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Mini Review

Oncologic and Safety Outcomes for Retrograde and Antegrade Endoscopic Surgeries for Upper Tract Urothelial Carcinoma: A Systematic Review and Meta-analysis

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Abstract

The aim of this study was to identify and summarize available data on oncologic and safety outcomes for retrograde versus antegrade endoscopic surgery in patients with upper tract urothelial carcinoma (UTUC). We systematically searched studies reporting on endoscopic surgery in patients with UTUC. The primary outcome of interest was oncologic control, including bladder and upper urinary tract recurrences. The secondary outcomes were any-grade and major complications. Twenty studies comprising 1091 patients were included in our analysis. The pooled bladder recurrence rate was 35% (95% confidence interval [CI] 28.0–42.3%; I^2 = 48%) after retrograde endoscopic surgery and 17.7% (95% CI 6.5–32.1%; I^2 = 29%) after antegrade endoscopic surgery. The pooled upper urinary tract recurrence rate was 56.4% (95% CI 41.2–70.9; I^2 = 93%) after retrograde endoscopic surgery and 36.2% (95% CI 25.5–47.6%; I^2 = 57%) after antegrade endoscopic surgery. The pooled complication rate was 12.5% (95% CI 0.8–32.8%; I^2 = 94%) for any-grade complications and 6.6% (95% CI 0.1–19.1%; I^2 = 89%) for major complications

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in the retrograde endoscopic cohort. In summary, our analyses suggest promising oncologic benefits of antegrade kidney-sparing surgery in terms of bladder and upper urinary tract recurrence rates in UTUC. Retrograde endoscopic surgery is a safe procedure with a minimal risk of complications and acceptable oncologic outcomes. Research should address the hypothesis that endoscopic antegrade surgery can be a safe and effective alternative for well-selected patients.

Patient summary: One of the surgical options for treatment of cancer of the upper urinary tract is removal of the tumor through a small telescope called an endoscope. The endoscope can be inserted via the urethra (called a retrograde approach) or through a small incision in the skin (antegrade approach). Our review shows that the antegrade approach seems to provide acceptable cancer control rates. Further research could help to identify the role for endoscope surgery in cancer of the upper urinary tract.

1. Introduction

Currently, kidney-sparing surgery for upper tract urothelial carcinoma (UTUC) is indicated for patients with low-risk tumors and for those with absolute contraindications to radical nephroureterectomy, such as advanced renal insufficiency and poor performance status. Depending on anatomic and/or technical parameters, management of renal pelvic tumors can be performed using a ureteroscopic (retrograde) or percutaneous (antegrade) endoscopic approach. Given the lack of evidence for comparisons between antegrade and retrograde endoscopic surgery, the primary aim of this systematic review and meta-analysis was to identify and summarize available data on oncologic and safety outcomes for retrograde versus antegrade endoscopic surgery for pyelocaliceal UTUC. Such a systematic comparison may help in understanding the true risks and benefits of each approach in order to guide adequate preoperative counseling and delivery of care.

2. Method

The PubMed, Web of Science, and Scopus databases were searched to identify studies reporting on endoscopic surgery in patients with UTUC. The primary outcome of interest was oncologic control in terms of bladder and upper urinary tract recurrences. The secondary outcomes were the rates of any-grade and major complications. A meta-analysis of proportions was conducted to calculate a weighted summary for the overall proportion. Detailed information on the study protocol, literature search, inclusion and exclusion criteria, and statistical analyses is reported in the Supplementary material.

3. Results

Twenty studies comprising 1091 patients met our inclusion criteria (Supplementary Fig. 1) [1–20]. Supplementary Table 1 summarizes the characteristics of the trials included. Fifteen studies reported on retrograde and five on antegrade endoscopic surgery. Most of the studies included in this meta-analysis were identified as having a moderate risk of bias according to the ROBINS-I risk-of-bias tool.

The pooled rate for bladder recurrence was 35% (95% confidence interval [CI] 28.0–42.3; I^2 = 48%) after retrograde and 17.7% (95% CI 6.5–32.1%; I^2 = 29%) after antegrade endoscopic surgery (Fig. 1A,B). The pooled rate for upper urinary tract recurrence was 56.4% (95% CI 41.2–70.9% I^2 = 93%) after retrograde and 36.2% (95% CI 25.5–47.6%; I^2 = 57%) after antegrade endoscopic surgery (Fig. 1C,D).

Among studies reporting safety outcomes, the pooled complication rates were 12.5% (95% CI 0.8–32.8%; I^2 = 94%) for any-grade complications and 6.6% (95% CI 0.1–19.1%; I^2 = 89%) for any-grade complications for the retrograde endoscopic surgery cohort (Fig. 2A,B). The pooled rate of ureteral stricture occurrence after retrograde endoscopic surgery for UTUC was 6.6% (95% CI 3.9–9.8%; I^2 = 7%; Fig. 2C). It should be noted that retrograde endoscopic surgery is associated with a high number of interventions (up to 18 procedures per patient) [18].

4. Discussion

Despite the superior oncologic outcomes achieved with the antegrade endoscopic approach, our results should be interpreted with caution owing to the high heterogeneity across studies regarding patient selection, tumor characteristics, and treatment strategies. For example, surgeon experience and use of adjuvant instillation chemotherapy may have affected the results. It is likely that adjuvant instillation chemotherapy was more commonly given to patients treated via the antegrade approach because of easier access. The limited number of studies reporting on antegrade endoscopic surgery and their small sample sizes limit the conclusions that can be drawn, and the results are therefore only hypothesis-generating. The lack of data on surgical complications and percutaneous site recurrence after antegrade endoscopic surgery did not allow for a systematic comparison. These points together reflect the fact that, mainly owing to the invasiveness of the procedure, antegrade endoscopic surgery is being underutilized and has almost been abandoned worldwide, whereas the popularity of the retrograde approach is rising owing to the availability of better instruments. Nevertheless, our analysis demonstrates that the antegrade endoscopic approach for low-risk UTUC tumors could be considered as an alternative to the retrograde approach for patients who might benefit from the former because of tumor location and volume. Percutaneous endoscopic surgery for UTUC is mainly used in the management of large multiple tumors and tumors located in the lower calyx, which present technical chal-

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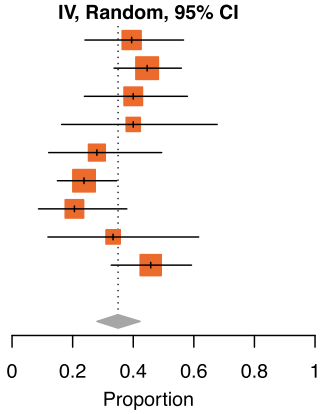
(A) Bladder recurrence: retrograde KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Keeley 1997	15	38	11.3%	0.395 [0.240; 0.566]
Thompson 2008	37	83	16.0%	0.446 [0.337; 0.559]
Cornu 2010	14	35	10.8%	0.400 [0.239; 0.579]
Tada 2010	6	15	6.3%	0.400 [0.163; 0.677]
Kalaitzis 2013	7	25	8.9%	0.280 [0.121; 0.494]
Scotland 2018	19	80	15.8%	0.238 [0.149; 0.346]
Hsieh 2020	7	34	10.7%	0.206 [0.087; 0.379]
Maruyama 2020	5	15	6.3%	0.333 [0.118; 0.616]
Shvero 2021	27	59	14.0%	0.458 [0.327; 0.592]
Total (95% CI)	**384**		**100.0%**	**0.350 [0.280; 0.423]**

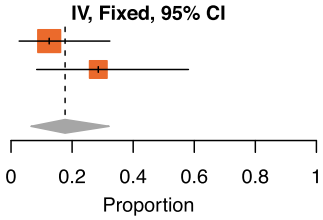
Heterogeneity: $Tau^2 = 0.0056$; $Chi^2 = 15.38$, df = 8 (P = 0.05); $I^2 = 48\%$



(B) Bladder recurrence: antegrade KSS

Study	Events	Total	Weight	IV, Fixed, 95% CI
Goel 2003	3	24	62.8%	0.125 [0.027; 0.324]
Sarmah 2020	4	14	37.2%	0.286 [0.084; 0.581]
Total (95% CI)	**38**		**100.0%**	**0.177 [0.065; 0.321]**

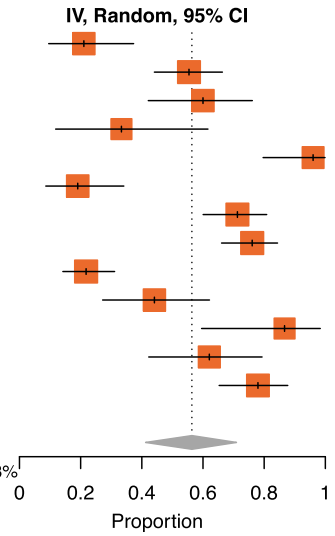
Heterogeneity: $Tau^2 = 0.0056$; $Chi^2 = 1.41$, df = 1 (P = 0.24); $I^2 = 29\%$



(C) Local recurrence: retrograde KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Keeley 1997	8	38	7.7%	0.211 [0.096; 0.373]
Thompson 2008	46	83	8.1%	0.554 [0.441; 0.663]
Cornu 2010	21	35	7.7%	0.600 [0.421; 0.761]
Tada 2010	5	15	6.8%	0.333 [0.118; 0.616]
Kalaitzis 2013	24	25	7.4%	0.960 [0.796; 0.999]
Musi 2018	8	42	7.8%	0.190 [0.086; 0.341]
Scotland 2018	57	80	8.1%	0.713 [0.600; 0.808]
Villa 2018	70	92	8.2%	0.761 [0.661; 0.844]
Defidio 2019	22	101	8.2%	0.218 [0.142; 0.311]
Hsieh 2020	15	34	7.7%	0.441 [0.272; 0.621]
Maruyama 2020	13	15	6.8%	0.867 [0.595; 0.983]
Proietti 2021	18	29	7.5%	0.621 [0.423; 0.793]
Shvero 2021	46	59	8.0%	0.780 [0.653; 0.877]
Total (95% CI)	**648**		**100.0%**	**0.564 [0.412; 0.709]**

Heterogeneity: $Tau^2 = 0.0669$; $Chi^2 = 169.43$, df = 12 (P < 0.01); $I^2 = 93\%$



(D) Local recurrence: antegrade KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Jabbour 2000	6	24	17.2%	0.250 [0.098; 0.467]
Goel 2003	12	24	17.2%	0.500 [0.291; 0.709]
Motamedinia 2016	50	141	31.2%	0.355 [0.276; 0.440]
Strijbos 2016	20	40	21.9%	0.500 [0.338; 0.662]
Sarmah 2020	2	14	12.5%	0.143 [0.018; 0.428]
Total (95% CI)	**243**		**100.0%**	**0.362 [0.255; 0.476]**

Heterogeneity: $Tau^2 = 0.0086$; $Chi^2 = 9.22$, df = 4 (P = 0.06); $I^2 = 57\%$

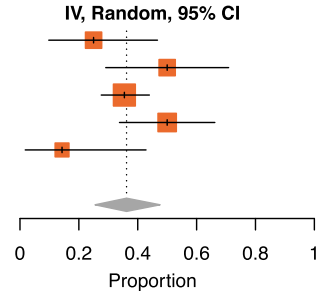


Fig. 1 – Forest plots showing pooled rates of (A,B) bladder and (C,D) upper urinary tract recurrences in studies reporting on patients undergoing endoscopic kidney-sparing surgery (KSS) for upper tract urothelial carcinoma. CI = confidence interval; df = degrees of freedom; IV = inverse variance.

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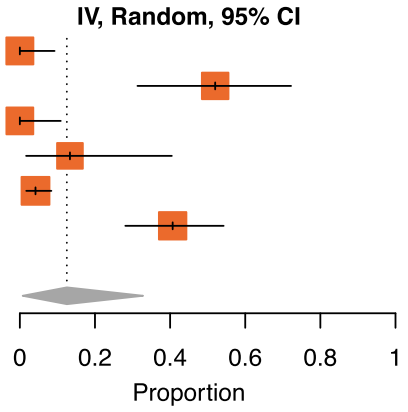
(A) Any complications: retrograde KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Keeley 1997	0	38	16.8%	0.000 [0.000; 0.093]
Kalaitzis 2013	13	25	16.2%	0.520 [0.313; 0.722]
Wen 2018	0	32	16.6%	0.000 [0.000; 0.109]
Maruyama 2020	2	15	15.2%	0.133 [0.017; 0.405]
Scotland 2020	7	168	17.9%	0.042 [0.017; 0.084]
Shvero 2021	24	59	17.3%	0.407 [0.281; 0.543]
Total (95% CI)		**337**	**100.0%**	**0.125 [0.008; 0.328]**

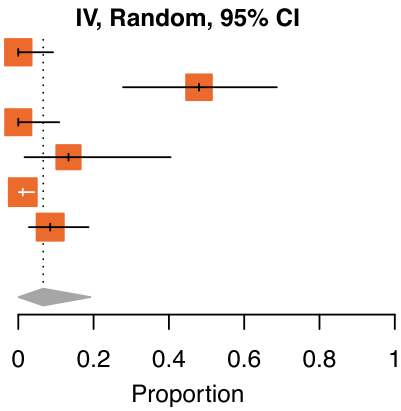
Heterogeneity: $Tau^2 = 0.0808$; $Chi^2 = 81.25$, df = 5 ($P < 0.01$); $I^2 = 94\%$



(B) Major complications: retrograde KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Keeley 1997	0	38	16.9%	0.000 [0.000; 0.093]
Kalaitzis 2013	12	25	15.9%	0.480 [0.278; 0.687]
Wen 2018	0	32	16.5%	0.000 [0.000; 0.109]
Maruyama 2020	2	15	14.2%	0.133 [0.017; 0.405]
Scotland 2020	2	168	18.8%	0.012 [0.001; 0.042]
Shvero 2021	5	59	17.7%	0.085 [0.028; 0.187]
Total (95% CI)		**337**	**100.0%**	**0.066 [0.001; 0.191]**

Heterogeneity: $Tau^2 = 0.0434$; $Chi^2 = 45.98$, df = 5 ($P < 0.01$); $I^2 = 89\%$



(C) Ureteral stricture: retrograde KSS

Study	Events	Total	Weight	IV, Random, 95% CI
Keeley 1997	2	38	11.1%	0.053 [0.006; 0.177]
Kalaitzis 2013	3	25	7.5%	0.120 [0.025; 0.312]
Wen 2018	4	32	9.4%	0.125 [0.035; 0.290]
Hsieh 2020	5	34	10.0%	0.147 [0.050; 0.311]
Maruyama 2020	1	15	4.6%	0.067 [0.002; 0.319]
Scotland 2020	10	168	40.8%	0.060 [0.029; 0.107]
Shvero 2021	2	59	16.6%	0.034 [0.004; 0.117]
Total (95% CI)		**371**	**100.0%**	**0.066 [0.039; 0.098]**

Heterogeneity: $Tau^2 = 0.0004$; $Chi^2 = 6.42$, df = 6 ($P = 0.38$); $I^2 = 7\%$

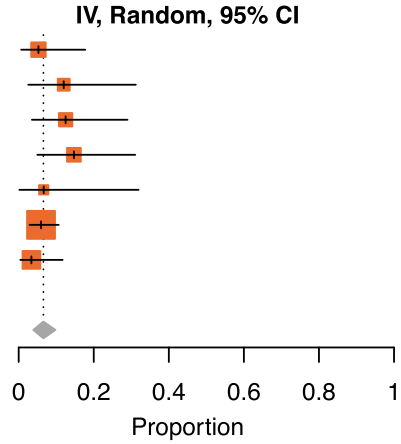


Fig. 2 – Forest plots showing pooled rates of (A) any complications, (B) major complications, and (C) ureteral stricture occurrence in studies reporting on patients undergoing retrograde endoscopic kidney-sparing surgery (KSS) for upper tract urothelial carcinoma. CI = confidence interval; df = degrees of freedom; IV = inverse variance.

lenges in ureteroscopic ablative surgery. Antegrade endoscopic surgery for UTUC is often considered the most effective approach for patients with urinary diversions.

According to our results, there was a relatively higher risk of bladder recurrence after ureteroscopy for UTUC. This might be explained by tumor seeding due to high-pressure backflow of cancer cells from the upper to the lower urinary tract during the procedure and/or ureteric stent placement. Nevertheless, this might be theoretically reduced via intensification of local therapy, such as single-dose chemotherapy instillations after retrograde endoscopic procedures. Multimodal kidney-preserving strategies, including sys-

temic therapy with or without local control after endoscopic management of intraluminal tumors, might be an option for patients with high-risk UTUC and contraindications for radical surgery [21].

Notably, retrograde endoscopic surgery for UTUC was associated with a good safety profile, including low rates of postoperative ureteral stricture and major complications. However, the high rate of upper urinary tract recurrences (up to 56%) after retrograde endoscopic surgery for UTUC might reflect the limitations of the ureteroscopic tools currently available for tumor visualization, resection, and extraction. This also highlights the importance of adherence to a strict surveillance scheme for patients with UTUC treated with kidney-sparing surgery. Further research is needed to identify appropriate concomitant/adjuvant therapy and follow-up schedules after endoscopic management of UTUC [22–24].

The main strength of our systematic review and meta-analysis is that, to the best of our knowledge, it is the first to assess pooled rates for recurrence in the bladder and upper urinary tract and for complications for retrograde and antegrade endoscopic surgeries in patients with UTUC. Among the limitations of the present study, inconsistencies in interventions across the studies and evaluation of the effect among all enrolled trials could lead to significant potential confounding and bias. In addition, the retrospective design of the studies included might mean that the follow-up data are incomplete. Therefore, well-designed trials are required to validate the findings from our study. Finally, selection and expertise bias may have impacted the results.

5. Conclusions

Our analyses suggest promising oncologic results for antegrade endoscopic management of UTUC in terms of the rates of recurrence in the bladder and upper urinary tract. However, there is still a lack of evidence regarding the safety profile for this approach. Retrograde endoscopic surgery appears to be a safe procedure with a minimal risk of any-grade or major complications and with acceptable oncologic outcomes. Hence, antegrade endoscopic surgery for UTUC tumors should be further investigated as an alternative to the retrograde approach in well-selected patients. Identification of the patients who are the most likely to benefit from each endoscopic approach is key. The development of a safe surgical strategy and adherence to appropriate follow-up schemes are important for the delivery of evidence-based safe and effective clinical care in UTUC.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.11.014.

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