Review

Segmental Ureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review and Meta-analysis of Comparative Studies

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Abstract

Radical nephroureterectomy (RNU) represents the standard of care for high-risk upper tract urothelial carcinoma (UTUC). In selected patients with ureteral UTUC, a conservative approach such as segmental ureterectomy (SU) can be considered. However, this therapeutic option remains controversial. The aim of this study was to perform a systematic review and meta-analysis of studies assessing the outcomes of SU versus RNU in patients with UTUC. Three search engines (Scopus, Embase, and Web of Science) were queried up to May 2019. The Preferred Reporting Items for Systematic Review and Meta-analysis Statement (PRISMA Statement) was used as a guideline for study selection. The clinical question was established as stated in the PICO (Population, Intervention, Comparator, Outcome) process. Patients in the SU group were more likely to have history of bladder cancer (odds ratio [OR], 1.99; 95% confidence interval [CI], 1.12-3.51; $P = .02$), but less likely to present with preoperative hydronephrosis (OR, 0.52; 95% CI: 0.31-0.88; $P = .02$). A higher rate of ureteral tumor location was found in the SU group (OR, 7.54; 95% CI, 4.15-13.68; $P < .00001$). The SU group presented with a lower rate of higher (pT $\geq$ 2) stage (OR, 0.66; 95% CI, 0.53-0.82; $P = .0002$), and high-grade tumors (OR, 0.62; 95% CI, 0.50-0.78; $P < .0001$). The SU group was found to have shorter 5-year relapse-free survival (OR, 0.64; 95% CI, 0.43-0.95; $P = .03$), but higher postoperative estimated glomular filtration rate (weighted mean difference, 10.97 mL/min; 95% CI, 2.97-18.98; $P = .007$). Selected patients might benefit from SU as a therapeutic option for UTUC. In advanced high-risk disease, RNU still remains the standard of care.

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Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision remains the standard of care for high-risk upper tract urothelial carcinoma (UTUC).[1] Traditionally, more conservative management options have been reserved for patients unfit for RNU, or with anatomical/functional conditions requiring kidney-sparing surgery (solitary kidney, baseline chronic kidney disease, or bilateral pathology).[2] Several kidney-sparing surgery techniques have been described and implemented, but their oncologic safety remains debatable.[3,4]

In this setting, segmental ureterectomy (SU) represents an option in selected patients, such as those with low-risk ureteral tumors or those with high-risk disease who might benefit from a conservative approach.[5] The aim of this study was to perform a systematic review and meta-analysis of comparative studies assessing the oncologic outcomes of SU versus RNU.

Material and Methods

Literature Research Strategy

Two authors (A.V. and E.C.) screened literature regarding SU versus RNU. The results were assessed by a third author (R.A.). Three search engines (Scopus, Embase, and Web of Science) were

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queried up to May 2019. The following strategy was deemed as the best for this study: ((((segmental ureterectomy) OR partial ureterectomy) OR distal ureterectomy) OR kidney sparing ureterectomy) AND nephroureterectomy).

The time frame of the included studies ranged from 2000 to 2019. The research was focused on English language studies and did not include conference abstracts, conference papers, notes, letters, editorials, and short surveys. Reviews were included only to screen the reference list to avoid missing articles.

Study Selection

The Preferred Reporting Items for Systematic Review and Meta-analysis Statement (PRISMA Statement; www.prisma-statement.org)[6] was used as a guideline for study selection. The clinical question was established as stated in the PICO (Population, Intervention, Comparator, Outcome) process[7]: patients with UTUC (P) undergoing SU (I) or RNU (C) to compare pathologic and survival outcomes (O).

First, the title of the studies was evaluated to exclude those inconsistent with the PICO question. Second, the abstracts of each potentially eligible study were carefully assessed, and those meeting the eligible criteria were included.

Data Extraction

Data included in the meta-analysis were the following:

(1) Baseline features: age, gender (male), race (Caucasian), current smoking history, American Society of Anesthesiologists score $\geq$ 3, history of bladder cancer, tumor side (right), tumor location (pelvicalyceal and ureteral);
(2) Pathologic outcomes: pT $\geq$ 2, tumor grade (high-grade), N+, associated Tis, positive surgical margins;

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart

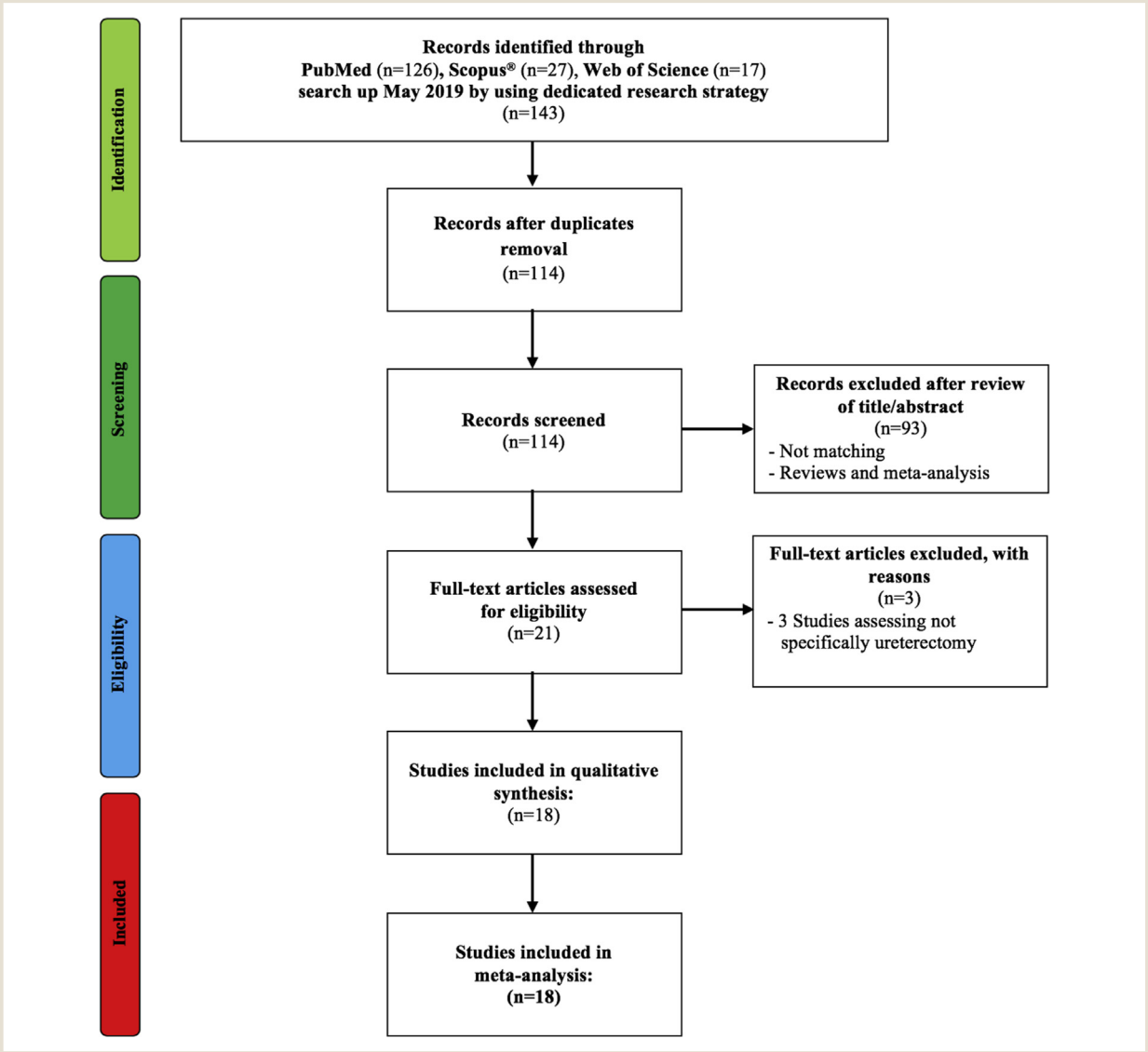


Table 1 Characteristics of the Studies

Author	Study Period	Centers	Study Design	SU	RNU	Endpoints	LE	SQ
Giannarini et al[13]	1974-2004	Single	Retrospective analysis	19	24	- Pathologic outcomes - Survival outcomes	3	********
Jeldres et al[14]	1988-2004	SEER Database	Retrospective analysis	569	1475	- Pathologic outcomes - Survival outcomes	3	*******
Silberstein et al[15]	1994-2009	Single	Retrospective analysis	33	87	- Pathologic outcomes - Survival outcomes	3	*******
Colin et al[16]	1995-2009	Multiple	Retrospective analysis	52	416	- Pathologic outcomes - Survival outcomes	2	********
Bin et al[17]	2000-2010	Single	Case series	17	33	- Pathologic outcomes - Survival outcomes	4	********
Bagrodia et al[18]	-	Single	Retrospective analysis	81	754	- Pathologic outcomes - Survival outcomes	3	*******
Dalpiaz et al[19]	1984-2011	Single	Retrospective analysis	49	42	- Pathologic outcomes - Survival outcomes	3	********
Hung et al[20]	2004-2010	Single	Retrospective analysis	35	77	- Pathologic outcomes - Survival outcomes	3	********
Fukushima et al[21]	-	Multiple	Retrospective analysis	43	86	- Pathologic outcomes - Survival outcomes	3	********
Pedrosa et al[22]	1999-2012	Single	Retrospective analysis	45	96	- Pathologic outcomes - Survival outcomes	3	********
Singla et al[23]	1998-2012	Multiple	Retrospective analysis	50	143	- Functional outcomes - Survival outcomes	3	*******
Seisen et al[24]	2004-2013	Multiple	Retrospective analysis	134	128	- Pathologic outcomes - Survival outcomes	3	********
Fang et al[25]	2003-2016	Single	Retrospective analysis	53	78	- Pathologic outcomes - Survival outcomes	3	********
Huang et al[26]	2011-2016	Single	Retrospective analysis	24	39	- Functional outcomes - Survival outcomes	3	*******
Zhang et al[27]	2005-2016	Single	Retrospective analysis	38	109	- Surgical outcomes - Survival outcomes	3	*******
Kato et al[28]	2004-2016	Single	Retrospective analysis	12	14	- Pathologic outcomes - Survival outcomes	3	*******
Jia et al[29]	2000-2014	Single	Retrospective analysis	40	179	- Pathologic outcomes - Survival outcomes	3	********
Campi et al[30]	2015-2018	Multiple	Retrospective analysis	15	66	- Surgical outcomes - Pathologic outcomes - Survival outcomes	3	*******

Abbreviations: LE = level of evidence; RNU = radical nephroureterectomy; SEER = Surveillance, Epidemiology, and End Results; SQ = study quality according to Newcastle-Ottawa Scale; SU = segmental ureterectomy.

(3) Survival outcomes: adjuvant chemotherapy, recurrence (overall and bladder), metastasis, cancer-related death, 5-year recurrence-free survival (RFS), metastasis-free survival (MFS), and cancer-specific survival (CSS), hazard ratio (HR) of RFS, and CSS surgical technique related (SU vs. RNU);
(4) Functional outcomes: preoperative estimated glomerular filtration rate (eGFR), postoperative eGFR, and delta eGFR.

Study Quality Assessment

Level of evidence as stated in the Oxford Level of Evidence Working Group 2011 was used to stratify each study.[8] The Newcastle-Ottawa Assessment Scale for non-randomized controlled trials was used to evaluate the studies' quality.[9] A score of 5 was considered low, 6 to 7 intermediate, and 8 to 9 high quality. The bias assessment was performed using the Cochrane Collaboration Risk of Bias Tool.[10]

Data Analysis

Continuous and dichotomous variables were considered: inverse variance weight mean difference (WMD) was used to summarize continuous variables, whereas the Mantel-Haenszel test was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of binary values. The random effect model was deemed most suitable to evaluate the cumulative heterogeneity among the studies.[11] The level of heterogeneity was stratified as low (≤ 25%), intermediate (26%-75%), and high (> 75%). Given the possibility to perform cumulative analysis of mean ± standard deviation (SD) only, median (range) was converted to mean ± SD through the Hozo formula.[12] Cumulative analysis of HR (CI) was performed after extraction of lnHR and calculation of standard error (SE). Then, we performed a sensitivity analysis of 5-year RFS and CSS of those studies of distal tumors treated with SU and RNU.

Statistical pooled analyses were performed using Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical significance was set at $P < .05$.

Results

Features of the Studies

Figure 1 reports the study selection PRISMA flow chart. Eighteen comparative studies were deemed eligible for meta-analysis.[13-30] No randomized controlled trial was available, all the studies were retrospective, and only one was prospective.[16] All the studies included were of intermediate quality.

Overall, the meta-analysis included 4797 patients (1313 patients in the SU group and 3484 patients in the RNU group) (Table 1).

Baseline Features

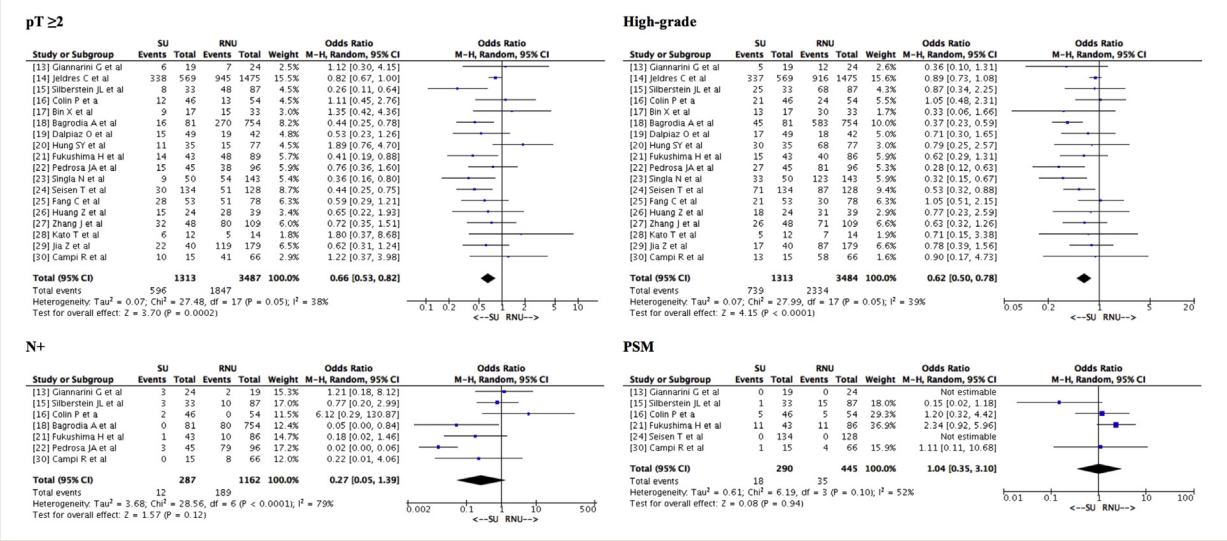
No statistically significant differences in terms of age, gender, race, smoking history, and American Society of Anesthesiologists score were recorded. More patients in the SU group had a history of bladder cancer (OR, 1.99; 95% CI, 1.12-3.51; $P = .02$)[13,15,16,19-22,25,26,28,30] but a lower probability of preoperative hydronephrosis (OR, 0.52; 95% CI, 0.31-0.88; $P = .02$).[13,15,19,21,24-26] A higher rate of ureteral tumor location was found in the SU group (OR, 7.54; 95% CI, 4.15-13.68; $P < .00001$)[18,28,30] (Table 2).

Table 2 Baseline Features

Variables	Studies	SU	RNU	τ^2	χ^2	df	*P* Value	I^2, %	ES	95% CI	*P* Value
Age (y)	12	1043	2327	6.52	77.96	11	<.00001	86	0.98[a]	−0.81 to 2.76	.28
Gender (male)	15	764	1842	0.00	13.79	14	.47	0	1.10[a]	0.95-1.27	.21
Race (Caucasian)	3	581/647	1478/1658	0.00	1.26	2	.53	0	1.05[b]	0.78-1.42	.73
Current smokers	2	99/149	105/194	0.27	2.21	1	.14	55	1.30[b]	0.52-3.28	.58
Tumor side (right)	7	121/237	288/570	0.15	10.59	6	.10	43	0.99[b]	0.64-1.52	.95
ASA score ≥ 3	3	63/184	69/248	0.47	7.08	2	.03	72	1.47[b]	0.58-3.71	.42
History of bladder cancer	11	158/380	305/1025	0.62	36.86	10	<.0001	73	1.99[b]	1.12-3.51	**.02**
Preoperative hydronephrosis	7	196/355	329/484	0.30	16.45	6	.01	64	0.52[b]	0.31-0.88	**.02**
Tumor location (ureter)	3	83/108	241/834	0.04	2.16	2	.34	7	7.54[b]	4.15-13.68	**<.00001**
Lymph node dissection	8	70/419	18/66	1.73	35.28	6	<.00001	83	0.77[b]	0.24-2.43	.65

Bold values are statistically significant.
Abbreviations: ASA = American Society of Anesthesiologists; CI = Confidence interval; df = degree of freedom; ES = effect size; OR = odds ratio; RNU = radical nephroureterectomy; SU = segmental ureterectomy; WMD = weighted mean difference.
[a]WMD.
[b]OR.

Figure 2 Pathologic Outcomes



Abbreviations: CI = confidence interval; M-H = Mantel-Haenszel; RNU = radical nephroureterectomy; SU = segmental ureterectomy.

Pathologic Outcomes

Patients in the SU group had less advanced disease, with a lower rate of pT ≥ 2 (OR, 0.66; 95% CI, 0.53-0.82; $P = .0002$)[13-30] and high-grade tumors (OR, 0.62; 95% CI, 0.50-0.78; $P < .0001$).[13-30] No statistically significant difference was recorded in terms of positive surgical margin (Figure 2).

Survival Outcomes

No statistically significant difference was found between the SU and RNU groups in terms of recurrence (overall [$P = .13$] and bladder [$P = .50$]), metastasis ($P = .18$), and cancer-related death ($P = .95$). No statistically significant difference was found regarding adjuvant chemotherapy. The SU group showed lower 5-year RFS (OR, 0.64; 95% CI, 0.43-0.95; $P = .03$).[16,18-21,24,26,28,29] This was confirmed in the cumulative analysis of HRs, where the RNU group was associated with higher RFS (HR, 1.26; 95% CI, 1.07-1.49; $P = .006$).[16,21,24,29] On the other hand, there was no statistically significant difference in terms 5-year MFS and CSS (Figure 3). Survival analysis of distal tumors showed no statistically significant difference in terms of 5-year RFS and CSS between the SU and RNU groups (Figure 4).

Functional Outcomes

No statistically significant difference was found in preoperative eGFR, whereas the SU group showed higher postoperative eGFR (WMD, 10.97 mL/min; 95% CI, 2.97-18.98; $P = .007$).[21,23,26-28] Despite the fact that SU seemed to be clinically associated with an improvement of eGFR, it did not achieve the conventional level of statistical significance (WMD, 7.18 mL/min; 95%CI, −1.68 to 16.04; $P = .11$)[20,21,23,26,29] (Table 3).

Publications Bias

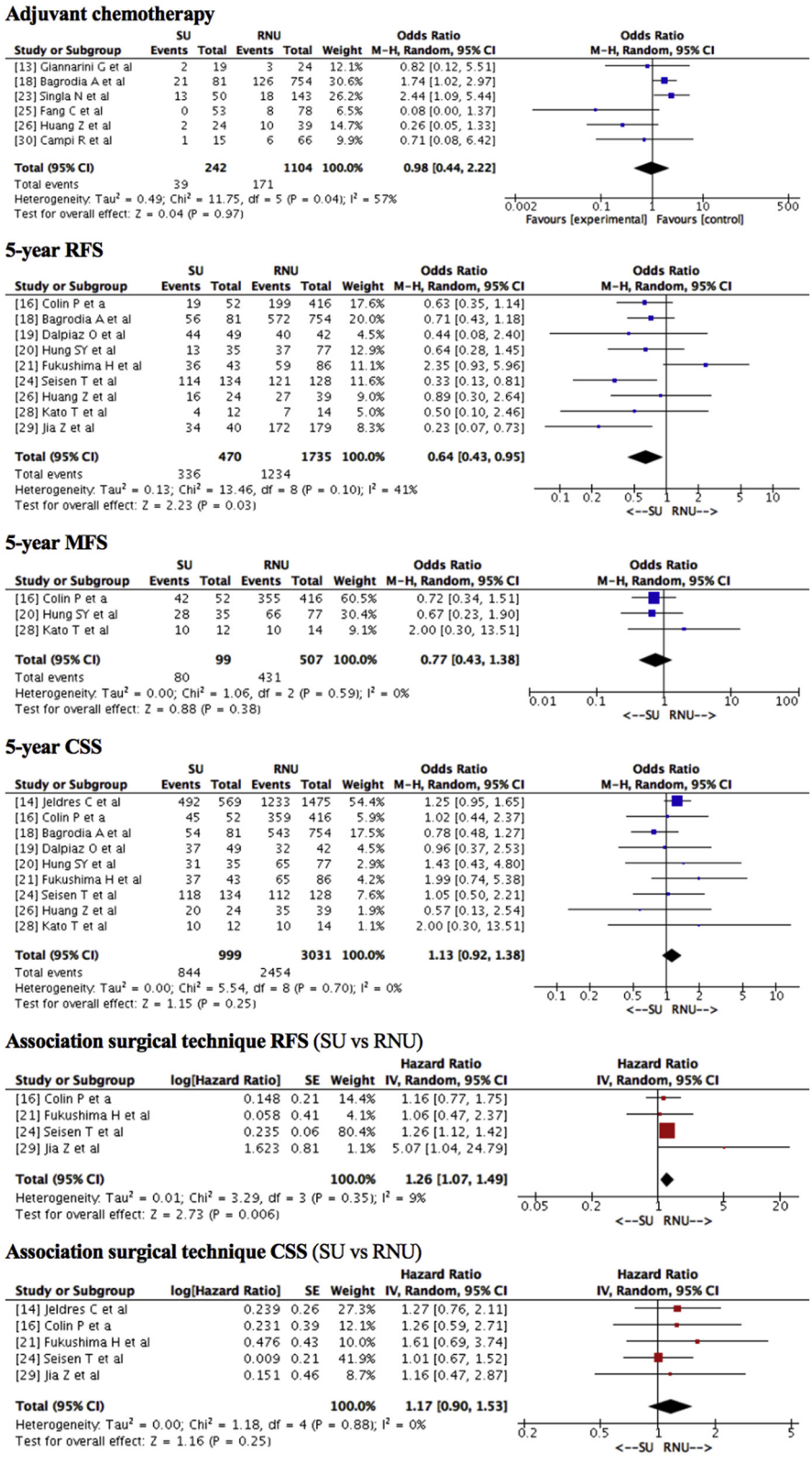
Overall, each study was affected by a high risk of selection, performance, and detection bias. No other obvious bias was clearly recognizable (see Supplemental Figures 1 and 2 in the online version).

Discussion

Herein we present the largest analysis assessing pathologic and survival outcomes of SU versus RNU in patients with UTUC. Compared with the most recent systematic review on this topic,[31] we included 6 additional studies for a total of 18 studies. Our findings give rise to some interesting points of discussion.

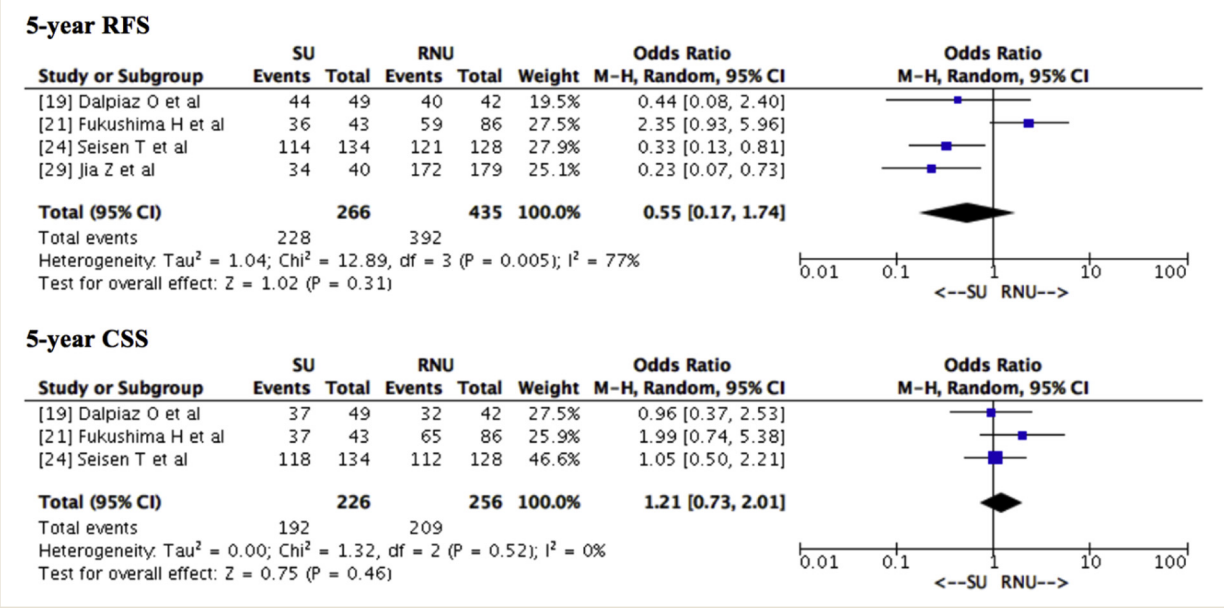
The SU and RNU groups had similar baseline characteristics, but there was a higher rate of patients with history of bladder cancer in the SU group. This finding is consistent with previous literature. Silberstein et al conducted a comparative analysis of SU versus RNU and found 70% of patients who underwent SU had a previous history of bladder cancer.[15] Recently, a multicenter analysis on robotic SU versus RNU found a history of bladder cancer in 40% of the SU cases.[30] Moreover, this higher rate could be owing to bladder tumor seeding when localized near ureteral orifices.[19] As expected, we found that SU was mostly performed in patients with ureteral carcinoma, and this was consistently reported in all the studies.[18,28,30] Preoperative hydronephrosis was more frequent in the RNU group. Kohada et al assessed the impact of hydronephrosis and elevated neutrophil/lymphocyte ratio within a cohort of 148 patients undergoing RNU and found that these parameters were associated with advanced pathologic stage.[32] Our analysis indirectly confirms this finding, as RNU patients were more likely to present with preoperative hydronephrosis but also to have more advanced disease. To note, 6 studies reported similar pathologic stage between the 2 groups,[13,16,17,20,28,30] but this was not the case for the tumor grading, which was similar in only 2 reports.[16,25] The advanced disease stage did not translate into any difference in terms of CSS, but the SU group had a shorter RFS. Several factors might explain

Figure 3 Survival Outcomes



Abbreviations: CI = confidence interval; CSS = cancer-specific survival; MFS = metastasis-free survival; M-H = Mantel-Haenszel; RFS = relapse-free survival; RNU = radical nephroureterectomy; SU = segmental ureterectomy.

Figure 4 Survival Outcomes Distal Ureterectomy



Abbreviations: CI = confidence interval; CSS = cancer-specific survival; M-H = Mantel-Haenszel; RFS = relapse-free survival; RNU = radical nephroureterectomy; SU = segmental ureterectomy.

this finding. As recommended by current guidelines, SU can be offered for high-grade tumors distally located in the ureter.[1] On the other hand, ureteral tumor location, especially distal location, as well as previous history of bladder cancer, was shown to be associated with shorter RFS.[33] These characteristics perfectly mirror those of the patients in the SU group of our analysis.

In addition, the lack of strong evidence regarding survival outcomes for SU requires a strict follow-up for these patients, with periodic ureterorenoscopies.[4] The literature has already highlighted the negative impact of diagnostic ureteroscopy on prognosis. Indeed, has been hypothesized that the application of high endoluminal pressure during the procedure might be responsible of pyelolymphatic and pyelovenous backflow, which could explain tumor seeding.[34] Marchioni et al corroborated this hypothesis within a systematic review and meta-analysis regarding the impact of diagnostic ureterorenoscopy (URS) on intravesical recurrence. With a pooled analysis of 5 retrospective comparative studies, they underlined a higher hazard of recurrence in those patients undergoing URS.[35] Despite this, we could not assess the use of preoperative URS because it was not routinely used in all the studies included. Another proof of the lower RFS in the SU group was the finding of a statistically significant association of RNU with RFS (HR, 1.26; 95% CI, 1.07-1.49; $P = .006$). This was not the case for SU and RNU performed for distal tumors. Sensitivity analysis showed no statistically significant difference between the 2 procedures, and this was consistent with previous evidence. Dalpiaz et al compared SU and RNU for distal urothelial tumors and found 5-year CSS and RFS rates of 77% and 91% for SU and 78% and 96% for RNU, respectively.[19] Again, Seisen et al compared distal ureterectomy and RNU and achieved the same results as our meta-analysis.[24]

Regarding functional outcomes, not surprisingly, SU was found to be associated with better postoperative eGFR compared with RNU. Indeed, our pooled analysis showed a higher level of eGFR, and an improvement of eGFR in the SU group (albeit this was statistically significant).

The above-mentioned finding might help to establish the best treatment tailored to each patient. Indeed, some patients might need adjuvant chemotherapy after surgery, and kidney function preservation could be mandatory.[36] On the other hand, in some cases, RNU is the only possible option, and in these cases, neoadjuvant therapy should be considered.[37] In our analysis, 16% of SU patients and 15% of RNU patients received adjuvant chemotherapy ($P = .97$).

To the best of our knowledge, this is the largest and most updated systematic review and meta-analysis on SU versus RNU. Despite this, some intrinsic limits require its results to be interpreted cautiously. Indeed, the retrospective nature of the studies makes it subject to selection and reporting bias. In addition, it was not possible to account for the surgical techniques used, and this might have influenced the results. Furthermore, this analysis address only the comparison of SU and RNU and does not consider other conservative techniques.[3] Another important limitation was the impossibility of stratifying the surgical techniques according to tumor position, so the results give a partial view of the picture. Indeed, only 4 studies reported survival outcomes of distal ureterectomy compared with RNU, but their limited number did not enable us to draw meaningful conclusions.[19,21,24,29] Moreover, it was not possible to discriminate standard distal SU (bladder cuff and ureteroneocystostomy) from a true SU (portion of ureter excision with uretero-ureterostomy). Notwithstanding these limitations, the results achieved suggest that both treatments could provide at least equivalent outcomes if tailored to the patient.

Table 3 Functional Outcomes

Variables	Studies	SU	RNU	τ^2	χ^2	df	*P* Value	I^2, %	WMD	95% CI	*P* Value
Preoperative eGFR (mg/mL)	6	177	391	24.15	9.30	5	.10	46	1.84	−3.99 to 7.67	.54
Postoperative eGFR (mg/mL)	5	169	387	62.82	21.33	4	.0003	81	10.97	2.97-18.98	**.007**
Δ eGFR (mg/mL)	5	192	524	93.44	65.49	4	<.00001	94	7.81	−1.68 to 16.04	.11

Bold value is statistically significant.
Abbreviations: CI = confidence interval; df = degree of freedom; eGFR = estimated glomerular filtration rate; RNU = radical nephroureterectomy; SU = segmental ureterectomy; WMD = weighted mean difference.

Conclusions

SU can be considered as a treatment option for patients with UTUC in selected cases as it offers better preservation of renal function. However, a strict follow-up is mandatory in these cases to avoid jeopardizing the oncologic outcome. In advanced high-risk disease, RNU remains the standard of care. The evidence in this field is based on intermediate- to low-quality non-randomized studies, and further research efforts are warranted.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.10.015.

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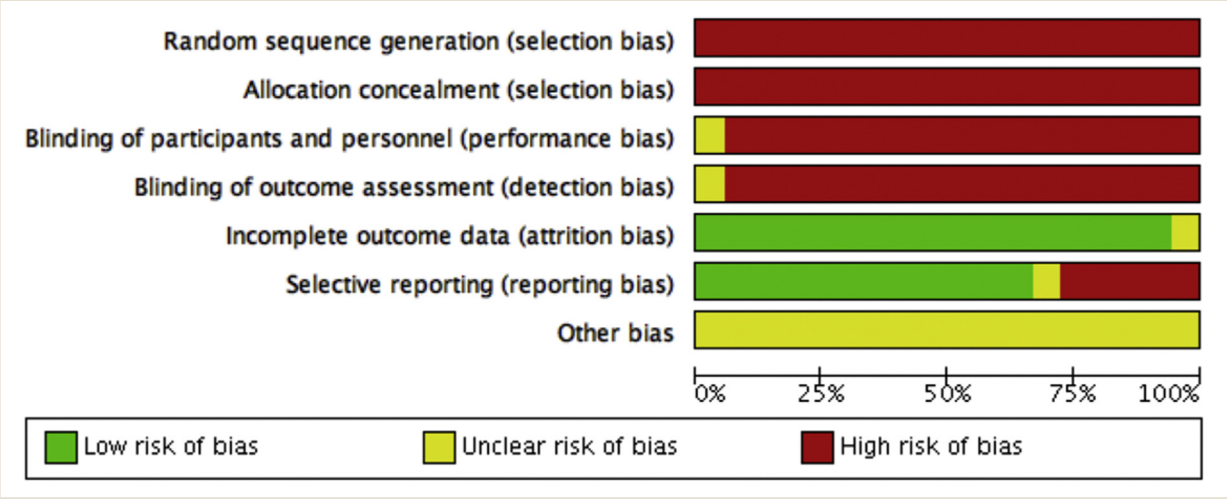
Supplemental Figure 1 Risk of Bias Graph. Review Authors' Judgments About Each Risk of Bias Item Presented as Percentages Across all Included Studies



Supplemental Figure 2 **Risk of Bias Summary. Review Authors' Judgments About Each Risk of Bias Item for Each Included Study**