering, an optical performance 365 μm laser (Quanta System, Samarate, Italy) was utilized. It was stabilized from the outside with a "Luer-lock" (Tuohy-Borst

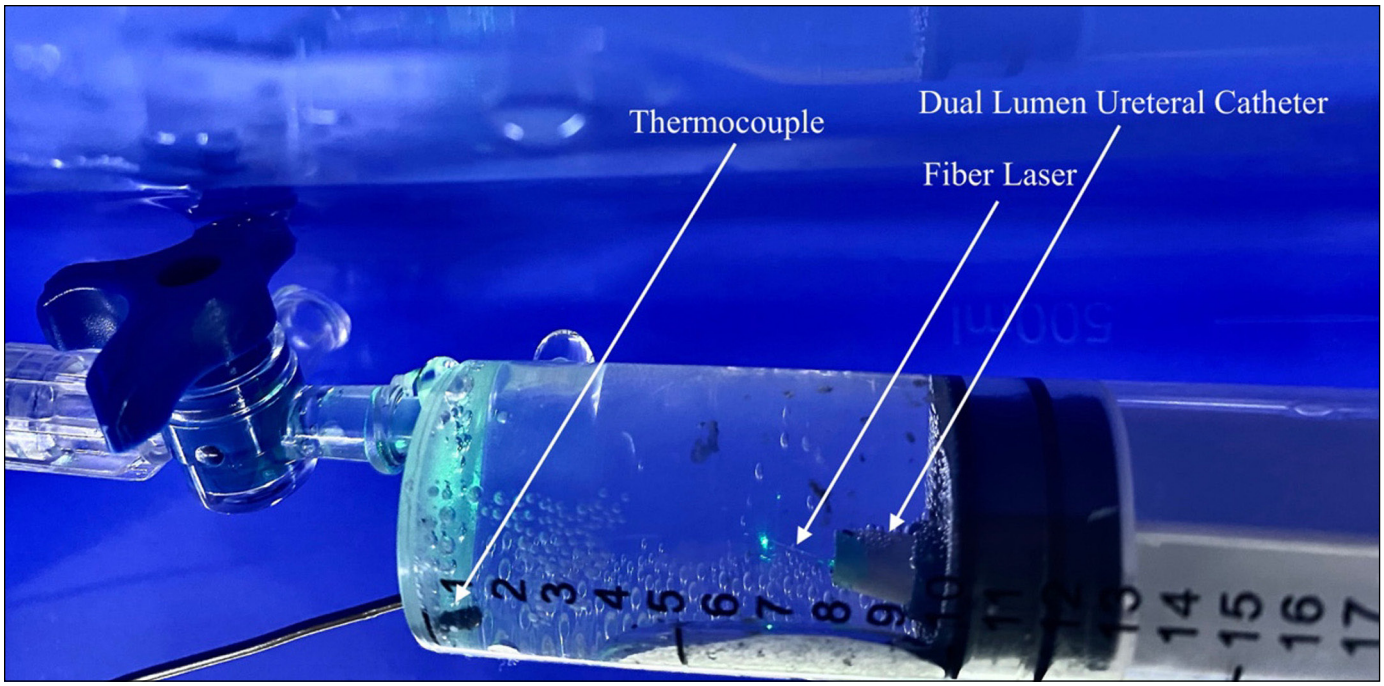

Figure 1. *Experimental setup. The tip of the dual-lumen catheter can be observed through the ureteral access sheath.*

Adapter, Cook Medical, Cook Ireland Ltd., Limerick, Ireland) which also ensured the absence of any fluid leakage from the channel.

The dual lumen catheter was then inserted in the 12/14 Fr UAS, which was prior introduced into the syringe and fixed at the level of the black rubber. To have an adequate volume chamber, the piston of the syringe was set at the 10 ml marking and fixed to prevent any inadvertent movement of the piston due to laser-firing or irrigation flow. For measuring the intrafluid temperatures, a K-type thermocouple (SE001, Pico Technologies, Cambridgeshire, UK) was inserted through a separate hole made on the front side of the syringe (Figure 1).

For irrigation, two saline 3 l bags set at 1 meter above the working table were used. A 10 ml/min continuous irrigation flow rate, calculated every 15_{th} minute, was set for all trials. To achieve fluid outflow only from the UAS, the tip of the syringe, that were usually designed to connect the needle, was connected with a 3-way connected system, and it was closed as shown in Figure 1. The laser was activated for 30 seconds, followed by deactivation till the return of the irrigation fluid temperatures to normal baselines.

Utilized laser devices

The experiment was conducted using a Fiber Dust® Thulium Fiber Laser (Quanta System, Samarate, Italy) and a high-power Ho:YAG Quanta Ho150 laser (Quanta System, Samarate, Italy).

Power settings

The temperature changes were documented with laser firing at the total power of 10 W, 20 W, 40 W and 60 W. We tested 4 variations of energy (0.5 J, 1 J, 2 J and 4 J) with the corresponding frequencies ranging from 5–120 Hz as shown in (Table 1). We also investigated the effect of the peak power of the TFL device stabilizing the energy on the 1 J with the corresponding frequencies for each power setting (10 W, 20 W, 40 W, 60 W).

Firing time

In all of each settings in the two devices we were firing the laser just for 30 seconds.

Comparison of Ho:YAG and thulium fiber laser devices

A further comparison between TFL and Ho: YAG laser using the latter settings was performed. The same 10 W, 20 W, 40 W and 60 W (energy = 1 J, frequency = 10–60 Hz) and firing for 30 seconds to see how evaluate were used for comparing the TFL and high-power Ho:YAG lasers in each device. We also conducted a statistical analysis using the SPSS program, starting with a descriptive analysis (Table 2), correlation, and threshold statistics.

Table 1. *Temperature response of the irrigation fluid at various power settings over 30 seconds, comparing TFL and Ho:YAG*

HPP		TFL		Ho:YAG
		LPP		
Power (W)	Energy (J) × Frequency (Hz)	T_{30}s (°C)		
10	0.5 × 20	30.4	–	–
	1 × 10	30.1	29.55	31.3
	2 × 5	29.2	–	–
20	0.5 × 40	35.5	–	–
	1 × 20	35	36.3	36.2
	2 × 10	32.6	–	–
	4 × 5	34.2	–	–
40	0.5 × 80	43.3	–	–
	1 × 40	45.8	47.5	45.3
	2 × 20	46.4	–	–
	4 × 10	46	–	–
60	0.5 × 120	53.8	–	–
	1 × 60	56.7	57.9	59.3
	2 × 30	55.8	–	–
	4 × 15	56.6	–	–

HPP – high peak power; LPP – low peak power; TFL – thulium fiber laser

Table 2. *Descriptive statistics for laser temperatures*

Laser	Power	Mean	SD	Min	Max
Ho:YAG	10	31.3	–	31.3	31.3
	20	36.2	–	36.2	36.2
	40	45.3	–	45.3	45.3
	60	59.3	–	59.3	59.3
TFL (HPP)	10	29.9	0.6	29.2	30.4
	20	34.3	1.3	32.6	35.5
	40	45.4	1.4	43.3	46.4
	60	55.7	1.3	53.8	56.7
TFL (LPP)	10	29.5	–	29.5	29.5
	20	36.3	–	36.3	36.3
	40	47.5	–	47.5	47.5
	60	57.9	–	57.9	57.9

HPP – high peak power; LPP – low peak power; SD – standard deviation; TFL – thulium fiber laser

Bioethical standards

This study was conducted entirely *in vitro* and does not involve human subjects, human material, human data, or *in vivo* experiments on animals. The ethical approval was not required.

RESULTS

Temperature with various power settings of thulim fiber laser

The temperature of the irrigation fluid increased in a linear manner as the power increased from 10 W to 60 W. For power settings 10 W, 20 W, and 40 W, the temperatures remained below 46°C. However, at a power setting of 60 W, a significantly higher temperature of approximately 55°C was observed. When the frequencies and energies were varied while keeping the power settings constant, no significant differences were found. This indicates that changing the frequencies and energies does not affect the maximum temperature or the profile of temperature rise. The recorded maximum temperatures were as following, at 10 W was from ~29°C to ~30°C, at 20 W was from ~32°C to ~35°C, at 40 W was from ~43°C to ~46°C and at 60W was from ~54°C to ~57°C, as shown in the (Figure 2), and with no significant difference were was detectible when the laser was fired with low or high peak power, as shown in the (Figure 3).

In the correlation study for all laser types, showed that power and the temperature were strongly linked in a good way. The Pearson correlation coefficient for the Ho:YAG laser was $r = 0.994$ ($p = 0.006$). The correlation coefficients for the TFL (HPP) and LPP were $r = 0.994$ ($p < 0.001$) and $r = 0.999$ ($p = 0.001$) respectively. This shows that power is a strong predictor of temperature increase for all laser types.

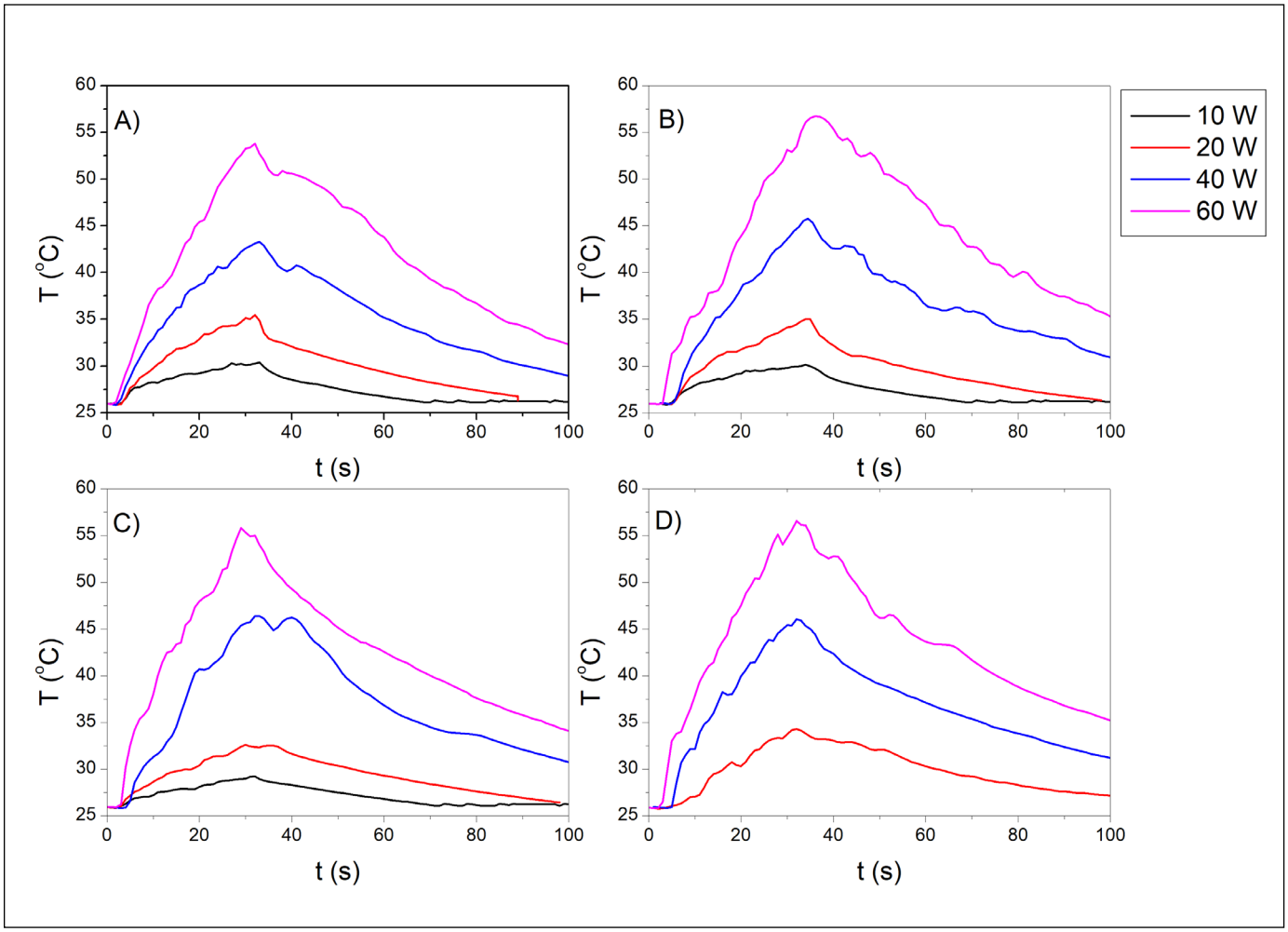

Figure 2. *The temperature increases with different power settings:* **A)** *0.5 J energy with the frequency 20–120 Hz;* **B)** *1 J energy with the frequency 10–60 Hz;* **C)** *2 J energy with the frequency 5–30 Hz;* **D)** *4 J energy with the frequency 5–15 Hz.*

Comparison of Ho:YAG and thulium fiber laser devices

The comparison of the temperature response of irrigation fluid at various power settings over a 30-second period is the main focus of the TFL and Ho:YAG lasers. We investigate 10 W, 20 W, 40 W, and 60 W power settings with different energy and frequency combinations.

At 10 W, Ho:YAG recorded 29.55°C and 31.3°C for the same (1 J × 10 Hz) setting, while TFL recorded 30.4°C (0.5 J × 20 Hz), 30.1°C (1 J × 10 Hz), and 29.2°C (2 J × 5 Hz). Ho:YAG recorded slightly higher temperatures of 36.2°C and 36.3°C for (1 J × 20 Hz), while TFL results at 20 W ranged from 32.6°C to 35.5°C across various energy-frequency combinations. On the other hand, Ho:YAG gave the reading of 45.3°C and 47.5°C for (1 J × 40 Hz), whereas the TFL was within the range of 43.3°C to 46.4°C at 40 W. At the highest power setting of 60 W, TFL touched maximum temperature ranging from 53.8°C to 56.7°C; however, Ho:YAG recorded relatively higher values of 57.9°C and 59.3°C for (1 J × 60 Hz).

Based on available data of this experimental study, TFL might raise temperature more subtly than Ho:YAG, which seems to reach higher temperatures at similar power levels. (Figure 4). But for further investigation to find out if these lasers can be safe to use, a threshold analysis was done to see how often temperatures went above 43°C, which could be harmful to the tissue. The Ho:YAG laser exceeded this limit in 50% of the settings, which means there is a moderate risk of overheating. TFL (HPP) and TFL (LPP), on the other hand, exceeded 43°C in 53.3% and 50% of settings, respectively. This shows that Ho:YAG and TFL lasers are less likely to reach temperatures that can damage tissue.

DISCUSSION

The rapid development of laser technologies introduces a need for deeper investigations of the safety profiles of different laser devices and settings. Temperature rise during laser lithotripsy is an important concern because temperatures above 43°C might induce tissue thermal damage [7]. Our team had previously determined the safety of high-power

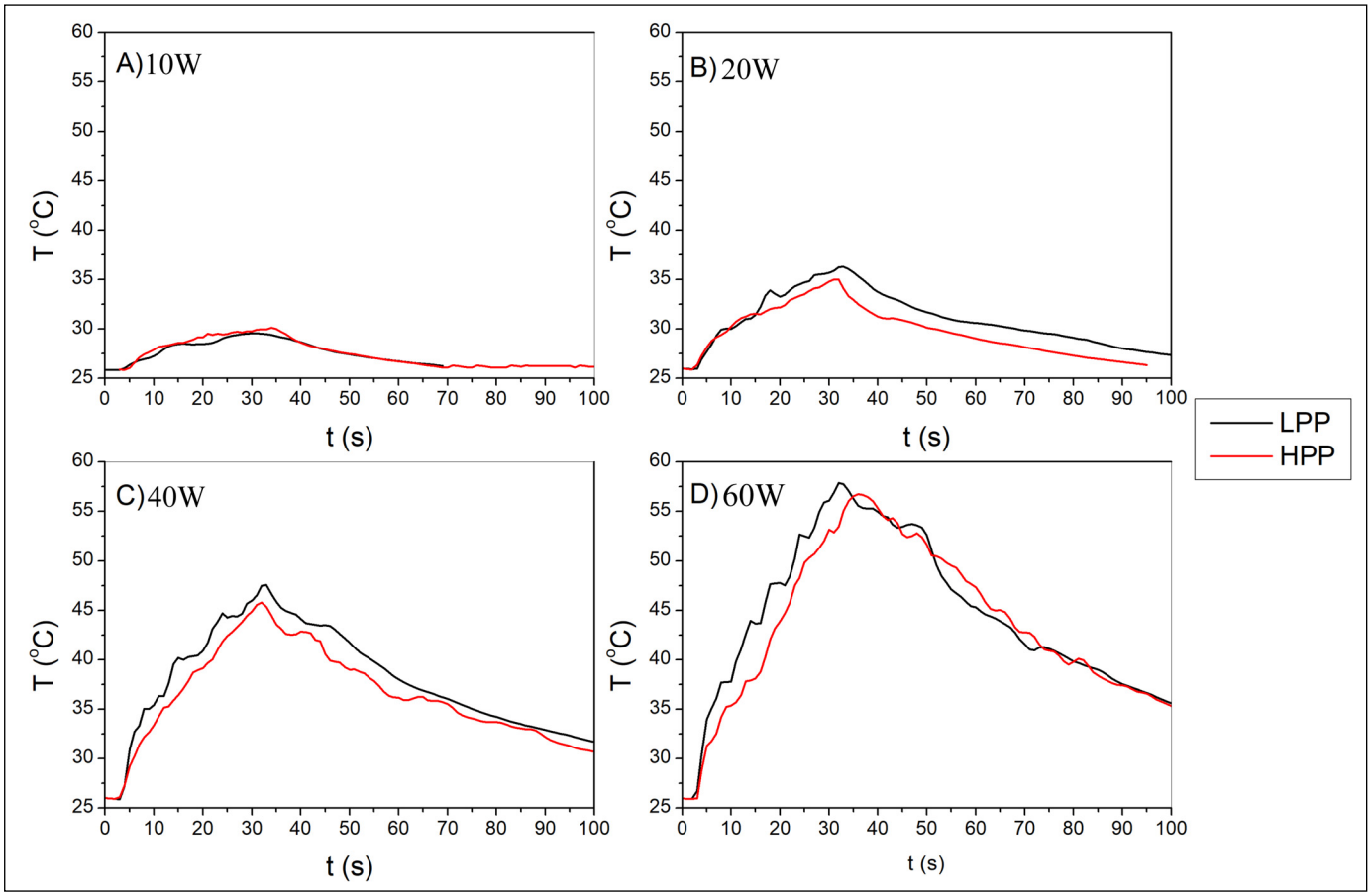

Figure 3. *Temperature increases with high and low peak power settings.*

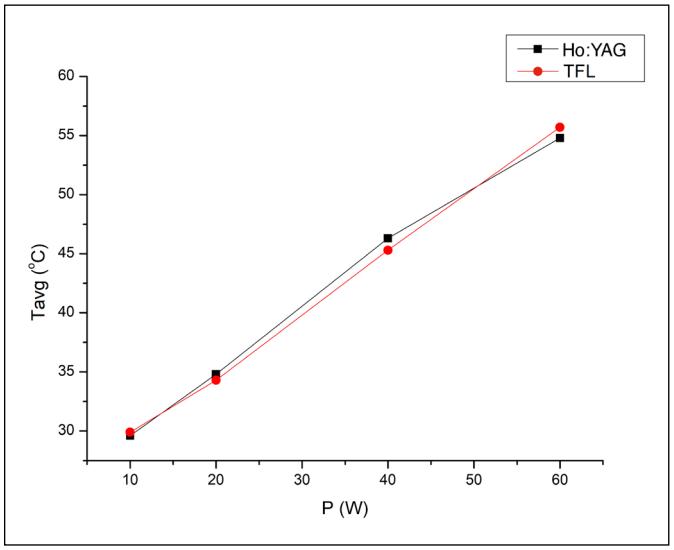

Figure 4. *Temperature increases with TFL and Ho:YAG lasers.*

lithotripsy utilizing the Ho:YAG laser [8, 9]. However, the process of heat generation by the TFL is still a matter of debate in the literature [10], since this laser has several different features that might influence temperature when compared to the Ho:YAG laser [11]. Firstly, the TFL has a wavelength of 1940 mm, which provides a 3–4 times higher water absorption coefficient [12]. Additionally, the TFL pulse is continuous as opposed to the peak power seen in the Ho:YAG laser pulse [11]. The continuous pulse allows uniform heating of the stone, with the vaporization of interstitial water inside the stone. Whether these features of the TFL significantly impact temperatures is still not clear.

This investigation evaluated the thermal generation of both the Fiber Dust® Quanta Thulium Fiber Laser and the Ho:YAG Quanta Ho150 laser, by escalating power levels from 10 W to 60 W, altering energy and frequency parameters, yet holding all other variables constant. We have shown that using the same settings, the TFL and Ho:YAG laser did not show any differences in saline temperature increase. These results are in line with other studies, which also found equal temperature when using the two lasers with the same power settings. Andreeva et al. [13] performed an *in vitro* ablation study using artificial stones inside water cuvettes. The authors evaluated the Ho:YAG and TFL at the same power settings (8 W, 16 W and 40 W) and they reported similar temperature increases with both lasers (4.9°C, 9.8°C and 14.6°C). Using a similar model without the use of artificial stones, Taratkin et al. [14] evaluated the temperature increase with a single setting (0.2 J × 40 Hz = 8 W) and found that after the 60 s of laser firing, both Ho:YAG and TFL presented a similar temperature increase (14.9°C for Ho:YAG and 15.4°C for TFL) and similar energy introduced into the experimental system (447.3 J for Ho:YAG and 459.8 J for TFL). Hardy et al. [15] reported higher temperatures while using the TFL at 500 Hz. However, the power settings used in the TFL did not match the ones used for Ho:YAG, so no direct comparison can be derived from this study. Molina et al. [16] performed an *ex vivo* experimental study using porcine kidneys and inserting artificial stones inside. The authors investigated dusting settings (0.3 J × 70 Hz = 21 W for Ho:YAG and 0.1 J × 200 Hz = 20 W for TFL) and fragmentation settings (0.8 J × 8 Hz = 6.4 W for both Ho:YAG and TFL). They found an equal temperature increase using dusting settings but a higher temperature increase in the TFL when fragmentation settings were being used (29.30°C for Ho:YAG and 31.87°C for TFL). No ureteral lesions were found in the histological examination.

A study conducted by Okhunov et al. [17] outlined methods for reducing the increase in intrarenal temperature during laser lithotripsy such using ureteral access sheaths to be helpful in preserving lower temperatures, most likely through improved flow rates. Moreover, Peng et al.'s [18] research reaffirmed the importance of irrigation rate in temperature regulation. According to their research, even at a lower power of 15 W, the lack of irrigation could cause dangerous temperature thresholds to be quickly reached after just 20 seconds of laser activation. On the other hand, even when using greater power settings for longer periods of time, it has been demonstrated that maintaining an irrigation rate of 25 ml/min will keep temperatures within acceptable limits [18]. These insights were taken into account in our experiment, where we consistently applied a fixed outflow rate of 10 ml/min across all trials to manage thermal effects.

In 2021, Belle et al. [19] performed an experiment with a 3D printed ureter to compare the evaluation of fluid temperature between TFL and Ho:YAG. The maximum temperature for the TFL was higher than the Ho:YAG at all power settings tested and the TFL exceeded the threshold for tissue damage at 30 W with at 43°C. Oppositely, as already stated, in our study, a similar temperature increase for the same power settings was detected. Our findings support the thermodynamical concept that 1 J always produces the same temperature increase, regardless of the energy source [10, 14]. Moreover, we have also found that none of the parameters (frequency, energy and pulse length) had any significant association with the temperature rise. Therefore, only the total amount of energy delivered in a specific period

of time (power) has an impact on temperature, for both Ho:YAG laser and TFL.

Currently, there is no clear understanding and recommendation on which laser settings are the best for effective and safe lithotripsy. A recent interesting study on TFL settings using experts' Tweets showed great differences in the proposed settings, with most experts recommending dusting settings [20]. In light of the divergent views on optimal power settings, it has been observed that operating at lower power levels, specifically below 40 W, is a common approach to mitigate the potential risk of thermal injury. This practice is typically coupled with adequate fluid irrigation as well as appropriate intervals for laser firing and flushing, to maintain a balance between efficacy and safety [21].

Several limitations are still associated with our study. As with every *in vitro* model, a complete, realistic replication of different clinical scenarios is not possible. In particular, several factors, including anatomical and physiological variations, blood circulation, and baseline body temperature, presence, and composition, may affect the outcomes in clinical practices. In addition, working parameters such as the use of UAS, the diameter of the flexible ureteroscope, and the volume of the pelvicalyceal system may influence the irrigation flow rate, thus affecting the temperature changes. In addition, the presence of artificial stones or real renal calculi might alter the fluid dynamics and the temperature patterns observed. The addition of stones would be a great idea for a future experimental study. Nonetheless, by maintaining constancy in the surrounding factors, our model serves as a beacon, illuminating the typical patterns of activity within the system. Also there were no diagram for the 10 W with the sittings using below the 5 Hz. It was not acceptable from the device to decrease the frequency below the 5 Hz.

CONCLUSIONS

Reflecting on the conclusions of our analysis temperatures >43°C were recorded for power settings ≥40 W after continuous laser firing of 30 seconds using TFL. Changing the frequency, energy and peak power, as well as firing with the same power setting with Ho:YAG laser did not affect the patterns of temperature increase.

Generally, the TFL shows more regular thermal behavior in comparison with the Ho:YAG laser. This indicates that it may be used safely in clinical settings. This regular thermal behavior decreases the heat impact and improves both efficacy and safety. More research is necessary to confirm the benefits of TFL in different surgical contexts and to investigate the clinical implications of these findings.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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ORIGINAL PAPER

UROLITHIASIS

Single-J versus double-J stents after ureterorenoscopy for renal stones: A randomized comparison of safety and tolerability

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Introduction Ureteral stents are generally used after ureterorenoscopy (URS) procedures, even in uncomplicated ones. We aimed to compare the safety and tolerability of single-J (SJ) stents and double-J (DJ) stents in patients submitted to flexible URS for renal stones.

Material and methods This prospective, randomized, unblinded, single-center study was conducted between July 2022 and May 2024, involving patients undergoing flexible URS with holmium laser lithotripsy for renal stones. Patients were randomized to either SJ stents (removed within 24 hours) or DJ stents (removed 2-4 weeks post-surgery). Primary endpoints included emergency department admissions, postoperative complications, and reintervention rates. Secondary endpoints included stent tolerability and surgery efficacy. A symptom questionnaire was applied at postoperative weeks 1 (W1) and 4 (W4).

Results We included 125 patients (60 in group SJ and 65 in group DJ), with comparable baseline characteristics. Emergency department admissions were similar (18.3% vs 16.9%, p = 0.84), as were complications (18.3% vs 21.5%, p = 0.65) and reintervention rates (1.7% vs 3.1%, p = 1.0). SJ stents showed better tolerability, with lower scores for lower urinary tract symptoms (LUTS) and pain at both time points.

Conclusions SJ stents placed for less than 24 hours after complete flexible URS are comparable to DJ stents regarding safety and are better tolerated, particularly 4 weeks after the surgery. SJ stents should be prioritized, reducing costs and hospital visits for stent removal.

Key Words: urolithiasis ‹› urinary catheters ‹› ureteroscopy ‹› lithotripsy ‹› laser ‹› patient safety

INTRODUCTION

Ureteral stenting after ureterorenoscopy (URS) is frequently used worldwide, even though major guidelines suggest it is optional for uncomplicated procedures [1, 2]. Studies with large samples have shown that ureteral stenting is performed at the end of over 80% of the surgeries [3, 4]. This can be attributed to several factors, including the surgeon's personal convictions, hospital logistical reasons, and accessibility to emergency services. Although findings of a systematic-review suggested that stenting reduced the number of emergency department visits, the investigators alerted to the uncertainty of the data behind those results, as most studies were small and retrospective [5]. Despite the widespread use of ureteral catheters, stent-related symptoms, like hematuria or urinary frequency, remain a significant problem, as extensively studied in the literature [5, 6]. Some stents, such as the Polaris™, are specifically designed to mitigate these symptoms [7].

Even when the surgeon has decided to use a ureteral stent, there is limited literature to guide the decision on which catheter to use. Therefore, our aim was

to provide good quality evidence on this subject. With this prospective randomized unblinded study, our objective was to compare the safety and tolerability of the 2 most common ureteral catheter types used in our hospital, the single-J loop (SJ) stents and the double-J loop (DJ) stents.

MATERIAL AND METHODS

Study design and participants

This randomized unblinded prospective study was carried out at Hospital de Braga, between July 2022 and May 2024. Patients submitted to flexible ureteroscopy with holmium laser lithotripsy of renal stones without ureteral access sheath use were randomized to ureteral catheterization with SJ stents (Coloplast Vortek® single loop ureteral stent, with 6Fr diameter; group SJ) or DJ stents (Coloplast Biosoft® duo double loop ureteral stent, with 6Fr diameter and 24–26 cm length; group DJ). SJ stents had an early removal less than 24 hours after the surgery, before hospital discharge, while DJ stents were removed in a subsequent appointment, 2–4 weeks after surgery.

For logistical reasons, randomization was conducted weekly (starting on Monday), alternating between group SJ and group DJ. The catheter group for the first week was randomly selected using a computer program. The surgeons were not informed of the randomization strategy; they were only informed of the group the patients were allocated to on the day of the surgery. Deviations from randomization were permitted only in cases of stent unavailability, not based on the surgeon's decision.

Written informed consent was obtained from all participants before enrolment. Exclusion criteria were concomitant bladder or ureteral stones, urinary tract alterations (congenital malformations, previous reconstructive procedures, or history of urothelial cancer), bilateral procedures, and inability/impossibility to answer questionnaires.

Outcomes

The primary endpoints, evaluated in the first postoperative month, were admission to the emergency department, postoperative complications, and reintervention rate. Secondary endpoints were stent tolerability and surgery efficacy.

Data collection

Patients' charts were reviewed frequently to monitor complications. Tolerability was studied with a simple phone symptom questionnaire at postoperative weeks 1 and 4. This questionnaire included 2 numeric pain scales (0–10 points, with 10 being the most extreme pain ever experienced) for lumbar and supra-pubic pain, and 5 questions focused on lower urinary tract symptoms (LUTS) – dysuria, hematuria, urinary incontinence, urgency, and urinary frequency; patients rated the frequency of the symptoms on a scale from zero (never) to five (almost always), and the total score for the LUTS questions was 25. It was based on the validated ureteral stent symptom questionnaire by Joshi et al. [8].

Efficacy was also evaluated by the stone-free rate (SFR), which was defined by the absence of residual stones >4 mm in imaging postoperative examination (computed tomography). We also included a secondary SFR that considered patients who underwent a postoperative ultrasound (US) or were assessed through the surgeon's clinical evaluation when no radiographic examination was performed.

Postoperative follow-up encompassed the first month after surgery. Complications were reported according to the Clavien-Dindo classification [9].

The sample size for this study was calculated using the application G*Power® V3.1.9.7, and a minimum of 82 patients should be included. After achieving the necessary number, study termination was decided for a specific date (end of May 2024).

Statistical analysis

Statistical analysis was performed using IBM® SPPSS® Statistics Software (version 28). Descriptive analysis included representation of categorical variables by frequencies (n) and proportions (%), while continuous variables were described by means (M) and standard deviations (SD), or medians (Mdn) and interquartile ranges (IQR), when applicable. Comparison between groups was performed using a χ^2 test or Fisher's exact test for categorical variables (depending on the expected cell counts), the independent t-test for standard distribution variables, and the Mann-Whitney U test as a non-parametric alternative. As-treated and intention-to-treat (ITT) analyses were both performed.

A $p < 0.05$ was considered statistically significant with a 95% confidence interval (CI).

Bioethical standards

The study was approved by the Ethics Committee of the Hospital de Braga and University of Minho in Braga, Portugal (approval number: CEHB_64_2024).

RESULTS

We included 125 patients (60 in group SJ and 65 in group DJ). Twelve patients (10%) did not receive the allocated stent due to stent unavailability at the date. Of these, 7 (58%) received SJ stents and 5 (42%) received DJ stents, despite being randomized to the opposite group. Both As-treated and ITT analyses were performed with similar results. The following results were obtained with the As-treated analysis; we included the ITT analysis of primary and secondary outcomes in the Suppl. Tables 1 and 2.
Baseline characteristics were comparable between groups, as illustrated in Table 1.

Primary outcomes – safety

Twenty-two patients (17.6%) were admitted to the emergency department. The reasons were: pain (n = 15, 12.0%), fever (n = 3, 2.4%), hematuria (n = 2, 1.6%), nausea (n = 1, 0.8%), and skin rash (n = 1, 0.8%).

Twenty-five patients (20.0%) suffered complications, 11 (18.3%) in group SJ and 14 (21.5%) in group DJ (p = 0.65). Complications were mostly grade I (pain requiring analgesics or bleeding) or grade II (steinstrasse treated with analgesics and α-blockers or pyelonephritis needing antibiotics).
Reintervention rate was low and not statistically different between groups. The motive for reintervention was an obstructive pyelonephritis needing stenting in a patient from group SJ and 2 incrusted stents in patients from group DJ.
Group-specific results are shown in Table 2.
Complications were more frequent in non-pre-stented patients (26.8% vs 11.1%, p = 0.03). Nevertheless, even in the non-pre-stented subgroup (n = 71), complications were comparable between Group SJ and Group DJ (29.4% vs 24.3%, respectively; p = 0.63); the reintervention rate was also similar (0% vs 2.7%, p = 1.0).
There were no reported intraoperative complications.

Table 1. *Patient demographic and surgical characteristics*

	Sample (n = 125)	Group SJ (n = 60)	Group DJ (n = 65)	p
Demographic characteristics				
Sex, n (%) Male	70.0 (56.0%)	31.0 (51.7%)	39 (60.0%)	0.35
Age (years), M ±SD	57.2 ±12.2	56.8 ±12.0	57.5 ±12.4	0.60
BMI (kg/m^2), Mdn (IQR)	27.4 (24.8–31.2)	26.4 (24.5–30.1)	27.8 (25.0–32.4)	0.10
Comorbidities				
Previous urolithiasis, n (%)	86.0 (68.8%)	44.0 (73.3%)	42.0 (64.6%)	0.29
Previous urolithiasis surgery, n (%)	80.0 (64.0%)	40.0 (66.7%)	40.0 (61.5%)	0.55
Arterial Hypertension, n (%)	52.0 (41.6%)	26.0 (43.3%)	26.0 (40.0%)	0.71
Diabetes mellitus, n (%)	25.0 (20.0%)	10.0 (16.7%)	15.0 (23.1%)	0.37
Depression, n (%)	16.0 (12.8%)	9.0 (15.0%)	7 (10.8%)	0.48
ASA Score, n (%) ASA I ASA II ASA III	 13 (10.4%) 90 (72.0%) 22 (17.6%)	 6 (10.0%) 43 (71.7%) 11 (18.3%)	 7 (10.8%) 47 (72.3%) 11 (16.9%)	0.97
Lithiasis and surgery data				
Side, n (%) Left	72 (57.6)	39 (65.0)	33 (50.8)	0.11
Stone number, n (%) One Multiple	 87 (69.6) 38 (30.4)	 36 (60.0) 24 (40.0)	 51 (78.5) 14 (21.9)	**0.03**
Stone maximum diameter (mm), Mdn (IQR)	11.0 (9.0–14.0)	10.0 (9.0–13.0)	12.0 (9.0–15.0)	0.06
Stone density (HU), Mdn (IQR)	980.0 (525.0 –1343.3)	1,060.0 (525.0 – 1363.0)	900.0 (500.0 –1341.0)	0.63
Pre-stenting – ureteral stent in place at the time of surgery, n (%)	54 (43.2)	26 (43.3)	28 (43.1)	0.98
Surgery duration (min), Mdn (IQR)	27.0 (20.5–34.5)	27.0 (21.0–34.0)	27.0 (20.0–36.0)	0.84

ASA – American Society of Anesthesiologists; HU – Hounsfield units; IQR – interquartile range; M – Mean; Mdn – Median; SD – standard deviation

Secondary outcomes – tolerability

Nine patients from group SJ and 12 from group DJ (15.0% vs 18.5%, p = 0.61) did not complete at least one of the questionnaires and were excluded from the tolerability assessment.

The main results from the questionnaire assessment are described in Table 3.

The most frequently reported LUT symptom was urinary frequency for both groups at both timepoints. Detailed answers to each LUTS question can be found in Suppl. Tables 3 and 4.

Regarding therapeutic regimens, at W1, no statistically significant differences were demonstrated between groups in analgesic medication (60.8% in group SJ and 60.4% in group DJ, p = 0.97) or α-blockers (76.5% in group SJ and 64.2% in group DJ, p = 0.17), but antispasmodics like trospium chloride or mirabegron were more frequently used by DJ stent patients (7.8% in group SJ and 34.0% in group DJ, p = 0.001). At W4, less patients were taking medication, and only antispasmodics showed a statistically significant difference between groups (0.0% in group SJ and 13.5% in group DJ, p = 0.03). Twenty-one (39.6%) patients from group DJ had the stent removed before answering the W4 questionnaire. DJ stents were removed after a median of 29 days (IQR: 21.5–44.5).

Table 2. *Primary outcomes*

	Group SJ (n = 60)	Group DJ (n = 65)	p
Safety – n (%)			
Emergency department admissions	11 (18.3%)	11 (16.9%)	0.84
Total complications	11 (18.3%)	14 (21.5%)	0.65
Grade I–II	10 (16.7%)	12 (18.5%)	
Grade ≥III	1 (1.7%)	2 (3.1%)	0.93
Reintervention rate	1 (1.7%)	2 (3.1%)	1.00

Table 3. *Secondary outcomes*

		Group SJ (n = 51)	Group DJ (n = 53)	p
Tolerability / Symptom Questionnaire – Mdn (IQR)				
LUTS – Symptom Score Total	W1	6 (3–9)	10 (5–13)	0.01
	W4	2 (0–5)	7 (2.5–13.5)	<0.001
Lumbar Pain	W1	1 (0–4)	3 (0–5)	0.14
	W4	0 (0–1)	1 (0–5)	0.02
Supra-pubic Pain	W1	1 (0–4)	3 (0–6)	0.002
	W4	0 (0–0)	1 (0–5)	<0.001

IQR – interquartile range; Mdn – median; W1 – postoperative week 1; W4 – postoperative week 4

Secondary outcomes – procedure efficacy

Only 29.6% of the patients had a control image within 30 days of the surgery: 32 with CT and 4 with US. Considering only the patients reviewed by CT, the global stone-free rate was 75.0% (82.4% in group SJ and 66.7% in group DJ, p = 0.42). Ten patients had no stone (31.3%), 4 patients had fragments smaller than 2 mm (12.5%), and 10 patients had residual fragments with 2.1–4 mm (31.3%). A secondary SFR including all patients revealed that only 6.4% had confirmed residual stones >4 mm, corresponding to a global 93.6% stone-free rate (95.0% in group SJ and 92.3% in group DJ, p = 0.72).

DISCUSSION

Ureteral stents are generally used after URS procedures, even in uncomplicated ones. However, there is still limited evidence on the optimal type and duration of stent usage. To our knowledge, this is the first randomized study comparing SJ vs DJ stents after flexible URS. The FaST studies also compared these stents in different settings, but none included solely flexible URS, and their focus was specifically urinary symptoms related to both stents [10, 11]. There is also a previous retrospective study comparing these stents after treatment of ureteral stones [12].

The baseline characteristics of our two groups were generally comparable. However, there was a statistically significant difference in the number of stones, with multiple stones being more frequent in group SJ. Additionally, there was a trend towards slightly larger stones in group DJ.

Our main objective was to compare the safety of both stents in terms of emergency department admission, overall complications, and reintervention rate. This study's complication rate of 20% was higher than global studies, like the ones by the Clinical Research Office of the Endourological Society (CROES) [4, 13], but similar to the comparative studies between these two stents [10–12]. Most complications were minor, and no patients experienced severe complications (Clavien-Dindo's grade >III).

Notably, the complication rate was not statistically different between group SJ and DJ, and the most frequent complication was pain requiring analgesics in both groups. Reintervention rate was 1.7% in group SJ and 3.1% in group DJ, which was lower than reported by previous studies [10, 11]. In contrast to the findings of FAST 3 [11], which was terminated early due to an unexpectedly high reintervention rate when SJ stents were placed, the reintervention rate in group SJ was rare, even

when considering only primary URS (without pre-stenting). Therefore, our findings suggest SJ stents are at least as safe as DJ stents.

As demonstrated by the questionnaire results, LUTS were significantly less frequent in group SJ at both time points. Although lumbar pain was not significantly more intense in group DJ at W1, it became more severe after 4 weeks. Additionally, suprapubic pain was greater in group DJ at both W1 and W4. These findings corroborate those of the FAST trial [10].

Regarding questionnaire results at W4, nearly 40% of the group DJ patients had already removed their stents before answering the questionnaire, potentially underestimating differences between groups. Conversely, the observed differences at W4 might be attributable solely to the earlier removal of SJ stents rather than the stent type itself. Regardless, given the easier removal and less associated costs with SJ stents, they offer advantages over early removed DJ stents; however, this study was not designed to compare early removal of DJ stents, so this question remains to be answered, and should be addressed in future trials.

Lastly, SFR was also concordant with the literature [4, 6], although only a few patients had a postoperative imaging study.

One of the main limitations of this study is the unblinding of both surgeons and patients, with its inherent biases – the randomization process intended to reduce surgeon bias, as each surgeon placed both types of stents. Additionally, patients were scheduled by an external urologist who was unaware of the randomization process and did not perform the surgeries, ensuring that case characteristics did not influence patient selection. It is also important to note that deviations from randomization were only permitted if the randomized stent was not available at the time; to further control this limitation, both as-treated and ITT analyses were performed and presented.

While not formally validated, the questionnaire used was derived from the USSQ [8] and was abbreviated to include only the urinary domain symptoms deemed most relevant by the investigators. Another limitation is the absence of a baseline assessment of LUTS and pain. This prevents us from determining whether the groups differed in their initial symptoms or if pre-existing symptoms were influenced by stent placement. Although we believe these limitations do not significantly impact our results, acknowledging them is essential for the design of future studies.

CONCLUSIONS

Our study demonstrates that SJ stents placed for less than 24 hours after complete flexible URS are comparable to DJ stents regarding emergency department admission, complications, and reintervention rates. Furthermore, SJ stents were better tolerated, particularly at 4 weeks post-surgery. Consequently, urologists should prioritize SJ stents, reducing costs and hospital visits for stent removal. Additional randomized trials with larger sample sizes are needed to reinforce this practice.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of the Hospital of Braga and University of Minho in Braga, Portugal (approval number: CEHB_64_2024).

SUPPPLEMENTARY MATERIALS

Suppl. Table 1. *Primary outcomes – intention to treat analysis*

	Group SJ (n = 58)	Group DJ (n = 67)	p
Safety, n (%)			
Emergency department admissions	13 (22.4%)	9 (13.4%)	0.19
Total complications	13 (22.4%)	12 (17.9%)	0.53
Grade I–II	12 (20.7%)	10 (14.9%)	
Grade ≥III	1 (1.7%)	2 (3.1%)	0.61
Reintervention rate	1 (1.7%)	2 (3.1%)	1.00

Suppl. Table 2. *Secondary outcomes – intention to treat analysis*

		Group SJ (n = 48)	Group DJ (n = 56)	p
Tolerability / Symptom Questionnaire – Mdn (IQR)				
LUTS Symptom Score Total	W1	6.5 (3–10)	9 (5–12.75)	0.080
	W4	3 (0–6.75)	6 (2–10)	0.005
Lumbar Pain	W1	2 (0–4.75)	2.5 (0–5)	0.510
	W4	0 (0–1)	1 (0–5)	0.008
Supra-pubic Pain	W1	2 (0–4)	3 (0–5)	0.210
	W4	0 (0–0.75)	1 (0–4)	0.004
Efficacy, n (%)		**Group SJ (n = 17)**	**Group DJ (n = 15)**	**p**
Stone-free rate		13 (76.5)	11 (73.3)	0.840

IQR – interquartile range; Mdn – median; W1 – postoperative week 1; W4 – postoperative week 4

Suppl. Table 3. *LUTS Questionnaire answers at week 1*

Question	Group SJ (n = 51)	Group DJ (n = 53)	p
Dysuria, n (%)			
Never	29 (56.9)	16 (30.2)	
Very rarely	8 (15.7)	6 (11.3)	
Rarely	8 (15.7)	4 (7.5)	<0.001
Sometimes	5 (9.8)	12 (22.6)	
More than half of the times	0 (0.0)	4 (7.5)	
Almost always	1 (2.0)	11 (20.8)	
Hematuria, n (%)			
Never	27 (52.9)	31 (58.5)	
Very rarely	8 (15.7)	8 (15.1)	
Rarely	9 (17.6)	6 (11.3)	0.64
Sometimes	5 (9.8)	4 (7.5)	
More than half of the times	1 (2.0)	0 (0)	
Almost always	1 (2.0)	4 (7.5)	
Urinary incontinence, n (%)			
Never	40 (78.4)	45 (84.9)	
Very rarely	2 (3.9)	0 (.0)	
Rarely	5 (9.8)	3 (5.7)	0.58
Sometimes	2 (3.9)	3 (5.7)	
More than half of the times	2 (3.9)	1 (1.9)	
Almost always	0 (.0)	1 (1.9)	
Urinary frequency, n (%)			
Never	10 (19.6)	7 (13.2)	
Very rarely	2 (3.9)	5 (9.4)	
Rarely	7 (13.7)	3 (5.7)	0.04
Sometimes	21 (41.2)	12 (22.6)	
More than half of the times	8 (15.7)	19 (35.8)	
Almost always	3 (5.9)	7 (13.2)	
Urinary urgency, n (%)			
Never	20 (39.2)	15 (28.3)	
Very rarely	2 (3.9)	5 (9.4)	
Rarely	10 (19.6)	9 (17.0)	0.02
Sometimes	11 (21.6)	4 (7.5)	
More than half of the times	6 (11.8)	7 (13.2)	
Almost always	2 (3.9)	13 (24.5)	
Total LUTS Score, Mdn (IQR)	6 (3–9)	10 (5–13)	0.01

IQR – interquartile range; LUTS – lower urinary tract symptoms; Mdn = Median

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EDITORIAL

UROLITHIASIS

Editorial comment to: Tinoco CL, Martins L, Costa F, et al. Single-J versus double-J stents after ureterorenoscopy for renal stones: A randomized comparison of safety and tolerability. Cent European J Urol. 2025; doi: 10.5173/ceju.2024.0212

Another step toward a better understanding of urinary drainage after upper tract endoscopy

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This prospective randomized study addresses with objective data a long-standing issue in upper tract endourology: the choice of urinary drainage following endoscopic treatment. This topic is characterized by significant variability among centers and individual surgeons, a variability also mirrored in the still inconclusive literature on the subject.

Despite some methodological limitations, the study enables a comparison between two homogeneous groups of patients receiving either a single-J (SJ) or a double-J (DJ) stent. In my view, the most clinically relevant finding is the absence of statistically significant differences in reintervention and emergency readmission rates between the two groups, suggesting that, in the management of renal stone disease, the use of SJ stents may reasonably be favored.

The inclusion of a third, tubeless group – patients discharged without any form of postoperative drainage – would have added further value and completeness to the study design.

While stent-related symptom questionnaires provide useful data, their practical relevance may be limited, particularly when early stent removal is planned. In most cases, the decision to place a stent is driven not by patient comfort, but by the need to prevent infectious complications or to manage ureteral trauma identified during the procedure. In such contexts, the risk-benefit ratio generally supports stent placement despite the associated discomfort.

It would be highly valuable to see an expanded version of this study in the future, including a tubeless arm and a longer follow-up period, particularly aimed at assessing the potential development of ureteral strictures – an outcome that remains underexplored in the long-term safety evaluation of different drainage strategies.

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ORIGINAL PAPER

UROLITHIASIS

Relocation and evacuation of stone fragments using 7.5 Fr flexible ureteroscope with direct-in-scope suction: an experimental study

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Introduction Aim of the study was to evaluate and illustratively depict the aspiration properties of a single-use 7.5 Fr flexible ureteroscope with direct-in-scope suction (DISS) in a specifically designed *in vitro* setting.

Material and methods An experimental *in vitro* study using a 6.5 size sterile glove, natural stone fragments and part of a porcine ureter was performed. A single use 7.5 Fr digital flexible ureteroscope with integrated direct-in-scope suction (PU3033AH, Zhuhai Pusheng Medical Technology Co., Ltd., Zhuhai China) was used for all trials. Five stone fragments ranging from 3 to 5 mm in maximal diameter were used. For each stone, three trials were performed; stones placed in the upper, middle and lower calyx. The experimental trial was defined as partially successful if stone relocation using suction (SRS) was present and successful when subsequent evacuation was reported.

Results Relocation of stone fragments (partial success) was observed for all stones in different locations. Easy evacuation of the 3 mm stone fragment occurred from all calyces. Complete success was also reported for all 4 mm stones. Complete success was documented with the 5 mm stone positioned in the upper and middle calyces, whereas evacuation of the stone from the lower calyx was not achieved after 5 attempts.

Conclusions With the 7.5 Fr Pusen DISS integrated scope, stone fragments 3–5 mm in all calyces were successfully relocated. Whilst evacuation from any calyx was successfully done in 3–4 mm fragments, this was only possible for 5 mm fragments located in upper calyx or interpolar region. The lower pole and greater fragment size need further evaluation for optimal management by DISS.

Key Words: direct in scope suction ‹› single-use flexible ureteroscopy ‹› experimental study ‹› stone-free

INTRODUCTION

Retrograde intrarenal surgery (RIRS) is the accepted standard of care for small and mid-sized renal stones smaller than 2 cm [1]. With the continuous advancement of technology and materials and relatively lower risk of complications compared to percutaneous nephrolithotomy (PCNL) [2], the modality is gaining popularity also for larger stone burden [3] and complicated anatomies [4].

Several advancements and/or techniques have been reported to improve stone-free rate (SFR) following RIRS and reduce the rate of residual fragments. Among them, the use of high-power and thulium fiber (TFL) lasers was associated with shorter operative time, better efficiency, and production of finer dust [5, 6]. Additional surgical modifications include table tilting techniques [7], percussion inversion diuresis [8], use of external physical vibration lithecbole [9], the use of standard and flexible and navigable suction ureteral access sheaths (SUAS and FANS) [10], specific direct-in-scope suction (DISS) devices [11] and steerable multi-lumen irrigation/aspiration devices [12].

Performing direct aspiration under vision seems the easiest and most logical approach to eliminating minor fragments. In a recent survey sent to the members of Endourological Society, suction feature was considered the future essential development. Out of 208 respondents, 94.3% and 92.3% agreed that fragment and fluid suctioning, respectively, are important future concepts for single-use ureteroscopy [13]. Theoretically, aspiration with SUAS and FANS could evacuate larger stone fragments compared to DISS, since the working channel of DISS is smaller and can accommodate smaller stone particles <1 mm in size [14]. A question that arises and would be worth investigating is whether the aspiration with DISS could potentially attract the bigger stone fragments to the scope and relocate or evacuate them from the collecting system without using a basket or other accessories. The aim of the current study is to evaluate and illustratively depict the aspiration properties of a single-use 7.5Fr flexible ureteroscope with DISS in a specifically designed *in vitro* setting.

MATERIAL AND METHODS

Study design and setup configuration

We conducted an experimental *in vitro* study. The experimental setup included a 6.5 size sterile glove, natural stone fragments, and part of a porcine ureter. No pig was sacrificed for the study purpose. Instead, porcine ureter was harvested from the slaughter, thus no ethical approval was required for this study. To mimic the pelvicalyceal system (PCS) of a human kidney, one out of five fingers of the sterile glove (small finger) was tied close to the palm part of the glove, leaving no space for this finger to fill with the saline. The thumb part of the glove was used to introduce a 12/14 Fr ureteral access sheath (UAS). A small incision was made on the tip of the thumb finger. A hydrophilic guidewire (Bioteq Blackwire, Bioteque corporation, Taipei, Taiwan) was introduced first through the lumen of the pig ureter and then into the glove through the artificial opening through the thumb finger. Following the guidewire course, a 12/14 Fr UAS (Cook Medical, Indiana, USA) was introduced from the glove's opening. The glove opening was circumferentially sutured to the part of the harvested porcine ureter over the 12/14 UAS. The remaining three fingers (index, middle, and ring fingers) were tied to decrease their volume and then fixed to the table to form upper, middle, and lower calyces. As a result of the following setup configuration, we constructed a transparent model with hypothetical 3 calyces, dilated pelvis and ureteropelvic junction (the sutured area of the glove to the porcine ureter). This setup allowed realistic movement of the UAS in and out, with a natural tight feel, as a result of used porcine ureter. In addition, when the UAS was pulled to the level of the suture (imaginary uretero-pelvic junction (UPJ)), a narrowing of that segment was present, resembling real UPJ narrowing (Figure 1).

Flexible ureteroscope

A single-use 7.5 Fr digital flexible ureteroscope with the integrated direct-in-scope suction (PU3033AH, Zhuhai Pusheng Medical Technology Co., Ltd., Zhuhai, China) was used for all trials. The features of the scope include maximum up and down bending flexibility of 270 degrees, a LED light source, and an innovative feature of integrated direct in scope suction (DISS) channel controlled by a suction button attached to the handpiece of the scope. Pressing the button when needed provides easy and intuitive control of the aspiration. The suction channel is 3.6Fr wide, which can aspirate dust and approximately 1 mm particles.

Evaluated parameters

To perform the study, one stone fragment for each trial was placed through the UAS using a flexible ureteroscope and basket. These stone fragments

were collected from real-life RIRS with patients' consent. Five calcium-oxalate dehydrate stone fragments ranging from 3 to 5 mm in maximal diameter of different shapes were used. For each stone, three trials were performed; stones placed in the upper, middle and lower calyx. The number of attempts for each trial were separately calculated. Trials were stopped after a maximum of 5 attempts. For the study purposes, two irrigation modes were tested, aspiration with the irrigation "on" and "off". Two 3 l saline bags were fixed 1 meter above the experimental table. A manual hand-pump (Cook Medical, Indiana, USA) was used for irrigation. Each attempt was initiated following the filling of the "hypothetical pelvicalyceal system". The suction was connected to the scope and the suction device was set at 100 mBar (× 100 Pa).

The experimental trial was defined as completely successful if stone relocation using suction (SRS) with subsequent evacuation of the was observed. Relocation of the stone fragment from the calyx into the pelvis of the hypothetical pelvicalyceal system was defined as partial success.

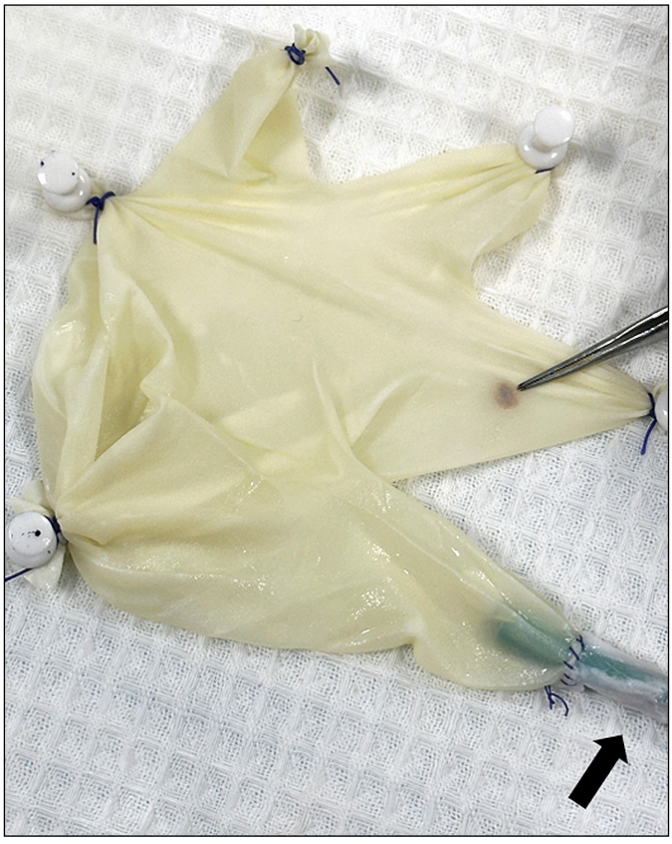

Figure 1. *Experimental model. Arrow shows the porcine ureter sutured to the thumb of the glove to form pelvi-calyceal system. The stone is positioned in the lower calyx shown with the tip of the forceps.*

Statistical analysis

SPSS v25 software (IBM Statistics, NY, USA) was used for the descriptive statistical analysis.

RESULTS

In total, 15 trials were performed for 5 stones. One stone was 3 mm, 3 stones were approximately 4 mm, and 1 stone was 5 mm in diameter. Relocation of stone fragments (partial success) was observed for all stones in different locations. Suction activation with the irrigation mode "on" and "off" did not affect the success of any of the trial. Easy SRS and evacuation of the 3 mm stone fragment occurred from all locations in the PCS. Two attempts were needed with the stone positioned in the upper and lower calyces, and only one attempt with the stone in the middle calyx. Complete success was also reported for all 4 mm stones, with the attempts ranging from 1 to 4. A five mm stone fragment was more difficult to relocate and evacuate via suction force. Complete success was documented with the 5 mm stone positioned in the upper and middle calyces, whereas SRS and evacuation of the 5 mm stone from the lower calyx was not achieved after 5 attempts (Table 1).

DISCUSSION

In our current *in vitro* experimental study, we evaluated the aspiration potential of a 7.5Fr single-use digital ureteroscope with an integrated direct-in-scope suction to relocate and evacuate stone fragments without the use of any adjunct instruments. We designed to construct a cheap and easily reproducible *in vitro* model to emulate the human PCS.

Table 1. *Stone relocation using suction and subsequent evacuation of stone fragments from different in vitro calyces using the 7.5Fr single-use digital PU3033AH flexible ureteroscope with DISS system*

Stone	1st trial* (upper calyx)	2nd trial* (middle calyx)	3rd trial* (lower calyx)
N1 (3 mm)	√	√	X√
N2 (4 mm)	XX√	X√	XX√
N3 (4 mm)	√	X√	XXX√
N4 (4 mm)	XX√	√	X√
N5 (5 mm)**	XXX√	XX√	XXXXX

No difference was observed with the irrigation mode "on" and "off"
* Maximum 5 attempts performed for each trial
** Relocation of the stone fragment was observed in all trials
DISS – direct-in-scope suction

Having a transparent model, the stone fragments were easily positioned in the desired calyces. In addition, it allowed an illustrative investigation of the suction effect on the constructed PCS and stone relocation.

With the increasing number of RIRS procedure worldwide, achieving stone-free status still remains a challenge. Despite the advantages of RIRS, in a recent study a SFR defined as the absence of any stone fragments was 56.7% following a single RIRS session for stones >2 cm [15], and as per the FLEXOR Registry, 51.5% of patients with residual fragments would eventually require re-intervention following RIRS [16]. Anomalous kidneys represent another entity; the reports have shown a SFR of 76.6% with almost 1/4 of the patients suffering from residual fragments [17]. While 2 to 4 mm residual stones have been considered as clinically insignificant fragments [18], the risk of reintervention ranges from 12% to 35% when residual fragments are present [19].

Several surgical methods have been described to improve the SFR. In addition, there have been recent advancements in endourological instrumentation. FANS and DISS [10, 11] are believed to be one of the promising features added to the endourological armamentarium. In case of DISS, the scope itself acts as the aspiration conduit. In an *in vitro* experimental study, Schneider et al. evaluated the feasibility of suctioning of sub-millimeter fragments through the working channel of the flexible ureteroscope [14]. A Luer Lock syringe was used to aspirate the phantom stone fragments of ≤1 mm and ≤0.5 mm sizes. In both of the groups, the mean percentage of suctioned fragments was 86%. Trapping of the working channel requiring further cessation of the procedure occurred in 64% and 78% of stones in the ≤0.5 mm and ≤1 mm groups, respectively [14]. A recent *in vitro* comparison of endoscopic clearance rates between manual syringe suction and integrated direct in-scope suction demonstrated significantly faster rates in favor of DISS (3.01 g/min vs 0.41 g/min). The authors reported complete stone clearance for dust particles <250 μm [20].

In a clinical setting, vacuum-assisted ureteroscopic lithotripsy has been shown to improve the SFRs significantly. Zhang et al. [21] compared vacuum suction rigid ureteroscopy with standard ureteroscopy and flexible ureteroscopic lithotripsy for impacted upper ureteral stones. Modified vacuum suction ureteroscopy group demonstrated significantly higher SFRs both at 3–5 days (90.0% vs 61.9% vs 55.6%) and 1-month (96.4% vs 77.7% vs 74.0%).

Gauhar et al. [11] were the first to coin and describe the DISS technique using a modified flexible ureteroscopy with in-scope suction potential. In their study, two 3-way stoppers were connected to each other and subsequently to the used scope. In a direct comparison of SUAS and DISS, Gauhar et al. reported no significant differences in residual fragments [11]. With the significantly bigger stone burden, comparable SFR were reported between the group, the DISS group showing 33.3% residual fragments. Yet, significantly more patients treated with DISS were shown to have multiple residual fragments and required subsequent treatment. It was also highlighted that the dusting technique should be used to evacuate the generated dust with DISS. The feasibility of the DISS technique using similar add-on instruments was also challenged in a patient with a transplanted kidney with a large ureteral stone [22]. The authors reported a successful procedure achieving complete stone-free status following antegrade ureteroscopic lithotripsy with DISS technique. Recently, a prospective multicentric study using the DISS scope in 57 patients showed a stone-free rate (SFR) of 84% with integrated suction deemed helpful by 94.7% of users, and all surgeons were willing to use the scope in the future [23].

Despite the promising results, the DISS technique may be associated with several drawbacks. The method may require an increased irrigation flow rate and some additional learning curve. During the active suction, not only dust, but also blood clots can be aspirated, blocking the working channel and requiring further maneuvers [11]. In addition, due to the smaller size of the suction/working channel, stone fragments smaller than 1mm can potentially be considered to be aspirated through the scope [14]. Our paper introduces a new concept of the action of flexible ureteroscopes with the DISS feature. We were able to show that the suction force was sufficient to relocate and in most of the cases to evacuate stone fragments 3–5 mm in size. In all experimental trials, naturally collected calcium oxalate stones were used, which further strengthens our paper.

Several limitations can be encountered in our paper. Our current study was performed in an artificially constructed *in vitro* model. Although the model was specifically designed to mimic human PCS, not all the factors could be controlled. Additional criticism may include the use of only one stone type and one size of the glove to construct the PCS. In the clinical setting, we deal with patients with different anatomy of the PCSs and stone composition, which may affect the outcomes. Nevertheless, this experiment spreads light on the aspiration properties of newly introduced single-use ureteroscope with integrated

DISS. Further *in vivo* experimental and clinical studies are warranted.

CONCLUSIONS

The 7.5 Fr Pusen DISS integrated scope successfully relocated stone fragments 3–5 mm in all calyces. Whilst evacuation from any calyx was successfully done in 3–4 mm fragments, this was only possible for 5 mm fragments located in the upper calyx or the interpolar region. The lower pole and bigger fragment size need further evaluation by DISS for optimal management.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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ORIGINAL PAPER

UROLITHIASIS

Comparison of the microbiome of bladder urine, upper urinary tract urine, and kidney stones in patients with urolithiasis

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Introduction It is believed that bacteria can be involved in the formation of all types of stones. The aim of study was to assess the urinary microbiome in patients with urolithiasis.

Material and methods The study group included 50 patients qualified for endoscopic treatment of urinary tract stones using: ureteroscopic lithotripsy (URSL), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotripsy (PCNL), endoscopic combined intrarenal surgery (ECIRS). Before the procedure, patients were asked to collect urine and stool for analysis. Urine from the upper urinary tract and stone fragments were collected intraoperatively. The research material was subjected to 16S rRNA sequencing. The chemical composition of stones was assessed using Raman spectroscopy.

Results In the urinary bladder, upper urinary tract, and kidney stone microbiomes of patients with urolithiasis the predominant bacteria identified were: *Acinetobacter, Bifidobacterium, Corynebacterium, Cutibacterium, Paracoccus, Pseudomonas, Staphylococcus* and *Streptococcus*. Further analysis showed the relative similarity of the urinary bladder and upper urinary tract microbiomes and the dissimilarity of the kidney stone microbiome. A comparison of the upper urinary tract microbiome based on the method of urine collection and a comparison of urinary bladder and upper urinary tract microbiomes based on the presence of a DJ stent prior to the procedure showed no statistically significant differences.

Conclusions The microbiome of stones differs from the microbiome of urine, which may play a role in the pathogenesis of urolithiasis. Bladder urine and upper urinary tract urine microbiomes do not differ. Therefore, bladder urine can replace upper urinary tract urine in microbiome studies.

Key Words: microbiome ‹› urolithiasis ‹› 16S rRNA sequencing ‹› kidney stones

INTRODUCTION

Urolithiasis is one of the most common urological diseases affecting up to 20% of the population. The recurrence rate of stones within five years in first-time stone formers is 26% [1]. For many years, only urease-producing bacteria, associated with the formation of struvite stones, were considered to be the bacterial etiology of urolithiasis [1]. However, patients with urolithiasis often experience concomitant urinary tract infections and often have positive urine cultures in the pre- or postoperative period, regardless of the chemical composition of the stone [2, 3]. Therefore, it is suspected that bacteria may be involved in the development of all types of stones, including non-struvite stones.

Thanks to advances in DNA sequencing, it has been shown that the urinary tract has its own endogenous

microbiome, and the dogma that urine bomust be sterile has been disproved [4]. Considering the postulated role of bacteria in the development of stones, it is believed that not one specific bacterium, but microbiome dysbiosis plays a role in the pathogenesis of urolithiasis.
Therefore, the aim of our study was to assess the urinary and stool microbiome in patients with urolithiasis and to compare bladder, upper urinary tract and stones microbiomes. Furthermore, we assessed whether there is an association between the composition of the microbiome in patients with urolithiasis and patient- and urolithiasis-related features.

MATERIAL AND METHODS

Study design and specimen collection

The study group included patients hospitalized at the University Center of Excellence in Urology in 2022–2023, qualified for endoscopic treatment of urinary tract stones using: ureteroscopic lithotripsy (URSL), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL) or endoscopic combined intrarenal surgery (ECIRS). Exclusion criteria included: recent/active sexually transmitted infection, recent/active urinary tract infection, use of antibiotics in the past month.
Before the procedure, patients were asked to collect urine and stool for analysis. Urine was collected from the midstream. Stool was collected using a Kałszyk stool sample collection kit (KOSOWSKI®). Intraoperatively, urine was collected from the upper urinary tract, through the ureterorendoscope during URSL and RIRS or right after percutaneous puncture during PCNL and ECIRS. Fragments of stones were also collected to analyze microbiome and its chemical composition. The biological material for microbiome analysis was stored at –80°C until DNA isolation. Stones collected for the assessment of chemical composition were stored at room temperature. The chemical composition was assessed using Raman spectroscopy.
Samples collected for microbiome analysis were divided into 4 groups: urine from the bladder (U), urine from the upper urinary tract (UT), stones (KS) and stool (S).

DNA isolation

The patient's U, UT, S samples were used to isolate bacterial DNA as previously described [5].
For KS DNA isolation, received samples were washed with filtered PBS, snap-freezed in liquid nitrogen, and crushed with the use of mortar and pestle. 200 mg of the obtained powder was treated with a DNeasy Blood & Tissue Kit (cat. no. 69506, QIAGEN). First, the sample was incubated in an ATL buffer (supplemented with proteinase K, mutanolysin and lysozyme) for 1 hour, at 37°C (with shaking). Before transfer to the column, the suspension was treated with AL buffer followed by pure ethanol. AW1 and AW2 buffers were used for washing steps and 50 μl AE buffer allowed DNA elution. All buffers necessary for the procedure were included in the kit.

DNA library preparation and sequencing

DNA library and sequencing were performed by Novogene company (China) according to their standardized procedures.
Briefly, all the DNA samples that passed the quality control were subjected to 16S rRNA library preparation. Briefly, 16S rRNA/18SrRNA/ITS genes of distinct regions (16SV4/16SV3/16SV3- V4/16SV4- V5, 18SV4/18SV9, ITS1/ITS2, ArcV4) were amplified by polymerase chain reactions (PCR). To select PCR products of the intended size, 2% agarose gel electrophoresis was performed. In the next step, the same amount of PCR products from each sample was pooled, end-repaired, A-tailed, and ligated with Illumina adapters.
Finally, to achieve the highest quality of the obtained library, it was checked with Qubit and real-time PCR for quantification, while a bioanalyzer was used for size distribution detection. Quantified libraries were pooled and sequenced on a pair-end Illumina platform to generate 250 bp paired-end raw reads.

Bioinformatic analysis

Quality control and preprocessing

Raw paired-end sequences in FASTQ format were processed in R (v4.1.2) using the dada2 package for quality control, trimming, and filtering [6]. Sequences were truncated to a fixed length of 210 bp for forward and 220 bp for reverse reads, with a maximum allowable number of expected errors set to 2 [6]. Sequences were dereplicated, and error models were learned independently for forward and reverse reads. Paired-end reads were merged, and chimeric sequences were removed. Resulting sequences were organized into an amplicon sequence variant (ASV) table.

Taxonomic assignment

The "dada2" package was used for taxonomic assignment of ASVs using the Silva v138.1 reference

database [6]. Taxonomy was assigned using the naive Bayesian classifier with a minimum bootstrap value of 80 [7]. Taxonomic tables were combined with sequence data to create a phyloseq object for further processing [8].

α- and β-diversity analysis

To evaluate microbial diversity within each subgroup, α-diversity indices, including the Chao1 richness index, Shannon diversity index, Simpson evenness index, and Gini index, were computed using the "mia" package and t-test [9]. β-diversity was assessed through principal component analysis (PCA) using the microbiome package and unsupervised clustering using "ComplexHeatmap" package [10, 11]. Briefly, data were log-transformed and visualized at the genus level, focusing on the top 50 genera across samples. Core microbiome analysis was conducted by defining prevalent taxa (present in at least 10% of samples) and aggregating rare taxa below the genus level. Relative abundances were calculated and visualized to illustrate composition patterns within each subgroup.

Confounding factors and multivariate analysis

To account for potential confounding factors, multivariate analyses were performed using PERMANOVA with the "microViz" package [12]. Confounding variables such as age, gender, BMI, and comorbidities (e.g., hypertension, diabetes) were tested for associations with microbial composition. Additional confounding analysis was performed using "swamp" package to evaluate potential clustering based on metadata variables [13].

Differential abundance and statistical testing

Differences in bacterial composition across subgroups were assessed using SIAMCAT [14]. Specific pairwise comparisons, between UT and U, KS and U, and KS and UT, were conducted to identify significantly differentially abundant genera. Differential abundance was determined using Wilcoxon rank-sum tests, and p-values were adjusted for multiple comparisons using the Benjamini-Hochberg method. Results were visualized with association plots.
Spearman correlation was applied to assess relationships between microbial genera and selected clinical variables. The analysis focused on the top genera at the genus rank present in at least of 50% of selected samples from given subgroup (U, UT, KS or S). Taxonomic abundance data was transformed using centered log-ratio (CLR) transformation with replacing zeros with half the minimum non-zero value. A correlation heatmap was generated using the corrplot package, with correlations below an absolute value of 0.49 and FDR-adjusted p-value >0.05 masked to highlight moderate to strong correlations [15]. The modified heatmap was visualized using NMF package [16].

Bioethical standards

The study was approved by the Bioethics Committee of the Wroclaw Medical University (KB-252/2022).

RESULTS

Patient characteristics

50 patients were qualified for the study, including: 33 women (66%) and 17 men (34%), aged 23–89 years (mean 55,64). The RIRS procedure was performed most frequently (42%). Half of the patients had a double J (DJ) stent inserted before the procedure. Most of the stones (34) were composed of calcium oxalate monohydrate.
Detailed characteristics of patients is presented in Table 1.
Of the 200 samples, 175 were included in the analysis, including 50 S, 50 U, 39 UT and 36 KS. The remaining samples were excluded due to insufficient genetic material for sequencing.

General characteristics of the microbiome

In the U, UT and KS microbiomes the predominant bacteria identified were: *Acinetobacter, Bifidobacterium, Corynebacterium, Cutibacterium, Paracoccus, Pseudomonas, Staphylococcus* and *Streptococcus* (Figure 1). At the level of α-diversity, no differences were demonstrated between the groups ($p > 0.05$) (Figure 2).

Comparison of the urine from the bladder, upper urinary tract and stones microbiomes

Hierarchical clustering analysis and principal component analysis (PCA) of the microbiome showed the relative similarity of the U and UT microbiomes and the dissimilarity of the KS microbiome (Figures 3, 4).

Detailed comparison of the urine from the bladder and upper urinary tract microbiomes

As a result of statistical comparison of abundances between the UT and U subgroups, 29 genera were

found to be significantly differentially abundant between the compared groups (adjusted p-value ≤0.05) (Figure 5 and Supplementary material 1).

Detailed comparison of the stones and urine from the bladder microbiomes

A total of 83 genera were identified as significantly differentially abundant between KS and U (Figure 6 and Supplementary material 2). Genera significantly more abundant in KS included *Chryseobacterium, Brevundimonas, Microbacterium, Acidocella, Rhodococcus, Brucella*, and *Flavobacterium*. Genera enriched in U included *Reyranella, Acidovorax, Legionella, Dialister, Pajaroellobacter*, and *Sphingomonas*. Genera such as *Pseudomonas* and *Rothia* were prevalent in both KS and U.

Detailed comparison of the stones and upper urinary tract microbiomes

A statistical comparison of abundances between the KS and UT subgroups identified 63 genera with significantly differential abundance (Figure 7 and Supplementary material 3). Genera significantly more abundant in KS included *Chryseobacterium, Acidocella, Rhodococcus, Stenotrophomonas, Brevundimonas, Brucella*, and *Flavobacterium*. Genera enriched in UT included *Burkholderia–Caballeronia–Paraburkholderia, Methylobacterium–Methylorubrum, Sphingomonas*, and *Neisseria*. Genera such as *Cloacibacterium* and *Bifidobacterium* were found in both sites but were more prevalent in KS. Pseudomonas was highly prevalent in both KS and UT, with a slight reduction in UT.

Assessment of the correlation between the urine from the bladder, upper urinary tract, stones, stool microbiomes and patient-related and urolithiasis-related features

We analyzed correlations between microbiome and patient-related features such as age, weight, BMI and comorbidities and correlations between microbiome and urolithiasis-related features including stone dimensions, mean Hounsfield Units (HU), and DJ stent presence. We found no statistically significant correlations for U, UT and S subgroups. The correlation analysis of KS microbiome revealed several significant relationships (Figure 8). *Microbacterium* showed a strong positive correlation with weight (r = 0.696) and BMI (r = 0.564). *Rhodococcus* and *Brucella* exhibited a negative correlation with stone depth (r = –0.494; r = –0.571). *Methylobacterium-Methylorubrum* showed a negative correlation with stone width (r = –0.567). *Rothia* and *Flavobacterium* demonstrated positive correlations with stone width (r = 0.514) and stone depth (r = 0.520), respectively. A comparison of the UT microbiome based on the method of urine collection, whether antegrade or percutaneous and a comparison of the U and UT microbiomes based on the presence of a DJ stent prior to the procedure showed no statistically significant differences.

Table 1. *Patient characteristics*

No. of Patients	50	
Women	33	66%
Men	17	34%
Age, mean (range)	55.64	23–89
BMI, mean (range)	28.02	19.13–35.08
Comorbidities		
Obesity	8	16%
Hypertension	11	22%
Diabetes mellitus	6	12%
Dyslipidemia	1	2%
Metabolic syndrome	6	12%
Hypothyroidism	8	16%
Hyperthyroidism	1	2%
Procedure		
URSL	5	10%
RIRS	21	42%
PCNL	11	22%
ECIRS	13	26%
Stone characteristics		
Location		
Ureter	13	
Pelvis	21	
Upper calyx	5	
Middle calyx	13	
Lower calyx	24	
Staghorn	7	
Side		
Right	22	44%
Left	16	32%
Bilateral	12	24%
Size [mm], mean (range)		
Height	13.56	3.59–48.8
Width	17.56	5.16–58.36
Depth	11.97	4.4–27.6
HU, mean (range)	1,016	312–1703
DJ stent preoperatively		
Yes	25	50%
No	25	50%
Stone composition		
Uric acid	6	
Calcium oxalate monohydrate	34	
Calcium oxalate dihydrate	18	
Carbapatite	15	
Magnesium ammonium phosphate	4	
Mixed	22	

BMI – body mass index; DJ – double-J; ECIRS – endoscopic combined intrarenal surgery; HU – Hounsfield Units; PCNL – percutaneous nephrolithotripsy; RIRS – retrograde intrarenal surgery URSL – ureteroscopic lithotripsy

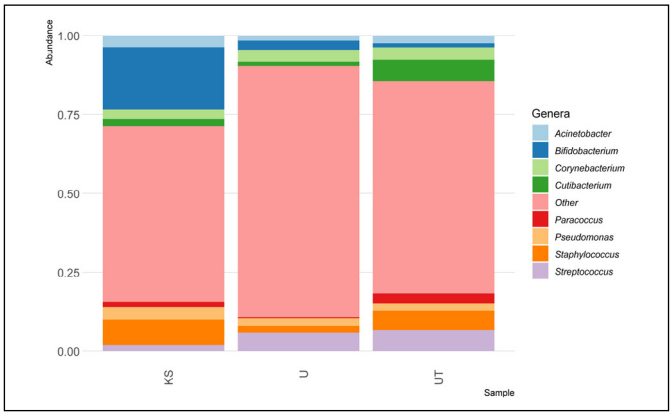

Figure 1. *Relative abundance of selected microbial genera across three subgroups: kidney stones (KS), urine (U), and urinary tract (UT). The data was averaged within each subgroup and agglomerated at the "Genus" level. Clear differences in the microbial composition are observed between the subgroups, highlighting distinct community structures in each environment. Rare taxa, defined as those present in fewer than 50% of the samples, were excluded from the analysis to focus on more prevalent genera.*

DISCUSSION

Until recently, it was believed that only urease-producing bacteria were involved in the pathogenesis of urolithiasis and are responsible for the formation of struvite stones [1]. Considering the rare occurrence of struvite stones and the common occurrence of urinary tract infections and positive urine cultures in patients with urolithiasis, it is believed that bacteria can be involved in the formation of all types of stones, including non-struvite stones [2, 3].

In our study, we assessed the U, UT, KS and S microbiomes. In the U, UT and KS microbiomes, the most abundant bacteria were *Acinetobacter*, *Bifidobacterium*, *Corynebacterium*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Cutibacterium*, and *Paracoccus*. These results are similar to those obtained by other authors. Dornbier et al. also assessed KS, U and UT microbiomes, and the dominant taxa were *Staphylococcus*, *Streptococcus*, *Corynebacterium*, *Bifidobacterium*, as well as *Veillonella*, *Haemophilus*, *Proteus*, *Lactobacillus*, and

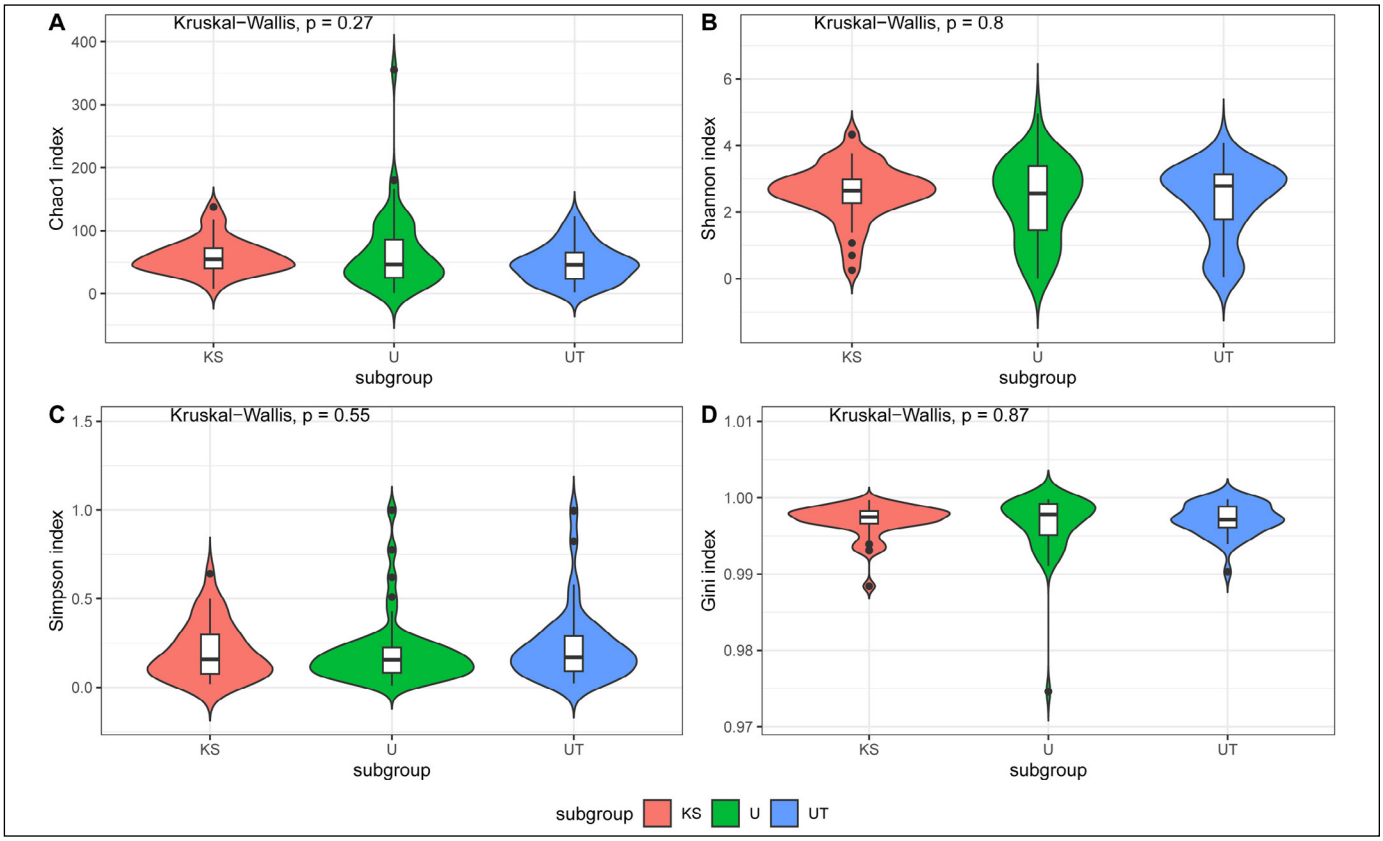

Figure 2. *The major alpha-diversity measures in the analysis of the V3-V4 16S region in KS (stones), U (urinary bladder), and UT (upper urinary tract). Alpha diversity measures* **(A)** *Chao1 index,* **B)** *Shannon index,* **C)** *Simpson index, and* **D)** *Gini index) representing key aspects of microbial diversity, including species richness, evenness, and overall diversity. Each plot displays the distribution of diversity indices across different sample groups. No significant differences were detected among groups for any of the diversity measures, as determined by the Kruskal-Wallis test (p >0.05).*

the *Enterobacteriaceae* family [17]. Liu et al. [18] compared the U and UT microbiomes. They found a high prevalence of the genera *Acinetobacter, Bifidobacterium, Corynebacterium, Staphylococcus, Streptococcus*, as well as *Delftia, Propionibacterium, Pontibacter, Sphingomonas*, and *Prevotella*. The high prevalence of *Acinetobacter, Pseudomonas*, and *Staphylococccus* in U and KS microbiomes was also described by Hong et al. [2] and Tavichakorntrakool et al. [19]. Xie et al. [20] reported a higher prevalence of the genus *Acinetobacter*.

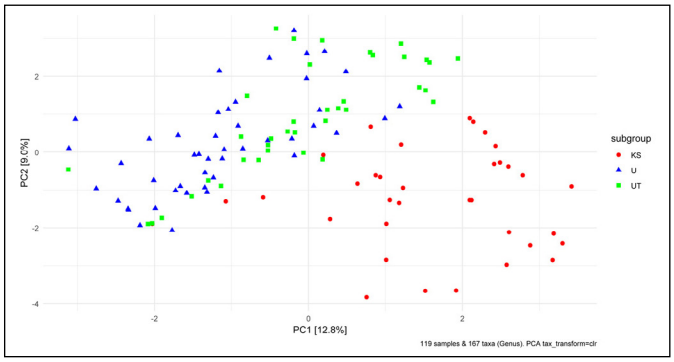

Figure 3. *Principal coordinate analysis (PCoA) of microbiome data from 125 samples across three subgroups: kidney stones (KS), urine (U), and urinary tract (UT). The PCoA plot shows clear separation of the KS subgroup, which forms a distinct cluster, while some U and majority of UT samples are more closely grouped. Intra-variability between the U and UT samples is much lower than the intra-variability between the KS samples.*

By comparing the U and UT microbiomes, we demonstrated their relative similarity. Only detailed analysis revealed differences in the abundance of some bacteria genera and the occurrence of a group of genera only in the U microbiome. These differences may result from improper urine collection by the patient. In addition, in our study, we did not demonstrate that the method of collecting urine from the renal pelvis, thorough the ureterorenoscope or percutaneously, had an effect on the composition of the UT microbiome. To our knowledge, this is the first study first study to assess this aspect. Other authors have also shown no differences between U and UT microbiomes [17, 18, 20]. Liu et al. [18], in order to minimize the risk of the influence of bacteria from the bladder performed bladder disinfection with iodophor before collecting urine from the renal pelvis. They also did not show any differences in the U and UT microbiomes. Therefore, it can be assumed that U is representative and can replace UT in microbiome studies.

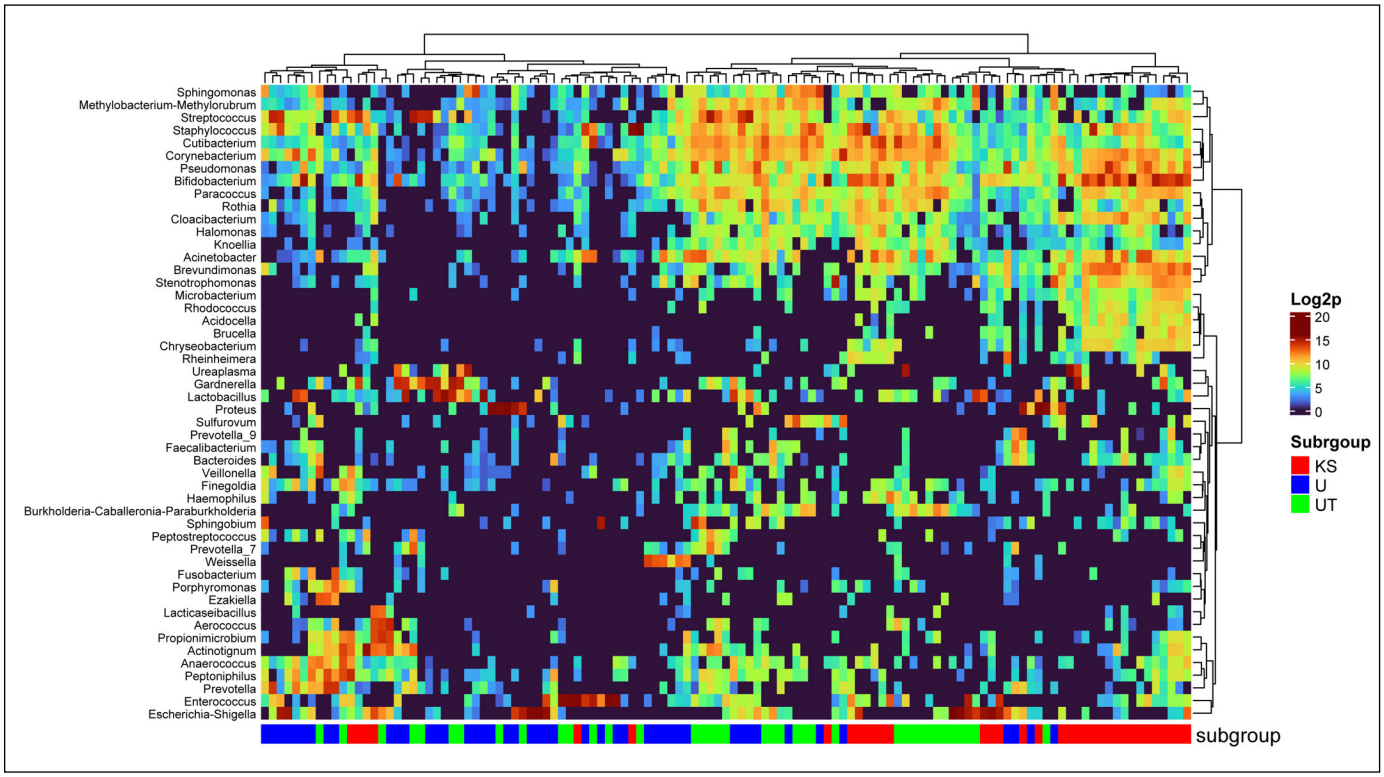

Figure 4. *Hierarchical clustering of microbiome data from 125 samples across three subgroups: stones (KS), urinary bladder (U), and upper urinary tract (UT). The dendrogram demonstrates that the KS subgroup forms a distinct cluster, while samples from the U and UT subgroups are intermixed, indicating a closer similarity between these two sample types.*

It allows for better comparison with a healthy controls in further studies, because collecting urine from the renal pelvis in healthy controls raises significant ethical concerns.

Comparison of the effect of the presence of a DJ stent on urinary microbiome also did not show any significant differences. In our study, a DJ stent was inserted 50% of patients preoperatively. In the study by Dornbier et al. [17], it was placed in 96.1% of patients at the time of stone extraction. They did not show any differences in the U, UT and KS microbiomes. In the study by Xie et al. [20], the presence of a ureteral stent preoperatively was an exclusion criterion. Again, no differences were found between the U and UT microbiomes. Buhmann et al. assessed the microbiome of ureteral stents placed 3 to 6 weeks after treatment for urolithiasis. The most common genera included *Actinomyces, Staphylococcus, Streptococcus, Corynebacterium, Lactobacillus, Achromobacter, Facklamia, Anaerococcus, Gardnerella, Atopobium, Actinotignum*, and the *Enterobacteriaceae* family [21]. The composition of the ureteral stent microbiome partially overlaps with the dominant taxa observed in our study. It therefore appears that the presence of the DJ stent may not affect the composition of the microbiome and that its microbiome does not differ from the U microbiome, but further studies are needed to confirm this thesis.

We also showed that KS microbiome differs from U and UT microbiomes. KS microbiome was more abundant in the genera *Chryseobacterium, Brevundimonas, Microbacterium, Acidocella, Rhodococcus, Brucella, Flavobacterium*, and *Stenotrophomonas*. These results are different from those reported by other authors. Neither Lemberger et al. [17] nor Dornbier et al. [22] showed differences between

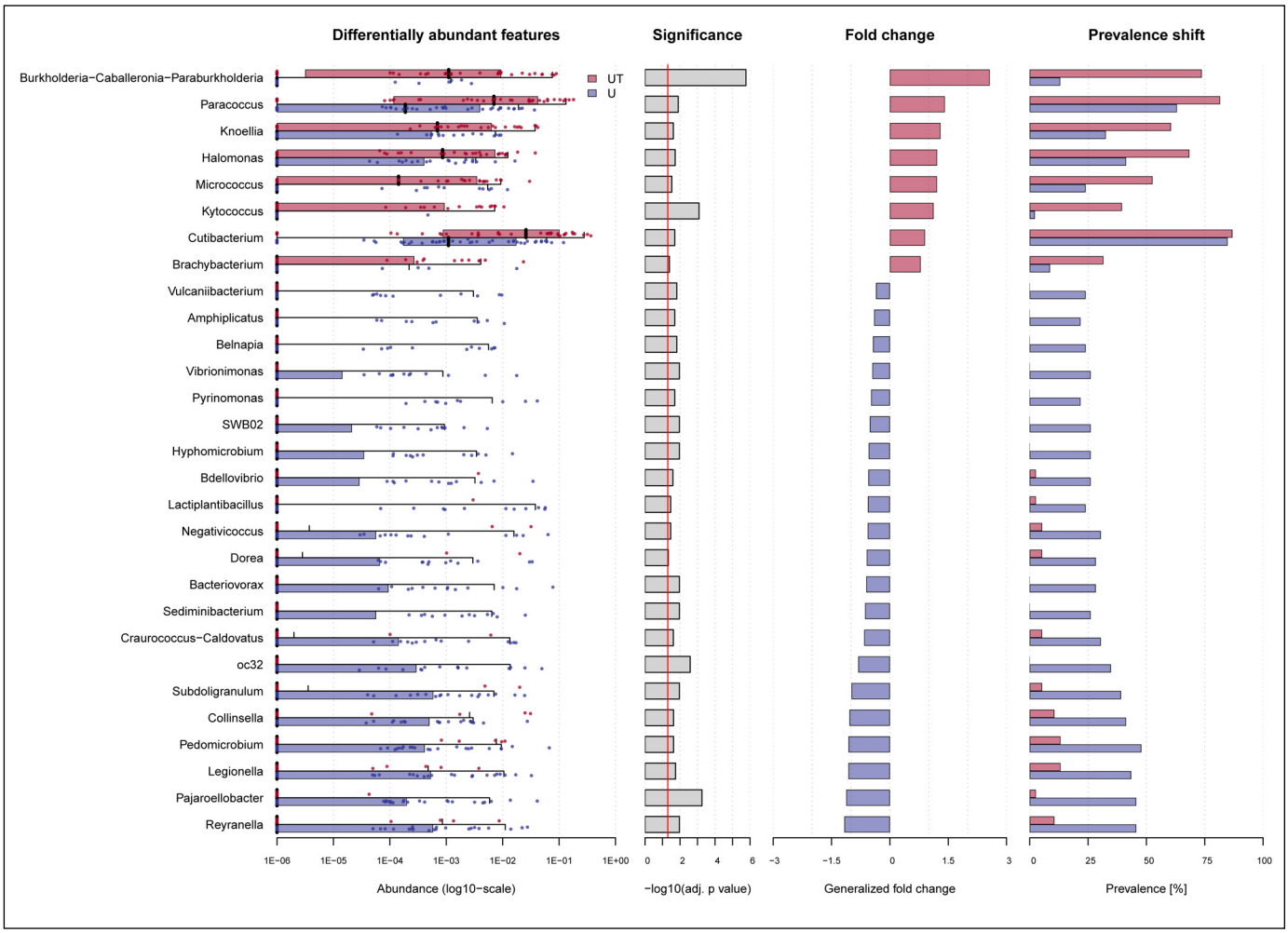

Figure 5. *Association between bacterial genera agglomerated to the "Genus" level and phenotype classes: upper urinary tract (UT) vs urinary bladder (U). The plot displays the log10-transformed abundances of each genus for both phenotype classes (UT and U) from left to right. Statistical associations are determined by an adjusted p-value (≤0.05) using the Wilcoxon test. Additionally, generalized fold change and prevalence shift between the two classes are shown.*

KS microbiome and U and UT microbiomes, only Dornbier et al. showed that KS microbiome was enriched in dominant taxa compared to the U microbiome. There is a hypothesis that bacteria responsible for stone formation are located in the stone nidus, while bacteria responsible for urinary tract infections in the course of urolithiasis secondarily cover the surface of the stone [2]. Our results seem to confirm this hypothesis. However, it is necessary to perform more studies with a detailed analysis of the stone microbiome from samples taken from different parts of the stone.

It is suspected that specific types of bacteria may be responsible for the development of specific types of urinary stones. Our research, as well as the study by Lemberger et al. [22] did not show such a relationship. However, in most studies, the dominant type of deposit is calcium oxalate, which makes it difficult to assess the relationship between the microbiome of U and KS and the formation of rarer types of non-struvite stones.

It is believed that risk factors for the development of urolithiasis may promote the development of urolithiasis by modifying the composition of the urinary microbiome [23]. However, we failed to demonstrate a relationship between the U, UT, KS, S microbiomes and almost all patient- and urolithiasis-related features. A similar lack of relationship has been reported by other authors [18, 22, 23]. We only showed correlations between the KS microbiome and patient weight and BMI and between the KS microbiome and stone dimensions. On this basis, we hypothesize that the composition of the stone microbiome may change with increasing stone dimensions. However, these results do not allow drawing broad conclusions, but they may suggest a direction for further research.

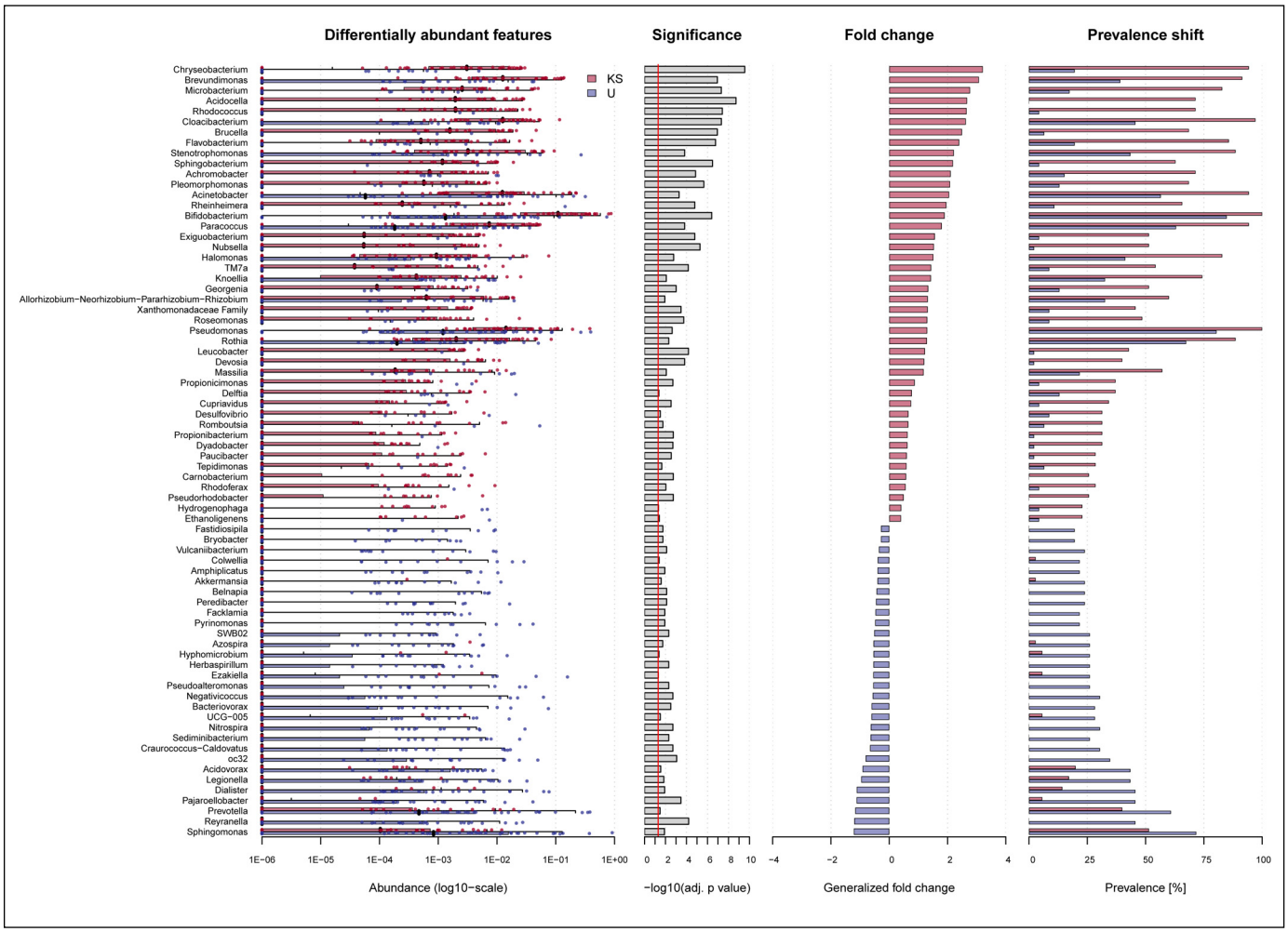

Figure 6. *Association between bacterial genera agglomerated to the "Genus" level and phenotype classes: kidney stones (KS) vs urinary bladder (U). The plot displays the log10-transformed abundances of each genus for both phenotype classes (KS and U) from left to right. Statistical associations are determined by an adjusted p-value (≤0.05) using the Wilcoxon test. Additionally, generalized fold change and prevalence shift between the two classes are shown.*

Our work has several limitations. First, the study group was small and single-center due to the costs of sequencing. We hope to conduct a multicenter study with a larger cohort in the future. Secondly, we did not include a control group in the study. This is due to the lack of possibility of noninvasive collection of urine from the upper urinary tract in healthy volunteers. We revealed that U and UT microbiomes do not differ significantly, which will allow the use of bladder urine from healthy controls for comparison in subsequent studies. Thirdly, collection of stone samples using a ureterorenoscope involves its passage through the urinary tract, which carries a risk of sample contamination. It may be limited by the routine use of ureteral access sheaths in further studies. Fourthly, we were able to obtain enough genetic material for sequencing only in 36 stones, which limits the possibility of comparing different types of stones. Fifthly, 16S rRNA sequencing does not detect microorganisms other than bacteria and archaea, such as fungi or viruses, which may play a role in the onset of the disease. Finally, like most microbiome studies, the study was descriptive in nature, which prevents us from establishing a causal relationship between the urinary microbiome and urolithiasis. Further studies are needed to determine whether changes in the urinary microbiome are involved in the pathogenesis of urolithiasis or are a consequence of the development of stones.

CONCLUSIONS

In conclusion, we compared the microbiomes of bladder urine, upper urinary tract urine, stones and stool in patients with urolithiasis. We showed that the stone microbiome differs from urine microbiome, which may play a role in the pathogenesis

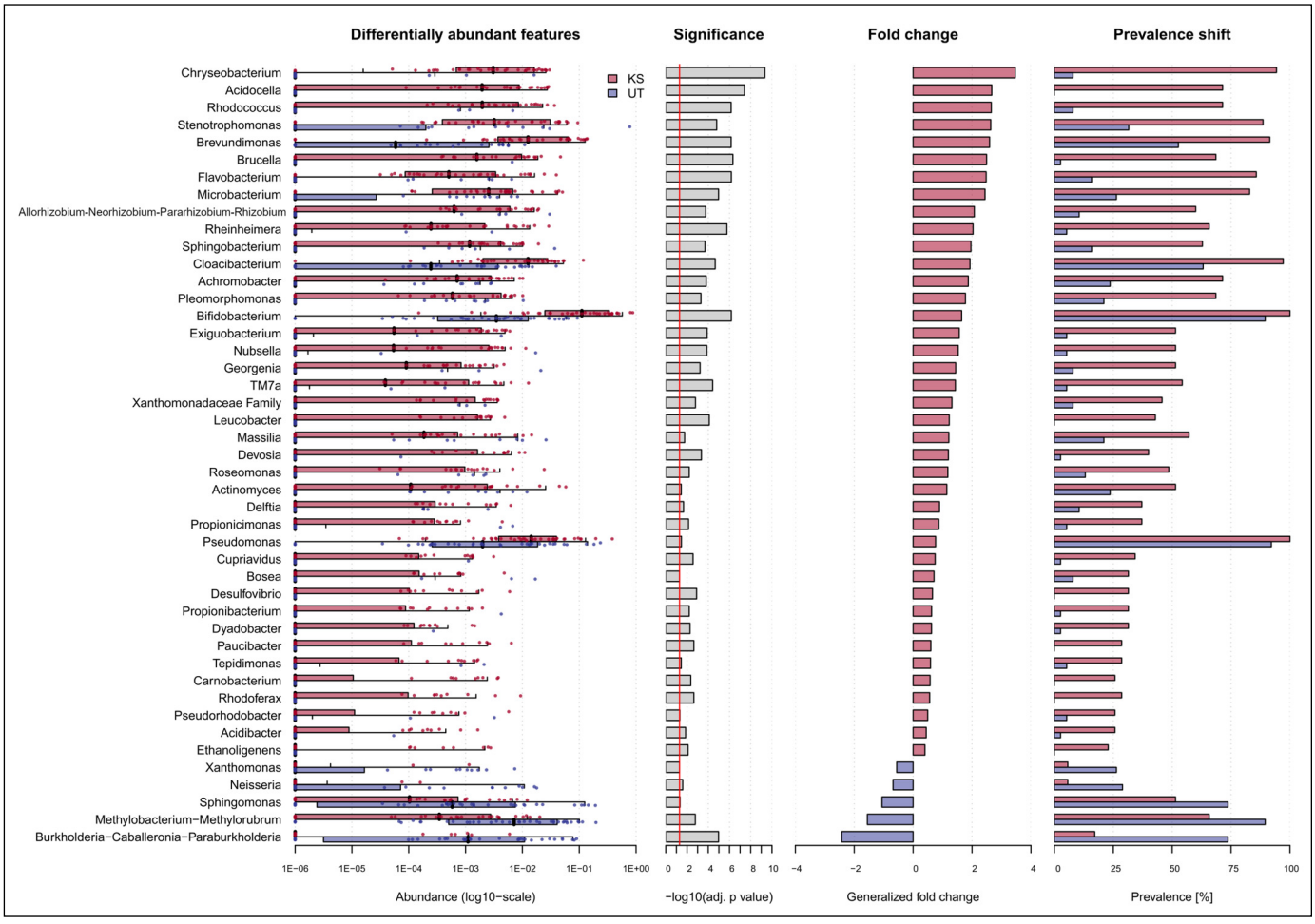

Figure 7. *Association between bacterial genera agglomerated to the "Genus" level and phenotype classes: kidney stones (KS) vs upper urinary tract (UT). The plot displays the log10-transformed abundances of each genus for both phenotype classes (KS and UT) from left to right. Statistical associations are determined by an adjusted p-value (≤0.05) using the Wilcoxon test. Additionally, generalized fold change and prevalence shift between the two classes are shown.*

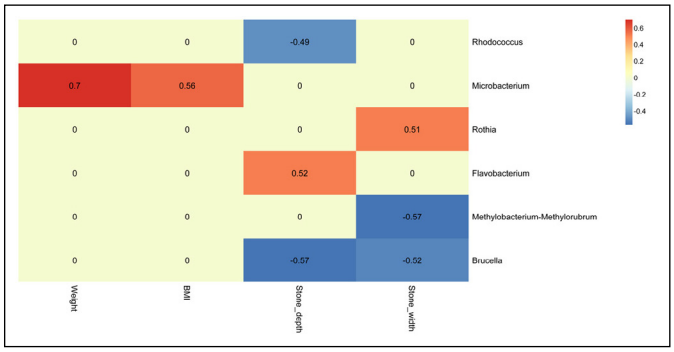

Figure 8. *Heatmap showing significant correlations between microbial taxa and clinical variables in kidney stone (KS) samples. The color intensity represents the strength and direction of the correlation, with positive correlations in shades of red and negative correlations in shades of blue. Correlations are displayed only for values with an absolute correlation coefficient ≥0.49 and an adjusted p-value <0.05. Numeric values within the heatmap cells indicate the rounded correlation coefficients. Rows represent microbial taxa, while columns correspond to clinical variables.*

of urolithiasis. In addition, we showed no effect of the presence of the DJ stent on the composition of the microbiome. Further studies are necessary on a larger cohort on this topic are necessary to confirm these results. Moreover, the comparison of bladder urine and upper urinary tract microbiomes showed their relative similarity. Therefore, it can be assumed that bladder urine is representative and can replace upper urinary tract urine in microbiome studies.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

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ETHICS APPROVAL STATEMENT

The study was approved by the Bioethics Committee of the Wroclaw Medical University (KB-252/2022).

SUPPLEMENTARY MATERIALS

Supplementary material 1. Detailed comparison of the urine from the bladder and upper urinary tract microbiomes

As a result of statistical comparison of abundances between the UT and U subgroups, 29 genera were found to be significantly differentially abundant between the compared groups (adjusted p-value ≤ 0.05) (Suppl. Table 1). The comparison showed that the genera *Brachybacterium, Burkholderia–Caballeronia–Paraburkholderia, Cutibacterium, Halomonas, Knoellia, Micrococcus* and *Paracoccus* were present in both subgroups, but their abundances were significantly higher in the UT group reaching prevalences above 50%. In addition, *Kytococcus was almost exclusively present in UT group reaching 39% of prevalence*. Large group of 15 genera (*Vulcaniibacterium, Amphiplicatus, Belnapia, Vibrionimonas, Pyrinomonas, SWB02, Hyphomicrobium, Bdellovibrio, Lactiplantibacillus, Negativicoccus, Dorea, Bacteriovorax, Sediminibacterium, Craurococcus–Caldovatus,* oc32 and *Pajaroellobacter*) were almost exclusively present in up to 25% of U samples. The remaining 5 genera, including *Reyranella, Legionella, Pedomicrobium, Collinsella* and *Subdoligranulum*, were predominantly present in U samples (approx. 40% of U samples), with only a few instances in the UT group.

Supplementary material 2. Detailed comparison of the stones and urine from the bladder microbiomes

A total of 83 genera were identified as significantly differentially abundant between KS and U (Suppl. Table 2). Genera significantly more abundant in KS included *Chryseobacterium, Brevundimonas, Microbacterium, Acidocella, Rhodococcus, Brucella,* and *Flavobacterium*. *Chryseobacterium* showed the highest fold change (3.21) and was present in 94.29% of KS samples compared to 19.57% in U, while *Brevundimonas*, with a fold change of 3.07, was prevalent in 91.43% of KS samples vs 39.13% in U. *Acidocella* was exclusive to KS with a prevalence of 71.43% and a fold change of 2.67, and *Rhodococcus* had a fold change of 2.65 and minimal presence in U (4.35%). *Brucella* (fold change = 2.49) and *Flavobacterium* (fold change = 2.40) also demonstrated higher prevalence in KS samples compared to U. Genera enriched in U included *Reyranella, Acidovorax, Legionella, Dialister, Pajaroellobacter,* and *Sphingomonas*. *Reyranella*, with a fold change of –1.20, was exclusive to U (prevalence 45.65%) and absent in KS. *Pajaroellobacter* (fold change = –1.12) and *Dialister* (fold change = –1.11) were significantly more prevalent in U (45.65%) but nearly absent in KS (5.71% and

14.29%, respectively). *Acidovorax* (fold change = –0.92) and *Legionella* (fold change = –0.96) were more abundant in U, with prevalences of 43.48% and 43.48% in U compared to 20.00% and 17.14% in KS, respectively. Genera such as *Pseudomonas* and *Rothia* were prevalent in both KS and U. *Pseudomonas*, with a fold change of 1.30, was found in all KS samples and most U samples (80.43%), while *Rothia* had a fold change of 1.29, with a prevalence of 88.57% in KS and 67.39% in U, showing their shared presence across the two environments with differing abundances.

Supplementary material 3. Detailed comparison of the stones and upper urinary tract microbiomes

A statistical comparison of abundances between the KS and UT subgroups identified 63 genera with significantly differential abundance (Suppl. Table 3). Genera significantly more abundant in KS included *Chryseobacterium, Acidocella, Rhodococcus, Stenotrophomonas, Brevundimonas, Brucella*, and *Flavobacterium*. Among these, *Chryseobacterium* had the highest fold change (3.47) with a prevalence of 94.29%

Suppl. Table 1. *Differentially abundant genera identified between urinary tract (UT) and urinary bladder (U) samples. Fold change values represent the log-transformed differences in abundance between the two sites, with positive values indicating higher abundance in UT and negative values indicating higher abundance in U. Prevalence values denote the proportion of samples in which a genus was detected in UT and U. Statistical significance of differences is indicated by adjusted p-values (p.adj). Only genera with significant differential abundance (p.adj <0.05) are included*

Genera	Fold change	P.adj	Prevalence in UT	Prevalence in U
Burkholderia-Caballeronia-Paraburkholderia	2.565633892	1.72098E-06	0.736842105	0.130434783
Paracoccus	1.411790319	0.012691747	0.815789474	0.630434783
Knoellia	1.301327126	0.024068651	0.605263158	0.326086957
Halomonas	1.214140487	0.018947631	0.684210526	0.413043478
Micrococcus	1.211317282	0.029433537	0.526315789	0.239130435
Kytococcus	1.121385489	0.000814289	0.394736842	0.02173913
Cutibacterium	0.90135918	0.020088907	0.868421053	0.847826087
Brachybacterium	0.791113444	0.039981511	0.315789474	0.086956522
Vulcaniibacterium	–0.356003071	0.015217793	0	0.239130435
Amphiplicatus	–0.404596323	0.020088907	0	0.217391304
Belnapia	–0.433585296	0.015217793	0	0.239130435
Vibrionimonas	–0.449081028	0.010847507	0	0.260869565
Pyrinomonas	–0.482612415	0.020088907	0	0.217391304
SWB02	–0.516473493	0.010847507	0	0.260869565
Hyphomicrobium	–0.541708916	0.010847507	0	0.260869565
Bdellovibrio	–0.551736892	0.02559233	0.026315789	0.260869565
Lactiplantibacillus	–0.565887784	0.034087007	0.026315789	0.239130435
Negativicoccus	–0.568884428	0.033934981	0.052631579	0.304347826
Dorea	–0.594983496	0.046664474	0.052631579	0.282608696
Bacteriovorax	–0.606984377	0.010847507	0	0.282608696
Sediminibacterium	–0.639978722	0.010847507	0	0.260869565
Craurococcus–Caldovatus	–0.660770332	0.024068651	0.052631579	0.304347826
oc32	–0.812495577	0.002630734	0	0.347826087
Subdoligranulum	–0.987443855	0.010847507	0.052631579	0.391304348
Collinsella	–1.037913004	0.023463593	0.105263158	0.413043478
Pedomicrobium	–1.064147922	0.023463593	0.131578947	0.47826087
Legionella	–1.067759796	0.017870127	0.131578947	0.434782609
Pajaroellobacter	–1.121239796	0.000554967	0.026315789	0.456521739
Reyranella	–1.170141567	0.010847507	0.105263158	0.456521739

in KS and 7.89% in UT. *Acidocella* was exclusive to KS (71.43%, fold change = 2.67), while *Rhodococcus* showed high prevalence in KS (71.43%, fold change = 2.65) and minimal presence in UT (7.89%). Brucella and Flavobacterium were also predominantly found in KS with fold changes of 2.50 and 2.48, respectively. Genera enriched in UT included *Burkholderia–Caballeronia–Paraburkholderia, Methylobacterium–Methylorubrum, Sphingomonas*, and *Neisseria*. *Burkholderia–Caballeronia–Paraburkholderia* had the highest negative fold change (–2.42), with a prevalence of 73.68% in UT compared to 17.14% in KS.

Suppl. Table 2. *Differentially abundant genera identified between kidney stone (KS) and urinary bladder (U) samples. Fold change values indicate the log-transformed differences in abundance between the two sites, with positive values indicating genera more abundant in KS and negative values indicating genera more abundant in U. Prevalence values represent the proportion of samples in which each genus was detected in KS and U. Statistical significance of differences is represented by adjusted p-values (p.adj). Only genera with significant differential abundance (p.adj <0.05) are included in the table*

Genera	Fold change	Prevalence in KS	Prevalence in U	p.adj
Chryseobacterium	3.2116705	0.942857143	0.195652174	2.85507E-10
Brevundimonas	3.073119547	0.914285714	0.391304348	1.14766E-07
Microbacterium	2.772512469	0.828571429	0.173913043	4.84005E-08
Acidocella	2.668013939	0.714285714	0	1.93947E-09
Rhodococcus	2.653689711	0.714285714	0.043478261	3.88317E-08
Cloacibacterium	2.625373344	0.971428571	0.456521739	4.76809E-08
Brucella	2.494321134	0.685714286	0.065217391	1.14766E-07
Flavobacterium	2.397236254	0.857142857	0.195652174	1.7065E-07
Stenotrophomonas	2.212614186	0.885714286	0.434782609	0.000150813
Sphingobacterium	2.186430443	0.628571429	0.043478261	3.36807E-07
Achromobacter	2.105979253	0.714285714	0.152173913	1.38854E-05
Pleomorphomonas	2.085858923	0.685714286	0.130434783	2.25464E-06
Acinetobacter	2.051382239	0.942857143	0.565217391	0.000506055
Rheinheimera	1.958520646	0.657142857	0.108695652	1.61725E-05
Bifidobacterium	1.899770835	1	0.847826087	3.96337E-07
Paracoccus	1.802514783	0.942857143	0.630434783	0.000150813
Exiguobacterium	1.56390584	0.514285714	0.043478261	1.61725E-05
Nubsella	1.52999373	0.514285714	0.02173913	5.13849E-06
Halomonas	1.51508167	0.828571429	0.413043478	0.001678905
TM7a	1.434934312	0.542857143	0.086956522	6.72138E-05
Knoellia	1.429505908	0.742857143	0.326086957	0.00843816
Georgenia	1.338523685	0.514285714	0.130434783	0.000964618
Allorhizobium–Neorhizobium–Pararhizobiu–Rhizobium	1.318521377	0.6	0.326086957	0.011648865
Xanthomonadaceae family	1.316212	0.457142857	0.086956522	0.000337856
Roseomonas	1.302796164	0.485714286	0.086956522	0.000182306
Pseudomonas	1.302463828	1	0.804347826	0.002349899
Rothia	1.291573524	0.885714286	0.673913043	0.004913594
Leucobacter	1.225735993	0.428571429	0.02173913	6.51178E-05
Devosia	1.196823852	0.4	0.02173913	0.000150813
Massilia	1.180130774	0.571428571	0.217391304	0.00843816
Propionicimonas	0.870494661	0.371428571	0.043478261	0.001993679
Delftia	0.774295689	0.371428571	0.130434783	0.042655307

Suppl. Table 2. *Conntinued*

Genera	Fold change	Prevalence in KS	Prevalence in U	p.adj
Cupriavidus	0.747291896	0.342857143	0.043478261	0.002989659
Desulfovibrio	0.657012229	0.314285714	0.086956522	0.03113351
Romboutsia	0.654557733	0.314285714	0.065217391	0.017621913
Propionibacterium	0.628356832	0.314285714	0.02173913	0.001810523
Dyadobacter	0.625164731	0.314285714	0.02173913	0.001974176
Paucibacter	0.600618193	0.285714286	0.02173913	0.002867887
Tepidimonas	0.590020876	0.285714286	0.065217391	0.0223693
Carnobacterium	0.576140056	0.257142857	0	0.001810523
Rhodoferax	0.561642398	0.285714286	0.043478261	0.00940123
Pseudorhodobacter	0.494305972	0.257142857	0	0.001810523
Hydrogenophaga	0.409733591	0.228571429	0.043478261	0.046513227
Ethanoligenens	0.401709452	0.228571429	0.043478261	0.039223595
Fastidiosipila	–0.280427475	0	0.195652174	0.017745457
Bryobacter	–0.282419335	0	0.195652174	0.017745457
Vulcaniibacterium	–0.354612871	0	0.239130435	0.007834667
Colwellia	–0.393239838	0.028571429	0.217391304	0.040620772
Amphiplicatus	–0.401065647	0	0.217391304	0.011648865
Akkermansia	–0.402783446	0.028571429	0.239130435	0.025959845
Belnapia	–0.432100549	0	0.239130435	0.007834667
Peredibacter	–0.455240232	0	0.239130435	0.007834667
Facklamia	–0.473596826	0	0.217391304	0.011648865
Pyrinomonas	–0.482985906	0	0.217391304	0.011648865
SWB02	–0.5146612	0	0.260869565	0.004913594
Azospira	–0.537626956	0.028571429	0.260869565	0.018588907
Hyphomicrobium	–0.538716603	0.057142857	0.260869565	0.041688167
Herbaspirillum	–0.540555985	0	0.260869565	0.004913594
Ezakiella	–0.54544366	0.057142857	0.260869565	0.048607431
Pseudoalteromonas	–0.545622026	0	0.260869565	0.004913594
Negativicoccus	–0.566830451	0	0.304347826	0.001993679
Bacteriovorax	–0.605209909	0	0.282608696	0.003148905
UCG-005	–0.607679005	0.057142857	0.282608696	0.031288463
Nitrospira	–0.632520613	0	0.304347826	0.001993679
Sediminibacterium	–0.638539303	0	0.260869565	0.004913594
Craurococcus–Caldovatus	–0.658972973	0	0.304347826	0.001993679
oc32	–0.807842299	0	0.347826087	0.000866322
Acidovorax	–0.915988732	0.2	0.434782609	0.028438662
Legionella	–0.959035061	0.171428571	0.434782609	0.014560994
Dialister	–1.113775496	0.142857143	0.456521739	0.012132818
Pajaroellobacter	–1.119407187	0.057142857	0.456521739	0.000341973
Prevotella	–1.167234465	0.4	0.608695652	0.03312955
Reyranella	–1.199857463	0	0.456521739	6.21782E-05
Sphingomonas	–1.214094912	0.514285714	0.717391304	0.012540092

Suppl. Table 3. *Differentially abundant genera identified between kidney stone (KS) and urinary tract (UT) samples. Fold change values indicate the log-transformed differences in abundance between the two sites, with positive values indicating genera more abundant in KS and negative values indicating genera more abundant in UT. Prevalence values represent the proportion of samples in which each genus was detected in KS and UT. Statistical significance of differences is represented by adjusted p-values (p.adj). Only genera with significant differential abundance (p.adj <0.05) are included in the table*

Genera	Fold change	Prevalence in KS	Prevalence in UT	p.adj
Chryseobacterium	3.46688663	0.942857143	0.078947368	4.63575E-10
Acidocella	2.669233421	0.714285714	0	3.89843E-08
Rhodococcus	2.654898832	0.714285714	0.078947368	7.00224E-07
Stenotrophomonas	2.636540999	0.885714286	0.315789474	1.59025E-05
Brevundimonas	2.597381169	0.914285714	0.526315789	7.00224E-07
Brucella	2.495811373	0.685714286	0.026315789	4.78393E-07
Flavobacterium	2.479236113	0.857142857	0.157894737	6.7113E-07
Microbacterium	2.440391343	0.828571429	0.263157895	1.05557E-05
Allorhizobium–Neorhizobium–Pararhizobium–Rhizobium	2.077356841	0.6	0.105263158	0.000177466
Rheinheimera	2.034651026	0.657142857	0.052631579	1.72676E-06
Sphingobacterium	1.963246636	0.628571429	0.157894737	0.000200044
Cloacibacterium	1.930996987	0.971428571	0.631578947	2.21467E-05
Achromobacter	1.873136492	0.714285714	0.236842105	0.000156058
Pleomorphomonas	1.776893022	0.685714286	0.210526316	0.000491392
Bifidobacterium	1.646609985	1	0.894736842	6.7113E-07
Exiguobacterium	1.564856939	0.514285714	0.052631579	0.000128011
Nubsella	1.531127884	0.514285714	0.052631579	0.000136317
Georgenia	1.445199443	0.514285714	0.078947368	0.000585522
TM7a	1.436217791	0.542857143	0.052631579	3.86037E-05
Xanthomonadaceae family	1.31691846	0.457142857	0.078947368	0.001615258
Leucobacter	1.226174159	0.428571429	0	8.1207E-05
Massilia	1.212481214	0.571428571	0.210526316	0.016924381
Devosia	1.197100504	0.4	0.026315789	0.000439779
Roseomonas	1.17808901	0.485714286	0.131578947	0.006211497
Actinomyces	1.145635818	0.514285714	0.236842105	0.034653306
Delftia	0.896119648	0.371428571	0.105263158	0.021230122
Propionicimonas	0.870995787	0.371428571	0.052631579	0.007233498
Pseudomonas	0.762825183	1	0.921052632	0.033595977
Cupriavidus	0.747642846	0.342857143	0.026315789	0.002704921
Bosea	0.708675731	0.314285714	0.078947368	0.049900237
Desulfovibrio	0.657349077	0.314285714	0	0.001242685
Propionibacterium	0.628592401	0.314285714	0.026315789	0.006211497
Dyadobacter	0.625704984	0.314285714	0.026315789	0.005222672
Paucibacter	0.601058341	0.285714286	0	0.0022685
Tepidimonas	0.59089744	0.285714286	0.052631579	0.034653306
Carnobacterium	0.576566802	0.257142857	0	0.004456682
Rhodoferax	0.562161029	0.285714286	0	0.0022685
Pseudorhodobacter	0.495026862	0.257142857	0.052631579	0.047436718
Acidibacter	0.444519037	0.257142857	0.026315789	0.01364999
Ethanoligenens	0.401882603	0.228571429	0	0.007908786

Suppl. Table 3. *Conntinued*

Genera	Fold change	Prevalence in KS	Prevalence in UT	p.adj
Xanthomonas	–0.558094406	0.057142857	0.263157895	0.049900237
Neisseria	–0.683164107	0.057142857	0.289473684	0.025411934
Sphingomonas	–1.057472563	0.514285714	0.736842105	0.045896812
Methylobacterium–Methylorubrum	–1.554175049	0.657142857	0.894736842	0.001666787
Burkholderia–Caballeronia–Paraburkholderia	–2.424046693	0.171428571	0.736842105	1.05557E-05

Methylobacterium–Methylorubrum was also more abundant in UT (89.47%, fold change = –1.55) but less prevalent in KS (65.71%). *Sphingomonas* showed higher prevalence in UT (73.68%, fold change = –1.06) than in KS (51.43%), while *Neisseria* was significantly more common in UT (28.95%) compared to KS (5.71%). Genera such as *Cloacibacterium* and *Bifidobacterium* were found in both sites but were more prevalent in KS, with *Cloacibacterium* showing a prevalence of 97.14% in KS and 63.16% in UT, and *Bifidobacterium* universally present in KS and UT but slightly reduced in UT (89.47%). *Pseudomonas* was highly prevalent in both KS and UT, with a slight reduction in UT (92.11%, fold change = 0.76).

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ORIGINAL PAPER

UROLITHIASIS

A cross-language analysis of urolithiasis patient online materials: Assessment across 24 European languages

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Introduction Urolithiasis is a prevalent condition with several etiological factors, affecting up to 20% of the population and exhibiting high recurrence rates. Its strain on healthcare systems, exacerbated by high incidence and recurrence, often results in insufficient time for thorough diagnostics and counselling. Consequently, many patients seek easily accessible online sources of information. This study aimed to assess the readability and availability of online urolithiasis materials across 24 official European languages to compare readability across different source types.

Material and methods The phrase "kidney stones" was translated into all official European languages, and the first 50 search results for each language were retrieved. Non-functional websites, those requiring accounts or payments, and duplicates were excluded. Relevance was assessed using Google Translate to filter out results lacking medical information. Only patient-oriented materials were included for analysis. Obtained results were then classified by source category, and their readability was assessed using LIX formula.

Results A total of 723 articles were analysed. The English term yielded the highest number of results, followed by Spanish and Portuguese. Overall, the English articles performed best, being the only language with a mean LIX score below 40, which marks the threshold between "somewhat hard" and "hard" to read. Finnish, Lithuanian, and Hungarian materials had LIX scores significantly exceeding the threshold of 50, classifying them as "very hard to read" and among the most difficult to comprehend.
A subgroup analysis revealed no statistically significant differences across the source classification.

Conclusions Online materials on kidney stones are generally too complex for patients, limiting their understanding and treatment adherence. Simplification of patient-oriented materials along with artificial intelligence utilisation could enhance comprehension. Improved awareness may promote adherence to preventive measures and help reduce the incidence and economic burden of urolithiasis.

Key Words: urolithiasis ‹› kidney stones ‹› patient oriented materials ‹› readability

INTRODUCTION

Urolithiasis is a multifactorial condition with a complex aetiology influenced by genetic, metabolic, environmental, and dietary factors, as well as comorbidities and their corresponding treatments [1–4]. Consequently, the same diagnosis encompasses patients with widely varying prognoses, ranging from individuals with incidental, asymptomatic stones to those progressing to end-stage kidney disease (ESKD). Moreover, this condition is relatively frequent. Depending on the demographic, urolithiasis affects up to 20% of the population, with its incidence steadily increasing over the past 30 years [5, 6].

Furthermore, the risk of kidney stone recurrence reaches as high as 50% within five years of the initial episode/finished treatment [7].

In the aforementioned context, overloaded and often inefficient healthcare systems, already facing long waiting lists for endoscopic procedures, frequently lack the time needed for comprehensive diagnostics and counselling on the causes of urolithiasis [8]. This results in an increase of patients turning to easily accessible online sources when seeking information about their condition. Considering that nowadays the internet has become a critical tool in patient decision-making [9], the need for credible and reliable information is of utmost significance. In this regard, it is essential not only to provide materials with high-quality content but also to ensure they are easily comprehensible.

The term "health literacy" refers to an individual's ability to understand and effectively use health information [10, 11]. While online patient education resources play a significant role in shaping patient decisions, their readability often exceeds the general public's health literacy levels [12–15]. This gap is concerning, as these resources influence patients' expectations prior to treatment, their satisfaction afterward, and, in cases of long-term care, the quality of patient-doctor collaboration.

The main objective of this study was a multilingual analysis of the comprehensibility of online patient education materials (PEMs) on urolithiasis and an assessment of their availability in different languages. An additional objective was to compare the level of readability of these materials depending on the source.

MATERIAL AND METHODS

Search algorithm and data acquisition

This manuscript follows an already established study protocol [16–18]. First, in order to obtain search inputs, the phrase "kidney stones" was translated using Google Translate services into all official European languages. Subsequently, initial searches were conducted. Each phrase was looked up using Google Search Engine. The queries were conducted using Google Chrome browser in Incognito mode to exclude potential confounding effects of the authors' search history. For each search, the first 50 records have been retrieved and further verified. At first, sites that were not functioning and ones that required the creation of an account, payment, or download of its content were excluded. Duplicate entries were ruled out. Next, each record has been assessed for its relevance. Using Google Translate add-on for entire website translation authors rejected results that did not contain medical information. Personal blogs, internet forums and websites dedicated to alternative treatment methods were not analysed. Due to the inability to assess the readability metrics we excluded videos and infographics. Moreover, we did not include medication or supplement advertisements, together with resources addressing animal owners and veterinary medicine professionals. Lastly, since this study aimed to determine the readability of materials dedicated to patients, scientific articles and literature addressed to healthcare professionals were excluded. The remaining articles were subject for detailed analysis.

Definitions and source classification

To enhance clarity and provide a more comprehensive understanding of the conducted analysis, we provide detailed definitions outlining the criteria used to classify included PEMs. The materials included in the analysis were grouped by their language of origin and the provided definitions, facilitating a thorough examination.

Commercial publisher

This category includes materials created by websites that do not offer products or services directly. However, these sites have clear indicators of other monetisation methods, such as advertisements or the option for a paid subscription.

Medical journal

Electronic patient material was classified under the Medical Journal category if it met the following criteria: it was published on a medical or scientific journal website, the content was not intended for healthcare professionals, and the article was not scientific in nature.

Medical service provider

This category includes PEMs issued by urology clinics, group practices, individual practitioners, or portals offering specialists' consultation services. It also contains materials prepared by diagnostic centres or dietitians.

Foundations

Online materials were considered suitable for this category, if a domestic or international scientific organisation prepared them, for example, European

Association of Urology or National Kidney Foundation. Furthermore, the website could not provide any service or product nor any method of income generation, other than donations.

Retailers

Evaluated articles published by websites directly selling medication or supplements, alongside websites connected with physical pharmacies fell under the Retailers category.

Pharmaceutical companies

Patient materials with solely educational purposes issued by companies producing medication or instrumentation used for the treatment or prevention of urolithiasis were classified in this section. If the website offered a purchase option, it was classified as an "Retailer".
Sources providing reliable information about urolithiasis that could not be assigned to the aforementioned were categorised as "Other".

Readability assessment

Numerous statistical measures are available for assessing the readability of the analysed materials. However, most of these methods have been validated solely in English, which restricts their applicability for comparing results across different countries due to linguistic constraints. Consequently, the only statistical method suitable for evaluating materials in all official European languages was the calculation of the LIX score. Results interpretation was conducted in accordance with the scale proposed by Anderson [19]. Accordingly, scores below 20 are classified as very easy to comprehend, scores below 30 as easy, scores below 40 as somewhat hard, scores below 50 as hard, and scores below 60 as very hard to comprehend.
The content of the included websites was copied into Microsoft Word (version 16.89.1) using the paste as plain text function. Irrelevant parts of PEMs, such as authors' information, affiliations, advertisements, figures, hyperlinks, disclaimers, and contact information, were removed. Prepared materials were saved as separate files using the "Save as Plain Text" feature. Each text was subsequently copied and pasted into the online LIX calculator at https://haubergs.com/rix. The calculator computes the LIX score, the number of words, the number of sentences, and the average number of words per sentence. All metrics were saved for analysis. Each step of the described analysis has been conducted by two individual researchers. The obtained results were compared, and in the event of discrepancies, the data were re-evaluated.
The obtained LIX scores were organised according to the provided definitions. Their distribution was assessed using IBM SPSS software version 27.0.1.0, and descriptive statistics were calculated. The individual groups were compared using appropriate statistical tests, with statistical significance set at a p-value of <0.05.

Bioethical standards

Due to the nature of the study, the consent of the ethics committee was not required.

RESULTS

Prevalence and inclusion rate

A total of 723 articles were analysed for readability. The English term yielded the highest number of results, followed by Spanish and Portuguese. Notably, the number of hits obtained in English was 13 times greater than that for Spanish, underscoring the significant dominance of English-language materials. In contrast, the Finnish term garnered the fewest hits (5,840), followed by Irish and Estonian, which had 16,800 and 18,400 hits, respectively. The highest inclusion rate of 90% was observed for Bulgarian, Dutch, and English, with 45 articles included from the initial 50 results. Conversely, the Estonian and Irish searches exhibited the lowest inclusion rates at 22% and 10%, respectively. Table 1 provides a detailed overview of the number of websites included in the analysis, the search queries used, and the total number of hits obtained.

Readability by origin

Out of the 723 materials analysed, only one had a LIX score below 30, classifying it as "easy" to read. All other analysed PEMs had LIX scores exceeding 30. Overall, the English articles performed the best, being the only language group with a mean LIX score below 40, which marks the threshold between "somewhat hard" and "hard" to read. Following English, the best results were seen in materials written in Dutch (42 ± 6), Swedish (44 ± 6), and Danish (45 ± 5), though these scores were still notably higher, placing them in the "hard to read" category. By contrast, Finnish (68 ± 6), Lithuanian (65 ± 6), and Hungarian (63 ± 5) PEMs had the worst outcomes, with LIX scores that far exceeded the threshold of 50, classifying them as "very hard to read" and

among the most difficult to comprehend. Figure 1 presents the mean LIX score values for the PEMs, categorised by their language of origin.

Complexity and length

Materials in Bulgarian (87 ±77), German (79 ±47), and English (79 ±61) recorded the highest average sentence counts, while French (1,443 ±1,042), Bulgarian (1,389 ±1,179), and Romanian (1,371 ±1,197) had the highest average word counts per article. The highest words-per-sentence ratios were observed in Italian (22 ±4), Irish (21 ±4), and Greek (20 ±4), whereas Finnish (11 ±3), Lithuanian (13 ±2), and Dutch (13 ±3) had the lowest ratios. Interestingly, despite the low words-per-sentence ratios, which would suggest conciseness and high readability, Finnish and Lithuanian are among the languages with the highest LIX scores. Further details on word counts, sentence counts, and words-per-sentence ratios are provided in Table 2.

Readability by category

A subgroup analysis based on the classification of PEM sources revealed that medical journals have the highest average LIX score (62 ±7). In contrast, materials from foundations and "other" category displayed lower LIX scores of 51 ±11 and 51 ±8, respectively, suggesting that these articles may be more accessible to a broader audience. Additionally, pharmaceutical companies produce patient-directed materials with the highest average counts, averaging 77 ±79 sentences and 1,307 ±1,322 words. Conversely, articles published by foundations tend to be shorter, with averages of 58 ±66 sentences and 891 ±1,019 words, indicating a more concise and focused communication style. However, no statistically significant differences were observed among these groups. Figure 2 depicts mean LIX score in regard to the allocated category. This is followed by Table 3, which provides detailed metrics for each subgroup analysed.

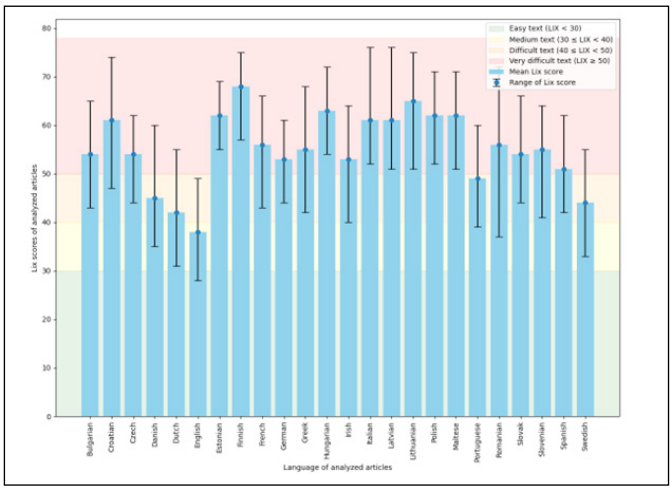

Figure 1. *Mean LIX score values for educational materials classified by language of origin.*

DISCUSSION

The internet has become one of the most common sources for information, especially when it comes to medical knowledge [20]. This is also true for patients suffering from kidney stones. However, stone form-

Table 1. *Overview of search terms, total number of hits and ratio of included materials*

Language	Search term	Total no. of hits	Included PEMs, n (%)
Bulgarian	камъни в бъбреците	630,000	45 (90)
Croatian	bubrežni kamenci	69,600	36 (72)
Czech	ledvinové kameny	79,600	25 (50)
Danish	nyresten	58,700	17 (34)
Dutch	nierstenen	155,000	45 (90)
English	kidney stones	99,900,000	45 (90)
Estonian	neerukivid	18,400	11 (22)
Finnish	munuaiskiviä	5,840	19 (38)
French	calculs rénaux	1,520,000	36 (72)
German	Nierensteine	1,180,000	35 (70)
Greek	πέτρες στα νεφρά	125,000	43 (86)
Hungarian	vesekövek	40,800	26 (52)
Irish	clocha duáin	16,800	5 (10)
Italian	calcoli renali	1,140,000	39 (78)
Latvian	nierakmeņi	90,900	23 (46)
Lithuanian	inkstų akmenys	76,200	39 (78)
Maltese	ġebel fil-kliewi	34,900	22 (44)
Polish	kamienie nerkowe	90,000	38 (76)
Portuguese	pedras nos rins	1,840,000	35 (70)
Romanian	pietre la rinichi	360,000	39 (78)
Slovak	obličkové kamene	56,700	25 (50)
Slovenian	ledvični kamni	26,400	22 (44)
Spanish	cálculos renales	7,690,000	34 (68)
Swedish	njursten	106,000	19 (38)

No. – number

ers often encounter various informational pitfalls. Although kidney stone disease may seem straightforward, it can stem from a range of issues, both metabolic and anatomical [1–5]. As a result, not all information found online applies to every individual case. This is further complicated by the spread of outdated information that contradicts current medical knowledge and is often presented in language that is difficult for non-medical professionals to understand [21].

The evaluation of the readability of Google-searched materials related to kidney stones showed that the level of comprehension of the texts exceeds what would be expected for materials designed for a broad readership. None of the tested languages achieved a LIX score at the "easy to read" level. Though English, according to the results, has the highest overall comprehensibility and favourable text structure; it is still classified as "a little hard to read" by the LIX score. Higher LIX ratings were assigned to articles written in Dutch, Swedish, Danish, and Portuguese, marking them as "hard to read". The articles in the remaining languages were classified as "very hard to read" due to their LIX ratings being higher than 50. Texts with such a high score are only comprehensible to readers with greater education. This is a challenge given that only approximately 30% of Europeans have a tertiary education [22]. The complexity of these articles undermines their primary goal: to provide inclusive access to information.

Although this study focused exclusively on urolithiasis, it is important to recognise that this issue is not limited to urology. Similar findings regarding poor readability of online materials have been observed in dermatology, gynaecology, and ophthalmology [16, 17, 23, 24]. The lack of easily accessible and understandable resources negatively impacts

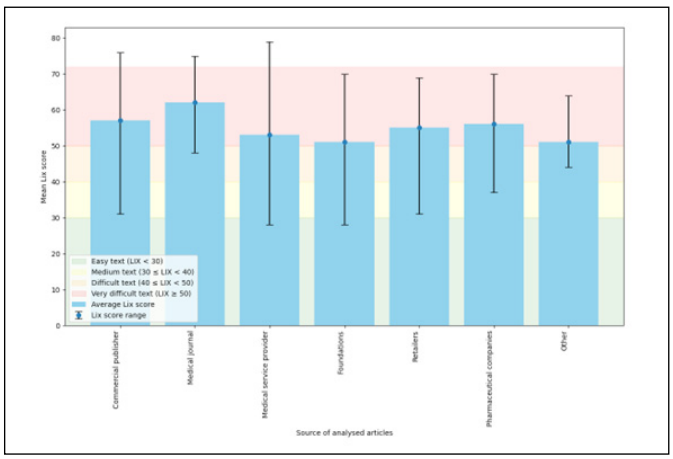

Figure 2. *Mean LIX scores by allocated category.*

Table 2. *Lix scores, word counts, sentence counts, and words per sentence ratios by language of origin*

Language	Lix score	No. sentences	No. words	Words/sentence ratio
Bulgarian	54 ±5	87 ±77	1,389 ±1,179	16±2
Croatian	61 ±6	50 ±32	805 ±481	17 ±4
Czech	54 ±5	74 ±50	979 ±686	15 ±4
Danish	45 ±5	55 ±37	797 ±475	16 ±2
Dutch	42 ±6	67 ±60	849 ±757	13 ±3
English	38 ±6	79 ±61	1,244 ±900	17 ±3
Estonian	62 ±4	40 ±13	564 ±177	14 ±3
Finnish	68 ±6	33 ±30	360 ±307	11 ±3
French	56 ±5	76 ±54	1,443 ±1,042	19 ±3
German	53 ±4	79 ±47	1,066 ±623	14 ±2
Greek	55 ±6	57 ±50	1,117 ±1,101	20 ±4
Hungarian	63 ±5	51 ±47	712 ±640	15 ±3
Irish	53 ±10	50 ±62	1,098 ±1,508	21 ±4
Italian	61 ±5	63 ±53	1339 ±1,,093	22 ±4
Latvian	61 ±7	52 ±34	765 ±459	16 ±4
Lithuanian	65 ±6	55 ±37	692 ±379	13 ±2
Maltese	62 ±6	31 ±23	446 ±273	15 ±4
Polish	62 ±4	71 ±36	1,014 ±503	15 ±3
Portuguese	49 ±5	48 ±24	871 ±426	19 ±3
Romanian	56 ±6	77 ±89	1,371 ±1,197	19 ±3
Slovak	54 ±6	59 ±47	775 ±538	14 ±3
Slovenian	55 ±6	53 ±52	801 ±717	16 ±3
Spanish	51 ±5	70 ±56	1,224 ±955	18 ±4
Swedish	44 ±6	78 ±49	1,122 ±710	14 ±4

No. – number

Table 3. *Detailed metrics by the category of PEMs*

Source	Lix score	No. sentences	No. words	Words/ sentence ratio
Commercial publisher	57±9	63 ±48	1,000 ±885	16 ±4
Medical journal	62 ±7	72 ±54	1,179 ±1,020	16 ±5
Medical service provider	53 ±10	62 ±53	976 ±752	17 ±4
Foundations	51 ±11	58 ±66	891 ±1,019	15 ±3
Retailers	55 ±7	72 ±45	1,079 ±651	16 ±4
Pharmaceutical companies	56 ±6	77 ±79	1,307 ±1,322	16 ±4
Other	51 ±8	69 ±27	1,028 ±430	15 ±3

No. – number

the treatment process. Additionally, difficult to read PEMs further contribute to healthcare disparities, as individuals with higher education and income are more likely to access and comprehend such information [25–27]. Unfortunately, this issue is exacerbated by those profiting from misinformation and false claims. A striking example identified in our analysis is the commercial sale of seahorse extract, falsely promoted as a preventive measure for kidney stones, which ranks among the top search results in Bulgarian. Lastly, social media have powerful impact over the younger generations. Unfortunately, they often present a skewed reality, further promoted by various media algorithms. Patients' perspective focuses mainly on negative and adverse events after the procedures, whereas the professional approach is often commercially oriented [28, 29]. As a result, misinformation prevails.

Publications like this are vital as they clearly highlight the problem while also identifying potential factors for improvement. In this case, a primary step would be to create materials that avoid complex vocabulary and paraphrase poorly evaluated sentences by statistical methods. Support from artificial intelligence could prove invaluable in this endeavour [30, 31]. Naturally, not every patient has the skills needed to effectively use the available large language models. In fact, these models often fail to generate accurate results [32]. However, content creators can leverage these tools to enhance readability without sacrificing the essence of their knowledge.

This study makes a significant contribution to the field by providing the first comprehensive analysis of urological PEMs across all 24 official European languages. It also presents a standardised approach to evaluating these materials based on their source. Nevertheless, our publication has certain limitations. First, we did not conduct a factual analysis of the content. The linguistic barrier and the absence of statistical methods suitable for such comparisons rendered this analysis unfeasible. We believe that thorough content analyses should be undertaken for each language individually, ideally by scientists and specialists in the field of endourology who are native speakers of the assessed languages. Only this approach can yield an adequate evaluation of the examined content. Second, while we analysed a substantial number of articles, our search was limited to results from the Google search engine. However, it is noteworthy that over 90% of internet users globally rely on this search engine, which lends some credibility to our findings [33]. Lastly, the readability assessment was conducted using only one statistical test. Unfortunately, this is the only measure validated in multiple languages [19, 34–36]. However, in studies that have examined the readability of PEMs using various tests, the results consistently align across different methodologies, demonstrating that the LIX score alone is a sufficient measure of readability [37].

CONCLUSIONS

The analysed online materials on kidney stones are overly complex for the intended audience, with only a portion of the English materials deemed acceptable. This complexity impedes patient understanding and hinder the treatment process. Simplifying the language and structure, along with leveraging artificial intelligence for content development, could help bridge this comprehension gap. Future research should focus on particular languages and their credibility to ensure the accuracy of the information provided. Improving patient awareness regarding their condition can improve adherence to healthy behaviours, ultimately contributing to a reduction in both the incidence and economic burden of kidney stones.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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REVIEW PAPER

UROLITHIASIS

Outcomes of ureteroscopy and laser lithotripsy with and without ureteral access sheaths for the treatment of renal calculi: A systematic review and meta-analysis

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Introduction The use of ureteral access sheaths (UASs) is an issue of contention among urologists, with their efficacy unclear in retrograde intrarenal surgery (RIRS). Therefore, we performed a systematic review and meta-analysis to assess RIRS with laser lithotripsy for the treatment of urolithiasis with and without the use of UASs.

Material and methods A systematic literature search was conducted in July 2023 using MEDLINE, EMBASE and the Cochrane library. The quality of the included studies was assessed using the Newcastle-Ottowa scale and Cochrane collaboration risk of bias tool. The primary outcome measures were stone-free rate (SFR), and post-operative complications. Secondary outcomes were operative time (OT), hospital length of stay (LOS) and ureteral injury rate. Effect sizes were calculated by pooled risk ratios (RRs) and mean differences (MDs) with confidence intervals (CIs).

Results In total, 16 studies met the inclusion criteria. There were 3,123 participants who had RIRS with a UAS and 1,478 without. Pooled analysis revealed no significant difference between groups in SFR (RR = 1.03, 95% CI: 0.99–1.07), complication rate (RR = 1.31, 95% CI: 1.00–1.73), ureteral injuries (RR = 1.13, 95% CI: 0.77–1.65) or LOS (MD = –0.01, 95% CI: from –0.08 to 0.11). OT was significantly longer in the UAS group (MD = 0.35, 95% CI: 0.01–0.7).

Conclusions The results of this meta-analysis demonstrate that the use of UASs during RIRS does not improve post-operative outcomes and is associated with a longer OT. While there are still times where the use of UASs may be beneficial, their routine use for patients undergoing RIRS is not currently indicated.

Key Words: urolithiasis ‹› endourology ‹› ureteral access sheath ‹› laser lithotripsy

INTRODUCTION

Urolithiasis is an increasingly prevalent and recurrent condition that poses a significant burden on both patients and healthcare systems worldwide, with a global incidence of approximately 10% [1]. The management of urolithiasis has evolved considerably over the years, encompassing a spectrum of interventions that range from conservative approaches to minimally invasive procedures [2]. One pivotal change in the field has been the introduction and widespread use of ureteral access sheaths (UASs) for patients undergoing retrograde intrarenal surgery (RIRS) [3].

RIRS with laser lithotripsy is a popular treatment modality for patients with symptomatic intrarenal calculi and is commonly performed with the ancillary aid of UASs [4]. The use of UASs gained popularity as they facilitate the repeated passage of flexible ureteroscopes to enable access to the proximal ureter and collecting system. This was particularly useful as the ureter was difficult to navigate with the first flexible ureteroscopes without the use of a guidewire. Although the ureter can often be easily

navigated under direct vision with modern-day flexible ureteroscopes, the reported benefits of UASs extend beyond merely navigating the ureter and include reduced rates of ureteral injury and reduced intra-operative intra-renal pressures, which likely lead to reduced post-operative infections. However, some studies have reported that UASs are associated with longer operative times (OT), increased healthcare costs and post-operative complications [5–7]. The conflicting results reported in the literature to date have prevented a global consensus on the role of UASs, and as a result their routine use remains controversial.

A previous systematic review and meta-analysis examined the outcomes associated with laser lithotripsy with UASs for the treatment of urolithiasis up to 2017, however a low number of included studies limit the reliability of the results [7]. Therefore, an updated pooled analysis of the literature is timely. The aim of this systematic review and meta-analysis is to quantify and compare the benefits and risks of UAS and non-UAS laser lithotripsy for the treatment of urolithiasis.

MATERIAL AND METHODS

Study design

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [8]. The protocol was registered in the PROSPERO database (CRD42023448523). The MEDLINE, Embase and Cochrane controlled trial databases were searched in July 2023. A combination of key words and MESH terms were used in the search string to identify all relevant studies. The search strategy is detailed in the supplementary material. No language or year of publication restrictions were placed on the search. The search was supplemented by searching the reference lists of selected articles as well as the grey literature through a Google Scholar search.

Eligibility criteria

Two authors (JC and SA) independently examined the search results, and disagreements on study selection were resolved through open discussion with the senior author (ND). Study selection was limited to randomised control trials (RCTs) and non-randomised comparative studies in which two independent groups received laser lithotripsy for the treatment of urolithiasis, one group with UASs, and a control group without. Participants with primary or recurrent renal stones, and with stones of any size and composition were eligible for inclusion. Studies were excluded if either arm had less than 10 participants, the population included non-adults, those with congenital urological anatomical abnormalities or active malignancy. Letters, review articles, laboratory studies, case reports, animal studies and journal supplements were also excluded.

Intervention

The intervention was laser lithotripsy with and without the use of UASs. All sizes, models and types of sheaths were considered. All types of laser modalities, as well as all durations of laser time were included. Studies were also included whether a basketing technique was used or not.

Outcome measures

The primary outcome measures were stone free rate (SFR), as determined by the trial investigators at any time using any modality or parameters, and post-operative complications using the Clavien-Dindo system as reported by the investigators, at any point in the post operative period. If complications were not reported in the Clavien-Dindo system, they were converted to a numerical value by the authors [9].

Secondary outcome measures included hospital length of stay (LOS), OT, and the rate of ureteral injury using the Post-Ureteroscopy Lesion Scale (PULS) as reported by investigators [10]. Where data in relation to outcomes of interest were omitted from the included studies, the corresponding authors were contacted directly in attempt to obtain this.

Risk of bias assessment

Studies were assessed for risk of bias using the Newcastle Ottawa scale for non-randomised studies and were considered high quality if they achieved a score of seven or higher [11]. The Cochrane collaboration risk of bias tool was used to critically appraise the RCTs [12].

Statistical analysis

Statistical analyses were conducted using STATA Statistical Software (STATA v17, College Station, Tx: StataCorp LLC). Results are reported as pooled risk ratios (RRs) with 95% confidence intervals (CIs) and mean differences (MD) with 95% CI for dichotomous and continuous outcomes respectively. When calculating risk ratios for binary outcomes, if a sit-

uation arose where no cases were reported in one of the groups, it was not included in the meta-analysis as to not skew the results [13]. A fixed-effects model was used when heterogeneity using I^2 was <50% and a random-effects model was used when I^2 was >50%, or when heterogeneity based on study design or outcome definitions was suspected.

RESULTS

Search results

The literature search yielded 807 potentially eligible studies, with two further papers being identified through other means (website, n = 1; citation searching, n = 1). Following removal of duplicates, 662 articles were screened by title and abstract, of which 50 were selected for full-text review. In total, 36 of these were excluded, resulting in 16 final studies. The reasons for study exclusion are outlined in the PRISMA flow chart (Figure 1).

Study characteristics and risk of bias assessment

The baseline characteristics of the included studies are presented in Table 1 [4, 14–28]. The studies that met the inclusion criteria were published between 2001 and 2023, and conducted in France [14], Italy [15], Spain [15], Argentina [16], Turkey [17–19, 24, 25, 28], UK [4], USA [20, 21, 27], Denmark [22], Romania [23] and India [26]. Sample sizes ranged between 47 and 1,808 patients. In total there were 3,123 participants who had RIRS with a UAS and 1,478 without. There were three RCT's, five prospective non-randomised comparative studies, and eight retrospective non-randomised comparative studies. Follow-up time for the outcomes of interest ranged from three days to 18 months. Multiple sizes of UAS were used with 12/14 Fr being the most common (n = 7; Table 1). None of the included studies used vacuum-assisted UASs. The most common definition for SFR was a lack of residual stone fragments >3 mm on imaging [4, 14–28]. Stone burden in mm^3, when reported, was similar between groups. In all cases where the type of laser was reported (n = 11), holmium laser was used.

The methodological quality of the included studies was generally good. The RCTs were of moderate to high quality with low risk of bias [15, 18, 26]. All of the included non-randomised studies had low risk of bias, scoring at least 7/9 on the Newcastle-Ottawa scale [11].

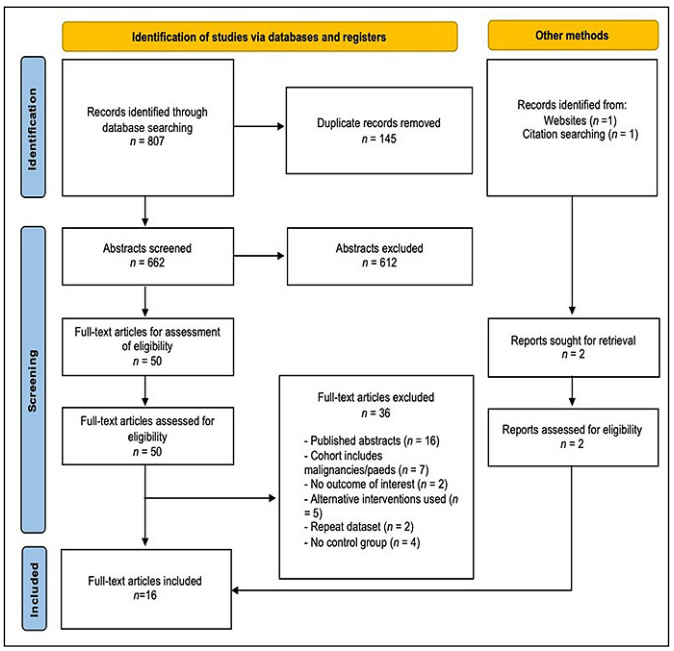

Figure 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies identified, excluded, or included in the review. There were three randomised controlled trials, five prospective studies, and eight retrospective studies.*

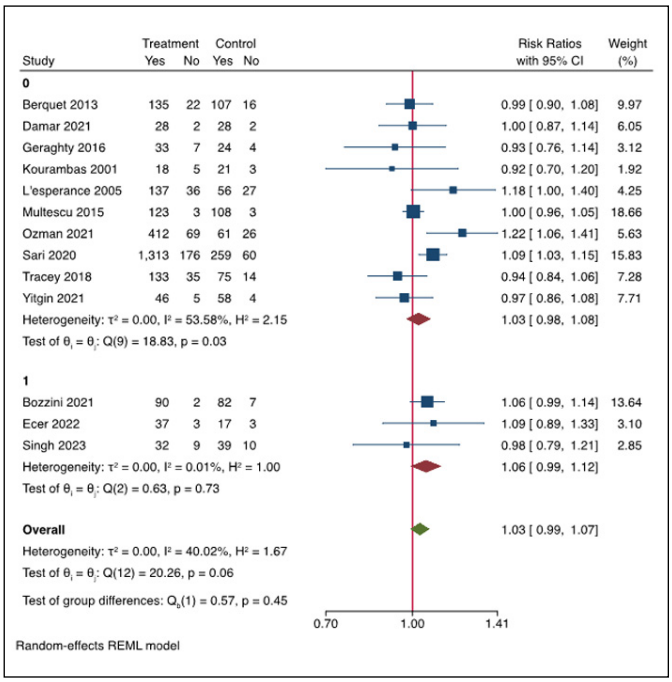

Figure 2. *Forest plots compare the stone-free rate for laser lithotripsy with and without ureteral access sheaths; (0) non-randomised control trials; (1) randomised control trials only. Procedures that used ureteral access sheaths were the reference approach, such that RR <1 indicated that procedures without a UAS have a lower SFR and RR >1 indicates that procedures without a have a higher SFR.*

CI – confidence interval; RR – risk ratio

Table 1. *Characteristics of studies comparing outcomes of laser lithotripsy with and without ureteral access sheaths*

Study and year	Study design	Country	SFR definition	Duration of follow-up	UAS Size	Sample size (n)	Patients per arm		Patient age (years)		Stone burden (mm)*	
							UAS	No UAS	UAS	No UAS	UAS	No UAS
Berquet et al. 2013 [14]	OBS	France	<3 mm	3 months	12/14 Fr	280	157	123	50	52	15.15 (9.8)	13.75 (8.0)
Bozzini et al. 2021 [15]	RCT	Italy, Spain	<3 mm	3 days	10/12 Fr	181	92	89	51.4	48.3	15.82 (4.12)	14.11 (4.89)
Cristallo et al. 2022 [16]	OBS	Argentina	NR	NR	12/14 Fr	241	43	198	54.1	53.2	11.5 (4.6)	9.2 (4.0)
Damar et al. 2021 [17]	OBS	Turkey	<3 mm	NR	9.5/11 Fr	60	30	30	49.6	48.4	NR	NR
Ecer et al. 2022 [18]	RCT	Turkey	<3 mm	14 days	9.5/13 Fr	60	40	20	47	50.5	13.65 (4.6)	14.95 (6.5)
Geraghty et al. 2016 [4]	OBS	UK	<2 mm	2–3 months	9.5/11 Fr 12/14 Fr	68	40	28	NR	NR	NR	NR
Karaaslan et al. 2019 [19]	OBS	Turkey	NR	NR	12/14 Fr	129	81	48	NR	NR	14.9 (5.7)	15.8 (6.0)
Kourambas et al. 2001 [20]	OBS	USA	NR	3 months	12/14 Fr	47	23	24	NR	NR	13.7	10.1
L'esperance et al. 2005 [21]	OBS	USA	NR	2 months	12/15 Fr	256	173	83	49	47	8.7	7.3
Lildal et al. 2018 [22]	OBS	Denmark	NR	NR	10/12 Fr	180	88	92	55	50	NR	NR
Mulţescu et al. 2015 [23]	OBS	Romania	NR	18 months	10/12 Fr	237	126	111	NR	NR	NR	NR
Özman et al. 2021 [24]	OBS	Turkey	<3 mm	1 month	10/12 Fr, 11/13 Fr	568	481	87	48.5	47.6	NR	NR
Sari et al. 2020 [25]	OBS	Turkey	<3 mm	2 months	11/13 Fr 9.5/11.5 Fr	1,808	1,489	319	46.2	44.9	15.6 (7.9)	12.53 (5.9)
Singh et al. 2023 [26]	RCT	India	<3 mm	1 month	9.5/11 Fr 12/14 Fr	90	41	40	39	39.1	14.7 (4.57)	15.3 (4.97)
Tracy et al. 2018 [27]	OBS	USA	TSB <100	3 months	12/14 Fr, 14/16 Fr	257	168	124	50.2	54	NR	NR
Yitgin et al. 2021 [28]	OBS	Turkey	<2 mm	3 months	10/12 Fr	113	51	62	45	46.1	NR	NR

*mm represents the mean diameter of stones noted on imaging of individual patients
NR – not reported; OBS – observational study; RCT – randomised control trial; SFR – stone free rate; UAS – ureteral access sheath

Outcome data

Stone-free rate

Thirteen studies reporting SFRs were included in the final meta-analysis. SFR as defined by the individual studies did not differ significantly between groups (Figure 2). A random effects model was used given the difference in definition of SFR and study designs, which generated a RR of 1.03, 95% CI: 0.99–1.07. There was moderate, but not significant heterogeneity among studies (Cochrane's $Q = 20.26$, $p = 0.06$, $I^2 = 40.02$).

Subgroup analysis of only RCTs is also presented in Figure 2. Again, no statistical difference was noted in the RR between UAS and non-UAS groups, with the pooled effect being 1.06, 95% CI: 0.99–1.12. There was no significant heterogeneity found in these studies (Cochrane $Q = 0.63$, $p = 0.73$, $I^2 = 0.01$). Further subgroup analysis of the difference in SFR based on UAS size (≤11/13 Fr compared to ≥12/14 Fr) showed no statistical difference (MD = 0.068 95% CI: from –0.10 to 0.24).

Operative time

Fourteen publications reported OT for both UAS and non-UAS groups (Figure 3). The mean OT was longer for the UAS group (60.7 ±18 minutes) compared to the non-UAS group (54.8 ±13.8 minutes), with a statistically significant mean difference (MD = 0.35, 95% CI: 0.01–0.7).

Subgroup analysis of RCTs only is also presented in Figure 3. The mean OT in the UAS group in RCTs was 48.98 ±11.42 minutes, and for non-UAS groups was 51.84 ±11.80 minutes. There was no significant difference between the groups (MD = –0.14, 95% CI: from –0.36 to 0.7).

Length of stay

Five studies reported LOS in both intervention and control groups as seen in Figure 3. The mean LOS for the UAS cohort was 1.45 ±0.41 days and was 1.48 ±0.38 days for the control group. The mean difference was not statistically significant (MD = –0.01, 95% CI: from –0.08 to 0.11).

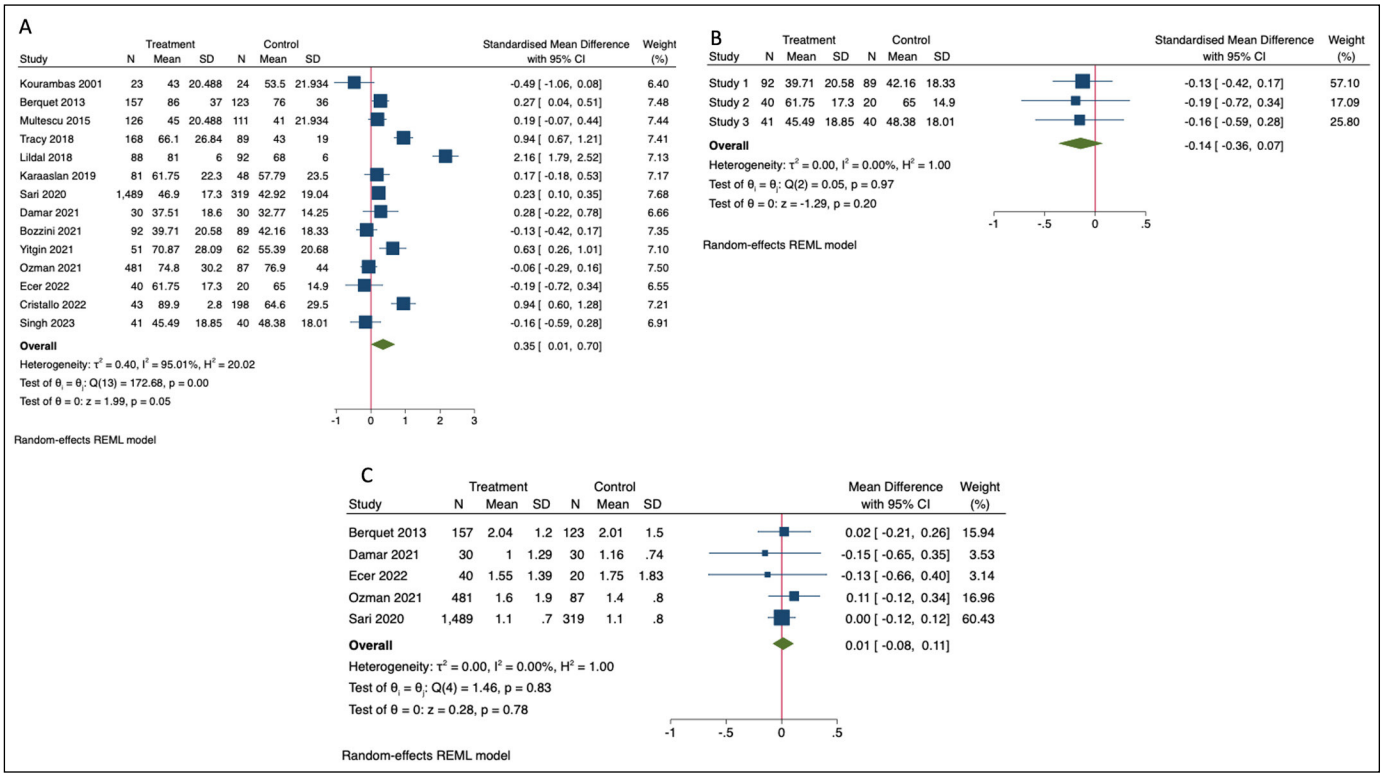

Figure 3. *Forest plots comparing standardised mean difference (SMD) in operations times for laser lithotripsy with and without ureteral access sheaths:* **A)** *all studies;* **B)** *randomised control trials; and mean difference in length of stay in hospital for patients undergoing laser lithotripsy with and without ureteral access sheaths.* **C)** *Procedures that did use ureteral access sheaths were the reference approach, such that a positive pooled value in SMD indicates the UAS cohort had a longer operation duration or LOS, and a negative result indicated the UAS group had a shorter operation duration or LOS.*

CI – confidence interval; N – number of participants per trial arm; SD – standard deviation

As only one RCT reported mean LOS a further subgroup analysis was not performed [18].

Clavien-Dindo complications

A total of twelve studies reported Clavien-Dindo complications. The meta-analysis of complication rates is presented in Figure 4. The overall incidence of post-operative complications was 13.4% in the UAS groups and 10.3% in the control groups. No statistically significant difference was seen between groups (RR = 1.10, 95% CI: 0.84–1.35).
A subgroup analysis was performed of RCTs only, and additionally found no significant difference in overall complications (RR = 1.97, 95% CI: 0.92–3.02). Further subgroup analysis of difference in complication rates based on UAS size (≤11/13 FR compared to ≥12/14 Fr) showed no statistical difference (MD = 0.37 95% CI: –1.40 to 1.48).

Post-Ureteroscopy Lesion Scale

Four publications reported PULS incidence. The overall incidence of ureteral lesions/injuries was 28.1% in the UAS group and 25.5% in the control group. A meta-analysis of the risk ratios of this data is presented in Figure 4. There was no significant difference in overall PULS incidence (RR = 1.13, 95% CI: 0.77–1.65).
A subgroup analysis of the two RCTs that reported PULS incidence also failed to demonstrate a significant difference between the two groups, as seen in Figure 4 (RR = 0.86, 95% CI: 0.62–1.19). Further subgroup analysis of difference in ureteral lesion rates based on UAS size (≤11/13 Fr compared to ≥12/14 Fr) showed a statistical difference in favour of smaller UASs (MD = 0.14, 95% CI: 0.09–0.19).

DISCUSSION

The incidence of urolithiasis is rising, and as such RIRS is being performed more commonly [2]. Although UASs have become routine ancillary endourological devices, there has been a paucity of robust evidence to support their use. This systematic review and meta-analysis provides a comprehensive review of post-operative outcomes such as SFR, OT, LOS, and post-operative complications, including all studies to date that compared laser lithotripsy with and without UASs in a well-matched cohort of urolithiasis patients.

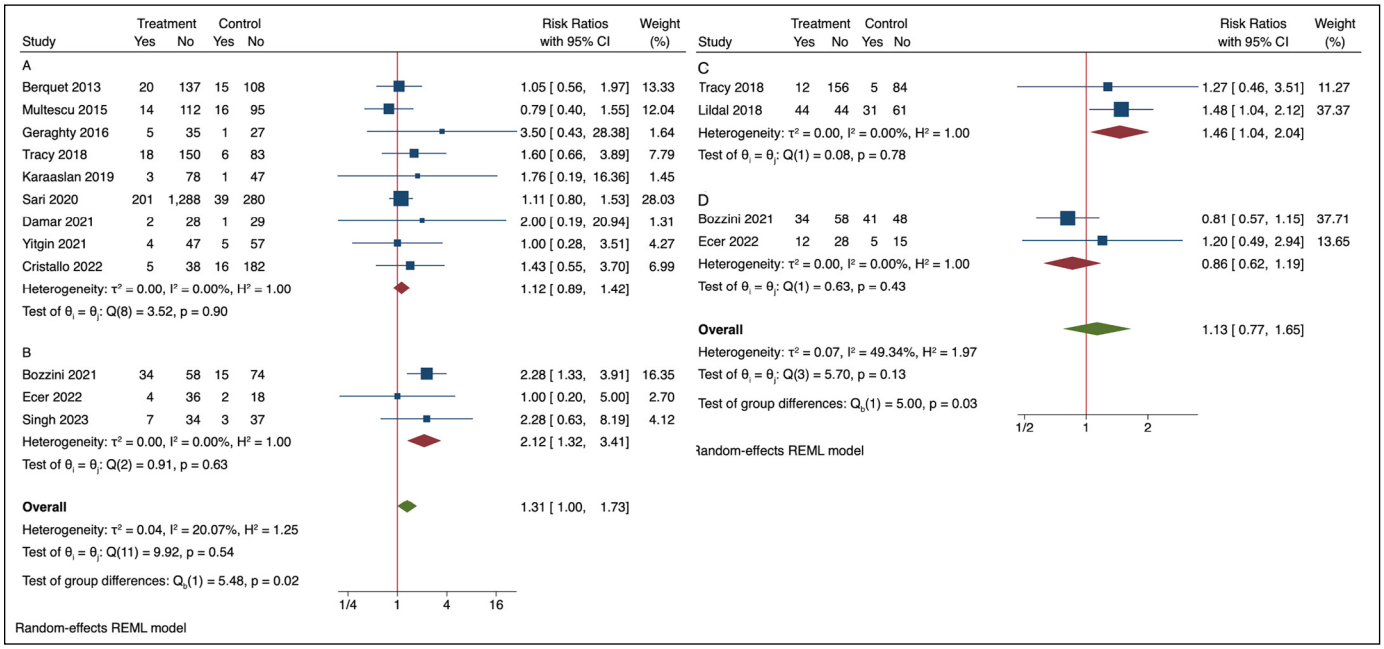

Figure 4. *Forest plots comparing Clavien-Dindo post-operative complication rates for patients undergoing laser lithotripsy with and without ureteral access sheath:* **A)** *all studies;* **B)** *randomised control trials only, and comparing ureteral injury rates for patients undergoing laser lithotripsy with and without ureteral access sheaths:* **C)** *for all studies;* **D)** *randomised control trials only. Procedures that used ureteral access sheaths were the reference approach, such that RR <1 indicated that procedures without a UAS have a lower post-op complication rate and RR >1 indicates that procedures with a UAS have a higher rate of post-op complications.*

CI – confidence interval; RR – risk ratio

The SFR was similar in both cohorts, with a pooled RR demonstrating no favourability towards one method over the other. A concordant literature review summarised that the use of UASs provides no clear benefit in terms of the success of RIRS for urolithiasis, attributing this to the advancement of laser therapy, as well as the downsizing of ureteroscopes [5]. A previous meta-analysis pooled the data until 2016 and reported comparable results; no significant difference in SFR, OT and LOS [7]. It has been hypothesised that the improved drainage associated with the use of a UAS can improve intra-operative visibility, however, the results of this meta-analysis have demonstrated that SFR are not significantly affected by the use of UASs, nor was the size of a given UAS used a determinant factor in the success of the procedure.

One limitation of our study is that we were not able to perform a subgroup analysis of SFR based on stone location. That said, an observational study by Berquet et al. 2014 found that stone location was not a significant factor in predicting SFR or post-operative complications in RIRS with the use of a UAS, but more research may be needed on this topic. There is no question that the use of UASs facilitates the repeated passage of ureteroscopes in cases where repeated basketing is required, and they also may provide some benefit in navigating anatomically challenging ureters. Interestingly, none of the included studies reported cases where the surgical technique was changed from not using a UAS to using one as a result of procedural difficulties. Some did report incidences where a UAS could not be safely placed and the procedure was therefore performed without one, suggesting that RIRS, when performed with modern-day flexible ureteroscopes, may be more easily performed without the use of a UAS compared to with one [4, 24]. However, access to the ureter was not a predefined outcome measure of any of the included studies, and so more studies are required to assess the impact of UASs on successful RIRS completion adequately.

While our study found an increased incidence of Clavien-Dindo complications in the UAS group, this difference did not reach statistical significance. Furthermore, we found that the size of the UAS used had no significant effect on the development of post-operative complications. These findings are in keeping with results from a previous meta-analysis, which concluded that post-operative complications were more prevalent in the UAS group [7]. There are however conflicting results reported in the literature, as many studies that report higher complication rates without the use of a UAS often find that UAS use reduces the risk of post-operative infection [15, 24, 29]. The likely explanation for this is the potential for reduced intra-operative pressures with the use of UASs. However, technological advances in ureteroscope diameter and laser technology allow modern RIRS for urolithiasis to be performed quicker and likely at lower intra-renal pressures. It is therefore unlikely that the routine use of UASs will reduce post-operative complications outside of specific cases, such as when repeated basketing is anticipated.

The rate of ureteral wall injury due to UAS placement has been reported to be as high as 46% [30]. Notably, the overall rate of ureteral wall injury was significantly lower in our systematic review, though this may be due to poor reporting of outcomes in the included studies. There was a higher rate of ureteral wall injury in the UAS group. However, this did not reach statistical significance. The lack of difference may be due to the experience level of the surgeons performing the procedure. The procedures were carried out by experienced urologists in the majority of the included studies, and perhaps a more significant difference would have been observed if the procedures were carried out by novice trainees. A subgroup analysis found a marginally higher incidence of ureteral lesions with smaller UASs, contrary to previous research, which demonstrated larger UAS size being associated with more ureteral lesions [31]. Though of note, only one study in this review reported ureteral lesions with the use of larger UASs (≥12/14 Fr), and therefore, this may be a limited representation of the actual distribution of ureteral lesions.

Our systematic review indicates that RIRS with laser lithotripsy can be performed safely and effectively without the use of a UAS. The main advantage of omitting routine UASs during RIRS is cost, as UASs can cost up to $300, and can contribute to nearly half the costs of a flexible ureteroscopy [32]. Furthermore, the shorter OT associated with omitting UASs may facilitate more procedures to be done in a similar timeframe. OTs are likely to be shorter in the non-UAS cohort because of the time needed at the beginning of the operation to insert the UAS. Our study found a difference of approximately 3 minutes in OT, favouring the non-UAS group, though it is unlikely that this would result in any clinical significance.

There are some important limitations to this meta-analysis to consider. Although the included studies were generally of high quality and low risk of bias, the majority of the included studies were

non-randomised, with only three RCTs satisfying the eligibility criteria. The included studies came from ten different countries, and regional differences may have been a confounder and skewed the data collected. Another important limitation is the lack of a standardised definition of SFR. There was no consistent method used for detecting residual fragments, and the follow-up times were generally poorly reported in the studies. Sepsis, pain, and intrarenal pressure as independent outcomes were infrequently reported in studies, so we were unable to do subgroup analyses between groups for these outcomes. Confounding factors that influence the risk of ureteral wall injury, such as prior RIRS or stenting, were poorly reported across the studies. Finally, our study did not examine the use of novel vacuum or suction-assisted or UASs, which research has suggested may improve SFR and decrease intra-renal pressure when compared to standard devices [33].

CONCLUSIONS

This study is the largest and most comprehensive systematic review and meta-analysis that assesses the role of UASs in RIRS for urolithiasis. No statistically significant differences in SFR, LOS or post-operative complications were seen. While there are specific instances where the use of UASs may help facilitate RIRS, this study suggests that, at present, there is insufficient evidence to support their routine use in the treatment of all patients with urolithiasis.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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ORIGINAL PAPER

TRAUMA AND RECONSTRUCTIVE UROLOGY

Comparison of MemoKath™ ureteral stent versus tumor ureteral stent: A single-center long-term analysis

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Introduction The MemoKath™-051 (MK) is a thermo-expandable spiral stent for the treatment of benign or malignant ureteral obstruction. Existing studies on outcome measurements, like complication rate or time to stent exchange for MK differ significantly. In this retrospective analysis, we investigated the supposed superiority of the MK over conventional tumor ureteral stent (TUS) insertion.

Material and methods In this monocentric retrospective analysis, 72 consecutive patients with benign or malignant extrinsic ureteral stenosis who either underwent insertion of a MK or TUS between 03/2008 and 12/2018 were analyzed. Indications for stent insertion were either chronic benign or malignant extrinsic obstruction in patients who were unsuitable for or refused definitive surgery. Patients who underwent urinary diversion were excluded. We compared the indwelling time, the complication rates and the time to occurrence of complications using Mann-Whitney-U-test and χ^2 test for categorical variables. Complication rates of both, the MK and the TUS were compared using Fisher´s test. Complications were classified according to Clavien-Dindo Classification (CDC).

Results The total number of ureteral units analyzed was 171, including 89 MK stents and 82 TUSs. No significant differences between both groups regarding age, stent indications, and stricture characteristics occurred. At a median follow-up of 32 and 27 months in the MK and TUS groups, postoperative complications occurred in 82 (92%) and 19 (23%) patients, respectively (p = 0.01). Almost all complications were major (CDC grade 3b) that required stent removal or replacement, with the exception of one patient in the MK group. Median time to complications was significantly longer for the MK group, 5.6 months, compared to 3.5 months in the TUS group (p = 0.01), and median time to stent replacement was 8 months for the MK group vs 5.2 months for the TUS group (p <0.001).

Conclusions Although the MemoKath™ is designed for a long indwelling time of up to years, it is associated with higher complication rates and premature replacement. However, compared to the TUS, the MK still has a significantly longer indwelling time. Further studies are needed to determine the predictors of failure and the best candidates for both stents.

Key Words: MemoKath™ stent ‹› tumour stent ‹› chronic ureteral obstruction

INTRODUCTION

Ureteral stents are often used as a palliative option for the treatment of patients with chronic ureteral obstruction due to either extrinsic (e.g., tumor compression, retroperitoneal fibrosis) or intrinsic causes (e.g., stricture, tumor) [1, 2]. The use of conventional polymeric double-J (DJ) stents for chronic obstruction is associated with high failure rates due to the lower resistance to compression, especially

in malignant obstruction. Moreover, a regular exchange in short periods is needed [2]. Thus, different types of metallic stents have been introduced to treat the chronic ureteral obstruction effectively and to avoid the drawbacks of conventional stent [3–5]. The MemoKath™ (MK) stent (PNN Medical A/S, Denmark) is one of the most commonly used metal stents. MK is a thermolabile ureteral stent that is inserted into the area of the ureteral obstruction in a non-expanded state and then expanded by flushing with warm saline solution. In principle, the MK can be used for several years and only needs to be replaced in the event of complications. Theoretically, this leads to a lower number of necessary interventions per patient, thus increasing the quality of life and reducing the burden of operations and costs [6]. However, the recent literature on MK stents is inconsistent with regard to the complication rates, indwelling time, and mostly smaller patient groups with a limited follow-up period have been studied [7–13]. Another type of ureteral stent that can be used for the treatment of chronic ureteral obstruction is the so-called tumor stent (TUS), a polymeric stent with a reinforced middle section that can withstand external compression and remain in place for up to 1 year. Moreover, it could be inserted easily like the regular DJ stent. A recent large study involving 556 reinforced stents showed their efficacy in the treatment of malignant obstructions [14]. In the present study, we aimed to compare the results of the MK vs TUS regarding their complication rate and indwelling time.

MATERIAL AND METHODS

We retrospectively reviewed medical records for patients who received a ureteral stent either as a permanent MK or TUS between March 2008 and December 2018. The indication for stent insertion was either chronic benign or malignant obstruction in patients who were unsuitable for or refused definitive surgery. Patients who underwent urinary diversion were excluded.

MK was used routinely in our center until December 2018. From 2018, we changed our policy and started to routinely use only the TUS (7F, Coloplast, Denmark). According to the manufacturer, the recommended indwelling time can be up to 1 year for the TUS. We used to replace the TUS every 9 months or if the patient developed complications. MK stents are permanent ureteral stents, which were only removed if complications such as obstructions by incrustations or stent dislocations occurred. After stent fixation, the patients underwent regular follow-up examinations using abdominal and renal sonography, urinalysis and renal function at the outpatient clinic. In the event of complications such as progressive hydronephrosis, deterioration in renal function or recurrent urinary tract infections (UTIs), patients were readmitted for removal or replacement of the stent. All procedures were performed inpatient under general anesthesia. Only patients with available complete follow-up data were included in the analysis.

A linear regression analysis was performed to examine the relationship between patient characteristics and stent type with time to stent removal.

Data collection

We retrospectively recorded preoperative patient data regarding age, gender, side of obstruction, and indication for surgery. The intraoperative findings regarding the length of the obstruction and the localisation of the stricture within the ureter (upper, middle, lower third of the ureter) were also recorded. Postoperative complications were recorded and categorized according to the Clavien-Dindo Classification (CDC) system [15]. The time until the occurrence of complications and removal of the stent was analyzed. The time to stent removal in TUS was calculated from insertion to replacement of the stent, either regularly or due to the development of complications.

Statistical analysis

Demographic and clinical data of all patients were analyzed descriptively using Student's t-test, Mann-Whitney U-test, and χ^2 test for categorical variables. Complication rates of both, the MK and the TUS were compared using Fisher´s tests and confidence intervals. A p-value of ≤ 0.05 indicated significance. All statistical analyses were performed using SPSS software version 26 (Chicago, IL, USA).

Bioethical standards

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and after written informed consent of the patients. The study was approved by Institutional Ethics Board of the University Duisburg-Essen (approval number 21-9863-BO).

RESULTS

Between March 2008 and December 2018, either MK or TUS was inserted in a total of 72 patients (34 men and 38 women) and 171 ureteral units

(UUs) at our hospital. MK and TUS were used in 89 (52%) and 82 (48%) UUs, respectively. The median age in the MK group was 70 years, significantly higher than in the TUS group at 60 years (p = 0.001). Most patients in the MK group were female (63%), while men were predominant in the TUS group (66%) (p = 0.013). Ureteral stents were inserted in 60% of patients on the right and 40% on the left. The stent was mostly used for benign indications (66%), including intrinsic strictures of different etiologies, after radiotherapy, endometriosis, and retroperitoneal fibrosis, while the remaining patients received ureteral stents for malignant obstruction. The length of the obstruction was <5 cm and ≥5 cm in 55% and 45%, respectively. The localisation of the obstruction was mostly the mid-third of the ureter (45%), followed by the distal and upper ureter (39% and 16%, respectively). There were no significant differences between the two groups in terms of side, cause, length, and location of ureteral obstruction (Table 1). Surgical outcomes was shown in Table 2.

In the MK subgroup, the median time to stent removal was 8.3 months compared to 7.5 months for benign and malignant indications, respectively (p = 0.8). Similarly, no significant difference was found in the TUS subgroup: The median time to stent removal was 5.7 months compared to 4.5 for benign and malignant cases, respectively (p = 0.55). In univariable analysis, MK was only seen to be associated with longer indwelling time (Table 3).

At a median follow-up of 32 and 27 months in the MK and TUS groups, postoperative complications occurred in 82 (92%) and 19 (23%) patients, respectively (p = 0.01). Median time to complications was significantly longer for MK group 5.6 months compared to 3.5 months in TUS group (p = 0.01). The most common major complication in both groups was stent occlusion, which occurred in 47 (53%) patients in the MK group and in 13 (16%) in the TUS group. Other complications such as stent dislocation (29.2%), stone formation (2.2%) and UTI (6.7%) were also reported in the MK group, whereas only UTI (7.3%) was reported in the TUS group. All complications in both groups were Clavien grade IIIb that included stent removal or replacement, with the exception of one complication in the MK group, which was UTI managed with antibiotic treatment only (Clavien grade II). Finally, in the TUS subgroup, 63 (77%) stents were exchanged in the regular time span (6–9 months) without harboring any complications. Nineteen (21%) ureteral units were still being treated with the initial MK at the time of the data analysis, and a total of 35 units (39%) received the MK for ≥12 months. The median time to stent removal or replacement was 8 months for the MK group vs 5.2 months for the TUS group (p <0.001). Supplementary Figure 1 shows the flow chart of the treated partners. By analyzing complication rates within the first nine months, as this is the maximum indwelling time of the tumor stent, a significantly higher complication rate was reported in the MK group, 53 (60%), compared to 19 UUs (23 %) in the TUS

Table 1. *Patient demographics*

Parameter	MK (n = 89)	TUS (n = 82)	p
Age (years), median (IQR)	59.5 (48–71.7)	69.5 (59–75)	0.001
Sex, n (%)			0.013
Male	33 (37)	54 (66)	
Female	56 (63)	28 (34)	
Side of obstruction, n (%)			0.62
Right	53 (60)	49 (60)	
Left	36 (40.4)	33 (40)	
Causes of ureteral obstruction, n (%)			0.36
Malignant	29 (32.5)	29 (35.3)	
Post radiotherapy	20 (22.4)	10 (12.2)	
Benign	40 (45)	43 (52.5)	
Stricture length, no. (%)			0.76
<5 cm	39 (43.8)	38 (46.3)	
≥5 cm	50 (56.2)	44 (53.7)	
Stricture site, n (%)			0.1
Upper ureter	20 (22.5)	9 (11)	
Middle ureter	35 (39.3)	41 (50)	
Distal ureter	34 (38.2)	32 (39)	

Table 2. *Surgical outcome*

Parameter	MK (n = 89)	TUS (n = 82)	p
Median follow-up, months (IQR)	31.8 (13–71.2)	27 (19.2–23.5)	0.02
Total complications, n (%)	82 (92)	19 (23)	0.01
Stent occlusion	48 (53.9)	13 (15.9)	
Stent dislocation	26 (29.2)	0	
Stone formation, patients	2 (2.2)	0	
UTI, patients	6 (6.7)	6 (7.3)	
Complications within first 9 months, n (%)	53 (59.6)	19 (23)	<0.001
Stent occlusion	31 (34.8)	13 (15.9)	
Stent dislocation	17 (19.1)	0	
Stone formation, patients	1 (1.1)	0	
UTI, patients	4 (4.4)	6 (7.3)	
Median time to complications (months)	5.6	3.5	<0.001
Median (IQR) time to stent removal, months	8 (2.3–20.7)	5.2 (3–7.1)	<0.001

UTI – urinary tract infection

(p = 0.01). In the TUS group, all patients underwent stent replacement due to complications, while in the MK group, 11 patients received a temporary nephrostomy tube, one patient underwent nephrectomy due to loss of kidney function, and one patient in the MK subgroup underwent ureteral reimplantation with psoas-hitch.

DISCUSSION

The MK ureteral stent was introduced in the treatment of ureteral strictures as a palliative treatment for non-operable patients in order to avoid high failure rates associated with regular DJ ureteral stents and, consequently, aimed to reduce the frequency of stent replacements [8, 9]. The studies available to date have shown variable results in terms of complication rates and indwelling time; moreover, there have been no studies comparing the results of the MK stent with another commonly used stent for the treatment of chronic obstructions, the TUS.

A recent review linked certain materials to stent-related symptoms, offering contradictory conclusions, and the majority of research does not specify the precise properties of the materials utilized [16]. Most patients in the MK group (92%) in our study experienced complications at a median follow-up of 5.6 months. In addition, complications in the MK group always required removal or replacement of the stent, and sometimes a temporary nephrostomy tube is required. By analyzing the complication rates within the first nine months, as this was the maximum time for the routine TUS replacement in our cohort, 60% developed complications compared to 23% in the TUS (p = 0.01). However, despite the higher complication rate in the MK group, MK was still associated with longer indwelling time than TUS. The median time to stent removal was 8 months for MK vs 5.2 months for TUS (p <0.001), and 39% received MK for ≥12 months.

However, the complication rate in our cohort is higher. In particular, the median indwelling time of the MK group in our study is significantly lower than expected in some previous reports, reporting complication rates between 25 and 70% and a median time to removal between 5 months and 4 years [7, 8, 10, 13, 17]. This large difference in complications and indwelling time between studies may be related to the retrospective nature of the studies and the differences between the centers in the included patients, follow-up protocols, and frequency of postoperative physical and radiographic examinations. Thus, comparing results between different studies is difficult, and the evidence regarding MK stents is still lacking. Klarskov et al. [8] published the results of MK in 33 patients with 37 stents in 2005. They reported stent malfunction requiring replacement in 22/37 (60%) stents after a median time of only 5 months, comparable to our study's early stent replacement. In addition, the median follow-up time for 15 stents that remained in place and did not require replacement was relatively short at 14 months (range 3–30 months) [8]. Papatsoris et al. [13] published a large cohort of 102 MK stents. After a median follow-up of 17 months, the authors reported complications in 26 (25%) patients, including stent manipulation due to dislocation in 15 patients and stent removal due to blockage in 5 patients. The cost of using MK stents was associated with annual savings of $7,539 from the second year after fixation compared with the cost of regular DJ replacement. However, the median follow-up time in this study is short, and 14% of patients experienced spontaneous resolution of the stricture, so the stents were removed after a median follow-up time of 9 months; this subset of patients was considered a success [13]. Recently, Forster et al. [7] published the largest series of MK stents with 100 patients who received 162 stents, while two researchers independent of the surgeons examined the long-term results. They reported a comparable high complication rate as in our study: at a mean follow-up of 5 years, a complication rate of 72% was found. The median time to first complication was

Table 3. *Univariable analysis of factors influencing stent indwelling time*

Variable	Coefficient (95% CI)	p
Age	–0.64 (from –0.21 to 0.08)	0.47
Gender		
Female	Ref.	0.95
Male	0.15 (from –4.5 to 4.5)	
Side		
Right	Ref.	0.46
Left	1.7 (from –2.8 to 6.2)	
Causes of ureteral obstruction		
Benign	Ref.	0.38
Malignant	–2.1 (from –6.9 to 2.68)	
Stricture length		
<5 cm	Ref.	0.18
≥5 cm	3 (from –1.4 to 7.5)	
Stricture site		
Upper ureter	Ref.	
Middle ureter	0.99 (from –3.54 to 5.53)	0.66
Distal ureter	0.07 (from –4.5 to 4.7)	0.97
Stent type		
TUS	Ref.	<0.001
MK	9.4 (5.1–13.6)	

MK – MemoKath™; TUS – tumor ureteral stent I am running a few minutes late; my previous meeting is running over.

12.5 months, and according to the Kaplan-Meier curve, the median stent life was 14.5 months.

Taken together, stent removal time in our cohort was shorter as in the studies of Forster et al. [18] and Moskovitz et al. [19] (using Allium stents), however comparable to Papatsoris et al. [13] (median 9 months).

Complications after MK stent insertion are usually major and require either removal, adjustment or replacement, which is considered to be the major disadvantage of MK stenting. In the present study, stent occlusion (54%) and dislodgement (30%) were the most commonly reported complications in the MK group, while stone formation (2.2%) and UTI (6.7%) occurred to a lesser extent. However, it is important to acknowledge that complications in the MK subgroup are more severe as compared to regular stenting, as 11 patients received a temporary nephrostomy tube before new stent insertion and one patient underwent nephrectomy due to loss of kidney function. Papatsoris et al. [13] reported 26 complications, including 57% stent dislocations, 20% stent occlusions and 23% UTIs. Similarly, Forster et al. [7] reported 46% stent migration, 34% obstruction, followed by lower rates of renal function loss, urosepsis and other complications including 1 postoperative mortality.

The factors influencing the outcome of MK have not yet been well studied in the literature. Agrawal et al. [12] tried to identify predictors of stent migration by comparing 13 patients who experienced stent migration to a control group including 61 patients without stent migration, no relationship was observed between stent migration and stricture related characteristic. Bier et al. [11] found that the median time to stent removal was longer in patients with adequate renal function than in patients with renal insufficiency (386 vs 317 days; $p = 0.007$) and in patients with active malignancy compared to benign disease (455 vs 190 days; $p = 0.006$). Otherwise, no further correlations were found between stent failure and patient and stricture characteristics. In contrary, Forster et al. [7] reported lower complication rate (62.7% vs 85.4%, $p = 0.04$) and longer mean indwelling time (14.5 months vs 13.4 months, $p = 0.02$) for malignant compared to benign obstruction. Further prospective studies on factors affecting outcome of MK are still needed. Taking into account the lower survival rates in patients with malignant obstruction and the longer indwelling time of MK compared to TUS, MK may be more suitable for such patients with malignant obstruction.

The outcome of TUS in our study is comparable with the largest series of tumour stent in the literature: Vogt and Blanchet [14] reported 23% failure rate at a mean of 4.4 months in a study including 556 tumour stents. One of the main disadvantages of the TUS, which we have not analyzed, is stent-associated urinary symptoms. Maan et al. reported severe urinary symptoms in 32% of DJ-stent patients compared to only 5.6% of MK patients. In the TUS group, 67% of patients reported stent-associated bother, like urinary symptoms, compared to 35% of MK patients. In addition, physical pain and impairment of daily activities were significantly higher in the TUS group. Finally, the patients were in favor of the MK stent for future stent insertion. However, it is worth noting that a subset of 10 patients who underwent MK stenting after TUS reported no improvement in pain or urinary symptoms [14]. Aziz et al. [20] reported a significant improvement in urinary symptoms after MK fixation in a small series of 16 patients who underwent MK stenting after DJ stenting for chronic ureteral strictures. The available findings indicate a better quality of life in favor of the MK stent, which is a significant advantage compared to TUS [20].

The strength of the study is the long follow-up period after application of the MK vs TUS system, and the significantly higher number of ureteral units compared to other studies. Another strength of this study is the utilization of the MK stent in a real-world scenario and comparing the MK and the more common tumour ureteral stent. Our study has limitations. First, its retrospective nature and small sample size limit further subanalyses on subgroup differences. This retrospective analysis was not powered to identify statistically significant differences between the two subgroups. Another limitation is that in our analysis, we compared the MK stent to the more common TUS and no other long-lasting stents, as Allium or Resonance stents. In addition, we did not examine other important factors, specifically changes in renal function that were measured by renal scintigraphy, stent-related symptoms, and costs. Further larger and/or prospective studies on this topic are still needed.

CONCLUSIONS

The MK was superior to TUS in terms of median time until stent replacement. However, there is a significantly increased risk of complications and time to MK exchange or removal is significantly shorter than reported in previous studies. These findings limit the anticipated advantages of the MK and should be taken into consideration. At least, patients should be informed that regular follow-up after MK insertion is mandatory.

CONFLICTS OF INTEREST

Boris Hadaschik: advisory boards for Janssen, Bayer, ABX, Lightpoint, Amgen, MSD, Pfizer, Novartis. Invited speaker for Accord, Astellas, Janssen R&D. Honoraria from Uromed. Research funding from AAA/Novartis, Bristol Myers Squibb, and German Research Foundation. Leadership roles for DKG AUO and DGU.
Jan Philipp Radtke: consulting – Saegeling Medizintechnik, Novartis, AAA, Dr. Wolf, Beckelmann und Partner: financial and non-financial donation – Astellas, Bayer, Janssen Pharmaceuticals, MedCom, Saegeling Medizintechnik, Philips Invivo, Bender Gruppe, Apogepha, AMGEN, Ipsen, Astra Zeneca; Clinical Studies – Janssen Pharmaceuticals, Bayer, Novartis AAA, SPL-01.
Christopher Darr: personal fees from Janssen-Cilag, IPSEN and travel fees from Janssen-Cilag, IPSEN and Bayer.
Ulrich Krafft: Grants to the author or organization: BMS, Novartis, Advanced Accelerator Applications. Personal fees: Janssen, Flatiron, MSD.
The other authors declare no conflict of interest.

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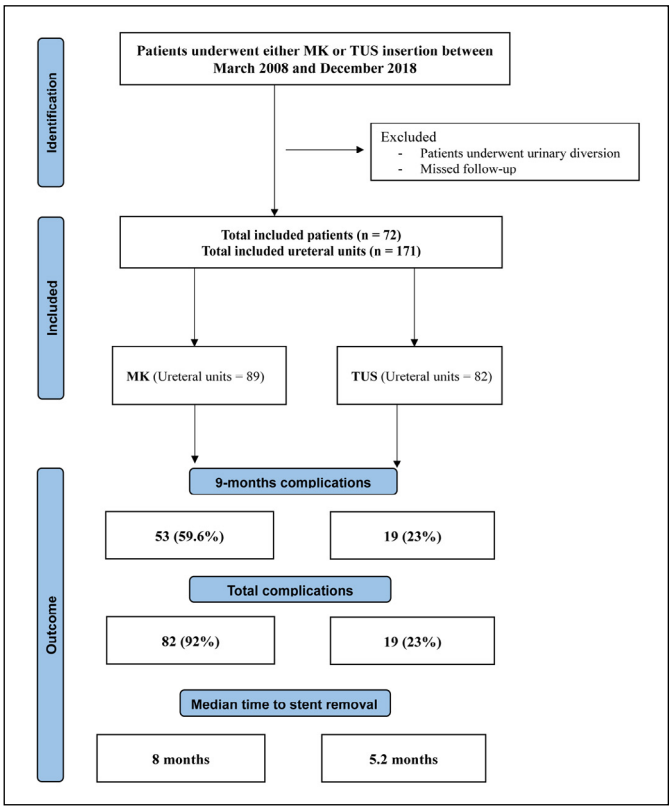
ETHICS APPROVAL STATEMENT

The study was approved by Institutional Ethics Board of the University Duisburg-Essen (approval number 21-9863-BO).

SUPPLEMENTARY MATERIAL



Suppl. Figure 1. *Flow chart of treated patients.*

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ORIGINAL PAPER

TRAUMA AND RECONSTRUCTIVE UROLOGY

Balancing technology and resources: Is robotic pyeloplasty always necessary?

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Introduction Ureteropelvic junction obstruction (UPJO) hinders urine flow from the renal pelvis to the ureter, causing renal dysfunction. Treatment focuses on relieving obstruction to restore urinary drainage and preserve renal function. Robotic-assisted laparoscopic pyeloplasty (RALP) offers enhanced precision compared to laparoscopic pyeloplasty (LP), but limited comparative data exist for adult patients. This study compares RALP and LP outcomes in an adult cohort from a tertiary care centre.

Material and methods A retrospective cohort analysis was conducted on adult patients who underwent RALP or LP between March 2018 and May 2024. Primary outcome measures included operative time, with secondary outcomes such as estimated blood loss (EBL), hospital length of stay (LOS), complication rates, and success (defined by symptom relief and diuretic renogram improvement). Statistical analysis included Mann-Whitney, χ^2, and Fisher's exact tests, with a significance threshold of $p < 0.05$.

Results The study included 128 patients (87 RALP, 41 LP). Operative time was significantly longer for RALP (200.92 ±59.26 minutes) vs LP (161.92 ±55.21 minutes, $p < 0.001$), largely due to robotic docking. Both groups had similar EBL (47.87 ml for RALP vs 45 ml for LP, $p = 0.45$) and success rates (97.7% for RALP vs 97.4% for LP). However, RALP patients experienced a longer LOS (3.91 days vs 3.41 days, $p = 0.001$).

Conclusions RALP demonstrates technical advantages but does not reduce operative time and incurs increased resource utilisation compared to LP. Both techniques achieve high success rates, though further research is needed to assess RALP's cost-effectiveness.

Key Words: UPJO ‹› PUJO ‹› pyeloplasty ‹› laparoscopy ‹› robotic

INTRODUCTION

Ureteropelvic junction obstruction (UPJO), a condition impeding urine flow from the renal pelvis to the ureter, is predominantly caused by congenital anomalies. However, acquired factors such as calculi and surgical history also play a role. Affecting 1 in every 1,000 to 2,000 live births, it manifests in symptoms ranging from acute renal colic to persistent lumbar pain, haematuria, recurrent urinary tract infections (UTIs), and secondary hypertension. Early identification using ultrasonography, contrast-enhanced computed tomography (CT), and diuretic renography is critical to preventing long-term renal dysfunction, as these techniques assess both renal function and the degree of obstruction [1] In addition to these imaging modalities, MR urography has been increasingly used in some centres to delineate anatomical details and assess kidney function [2]

The primary goal of UPJO treatment is to alleviate the obstruction, promote urinary drainage, and preserve renal function. While minimally invasive procedures such as laparoscopic pyeloplasty (LP) have gained widespread traction, the advent of robotic-assisted laparoscopic pyeloplasty (RALP) has introduced enhanced precision and dexterity through robotic technology [3]. However, despite the rising interest in RALP, much of the comparative literature focuses on paediatric populations, leaving a paucity of data on adult patients [4]. Moreover,

the inconsistency of findings related to operative efficiency, resource utilisation, and long-term outcomes warrants further scrutiny, especially within the adult cohort. This study, therefore, seeks to address this gap by presenting the largest adult cohort comparison of RALP and LP within a tertiary care setting. Furthermore, a focus on the learning curve and cost-effectiveness of each technique is critical for establishing their roles in clinical practice.

MATERIAL AND METHODS

We conducted a retrospective cohort study of all adult patients who underwent either RALP or LP at our institution between March 2018 and May 2024. Patient demographics, clinical presentations, and perioperative data were meticulously reviewed from medical records.

Inclusion criteria encompassed patients presenting with flank pain, recurrent UTIs, obstructive patterns on diuretic renography, renal stone formation, or progressive decline in renal function. Exclusion criteria included patients with advanced renal failure, those unfit for surgery due to comorbidities, and cases with previous failed pyeloplasty. Patients were assigned to RALP or LP based on surgical team preference, patient-specific factors (e.g., anatomical complexity), and resource availability. The surgeons' choice also depended on the availability of the robotic system on the surgery day.

Surgeon experience: All procedures were performed by two experienced urologists, each with over 10 years of experience in laparoscopic surgeries. One surgeon had performed over 100 robotic surgeries, while the other had equivalent laparoscopic experience but was newer to robotic surgery, reflecting the inherent learning curve.

Primary outcome measures included intraoperative time, while secondary outcomes assessed, hospital length of stay (LOS), estimated blood loss (EBL), complication rates, and overall procedural success. Success was defined by symptomatic relief and improvement on diuretic renograms at 6–12 months postoperatively. Operative times were measured from the first incision to the final closure, and perioperative complications were classified according to the Clavien-Dindo grading system.

Surgical procedure

Both groups underwent Anderson-Hynes dismembered pyeloplasty via an intraperitoneal approach. In the RALP group, the 4-arm da Vinci Xi system was utilised, while the LP group followed a standard 3-port technique. Right-sided pyeloplasties necessitated an additional port for liver retraction. All anastomoses were completed using 3-0 polyglactin 910 sutures, with an antegrade double-J (DJ) stent placed in all patients. The DJ stent used in all patients was of 6 Fr diameter, placed antegrade during surgery. The 6F stent was specifically used as it is our institutional policy. Foley catheters were removed postoperatively after 24–48 hours, and drainage tubes were removed once output decreased below 50 ml/day.

Follow-up

Postoperative follow-up occurred one week after surgery, including clinical evaluation and routine blood and urine tests. Ureteric stents were removed 4–6 weeks postoperatively, and follow-up diuretic renograms were performed at six-month intervals thereafter.

Statistical analysis

Continuous variables were compared between RALP and LP groups using the Mann-Whitney test, while categorical variables were analysed with the χ^2 or Fisher's exact test. A two-sided p-value of less than 0.05 was deemed statistically significant, and all analyses were conducted using SPSS software (version 23, IBM, Chicago, IL).

Bioethical standards

Ethical approval was obtained from the Institutional Ethics Committee under approval number IECA/2024/09/021, and informed consent was secured from all participants before the study commenced. The manuscript has been prepared in strict observation of the research and publication ethics guidelines. All studies, including human subjects or data, have been reviewed and approved. Principles embodied in the Declaration of Helsinki (2013) for all investigations involving human materials have been followed.

RESULTS

A total of 128 patients were included, with 87 undergoing RALP and 41 receiving LP. The baseline characteristics, including demographics and clinical presentations, were comparable between the two groups (Table 1).

In the RALP group, unique presentations included one patient with a horseshoe kidney and another with UPJO secondary to genitourinary tuberculosis, while the LP group had one patient with a malrotated kidney.

Operative time was significantly longer in the RALP group (200.92 ±59.26 minutes) compared to the LP group (161.92 ±55.21 minutes, p <0.001). Robotic docking/undocking accounted for an average of 25 minutes, indicative of the learning curve associated with robotic surgery (Figure 1). Although docking time was noted to average 8–15 minutes in experienced hands [8], the observed prolongation here reflects the surgeons' earlier phase of the robotic learning curve. EBL between the two groups was comparable (47.87 ml in RALP vs 45 ml in LP, p = 0.45). The median LOS was notably longer in the RALP group (3.91 days) compared to LP (3.41 days, p = 0.001), though both groups demonstrated similar high success rates (97.7% in RALP vs 97.4% in LP). Notably, no conversions to open surgery were required (Table 2).

Success rates were high in both groups (97.7% in RALP vs 97.4% in LP), and no conversions to open surgery were required. Clavien-Dindo complications were minor (Grade I–II) in 4.6% of RALP patients and 7.3% of LP patients, reflecting the safety of both techniques.

DISCUSSION

UPJO represents one of the most common causes of upper urinary tract obstruction in both pediatric and adult populations. Surgical intervention, primarily pyeloplasty, remains the definitive treatment for this condition. The emergence of minimally invasive techniques, such as LP and RALP, has transformed the management of UPJO. Our study aimed to compare these two approaches in terms of operative time, success rate, LOH, and postoperative complications, thus contributing to the growing body of literature on this subject [5, 12, 14, 15].

The findings of our study align with previous research in highlighting the advantages and limitations of both LP and RALP. LP, introduced in the

Table 1. *Showing the demographic characteristics and clinical presentation of the patients*

Demographics, characeteristics	RALP (n = 87)	LP (n = 41)
Median age [years (range)]	31 (15–58)	18/21
Sex (male/female)	37/50	18/21
Side (left/right/bilateral)	34/53/3	16/23/0
Presentations		
Pain	65	28
UTI/dysuria	29	13
Haematuria	6	2
Incidental finding	0	0
Crossing vessels (%)	30 (34.5%)	14 (35.9%)
Concomitant stones (%)	3 (3.4%)	1 (2.6%)
Previous procedures: PCN	6 (6.7%)	5 (12.8%)
DJS	6 (6.7%)	2 (5.1%)

DJS PCN
UTI

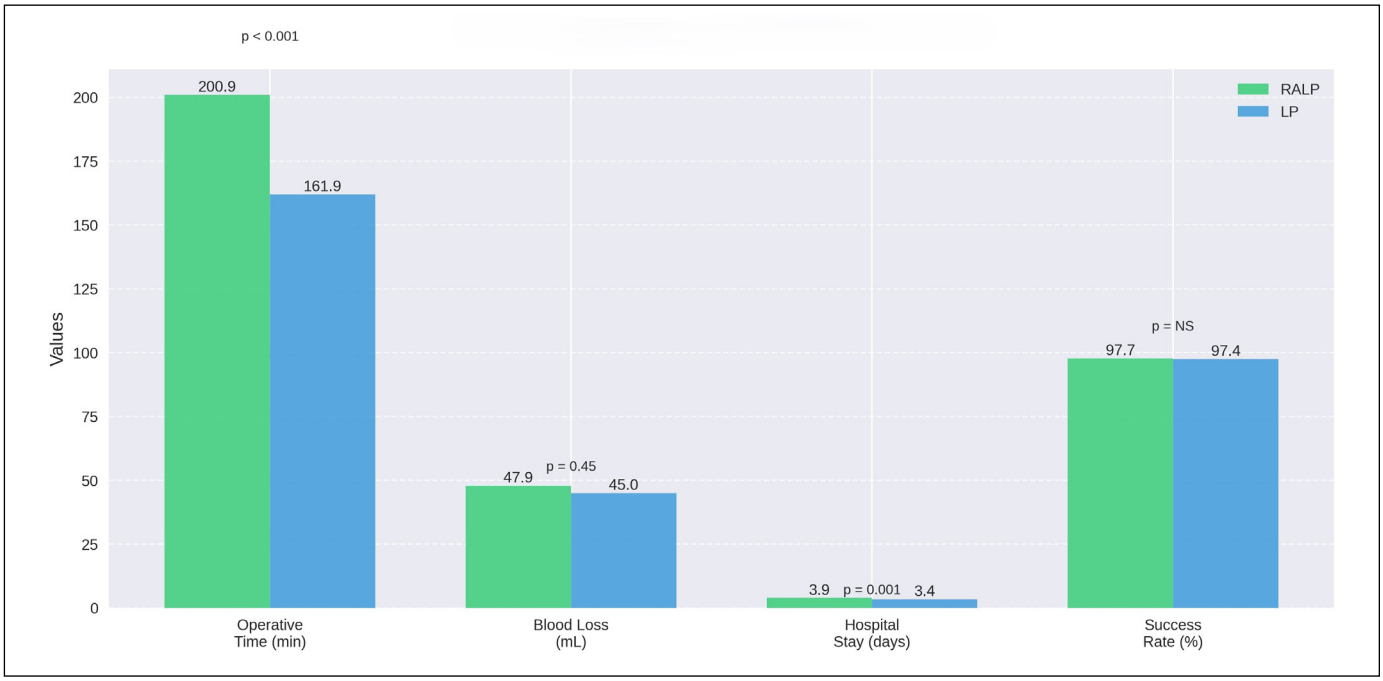

Figure 1. *Comparison of parameters between robotic and laparoscopic pyeloplasty.*

1990s, has been well-established as a minimally invasive approach with excellent success rates (Jarrett et al. [13], Hemal et al. [4]). RALP, introduced later, leverages robotic technology to improve precision and ergonomics during complex reconstructive procedures. While RALP has gained popularity in recent years, particularly in high-volume centres, the debate continues over whether its increased cost is justified by improved outcomes [4, 13].

One of the primary areas of comparison in our study was operative time. Our results indicate that RALP had a slightly shorter operative time than LP. This observation aligns with studies by Autorino et al. [3] and Link et al. [6], which reported reduced operative time with RALP due to enhanced dexterity, improved visualization, and shorter suturing times. However, the operative time in both approaches varies significantly depending on the surgeon's experience, highlighting the role of the learning curve. Studies by Guven et al. [9] and Singh et al. [22] emphasize that the learning curve for RALP tends to plateau more quickly than for LP. Our study's results corroborate these findings, suggesting that RALP may offer greater efficiency as surgeons gain experience, potentially reducing intraoperative complications and improving patient outcomes.

While the robotic docking process generally requires less than 10 minutes in experienced hands, our study reported an average of 25 minutes for docking and undocking, reflecting the surgeons' relative position on the robotic learning curve. Both operators were proficient in laparoscopic surgeries of the kidney and pelvis; however, the surgeon newer to robotic surgery required additional time for familiarisation with robotic console dynamics, especially during critical steps like precise dissection and intracorporeal suturing. Notably, the operator's relative inexperience with robotic controls may have mitigated the perceived advantage of robotic systems in tissue dissection and anastomosis. The extended operative time can thus be attributed to the combined effects of the robotic learning curve and case complexity, as some RALP patients presented with unique anatomical challenges, such as horseshoe kidneys or tuberculosis-associated UPJO.

Table 2. *Showing the outcomes and comparison between the two groups*

Outcome	RALP (n = 87)	LP (n = 41)	p
Mean docking/undocking time [min]	25 (10–27)	–	–
Total operative time [min, range]	200.92 ±59.26	161.92 ±55.21	<0.001
EBL [ml, range]	47.87 ±22.69	45.0 ±0.45	0.45
Hospital stay (days)	3.91 ±0.85	3.41 ±0.85	<0.001
Post-op complications (Clavien-Dindo grade)	3 (3.4%)	2 (4.87$)	
Success rate	85 (97.7%)	38 (97.4%)	

In terms of success rates, our study revealed no significant difference between LP and RALP. Both techniques demonstrated high success rates comparable to those reported in earlier literature (Minnillo et al. [10]; Zargar et al. [13]). This supports the notion that surgical technique, rather than the modality used, is the most critical determinant of success. However, RALP offers advantages in cases with complex anatomy or recurrent UPJO, as highlighted by Yang et al. [11] and Hung et al. [17], where the superior articulation and visualization of robotic instruments facilitate precise reconstruction.

The LOS in our study was slightly shorter for RALP compared to LP, though the difference was not statistically significant. This finding is consistent with systematic reviews by Bragga et al. [7] and Ball et al. [8], which also noted minimal reductions in hospital stay with RALP due to faster postoperative recovery. However, this modest reduction must be weighed against the higher cost of RALP, which remains a contentious issue. Our study observed a statistically significant increase in the LOS for RALP patients compared to LP patients (3.91 vs 3.41 days, $p = 0.001$). However, the discrepancy is relatively small (0.5 days) and could be attributed to postoperative protocols, including delayed mobilisation, prolonged observation due to perceived risks associated with the learning curve of robotic surgery, and owing to the small sample size in the cohorts. Optimising perioperative care, including enhanced recovery after surgery (ERAS) protocols, could help mitigate this issue. Standardising postoperative pathways, including earlier catheter and drain removal, may also reduce LOS, ultimately offsetting costs associated with robotic surgery.

Studies by Akbulut et al. [21] and Chang et al. [24] demonstrate that while RALP is associated with higher initial costs, these may be offset by reduced complication rates, shorter recovery times, and fewer readmissions over the long term. Our study underscores the need for a comprehensive cost-benefit analysis, particularly in low-resource settings, to determine the most appropriate modality for UPJO repair.

Postoperative complications in our study were comparable between the two groups, which aligns with the findings of multiple studies (Autorino et al. [3]; Molina et al. [10]) that report low complication rates for both LP and RALP. The robotic approach may offer a slight edge in reducing the likelihood of suture-related complications due to its precision, but this difference is not clinically significant. Moreover, studies by

Gundeti et al. [15] and Tan et al. [16] emphasize the safety and feasibility of both approaches in pediatric populations, further underscoring their versatility.

Another important consideration is the impact of surgeon expertise on outcomes. Link et al. [6] and Singh et al. [22] highlight that the learning curve plays a critical role in determining operative time, complication rates, and overall success. LP requires advanced laparoscopic skills, particularly for intracorporeal suturing, which can be challenging for less experienced surgeons. Conversely, RALP's intuitive controls and three-dimensional visualization may shorten the learning curve, making it more accessible for urologists without extensive laparoscopic experience. Our study confirms that surgeon experience is a key variable, regardless of the chosen modality, and emphasizes the importance of adequate training and mentorship programs.

Several studies have also explored long-term outcomes of LP and RALP. The meta-analysis by Bragga et al. [7] and long-term follow-up studies by Minnillo et al. [10] and Gettman et al. [25] demonstrate durable success rates for both techniques, with minimal risk of recurrence. These findings are consistent with our results, which showed no significant difference in long-term outcomes between LP and RALP. However, Yang et al. [17] suggest that RALP may offer better outcomes in highly complex cases, an observation that warrants further investigation.

Our study contributes to the growing body of evidence supporting both LP and RALP as effective options for UPJO repair. While RALP offers advantages such as shorter operative times, a potentially faster learning curve, and improved ergonomics for the surgeon, these benefits must be balanced against the significantly higher costs. Conversely, LP remains a cost-effective option with comparable success rates and outcomes, particularly in resource-constrained settings. The choice of modality should be individualized, taking into account patient factors, surgeon expertise, and institutional resources [18–21, 23].

In conclusion, while our study reinforces many of the findings in existing literature, it also highlights important nuances, such as the role of surgeon expertise and the need for cost-effectiveness analyses, in determining the most appropriate approach for UPJO repair. Future research should focus on randomized controlled trials with larger sample sizes and more extended follow-up periods to further delineate the comparative advantages of LP and RALP. Additionally, efforts to make robotic technology more affordable could help bridge the gap in accessibility, particularly in low- and middle-income countries.

This study has several limitations that warrant discussion. Firstly, there was an inherent selection bias for RALP patients, as inclusion depended on patient-specific factors such as anatomical complexity, which may have influenced both operative times and outcomes. Secondly, the study's retrospective design limits its ability to establish causal relationships. Thirdly, the operators' varying experience with robotic systems contributed to prolonged operative times, underscoring the impact of the robotic learning curve. Finally, the economic implications of robotic surgery in resource-constrained settings were not comprehensively addressed, which is an area requiring further investigation through cost-benefit analyses.

CONCLUSIONS

RALP represents a promising advancement in urological surgery, yet its prolonged operative times and heightened resource utilisation may limit its broader application, especially in settings where robotic technology is less accessible. LP, by contrast, remains an equally effective but less resource-intensive option, with comparable success rates. As the landscape of minimally invasive surgery evolves, future research must continue to evaluate the long-term value of RALP, particularly in light of its cost implications and the potential for optimising patient outcomes across various healthcare environments.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

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ETHICS APPROVAL STATEMENT

The study was approved by the Institutional Ethics Committee under approval number IECA/2024/09/021.

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VIDEOABSTRACT

VIDEOSURGERY

Video can be found at https://www.ceju.online/journal/2024/robotassisted-surgery-2419.php

Robot-assisted pyeloplasty with direct pyelo-ureteral anastomosis for retrocaval ureter

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Key Words: robot-assisted surgery ‹› indocyanine green ‹› robot-assisted pyeloplasty ‹› direct pyelo-ureteral anastomosis ‹› retrocaval ureter

Retrocaval ureter (RU) is a congenital venous anomaly due to an uncommon inferior vena cava (IVC) course and consequent entrapment and obstruction of the right ureter. It is caused by non-regression of the subcardinal vein forming the post-renal IVC segment, from the 4th to 7th weeks of pregnancy.

According to the literature, RU has a very low prevalence, which was found to be around 0.13%. The Bateson and Atkinson classification based on preoperative imaging identifies two types of RU: S-shape also called "fishhook sign" (type I) in which the obstructive syndrome is due to a intrinsic anomaly in the development of the retrocaval segment of the ureter requiring surgical resection and Sickle shape (type II) in which the obstruction is due to extrinsic compression of a normal ureter in its retrocaval portion, and for which the plasty is possible without resection. When the patient is symptomatic (flank pain, hematuria, or urinary infection) with a preserved renal function, a surgical correction is mandatory for ureteral uncrossing and continuity restoration.

We accomplished a robot-assisted right RU correction with direct pyelo-ureteral anastomosis in a 31-year-old Caucasian girl presenting with right flank pain.

The patient was first placed in a lithotomic position, therefore a right ureteral catheter was placed below the obstruction. Subsequently, the patient was placed in left flank decubitus. Robotic surgery was performed by an experienced robotic surgeon, using DaVinci Xi platform, in 3 arms configuration, with intraperitoneal approach according to the following surgical steps: incision of the right paracolic gutter along the Told line, medialization of the ascending colon and duodenum, opening of Gerota's fascia, identification and dissection of the right ureter and inferior vena cava; retrograde injection of Indocyanine green trough the ureteral catheter; identification of the retrocaval tract of the right ureter using Firefly mode; completion of the dissection of the right ureter; resection of the retrocaval stenotic tract; spatulation of the proximal ureter, placement of JJ ureteral stent, pyelo-ureteral anastomosis using two semicontinuous 5/0 running suture, leak test through infusion of carmine indigo via bladder catheter with verification of absence of urinary leakage, reperitonealization, placement of periureteral drainage.

Overall operative and console time were 150 and 90 minutes, respectively. Estimated blood loss was <50 ml. No intra-operative or post-operative complication was observed and the patient was discharged

on the 5th postoperative day. The JJ stent was removed 30 days after surgery. Follow up at 60 days after surgery demonstrated a complete resolution of symptoms and reduction of the hydronephrosis.

Robot-assisted RU correction is a feasible and safe surgical procedure for surgeons with previous experience in robotic renal surgery. Due to its rarity and wide interindividual variety, intraoperative study with indocyanine green can be useful to carefully identify and evaluate the length of the obstructed tract of RU to adapt reconstructive surgery to each case.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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VIDEOABSTRACT

VIDEOSURGERY

Video can be found at https://www.ceju.online/journal/2024/posterior-reconstruction-2418.php

Modified posterior reconstruction and vesicourethral anastomosis in robot-assisted radical prostatectomy and its impact on anastomosis stricture rate and clips migration

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Key Words: posterior reconstruction ‹› vesico-urethral anastomosis ‹› robot-assisted radical prostatectomy ‹› clips migration

Most of the surgeons dealing with the surgical treatment of prostate cancer apply a popularised kind of posterior reconstruction known as the Rocco stitch. It is an approximation of the remnants of the rectourethral muscles with the remnants of the Denonvilliers' fascia (DF). Originally, this technique was implemented in a retropubic radical prostatectomy, and in multiple published studies, authors concluded that it allows improvement of early confidence after surgery. Concurrently, multiple reports highlight a concept that DF is too weak to give sufficient support for a posterior reconstruction. Following this idea, some other concepts are being applied, for example, reapproximation of the urethra with the tendinous arch of the levator ani. Reapproximation of the urethral stump and the vesical opening promotes a tension-free anastomosis, allows achieving a longer membranous urethra, and creates a firm posterior support. After the transition from a classic laparoscopy to robot-assisted radical prostatectomies in our institution, an increased number of cases of vesico-urethral anastomosis strictures (VUAS) were noted. In most cases, polymer clip migration was revealed during endoscopic inspection. VUAS is not easy to treat and entails a risk of debilitating complications. That has prompted the authors to look for a solution. Our modification applies an approximation of the urethral stump with the vesical opening using a barbed running suture in two layers. The first layer is an equivalent of a Rocco stitch, which brings together the posterior aspect of the urethral stump and the external aspect of the bladder neck. After an adequate tightening of this first line of the sutures, an additional layer of the same running suture is placed to precisely reapproximate the mucosa of the urethra and the bladder opening. This reconstruction is followed by a regular vesico-urethral anastomosis using a standard van Velthoven technique. In the period from March 2020 to March 2024, there were 291 robot-assisted radical prostatectomies (RARP) performed in our Institution. The first 50 RARP were not included in the study as a learning curve group. In our retrospective observational study, we have compared an initial group of patients with the use of the classic Rocco stitch (n = 135) with a study group (n = 156) where the aforementioned modification of the posterior reconstruction

was applied. VUAS was noted in 9 cases (6.67%) in the initial group, and 3 (1.92%) in the study group. The endoscopic inspection revealed 7 cases with clip migration after the classic Rocco stitch and 1 after the modified method. In our opinion, such modification can be a valuable option for the robot assisted VUA due to many factors: a reduction of tension in the anastomosis, an increased number of tissue layers that may promote healing through an improved blood supply and create separation of the healthy tissue from the polymer clips, and finally a reduction of VUAS. Furthermore, the mucosa approximation and the multilayer posterior plate can guarantee an unobstructed catheterization if any unexpected catheter loss happens. Nevertheless, further studies are required for a stronger confirmation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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