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Article type : Original Article

Article category: Urological Oncology

Impact of ureteroscopy before radical nephroureterectomy for upper tract urothelial carcinomas on oncologic outcomes: a meta-analysis

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Abstract

Objectives: To investigate whether ureteroscopy (URS) before radical nephroureterectomy (RNU) for upper tract urothelial carcinomas (UTUC) has an impact on oncologic outcomes.

Materials and Methods: We performed a systematic literature search of PubMed, Web of Science, and EMBASE for citations published prior to September 2017 that described URS performed on patients with UTUC and conducted a standard meta-analysis on survival outcomes.

Results: Our meta-analysis included eight eligible studies containing 3,975 patients. The results were as follows: cancer-specific survival (CSS) (Hazard Ratio (HR) = 0.76, 95% CI: 0.59 - 0.99, $P = 0.04$), overall survival (OS) (HR = 0.76, 95% CI: 0.48 - 1.21, $P = 0.24$), recurrence-free survival (RFS) (HR = 0.89, 95% CI: 0.69 - 1.14, $P = 0.37$), metastasis-free survival (MFS) (HR = 1.06, 95% CI: 0.82 - 1.36, $P = 0.66$), and intravesical recurrence-free survival (IRFS) (HR = 1.51, 95% CI: 1.29 - 1.77, $P < 0.00001$). Excluding the previous bladder tumour history, the results of IRFS were HR = 1.81, 95% CI: 1.53-2.13, and $P < 0.00001$.

Conclusions: This meta-analysis indicated that URS before RNU did not have a negative impact on CSS, OS, RFS, or MFS in UTUC patients. However, patients were at higher risk of intravesical recurrence after RNU when they had undergone URS before RNU. Further studies are needed to assess the effects of post-URS intravesical chemotherapy on intravesical recurrence.

Keywords: recurrence, survival, upper urinary tract, ureteroscopy, urothelial carcinoma

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is an uncommon malignant disease, accounting for approximately 5 -10% of all urothelial carcinomas [1-3], with an estimated annual incidence in Western countries of ~2 cases per 100,000 inhabitants. Approximately 60% of UTUC patients are invasive at diagnosis [4-5]. The gold-standard treatment for UTUC is radical nephroureterectomy (RNU) with bladder cuff removal [1]. Recurrence in the bladder after standard treatment of UTUC occurs in 22 - 47% of UTUC patients [6-8] compared with 2 - 6% in the contralateral upper urinary tract [9-10].

Urinary cytology, cystoscopy, and computed tomography urography should be performed as the standard diagnostic work-up with the grade A of recommendation [1]. Diagnostic ureteroscopy (URS) and biopsy should be performed, especially in cases where additional information will impact treatment decisions. In the contemporary era, with the advances in medical equipment and the rapid development of endoscopic techniques, URS has become increasingly accessible and could be used to explore the entire upper urinary tract [11]. Furthermore, URS is a practical and powerful tool to diagnose and treat the patients with UTUC. Such ureteroscopic biopsies can determine tumour grade in 90% of cases, with low false-negative rates [12]. URS can prove to be invaluable in cases of suspected UTUC, especially when the diagnosis is equivocal or if nephron sparing surgery is considered. However, the URS procedure and relevant operation prior to RNU may increase the risk of renal tumour and urothelial carcinoma implantation, which may theoretically occur due to ureteroscope manipulation or tumour dissemination due to irrigation back-flow; anecdotal reports suggest tumour seeding as a consequence of URS [13-14].

In this article, we aimed to evaluate whether URS before RNU for UTUC has an impact on oncologic outcomes.

MATERIALS AND METHODS

Search strategy

A systematic literature search was performed using PubMed, Web of Science, and EMBASE. All the search articles were written in English. The latest search was updated in September 2017. The main keywords used for the search were ureteroscopy, nephroureterectomy, prognosis or survival or oncological outcome, and upper tract urothelial neoplasms or upper tract urothelial cancer or transitional cell carcinoma of the upper urinary tract. The detailed search terms and strategies are shown in the S1 Text. Additionally, we manually screened the references from the relevant literature, including all of the identified studies, reviews, and editorials. Two independent investigators (GUO and HONG) assessed the titles and abstracts of published studies, and divergences were settled by consensus.

Inclusion and exclusion criteria of trials

Studies were included if they met all of the following criteria: (1) studies analysing the relationship between URS and UTUC prognosis after RNU; (2) studies that clearly described outcome assessment by representing overall survival (OS), cancer-special survival (CSS), recurrence-free survival (RFS), metastasis-free survival (MFS), or intravesical recurrence-free survival (IRFS); (3) survival outcome was further explored considering hazard ratio (HR) and corresponding 95% confidence interval (CI) or sufficient information to achieve an estimated HR and 95% CI by using the methods reported by Tierney *et al* [15]; (4) retrospective or prospective study design; and (5) median follow-up time longer than 12 months. The excluded studies met one of the following criteria: (1) the article was a review or meta-analysis; (2) no available data could be extracted from the previously published studies;

(3) the article dealt with recurrent UTUC, metastatic carcinoma, previous or concurrent invasive bladder tumours, or neoadjuvant chemotherapy; and (4) (potentially) overlapping study populations were reported for the same outcome.

Data extraction

The data were extracted from full length articles by two reviewers (GUO and HONG) independently with a standardized items form. The extracted information included name of the author; year of publication; study region; type of study; sample size; median follow-up time; median age; number of patients receiving URS; tumour location and grade; tumour pathologic stage; previous bladder tumour history; outcomes, including CSS, OS, RFS, MFS, or IRFS. Divergences were settled through consensus.

Quality assessment

The quality of the selected studies was assessed independently by two reviewers (GUO and HONG) using the Newcastle Ottawa Scale, which was recommended for the assessment of non-randomized studies [16]. This scale assesses risk in three domains: patient selection, comparability of URS+ and URS- groups, and assessment of outcome. Any divergence was settled by discussion or through arbitration by a third reviewer if no agreement could be reached.

Data analysis and synthesis

We used log HR and the variance as the summary outcome measure from all trials in the meta-analysis. For each study, HR with the 95% CI of the survival rate was derived to evaluate the impact of URS on the survival of UTUC patients. When there was no evident heterogeneity existing among studies (I^2 > 50% and P value < 0.1 suggested obvious heterogeneity)[17], we used the fixed-effects model (Mantel-Haenszel method) to pool the results. Otherwise, the random-effects model (DerSimonian and Laird method) was applied, which provided more conservative estimates than the fixed-effects model when heterogeneity

was present [18]. Potential sources of heterogeneity, if significant, were explored using subgroup analysis and meta-regression analysis.

The publication bias of selected studies was detected using the funnel plot, and the Egger's test was used to assess publication bias statistically [19]. Review manager version 5.3 (Cochrane Collaboration, Oxford, UK) was used for data analysis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Study identification and quality assessment

As shown in the flow diagram (Fig 1), 552 potentially relevant studies were retrieved from our initial literature search. Using literature manager software (Endnote), 258 duplicated papers were excluded. After carefully screening titles and abstracts of identified records, 265 were excluded: 103 were not relevant, 101 were case series/case reports, and 61 were reviews/letters/comments. Twenty-nine were reviewed in depth, and a full examination of the text was performed. Twenty studies were excluded because of insufficient outcomes, and one was excluded due to potentially overlapping study populations. Finally, eight studies were included in the current meta-analysis [20-27]. Table 1 summarizes the characteristics of the included studies [20-27]. The eight studies contained 3,975 UTUC patients, including 1,070 patients who received URS before RNU. These UTUC patients came from different countries or regions (United States, Japan, Austria, Canada, Germany, Italy, Chinese Taipei, France, Korea, and China) with the duration of follow-up of more than 12 months. Of the eight eligible studies, five studies [21-24,27] containing 2,585 patients were carried out to investigate the impact of URS on the CSS of UTUC patients after RNU, two studies [20,27] containing 297 patients to investigate the OS, two studies [22,24] containing 1,780 patients to investigate the RFS, four studies [20,23,24,27] containing 1,205 patients to investigate the MRS, and five studies

[21,23,25-27] containing 2,099 patients to investigate the IRFS. Assessment of quality scores by the Newcastle Ottawa Scale demonstrated that the scores of selected studies ranged from 7 to 9, which were considered adequate for the following meta-analysis (Table 1). The summary of included studies (treatment, including surgery and neoadjuvant/adjuvant therapy) is shown in Table 2.

Meta-analysis results

Cancer-specific survival

Of the five studies that referred to CSS, there was no heterogeneity (I^2 = 2%, Chi^2 = 4.08, P = 0.40); thus, the fixed-effects model was used to calculate the pooled HR and corresponding 95% CI. As shown in Fig 2a, the combined HR of these studies revealed that URS before RNU was associated with better CSS in UTUC patients (HR = 0.76, 95% CI: 0.59 - 0.99, P = 0.04). To explore the source of better CSS in the URS+ group, we compared the differences in tumour stage and tumour grade between the groups, thereby demonstrating the features between the groups using Chi-square tests and Fisher's exact tests for categorical variables (Table 3). The results showed that there were remarkable significant differences in tumour stage between the URS+ group and URS- group (P < 0.001). However, no significance was found in tumour grade between the two groups (P = 0.104). While excluding the studies containing patients receiving adjuvant therapy, no significant difference was found between the two groups (HR = 0.83, 95%CI: 0.58 - 1.17, P = 0.28) without heterogeneity (I^2 = 17%, Chi^2 = 3.63, P = 0.30) (Fig 2b).

Overall survival

The data for OS were reported in only two studies, and there was no significant difference in the study heterogeneity (I^2 = 0%, Chi^2 = 0.11, P = 0.51); thus, the fixed-effects model was used to pool the results. The data showed that no significant difference was found between the URS+ group and the URS- group (HR = 0.76, 95% CI: 0.48 - 1.21, P = 0.24) (Fig 2c).

Recurrence-free survival

No significant heterogeneity was observed in the two studies that focused on RFS (I^2 = 0%, Chi^2 = 0.96, P = 0.33); thus, the fixed-effects model was used to pool the results. The pooled HR for RFS was 0.89 (95%CI: 0.69 - 1.14, P = 0.37), indicating that URS before RNU was not associated with poor RFS in patients with UTUC (Fig 2d).

Metastasis-free survival

There were five studies regarding MFS of URS+ vs. URS- before RNU. The results demonstrated that the risk of metastasis for UTUC patients with URS was not higher than those without URS (HR = 1.06, 95% CI: 0.82 - 1.36, P = 0.66) and that there was no significant heterogeneity observed (I^2 = 0%, Chi^2 = 0.53, P = 0.66) (Fig 2e).

Intravesical recurrence-free survival

Of the five studies that referred to IRFS irrespective of previous bladder tumour history, there was no inter-study heterogeneity (I^2 = 37%, Chi^2 = 6.34, P = 0.18); thus, the fixed-effects model was used to pool the results. The combined HR of these studies revealed that URS before RNU was associated with poorer IRFS in UTUC patients (HR = 1.51, 95% CI: 1.29 - 1.77, P < 0.00001) (Fig 3a). Excluding the previous bladder tumour history, patients in the URS+ group were still at higher risk of intravesical recurrence compared with those in the URS- group (HR = 1.81, 95% CI: 1.53 - 2.13, P < 0.00001), with no heterogeneity among the studies (I^2 = 0%, Chi^2 = 1.29, P = 0.73) (Fig 3b). We further confined included studies to those with bladder cuff management; the risk of intravesical recurrence for UTUC patients

with URS was higher than those without URS (HR = 1.61, 95% CI: 1.30 - 1.99, $P < 0.00001$), with no heterogeneity ($I^2 = 0\%$, $Chi^2 = 0.99$, $P = 0.61$) (Fig 3c).

Publication bias

Publication bias was detected using a funnel plot of the meta-analysis result. The basic symmetry of the funnel plots suggested that there was no obvious publication bias in this meta-analysis (Fig 4). The Egger's test for CSS, OS, RFS, MFS, and IRFS did not show any evidence of publication bias.

DISCUSSION

The relationship between URS and oncological outcomes in UTUC patients has attracted extensive attention and has been widely debated; however, the reports remain controversial, and there has yet to be a consensus on whether URS before RNU increases the risk of disease progression or death from disease. Thus, we reviewed the published studies to evaluate the impact of URS before RNU on UTUC survival and conducted a standard meta-analysis to assess whether URS before RNU showed a tendency towards a poor prognosis for UTUC patients.

In the present research, based on the inclusion and quality assessment criteria, eight studies were eligible, and the HRs of cumulative survival rates were summarized quantitatively by meta-analysis techniques. One potential criticism of ureteroscopic management before RNU for UTUC is the time delay of radical surgery. In a previously published study, Boorjian *et al* retrospectively reviewed the cases of 121 UTUC patients undergoing RNU with or without prior URS at New York–Presbyterian Hospital [28]. They further subdivided the URS group into those undergoing therapeutic laser ablation and those undergoing tissue biopsy. Although the time of delay between the ablation group and the biopsy group differed significantly (40.1 months vs. 28 days), no significant difference was found in the postoperative disease status

between patients undergoing RNU after ablation and those who received RNU after endoscopic biopsy or those who did not undergo URS before RNU. Our results indicated that URS did not have a significant negative impact on OS, RFS, or MFS for UTUC patients who finally underwent radical surgery. Interestingly, URS was significantly associated with better CSS (HR = 0.76, 95% CI: 0.59 - 0.99, P = 0.04). For this result, we contributed it to selection bias (Table 2). It was more likely that patients with advanced disease (>pT2) had apparent imaging findings, such as a solid mass on CT or a filling defect on contrast imaging and positive urinary cytology. In such cases, the surgeon would omit diagnostic URS and proceed to radical surgery, which may have resulted in worse survival in the URS- group. Aggressive disease may be more likely diagnosed without diagnostic URS even when it is ultimately categorized as the same pathological stage. A study by Ishikawa *et al* also showed that UTUC patients without prior URS for pT3 or greater disease were at higher risk of cancer-specific mortality compared with those with URS before RNU and that, on multivariate analysis, pathological stage and node status were independent prognostic factors [21]. When confined to patients without adjuvant therapy, URS before RNU was not associated with poor CSS, which indicated that adjuvant therapy could be a confounder. Thus, we believe that URS does not adversely affect oncologic outcomes as assessed by overall recurrence, metastasis, and mortality.

Regarding intravesical recurrence, our analysis demonstrated that URS was associated with poorer IRFS (HR = 1.51, 95% CI: 1.29 - 1.77, P < 0.00001) irrespective of prior bladder tumour history (HR = 1.81, 95% CI: 1.53 - 2.13, P < 0.00001), which is a well-known prognostic factor of intravesical recurrence [29-32] and was even confined to bladder cuff resection (HR = 1.61, 95% CI: 1.30 - 1.99, P < 0.00001). Similar results were also reported by Autorino *et al* [33]. Several theories have been suggested to explain intravesical recurrence following RNU, including intraluminal tumour seeding, intraepithelial cancer migration, and

urinary tract cancerization [23,34]. Patients with distal ureteral tumours, a site that is associated with increased risk of intravesical recurrence, were more likely to undergo URS before RNU [21,27]. These theories have also been applied to intravesical recurrence following prior URS. We suggest that care should be taken for UTUC patients at risk of intravesical recurrence. Intravesical chemotherapy following URS may prevent intravesical recurrence and prevent the need for additional surgical interventions. Randomized control trials are needed to assess the effects of post-URS intravesical chemotherapy on intravesical recurrence.

To the best of our knowledge, this is the first study to evaluate the relevance between prior URS and survival for UTUC patients using comprehensive and standard meta-analysis following the guideline proposed by PRISMA (S2 Text); however, limitations should be acknowledged when drawing conclusions. First, this research was based on retrospective studies. Although all of the eight eligible studies involving 3,998 patients were of high quality (>6 stars) according to the modified Newcastle-Ottawa Scale, intrinsic bias still existed, which might have rendered the results less reliable. Second, we failed to detect the relationship between different locations of tumours and survival due to lack of information. Pelvis and ureteral transitional carcinoma are not the same disease in terms of invasion and prognosis [35-36]. Third, there were only two studies investigating RFS and MFS of UTUC even by a comprehensive literature search, which might have inevitably increased the risk of random error; therefore, more large prospective studies are needed to further confirm our findings. Fourth, there was considerable confounding by indication of URS within the representative series. Only 26.9% of patients underwent URS prior to RNU and those patients who did not undergo URS were more likely to have a high volume tumour noted on axial imaging, which might influence the results of survival analysis. Furthermore, without pre-operative grade assessment by URS or clinical staging by axial imaging, it is difficult to ascertain suitability for neoadjuvant chemotherapy, which does not appear to have occurred

in the eight studies but still needs to be evaluated in the future study. Finally, in spite of the well-recognized advantages of meta-analysis, the results are affected by the quality of the included studies, and the reporting bias that papers with null or nonsignificant results are more difficult to publish than those with significant results might be unavoidable [37].

CONCLUSIONS

In conclusion, our meta-analysis of current evidence suggests that URS before RNU does not have a negative impact on CSS, OS, RFS, or MFS in UTUC patients. However, patients are at higher risk for intravesical recurrence after RNU when they have undergone prior URS. Further studies are needed to assess the effects of post-URS intravesical chemotherapy on intravesical recurrence.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Fig 1. Flowchart of study selection.

Fig 2. Forest plot comparing survival in patients receiving ureterscopy before radical nephroureterctomy versus those without ureterscopy before surgery. (a) cancer-specific survival; (b) cancer-specific survival excluding patients received adjuvant therapy; (c) overall survival; (d) recurrence-free survival; (e) metastasis-free survival.

Fig 3. Forest plot comparing intravesical recurrence-free survival according to preoperative ureterorenoscopy (a) in all patients following radical nephroureterectomy, (b) excluding prior bladder tumor history, and (c) further confined to those with bladder cuff management.

Fig 4. Funnel plot for the evaluation of potential publication bias. (a) cancer-specific survival; (b) overall survival; (c) recurrence-free survival; (d) metastasis-free survival; (e) intravesical recurrence-free survival.

Table 1 Summary of included studies (individual study characteristics and quality score)

Study	Region/ Country	Type of study	Gender	Patients (n)	Follow-up median (months)	Median age (years)	URS	Tumour location	Pathologic tumour stage	Tumour grade	Previous bladder tumour	Outcome	Quality score
Hendin BN *et al* 1999 [20]	USA	Retrospective	Male 68 Female 28	96	46.4	65.4	48	Pelvis 40 Ureter 37 Both 19	Tis 6 Ta 46 T1 16 T2 3 T3 22 T4 1	G1 15 G2 42 G3 36	30	OS MFS	9
Ishikawa S *et al* 2010 [21]	Japan	Retrospective	Male 139 Female 69	208	44	70	55	Pelvis 111 U-Ureter 43 L-Ureter 54	Ta-is 41 T1 59 T2 44 T3 56 T4 9	Low 142 High 66	39	CSS IRFS	9
Gurbuz C *et a*l 2011 [22]	USA, Austria, Canada, Germany, Italy, & Japan	Retrospective	Male 415 Female 853	1268	52.8	67.5	175	Pelvis 838 Ureter 430	Tis 22 Ta 259 T1 286 T2 234 T3 408 T4 59	Low 479 High 789	0	CSS RFS	7
Luo HL *et al* 2013 [23]	Chinese Taipei	Retrospective	Male 190 Female 206	396	40.7	66.4	115	Pelvis 285 Ureter 232	≤T2 289 >T2 107	Low 39 High 357	98	CSS IRFS MFS	9
Nison L *et al* 2013 [24]	France	Retrospective	Male 348 Female 164	512	23.1	69.7	170	Pelvis 277 Ureter 172 Both 63	Ta-is 141 T1 111 T2 53 T3 186 T4 31	G1 62 G2 154 G3 296	0	CSS RFS MFS	7

Table 1 Summary of included studies (individual study characteristics and quality score)

Sung HH *et al* 2015 [25]	Korea	Retrospective	Male 465 Female 165	630	34.3	64	282	Pelvis 146 Ureter 316 Both 168	Ta 109 T1 153 T2 103 ≥T3 265	≤G2 353 G3 277	123	IRFS	8
Liu P *et al* 2016 [26]	China	Retrospective	Male 295 Female 369	664	48	68	81	Pelvis 368 Ureter 296	≤T2 458 >T2 206	Low 381 High 283	0	IRFS	7
Sankin A *et al* 2016 [27]	USA	Retrospective	Male 110 Female 91	201	64.8	70.3	144	Pelvis 127 Ureter 47 Both 27	Tis 3 Ta 60 T1 36 T2 42 T3 53 T4 7	Low 40 High 161	0	CSS OS IRFS MFS	7

URS, ureteroscopy; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; IRFS, intravescial recurrence-free survival; MFS, metastasis-free survival.

Table 2 Summary of included studies (treatment)

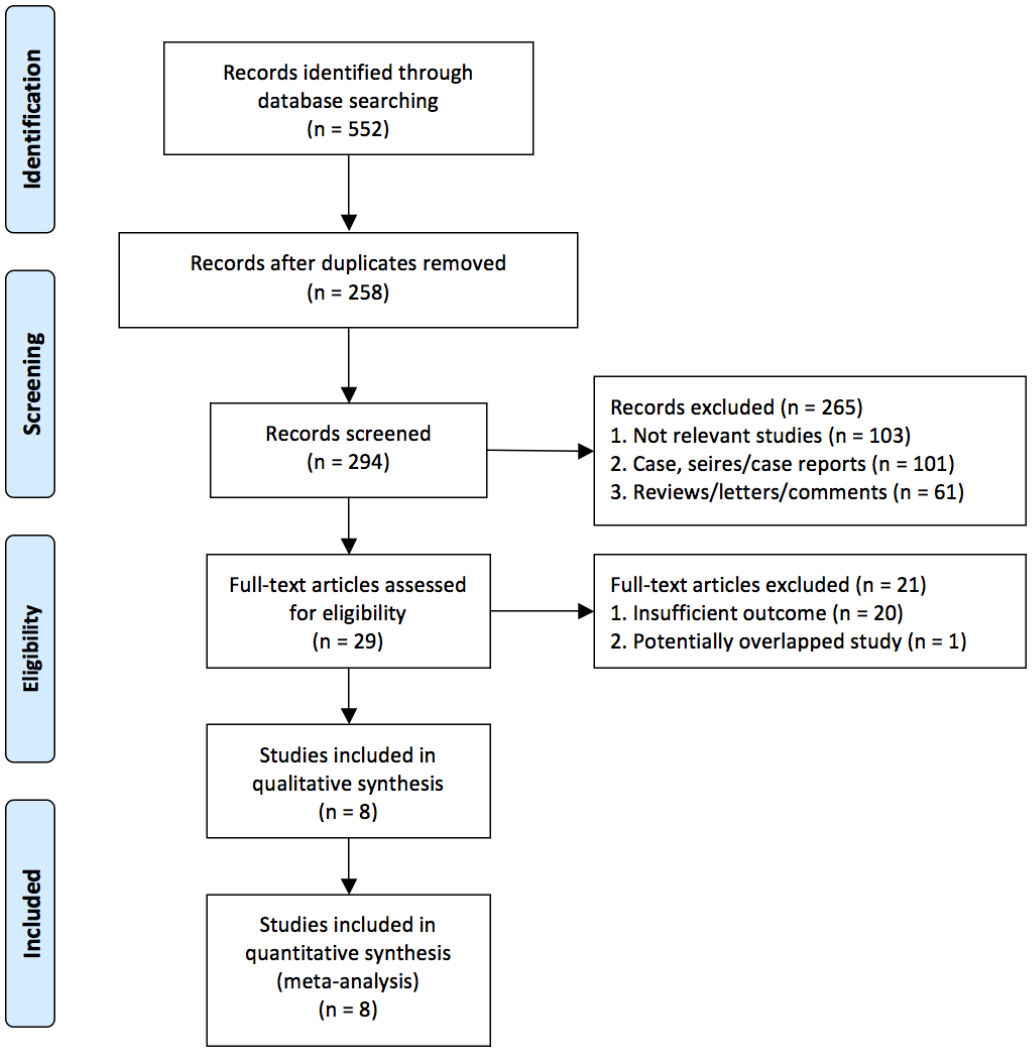
Study	Surgical approach	Bladder cuffing	Neoadjuvant/adjuvant therapy
Hendin BN *et al* 1999 [20]	RNU	Yes	NA
Ishikawa S *et al* 2010 [21]	RNU (165 open and 43 laparoscopic)	Yes	No
Gurbuz C *et a*l 2011 [22]	RNU (970 open and 298 laparoscopic)	NA	153 adjuvant therapy (immunotherapy and chemotherapy)
Luo HL *et al* 2013 [23]	RNU	Yes (156 endoscopic and 240 extravesical)	No
Nison L *et al* 2013 [24]	RNU	NA	No
Sung HH *et al* 2015 [25]	RNU (392 open and 238 laparoscopic)	Yes (361 intravesical and 269 extravesical)	128 adjuvant therapy
Liu P *et al* 2016 [26]	RNU	Yes	No
Sankin A *et al* 2016 [27]	RNU	NA	NA

RNU, radical nephroureterectomy; NA, not available.

Table 3 Chi-square tests for the two groups

Variable	URS+ (n, %)	URS- (n, %)	*P* value
Tumour stage			<0.001
≤T2	801 (74.9)	1782 (61.3)	
>T2	269 (25.1)	1123 (38.7)	
Tumour grade			0.104
Low grade or ≤G2	482 (45.0)	1225 (42.2)	
High grade or >G2	588 (55.0)	1680 (57.8)	

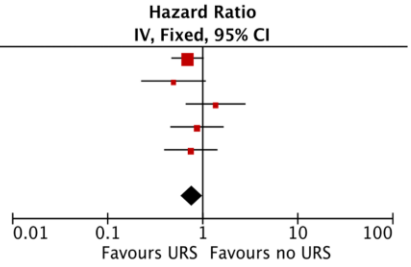
URS+, ureteroscopy before nephroureterectomy; URS-, without ureteroscopy before nephroureterectomy



A

Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Gurbuz 2011	−0.37	0.2	175	1093	43.9%	0.69 [0.47, 1.02]
Ishikawa 2010	−0.71	0.4	55	153	11.0%	0.49 [0.22, 1.08]
Luo 2013	0.31	0.37	115	281	12.8%	1.36 [0.66, 2.82]
Nison 2013	−0.14	0.33	170	342	16.1%	0.87 [0.46, 1.66]
Sankin 2016	−0.29	0.33	144	57	16.1%	0.75 [0.39, 1.43]
Total (95% CI)			**659**	**1926**	**100.0%**	**0.76 [0.59, 0.99]**

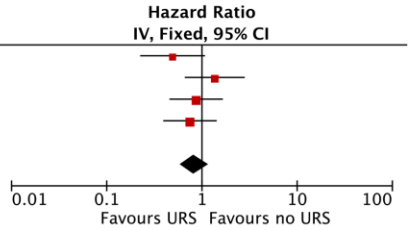
Heterogeneity: $Chi^2 = 4.08$, df = 4 (P = 0.40); $I^2 = 2\%$
Test for overall effect: Z = 2.04 (P = 0.04)



B

Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Ishikawa 2010	−0.71	0.4	55	153	19.6%	0.49 [0.22, 1.08]
Luo 2013	0.31	0.37	115	281	22.9%	1.36 [0.66, 2.82]
Nison 2013	−0.14	0.33	170	342	28.8%	0.87 [0.46, 1.66]
Sankin 2016	−0.29	0.33	144	57	28.8%	0.75 [0.39, 1.43]
Total (95% CI)			**484**	**833**	**100.0%**	**0.83 [0.58, 1.17]**

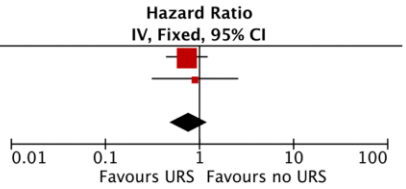
Heterogeneity: $Chi^2 = 3.63$, df = 3 (P = 0.30); $I^2 = 17\%$
Test for overall effect: Z = 1.08 (P = 0.28)



C

Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Hendin 1999	−0.31	0.26	48	48	81.2%	0.73 [0.44, 1.22]
Sankin 2016	−0.11	0.54	144	57	18.8%	0.90 [0.31, 2.58]
Total (95% CI)			**192**	**105**	**100.0%**	**0.76 [0.48, 1.21]**

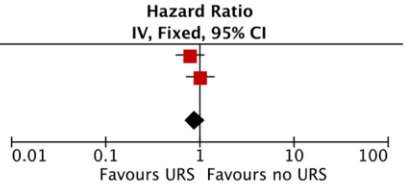
Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 1.16 (P = 0.24)



D

Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Gurbuz 2011	−0.24	0.18	175	1093	50.0%	0.79 [0.55, 1.12]
Nison 2013	0.01	0.18	170	342	50.0%	1.01 [0.71, 1.44]
Total (95% CI)			**345**	**1435**	**100.0%**	**0.89 [0.69, 1.14]**

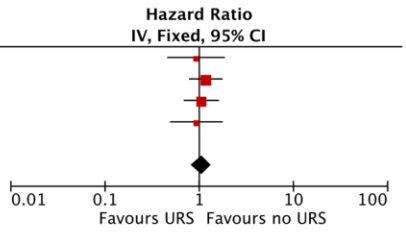
Heterogeneity: $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0\%$
Test for overall effect: Z = 0.90 (P = 0.37)



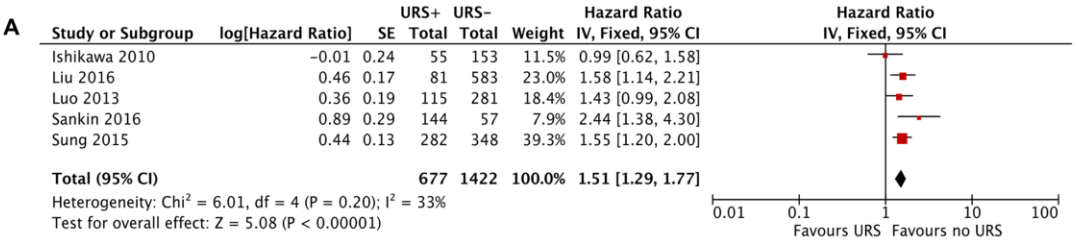
E

Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Hendin 1999	−0.08	0.36	48	48	12.8%	0.92 [0.46, 1.87]
Luo 2013	0.16	0.21	115	281	37.6%	1.17 [0.78, 1.77]
Nison 2013	0.05	0.22	170	342	34.3%	1.05 [0.68, 1.62]
Sankin 2016	−0.07	0.33	144	57	15.2%	0.93 [0.49, 1.78]
Total (95% CI)			**477**	**728**	**100.0%**	**1.06 [0.82, 1.36]**

Heterogeneity: $Chi^2 = 0.53$, df = 3 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = 0.44 (P = 0.66)



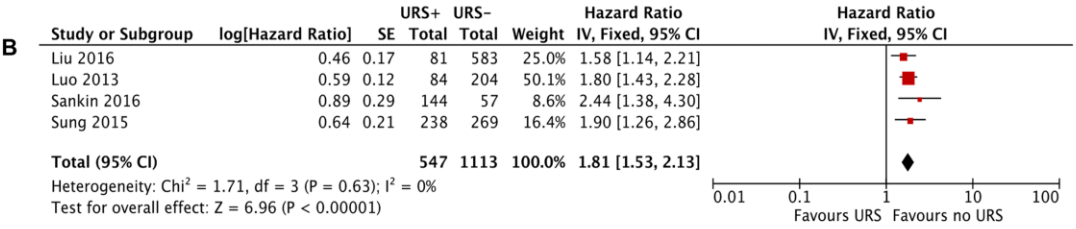
A



Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Ishikawa 2010	−0.01	0.24	55	153	11.5%	0.99 [0.62, 1.58]
Liu 2016	0.46	0.17	81	583	23.0%	1.58 [1.14, 2.21]
Luo 2013	0.36	0.19	115	281	18.4%	1.43 [0.99, 2.08]
Sankin 2016	0.89	0.29	144	57	7.9%	2.44 [1.38, 4.30]
Sung 2015	0.44	0.13	282	348	39.3%	1.55 [1.20, 2.00]
Total (95% CI)			**677**	**1422**	**100.0%**	**1.51 [1.29, 1.77]**

Heterogeneity: $Chi^2 = 6.01$, df = 4 (P = 0.20); $I^2 = 33\%$
Test for overall effect: Z = 5.08 (P < 0.00001)

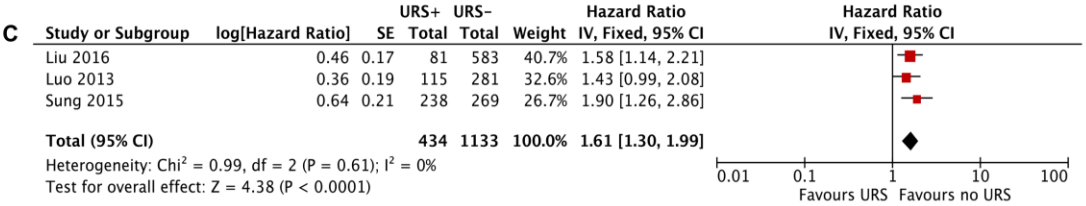
B



Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Liu 2016	0.46	0.17	81	583	25.0%	1.58 [1.14, 2.21]
Luo 2013	0.59	0.12	84	204	50.1%	1.80 [1.43, 2.28]
Sankin 2016	0.89	0.29	144	57	8.6%	2.44 [1.38, 4.30]
Sung 2015	0.64	0.21	238	269	16.4%	1.90 [1.26, 2.86]
Total (95% CI)			**547**	**1113**	**100.0%**	**1.81 [1.53, 2.13]**

Heterogeneity: $Chi^2 = 1.71$, df = 3 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 6.96 (P < 0.00001)

C



Study or Subgroup	log[Hazard Ratio]	SE	URS+ Total	URS− Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Liu 2016	0.46	0.17	81	583	40.7%	1.58 [1.14, 2.21]
Luo 2013	0.36	0.19	115	281	32.6%	1.43 [0.99, 2.08]
Sung 2015	0.64	0.21	238	269	26.7%	1.90 [1.26, 2.86]
Total (95% CI)			**434**	**1133**	**100.0%**	**1.61 [1.30, 1.99]**

Heterogeneity: $Chi^2 = 0.99$, df = 2 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 4.38 (P < 0.0001)