 doi:10.20944/preprints202107.0387.v1

Review

The impact of diagnostic ureteroscopy prior to radical nephroureterectomy on oncological outcomes in patients with upper tract urothelial carcinoma: a comprehensive systematic review and meta-analysis

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Abstract: Background: The incidence of intravesical recurrence (IVR) following radical nephroureterectomy (RNU) is reported in up to 50% of patients with upper tract urothelial carcinoma (UTUC). It was suggested that preoperative diagnostic ureteroscopy (URS) could increase the IVR rate after RNU, however, the available data are often conflicting. Thus, in this systematic review and meta-analysis we sought to synthesize that available data for the impact of pre-RNU URS for UTUC on IVR and other oncological outcomes; Materials and methods: A systematic literature search of the PubMed, Embase and Cochrane Library databases was performed in June 2020. Cumulative analyses of hazard ratios (HRs) and their corresponding 95% confidence intervals (CI) were conducted. The primary endpoint was intravesical recurrence-free survival (IVRFS), with the secondary endpoints being cancer-specific survival (CSS), overall survival (OS), and metastasis-free survival (MFS); Results: Among a total of 5489 patients included in the sixteen selected papers, 2387 (43.4%) underwent diagnostic URS before RNU and 3102 (56.6%) did not. Pre-RNU diagnostic URS was significantly associated with worse IVRFS after RNU (HR=1.44, 95% CI: 1.29-1.61, p<0.001) than RNU alone. However, subgroup analysis including patients without biopsy during URS revealed no significant impact of diagnostic URS on IVRFS (HR=1.28, 95% CI: 0.90-1.80, p=0.16). The results of other analyses showed no significant differences in CSS (HR=0.94, p=0.63), OS (HR: 0.94, p=0.56), and MFS (HR: 0.91, p=0.37) between patients who underwent URS before RNU and those who did

not. Conclusions: The results of this meta-analysis confirm that diagnostic URS prior to RNU is significantly associated with worse IVRFS, albeit with no concurrent impact on the other long-term survival outcomes. Our results indicate that URS has a negative impact on IVRFS only when combined with endoscopic biopsy. Future studies are warranted to assess the role of immediate postoperative intravesical chemotherapy in patients undergoing biopsy during URS for suspected UTUC.

Keywords: upper tract urothelial carcinoma; radical nephroureterectomy; ureteroscopy; oncological outcomes.

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare neoplasm accounting for approximately 5 - 10% of all urothelial cancers [1]. According to the current European Association of Urology (EAU) guidelines, radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision is the standard treatment for high-risk UTUC [2]. However, the incidence of intravesical recurrence (IVR) following RNU is considerable and has been reported in up to 50% of patients [2,3].

Identification of risk factors for IVR after RNU in UTUC patient is among the major challenges facing urologists. Several studies and previous meta-analyses have suggested that preoperative diagnostic ureteroscopy (URS) could increase the IVR rate after RNU, which might be related to malignant urothelial cells backflow and tumour seeding during URS evaluation [4,5,6]. Nevertheless, the existing data is still conflicting. Furthermore, some technical aspects of URS, such as performance of biopsy during URS in relation to IVR have not been closely evaluated to date. Thus, in this updated systematic review and meta-analysis with detailed exploratory analyses, we sought to comprehensively synthesize the available data regarding the impact of URS before RNU for UTUC on IVR, as well as other oncological outcomes.

2. Materials and Methods

The present systematic review and meta-analysis were performed according to the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [7] and methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [8].

2.1. Search Strategy

Two review authors (ŁN and WK) independently performed a computerized systematic literature search of the PubMed, Embase and Cochrane Library databases using combination of the following terms/key words: („upper tract urothelial carcinoma" OR „upper tract urothelial cancer" OR „upper urinary tract cancer" „upper tract urothelial neoplasm" OR „transitional cell carcinoma of the upper urinary tract" OR „UTUC" OR „UUTC") AND („ureteroscopy" OR „URS"). No specific time or language limitations were applied. The references of the relevant review articles were also manually screened to ensure that no additional eligible papers were inadvertently omitted. Additional screening was also performed from ahead of print articles published in the various urological journals. The last search was conducted on 30 June 2021.

2.2. Inclusion and Exclusion Criteria

Studies were evaluated for eligibility based on a predefined PICOS (Population, Intervention, Comparator, Outcome, and Study design) approach. The inclusion criteria were as follows:

- (P)opulation: Patients with UTUC treated with RNU. There were no restrictions to age, gender, race, pathological stage, pathological grade, and previous intravesical therapy.
- (I)ntervention: Diagnostic URS with or without biopsy prior to RNU (URS (+) group).
- (C)omparator: No diagnostic URS prior to RNU (URS (-) group).
- (O)utcome: The primary outcome was intravesical recurrence-free survival (IVRFS). The secondary outcomes were cancer-specific survival (CSS), overall survival (OS), and metastases-free survival (MFS). Studies were deemed eligible if they reported at least one of the above mentioned outcomes.
- (S)tudy design: Prospective and retrospective studies

The exclusion criteria of were as follows: (1) studies were meeting abstracts, review papers, case reports, letters, and editorials; (2) studies reported no sufficient data to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs); (3) studies included patients who underwent tumour ablation during URS; (4) studies included patients who underwent kidney-sparing surgery.

In the case of multiple reports of the same cohort, the one with the most complete data aggregated with the longest follow-up duration was selected.

2.3. Data extraction

Data extraction process was completed independently by two review authors (ŁN and WK). Following initial screening of the search strategy results by titles and abstracts, full text screening and study selection was carried out using a standardized item forms. Disagreements or discrepancies were resolved by discussion with a third author who was not involved in the initial screening process (TS).

Initially, the following study-related data were extracted: first author, year of publication, journal, country of origin, study design, study duration, sample size, and duration of follow-up. Subsequently, the following clinicopathological variables were retrieved: participants' age and gender, proportion of patients with bladder cancer prior to RNU, proportion of patients who underwent biopsy during URS, UTUC location, tumour multifocality, pathological tumour stage and grade, proportion of patients with pathologically confirmed lymph node invasion (LNI), proportion of patients with concomitant carcinoma *in situ* (CIS), proportion of patients who received intravesical installation after RNU, and proportion of patients who received perioperative systemic chemotherapy. Also, data regarding the technical details of URS and RNU were extracted.

Eventually, the outcome measurements of IVRFS, CSS, OS, MFS (including HRs and 95% CIs) were extracted. Missing information or clarifications were sought by contacting the primary authors, however, no additional data were received.

2.4. Methodological Quality and Risk of Bias Assessment

The quality of the selected studies was assessed independently by two review authors (ŁN and WK). All selected nonrandomized studies were assessed for their methodological quality using the Newcastle-Ottawa Scale (NOS), with the methodological quality stratified by score as: low (0–3), moderate (4–6), or high (7–9) [9].

 doi:10.20944/preprints202107.0387.v1

The risk of bias (RoB) was determined independently by two review authors (ŁN and WK) using a pragmatic approach to the evaluation of nonrandomized studies by examining the adjustments for confounders according to the Cochrane Handbook for Systematic Reviews of Interventions [8]. The articles were therefore reviewed based on their adjustment for the effects of the following confounders: age, gender, tumour location, tumour multifocality, pathological tumour stage, pathological tumour grade, and presence of concomitant CIS.

Finally, all eligible studies were evaluated for the potential publication bias. Give that visual interpretation of the funnel plot asymmetry is inherently subjective and should be interpreted carefully due to several possible explanations, publication bias assessment was mainly based on the results of the Egger's asymmetry test.

Throughout the whole process of methodological quality and RoB assessment, any disagreements and discrepancies were solved by consensus or recourse to the third author (TS).

2.5. Statistical Analysis

Effect measures for the outcomes of survival (IVRFS, CSS, OS, and MFS) were HRs and 95% CIs, which were extracted from included articles. We preferred to collect data from multivariate Cox proportional hazard regression models, otherwise (if not reported), data from univariate analyses were extracted. For publications that did not present HRs and 95% CIs, the methods reported by Tirney et al. were used to incorporate summary time-to-event data into meta-analysis [10]. The statistical significance of the pooled HRs was evaluated by the Z test. Statistical pooling of the effect measures was based on the level of heterogeneity among the studies. Significant heterogeneity was indicated by either a ratio of > 50% in I^2 statistics or a p-value of < 0.05 in Cochran Q test, which led to the use of the random-effect model. When no significant heterogeneity was observed, fixed-effect model was used for calculations.

For each oncological outcome of interest (IVRS, CSS, OS, and MFS) we planned to perform primary pooled analyses including data from the main cohorts of all eligible publications. Subsequently, we planned to perform exploratory subgroup analyses as stratified by biopsy status, URS technique, tumour location, bladder cancer history, bladder cuff excision, receipt of perioperative systemic chemotherapy, receipt of intravesical installation post RNU, and geographical region. Also, sensitivity analyses were conducted to assess the robustness of the results by excluding one study from each analysis. These analyses were performed to examine the impact of weighting and whether a single study was driving the conclusions.

All statistical analyses were performed using Review Manager 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark), Statistica 13.3 (Tibco Software Inc. CA, USA), and Stata 16.0 software (STATA Corporation, College Station, TX, USA). For all tests, a p-value ≤ 0.05 was considered a statistically significant difference.

3. Results

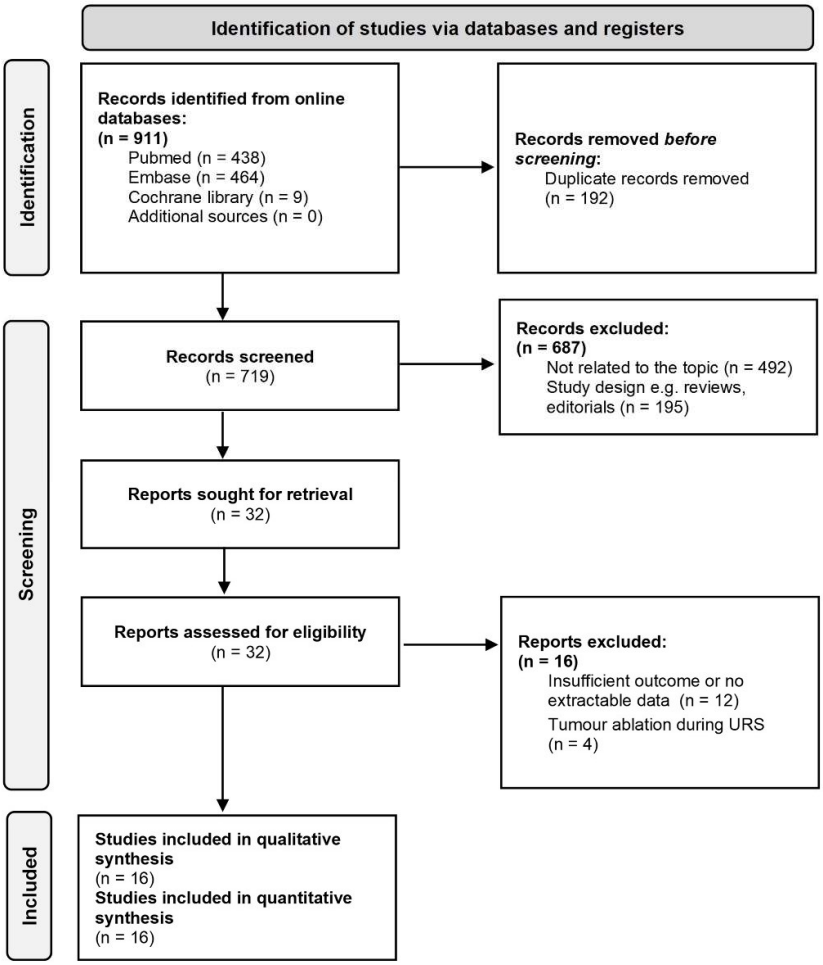
3.1. Literature Selection

The detailed flow diagram of study selection with subsequent exclusions is presented in **Figure 1**. Literature search using above mentioned methodology yielded a total of 911 articles (911 from online databases and 0 from additional sources). All citations were

 doi:10.20944/preprints202107.0387.v1

exported to the reference manager EndNote 20 (Clarivate Analytics) and duplicate references (n = 192) were removed. After screening of the titles and abstracts, 687 papers were excluded due to inappropriate article type (n = 195) or irrelevance to present topic (n = 492). The full text of 32 studies were read in detail to determine the eligibility. In accordance with the study inclusion criteria, 12 and 4 articles were excluded for insufficient outcome and inclusion of patients who received tumour ablation during URS, respectively. Finally, sixteen studies were included in this systematic review and meta-analysis [11-26].

Figure 1. Flow diagram of study selection.



3.2. Baseline Characteristics of Included Studies

The baseline characteristics of the sixteen studies included in the present systematic review and meta-analysis were presented in **Table 1**. All articles had retrospective design. Among a total of 5489 patients in the selected papers, 2387 (43.4%) and (%) underwent diagnostic URS before RNU [URS (+) group] and 3102 (56.6%) did not [URS (-) group]. Geographically, nine studies were conducted in Asia [13,15,17-21,25,26], four in North America [12,14,23,24], and three in Europe [11,16,22]. Included articles reported cases from the year 1985 to 2019. The median follow-up periods for whole or individual cohorts ranged from 21.4 months to 76.8 months. Among sixteen selected papers, thirteen provided data regarding IVRFS [11,13,15-21,23-26] whilst seven [13,15,17,20-23], seven [12,13,14,17,21,23,24] and five [14,17,20,22,23] studies reported CSS, OS and MFS, respectively.

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The NOS score for the included studies ranged from 6 to 9 with an overall mean score of 7.8. All studies were consequently of moderate or high quality (**Table 1**), which was considered appropriate for this systematic review and meta-analysis. All selected papers carried a high RoB, which was primarily related to their retrospective design. Assessment of confounding factors used for adjustments in Cox proportional hazard regression models for each study was presented together with forest plots.

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Table 1. Baseline characteristics and quality assessment of included studies

Author, year [reference]	**Journal**	**Country**	**Study design**	**Study duration,** years	**No. of patients, n** URS (+)/URS (-)	**Follow-up**, months URS (+)/URS (-)	**Reported outcomes of interest**	**Methodological quality** (NOS)
Baboudjian *et al.* 2020 [11]	*World Journal of Urology*	France	Retrospective Single-centre	2005 - 2017	70/23	Median: 35/34	IVRFS	8
Boorjian *et al.* 2005 [12]	*Urology*	United states	Retrospective Single-centre	1993 - 2003	75/34	Mean: 40.1/38.7	OS	6
Chung *et al.* 2020 [13]	*Investigative and Clinical Urology*	Korea	Retrospective Single-centre	2003 - 2018	226/227	Median: 46.1/36.9	IVRFS, CSS, OS	7
Hendin *et al.* 1999 [14]	*The Journal of Urology*	United States	Retrospective Single-centre	1985 - 1995	48/48	Mean: 50.4/42.4	OS, MFS	8
Ishikawa *et al.* 2010 [15]	*The Journal of Urology*	Japan	Retrospective Multi-centre	1990 - 2005	55/153	Median: 35/51	IVRFS, CSS	7
Izol *et al.* 2021 [16]	*Urologia Internationalis*	Turkey	Retrospective Multi-centre	2005 - 2019	95/99	Mean: 36.4/41.8	IVRFS	8
Lee HY *et al.* 2018 [17]	*World Journal of Surgical Oncology*	Taiwan	Retrospective Single-centre	1990 - 2013	206/296	Whole cohort Mean: 76.8	IVRFS, CSS, OS, MFS	9
Lee JK *et al.* 2016 [18]	*Clinical Genitourinary Cancer*	Korea	Retrospective Single-centre	2003 - 2012	74[#]/30	Whole cohort Mean: 34.4	IVRFS	8
Liu *et al.* 2016 [19]	*International Brazilian Journal of Urology*	China	Retrospective Single-centre	2000 - 2011	81/583	Whole cohort Median: 48	IVRFS	9
Luo *et al.* 2013 [20]	*Annals of Surgical Oncology*	Taiwan	Retrospective Single-centre	2004 - 2010	115/281	Mean: 42.4/38.9	IVRFS, CSS, MFS	9
Ma *et al.* 2019 [21]	*Journal of Peking University (Health Sciences)*	China	Retrospective Single-centre	2007 - 2016	110/53	Whole cohort Median: 40	IVRFS, CSS, OS	7
Nison *et al.*	*World Journal of Urology*	France	Retrospective	1995 - 2011	170/342	Median: 21.4/24	CSS, MFS	7

2013 [22]			Multi-centre					
Sankin *et al.* 2016 [23]	*Urology*	United States	Retrospective Single-centre	1994 - 2012	144/57	Whole cohort Median: 64.8	IVRFS, CSS, OS, MFS	7
Sharma *et al.* 2021 [24]	*The Journal of Urology*	United States	Retrospective Single-centre	1995 - 2019	567[##]/210	Whole cohort Median 29.3	IVRFS, OS	9
Sung *et al.* 2015 [25]	*PLOS One*	Korea	Retrospective Single-centre	1994 - 2013	282/348	Median: 30.1/39.3	IVRFS	8
Yoo *et al.* 2017 [26]	Journal of Endourology	Korea	Retrospective Single-centre	1998 - 2012	69/318	Whole cohort Median: 62	IVRFS	7

[#] number of patients who underwent URS regardless of following RNU time

[##] number of patients who underwent URS regardless of biopsy status

Abbreviations: **CSS** = cancer-specific survival **IVRFS** = intravesical recurrence-free survival; **MFS** = metastases-free survival; **NOS** = Newcastle-Ottawa Scale; **OS** = overall survival**; URS =** ureteroscopy

 doi:10.20944/preprints202107.0387.v1

3.3. Clinicopathological Characteristics of Included Studies

Clinicopathological characteristics of patients in selected articles are presented in **Table 2**. The median or mean age of patients in included studies ranged from 63.8 to 73 years, with no statistically significant differences observed between URS (+) and URS (-) groups. The male predominance was reported in twelve [11-16,18,22-26] out of sixteen articles. Six studies [11,13,16,18,19,23] presented populations without history of bladder cancer prior to RNU. The proportion of patients with history of bladder cancer in ten remaining articles [12,14,15,17,20,21,22,24,25,26] ranged from 4.5% - 42.7% and 0% - 44% in URS (+) and URS (-) groups, respectively. In four [12,17,21,26] out of sixteen articles all patients underwent URS with biopsy, whilst in eight articles [11,15,16,18,20,22,24,25] biopsy rates during URS ranged from 59.5% to 92.6%. Four publications [13,14,19,23] lacked data regarding performance of URS biopsy. Two studies [24,25] distinguished specific sub-populations based on performance of biopsy during URS and analysed differences in IVRFS in reference to patients who not underwent URS before RNU. In majority of eligible publications URS (+) and URS (-) groups were well matched in terms of pathological tumour characteristics. Only four [11,19,21,22] out of sixteen studies reported significant differences in pathological tumour stage between patients who underwent URS and those who did not (with a higher proportion of ≤ pT2 tumours in URS (+) groups). In one study [22], a lower proportion of G3 tumours was observed in URS (+) group. Some trials reported a significantly higher rates of ureteral tumours in patients who underwent URS before RNU [13,16,18,19,20,22,23]. If reported, LNI and concomitant CIS rates were similar in most studies. Proportion of patients receiving intravesical installation after RNU ranged from 9.7% to 16% and 1.9% to 22% in URS (+) and URS (-) groups, based on data collected from two articles [11,24]. Data regarding administration of perioperative systemic chemotherapy were presented in three papers [16,24,25], whereas in other articles patients receiving neoadjuvant or adjuvant systemic chemotherapy were initially excluded or no data were available. Additional information regarding technical details of URS and RNU were presented in **Supplementary Table 1**.

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Table 2. Clinical and pathological characteristics of included studies

Author, **year** [reference]	**Group**	**Age**	**Male gender**, n (%)	**History of bladder cancer before RNU**, n (%)	**Biopsy**, n (%)	**Tumour location**, n (%)	**Multifocal tumour**, n (%)	**Pathological stage**, n (%)	**Pathological grade**, n (%)	**LNI**, n (%)	**Concomitant CIS**, n (%)	**Intravesical installation post RNU**, n (%)	**Perioperative systemic CTX**, n (%)
Baboudjian *et al.* 2020 [11]	**URS ((+))** n = 70	72[a]	50 (71.4)	Excluded	62(88.6)	Pelvicalyceal: 40 (57.1) Ureter: 30 (42.9)	14 (20.0)	≤ pT2: 47 (67.1)* > pT2: 23 (32.9)	LG: 19 (27.1) HG: 51 (72.9)	2 (3.0)	7 (10.0)	11 (16.0)	NAC, AC: excluded
	URS ((-)) n = 23	73[a]	17 (73.9)	Excluded	-	Pelvicalyceal: 16 (69.6) Ureter: 7 (30.4)	2 (8.7)	≤ pT2: 9 (39.1) > pT2: 14 (60.9)	LG: 3 (13.0) HG: 20 (87.0)	2 (9.0)	0 (0.0)	5 (22.0)	NAC, AC: excluded
Boorjian *et al.* 2005 [12]	**URS ((+))** n = 75	68.4[b]	53 (70.7)	32 (42.7)	75 (100.0)	Pelvicalyceal: 38 (50.7) Ureter: 37 (49.3)	NR	≤ pT2: 55 (78.6) > pT2: 16 (21.4)	LG: 54 (72.0) HG: 21 (28.0)	NR	NR	0 (0.0)	NR
	URS (-) n = 34	67.1[b]	24 (70.6)	15 (44.1)	-	Pelvicalyceal: 18 (52.9) Ureter: 16 (47.1)	NR	≤ pT2: 28 (82.4) > pT2: 6 (17.6)	LG: 27 (79.4) HG: 7 (20.6)	NR	NR	0 (0.0)	NR
Chung *et al.* 2020 [13]	**URS (+)** n = 226	65.9[b]	155 (68.6)	Excluded	NR	Pelvicalyceal: 64 (28.3)* Ureter: 129 (57.1) Multiple: 33 (14.6)	33 (14.6)	≤ pT2: 146 (64.6) > pT2: 80 (35.4)	G1: 2 (0.9) G2: 122 (54.0) G3: 99 (45.1)	22 (9.7)	NR	NR	NR
	URS (-) n = 227	67.0[b]	165 (72.7)	Excluded	-	Pelvicalyceal: 97 (42.7) Ureter: 72 (31.7) Multiple: 58 (25.6)	58 (25.6)	≤ pT2: 139 (61.2) > pT2: 88 (38.8)	G1: 0 (0.0) G2: 103 (45.8) G3: 123 (54.2)	23 (10.1)	NR	NR	NR
Hendin *et al.* 1999 [14]	**URS (+)** n = 48	63.2[b]	37 (77.1)	14 (29.2)	NR	Pelvicalyceal: 15 (31.3) Ureter: 23 (47.9) Both: 10 (20.8)	NA	≤ pT2: 38 (80.6) > pT2: 9 (19.4)	G1: 9 (20.0) G2: 23 (51.0) G3: 13 (29.0)	NR	NR	NR	NR
	URS (-) n = 48	67.5[b]	31 (64.6)	17 (35.4)	-	Pelvicalyceal: 25 (52.1) Ureter: 14 (29.2) Both: 9 (18.7)	NA	≤ pT2: 33 (70.2) > pT2: 14 (29.8)	G1: 6 (12.5) G2: 19 (39.6) G3: 23 (47.9)	NR	NR	NR	NR
Ishikawa *et al.* 2010 [15]	**URS (+)** n = 55	71[a]	36 (65.5)	13 (23.6)	36 (65.5)	Pelvicalyceal: 27 (49.1) Ureter: 28 (50.9)	7 (12.7)*	≤ pT2: 43 (78.2) > pT2: 12 (21.8)	LG: 43 (78.2) HG: 12 (21.8)	1 (1.8)*	NR	NR	NAC, AC: excluded
	URS (-)	70[a]	103 (67.3)	26 (17.0)	-	Pelvicalyceal: 84 (54.9)	41 (26.8)	≤ pT2: 101 (66.0)	LG: 99 (64.7)	13 (8.5)	NR	NR	NAC, AC: excluded

	n = 153					Ureter: 69 (45.1)		> pT2: 52 (34.0)	HG: 54 (35.3)			
Izol *et al.* 2021 [16]	**URS (+)** n = 95	66.3[b]	74 (77.9)	Excluded	58 (61.1)	Pelvicalyceal: 46 (48.4)* Ureter: 35 (36.8) Both: 14 (14.7)	NA	≤ pT2: 48 (50.5) > pT2: 47 (49.5)	LG: 27 (28.4) HG: 68 (71.6)	6 (6.4)	8 (8.4)	Excluded	NAC: 8 (8.4) AC: 12 (12.6)
	URS (-) n = 99		80 (80.8)	Excluded	-	Pelvicalyceal: 74 (74.7) Ureter: 17 (17.2) Both: 8 (8.1)	NA	≤ pT2: 35 (45.5) > pT2: 54 (54.5)	LG: 33 (33.3) HG: 66 (66.7)	9 (9.1)	6 (6.1)	Excluded	NAC: 3 (3.0) AC: 19 (19.2)
Lee HY *et al.* 2018 [17]	**URS (+)** n = 206	66.1[b]	85 (41.3)	61 (29.6)	206 (100.0)	Pelvicalyceal: 76 (36.9) Ureter: 95 (46.1) Both: 35 (17.0)	44 (21.4)	≤ pT2: 137 (66.5) > pT2: 69 (33.5)	LG: 48 (23.2) HG: 158 (76.7)	16 (7.8)	NR	0 (0.0)	NR
	URS (-) n = 296	65.7[b]	135 (45.6)	87 (29.4)	-	Pelvicalyceal: 114 (38.5) Ureter: 126 (42.6) Both: 56 (18.9)	73 (24.7)	≤ pT2: 192 (64.8) > pT2: 104 (35.2)	LG: 63 (21.3) HG: 233 (78.7)	23 (7.8)	NR	0 (0.0)	NR
Lee JK *et al.* 2016 [18]	**URS (+)** n = 74[#]	67.3[b]	48 (64.9)	0 (0.0)	44 (59.5)	Pelvicalyceal: 68 (91.9)* Ureter: 6 (8.1)	11 (14.9)*	≤ pT2: 64 (86.5) > pT2: 10 (13.5)	LG: 18 (24.3) HG: 56 (75.7)	NR	13 (17.6)	NR	NAC: 0 (0.0) AC: 0 (0.0)
	URS (-) n = 30	67.5[b]	23 (76.6)	0 (0.0)	-	Pelvicalyceal: 21 (70.0) Ureter: 9 (30.0)	10 (33.3)	≤ pT2: 23 (76.7) > pT2: 7 (23.3)	LG: 7 (23.3) HG: 23 (76.7)	NR	3 (10.0)	NR	NAC: 0 (0.0) AC: 0 (0.0))
Liu *et al.* 2016 [19]	**URS (+)** n = 81	65.9[b]	31 (38.3)	Excluded	NR	Pelvicalyceal: 26 (32.1)* Ureter: 55 (67.9)	27 (33.3)*	≤ pT2: 65 (80.2)* > pT2: 16 (19.8)	LG: 51 (63.0) HG: 30(37.0)	3 (3.7)	4 (4.9)	NR	NAC: 0 (0.0) AC: 0 (0.0))
	URS (-) n = 583	66.6[b]	264 (45.3)	Excluded	-	Pelvicalyceal: 342 (58.7) Ureter: 241 (41.3)	132 (22.6)	≤ pT2: 393 (67.4) > pT2: 190 (32.6)	LG: 330 (56.6) HG: 253 (43.3)	44 (7.5)	15 (2.6)	NR	NAC: 0 (0.0) AC: 0 (0.0)
Luo *et al.* 2013 [20]	**URS (+)** n = 115	65.9[b]	54 (47.0)	31 (27.0)	85 (73.9)	Pelvicalyceal: 62 (53.9)* Ureter: 83 (72.2)	38 (33.0)	≤ pT2: 90 (78.3) > pT2: 25 (21.7)	LG: 13 (11.3) HG: 102 (88.7)	Excluded	39 (33.9)	0 (0.0)	NAC: 0 (0.0) AC: NR
	URS (-) n = 281	66.6[b]	136 (48.4)	77 (27.4)	-	Pelvicalyceal: 203 (72.2) Ureter: 149 (53.0)	92 (32.7)	≤ pT2: 199 (70.8) > pT2: 82 (29.2)	LG: 26 (9.3) HG: 255 (90.7)	Excluded	105 (37.4)	0 (0.0)	NAC: 0 (0.0) AC: NR
Ma *et al.* 2019 [21]	**URS (+)** n = 110	66.1[b]	51 (46.4)	5 (4.5)	110 (100.0)	Pelvicalyceal: 46 (41.8) Ureter: 59 (53.6) Both: 5 (4.2)	13 (11.8)	≤ pT2: 84 (76.4)* > pT2: 26 (23.6)	LG: 33 (30.0) HG: 77 (70.0)	3 (2.7)	NR	NR	NR

	URS (-) n = 53	69.0[b]	20 (37.8)	0 (0.0)	-	Pelvicalyceal: 27 (50.9) Ureter: 21 (39.6) Both: 5 (9.4)	9 (17.0)	≤ pT2: 32 (60.4) > pT2: 21 (39.6)	LG: 13 (24.5) HG: 40 (75.5)	2 (3.8)	NR	NR	NR
Nison *et al.* 2013 [22]	**URS (+)** n = 170	68.8[a]	112 (65.9)	39 (22.9)	117 (66.8)	Pelvicalyceal: 80 (47.1)* Ureter: 71 (41.8) Both: 19 (11.2)	NA	≤ pT2: 112 (65.9)* > pT2: 58 (34.1)	G1: 28 (16.5)* G2: 56 (32.9) G3: 86 (50.6)	7 (4.1)	NR	NR	NAC: excluded AC: NR
	URS (-) n = 342	70.1[a]	236 (69.0)	73 (21.4)	-	Pelvicalyceal: 197 (57.6) Ureter: 101 (29.5) Both: 44 (12.9)	NA	≤ pT2: 193 (56.4) > pT2: 149 (43.6)	G1: 34 (9.9) G2: 98 (28.7) G3: 210 (61.4)	32 (9.4)	NR	NR	NAC: excluded AC: NR
Sankin *et al.* 2016 [23]	**URS (+)** n = 144	70[a]	87 (60.4)*	0 (0.0)	NR	Pelvicalyceal: 83 (58.0)* Ureter: 40 (28.0) Both: 21 (15.0)	NA	≤ pT2: 105 (72.9) > pT2: 39 (27.1)	LG: 32 (22.0) HG: 112 (78.0)	NR	NR	NR	NR
	URS (-) n = 57	71[a]	23 (40.0)	0 (0.0)	-	Pelvicalyceal: 44 (77.0) Ureter: 7 (12.0) Both: 6 (11.0)	NA	≤ pT2: 36 (63.2) > pT2: 21 (36.8)	LG: 8 (14.0) HG: 49 (86.0)	NR	NR	NR	NR
Sharma *et al.* 2021 [24]	**URS (+)** n = 567[##]	72.8[a]	369 (65.1)	177 (31.2)	442 (78.0)	NA	179 (31.6)	≤ pT2: 347 61.2) > pT2: 220 (38.8)	LG: 190 (33.5) HG: 339 (59.8)	NR	45 (7.9)*	55 (9.7)*	NAC: 47 (8.3) AC: 75 (13.2)
	URS (-) n = 210	72.5[a]	145 (69.0)	68 (34.3)	-	NA	82 (39.6)	≤ pT2: 114 (54.3) > pT2: 96 (45.7)	LG: 76 (40.9) HG: 110 (59.1)	NR	4 (1.9)	4 (1.9)	NAC: 14 (6.7) AC: 36 (17.1)
Sung *et al.* 2015 [25]	**URS (+)** n = 282	64[a]	212 (75.2)	44 (15.6)*	261 (92.6)	Ureter involved: 145 (51.4)	81 (28.7)	≤ pT2: 191 (67.7) > pT2: 91 (32.3)	G1,G2: 158 (54.6) G3: 124 (45.4)	20 (7.1)	36 (12.8)	NR	NAC: NR AC: 54 (19.1)
	URS (-) n = 348	65[a]	253 (72.7)	79 (22.7)	-	Ureter involved: 171 (49.1)	87 (25.0)	≤ pT2: 174 (50.0) > pT2: 174 (50.0)	G1,G2: 195 (55.5) G3: 153 (44.5)	36 (10.3)	30 (8.6)	NR	NAC: NR AC: 74 (21.3)
Yoo *et al.* 2017 [26]	**URS (+)** n = 69	63.8[b]	52 (75.4)	13 (18.8)	69 (100.0)	Pelvicalyceal: 27 (39.1) Ureter: 42 (60.9)	14 (20.3)	≤ pT2: 52 (75.4) > pT2: 17 (24.6)	LG: 36 (52.9) HG: 32 (47.1)	3 (4.3)	12 (17.4)	0 (0.0)	NAC, AC: excluded
	URS (-)	63.9[b]	232 (73.0)	45 (14.2)	-	Pelvicalyceal: 158 (49.7)	55 (17.3)	≤ pT2: 223 (70.2)	LG: 159 (50.2)	23 (7.2)	43 (13.5)	0 (0.0)	NAC, AC: excluded

 doi:10.20944/preprints202107.0387.v1

n = 318	Ureter: 160 (50.3)	> pT2: 95 (29.8)	HG: 158 (49.8)	

[#] data is presented for patients who underwent URS regardless of following RNU time

[##] data is presented for patients who underwent URS regardless of biopsy status

[a] *median*

[b] *mean*

[*] Statistically significant difference between URS (+) and URS (-) groups

Abbreviations: **AC** = adjuvant chemotherapy; **CIS** = carcinoma *in situ*; **CTX** = chemotherapy; **HG** = high grade; **LG** = low grade; **LNI** = lymph node invasion; **NA** = not applicable; **NAC** = neoadjuvant chemotherapy; **NR** = not reported; **RNU** = radical nephroureterectomy; **URS** = ureteroscopy

 doi:10.20944/preprints202107.0387.v1

Data regarding characteristics of intravesical recurrences were provided in **Supplementary Table 2**. Rates of IVR reported in included studies ranged from 27.0% to 59.0% and 16.7% to 27.8 % in URS (+) and URS (-) groups, respectively. Only one study [11] provided pathological characteristics of bladder recurrences, reporting that all intravesical recurrences were <T2 stage, and majority of tumours were low-grade.

3.4. Meta-Analysis Results

3.4.1. Main Analyses

Data for IVRFS was extractable from 13 studies [11,13,15-21,23-26]. One study [18] presented HRs as stratified by timing of RNU after URS (RNU at the same day or later) and one study [24] presented HRs as stratified by performance of endoscopic biopsy during URS. Estimates in these studies were combined using a random-effects model and subsequently used in primary IVRFS analysis. A pooled results indicated that diagnostic URS prior to RNU was significantly associated with worse IVRFS after RNU compared to RNU alone (HR = 1.44, 95% CI: 1.29 - 1.61, $p < 0.001$) (**Figure 2A**). Heterogeneity between studies was considered non-significant with an $I^2 = 37\%$ ($p = 0.09$), thus, a fixed-effect model was used for data synthesis.

Data for CSS was extractable from 7 studies [13,15,17,20-23]. A pooled results indicated that compared to RNU alone, diagnostic URS prior to RNU was not significantly associated with worse CSS after RNU than RNU alone (HR = 0.94, 95% CI: 0.75 - 1.19, $p = 0.63$) (**Figure 2B**). Heterogeneity between studies was considered non-significant with an $I^2 = 29\%$ ($p = 0.21$), thus, a fixed-effect model was used for data synthesis.

Data for OS was extractable from 7 studies [12,13,14,17,21,23,24]. A pooled results indicated that compared to RNU alone, diagnostic URS prior to RNU was not significantly associated with worse OS after RNU than RNU alone (HR = 0.94, 95% CI: 0.75 - 1.17, $p = 0.56$) (**Figure 2C**). Heterogeneity between studies was considered non-significant with an $I^2 = 47\%$ ($p=0.08$), thus, a fixed-effect model was used for data synthesis.

Data for MFS was extractable from 5 studies [14,17,20,22,23]. A pooled results indicated that compared to RNU alone, diagnostic URS prior to RNU was not significantly associated with worse MFS after RNU than RNU alone (HR = 0.91, 95% CI: 0.74 - 1.12, $p = 0.37$) (**Figure 2D**). Heterogeneity between studies was considered non-significant with an $I^2 = 0\%$ ($p = 0.42$), thus, a fixed-effect model was used for data synthesis.

Examination of the funnel plots combined with analysis of the Egger's test results did not demonstrate a significant publication bias (**Figure 3**). In sensitivity analyses omitting enrolled studies in turn, the results showed that the pooled HRs did not differ significantly, suggesting that the findings of the primary analyses were stable (**Supplementary Table 3**).

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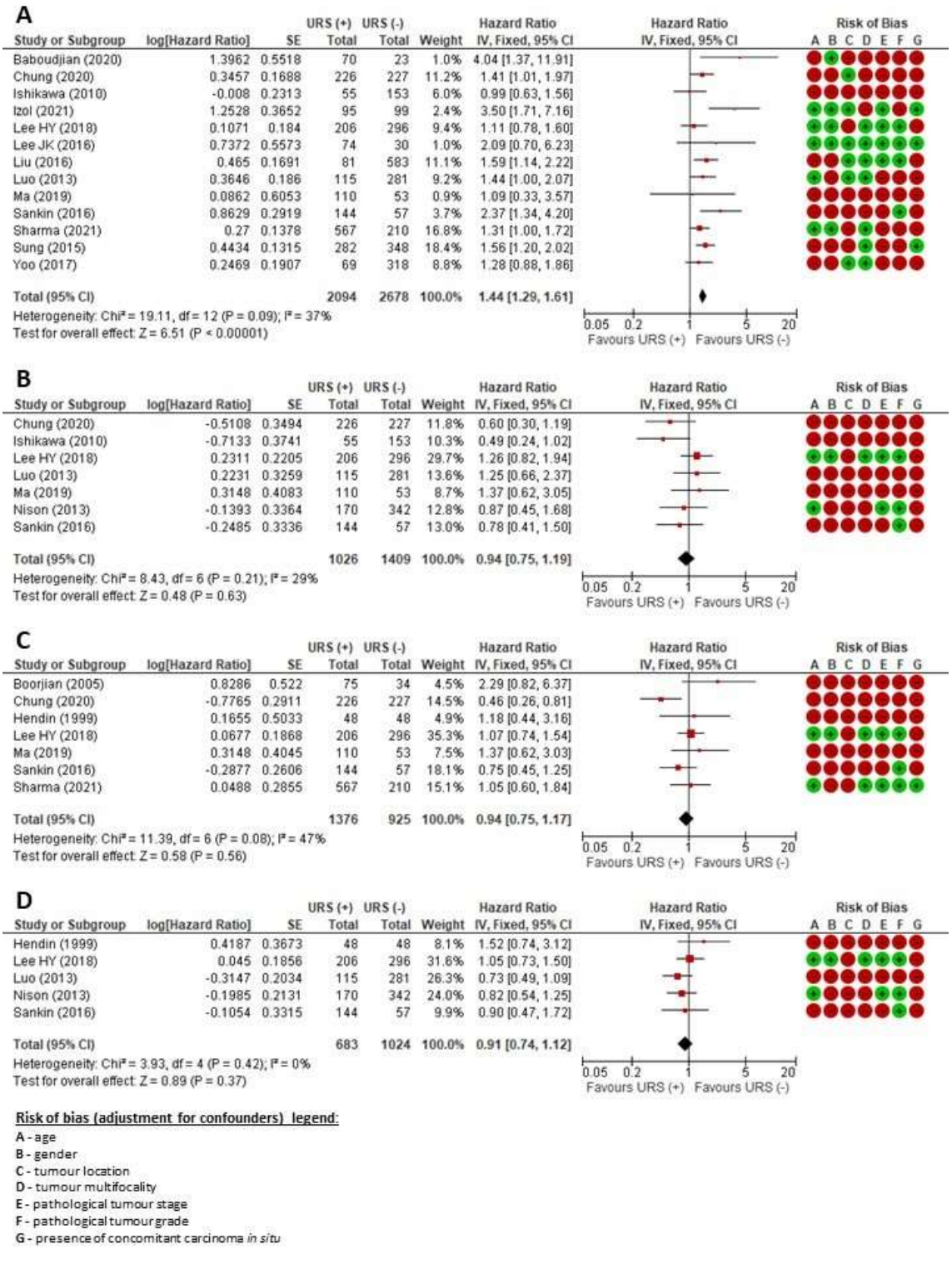
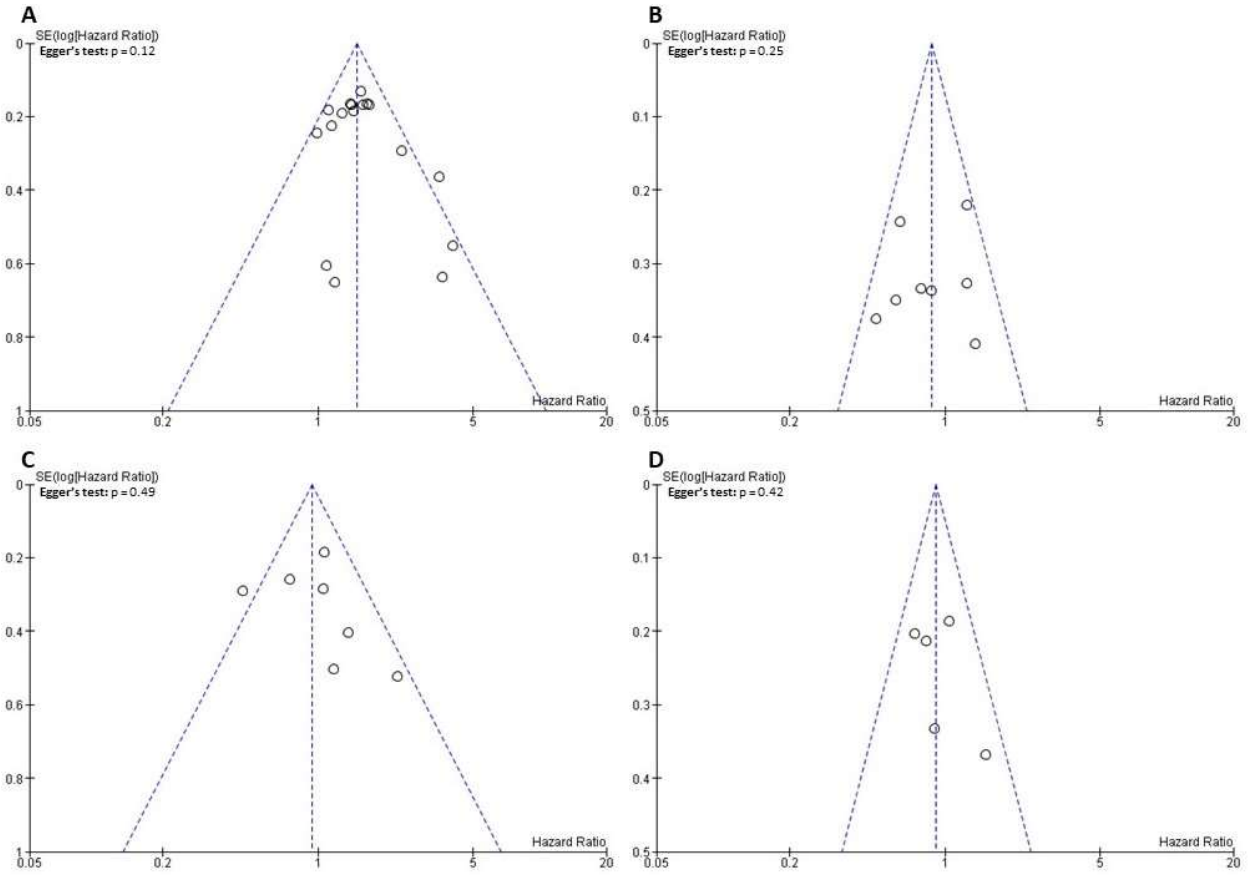
Figure 2. Forest plot comparing oncological outcomes in patients who underwent URS before RNU with those who did not. (**A**) intravesical recurrence-free survival; (**B**) cancer-specific survival; (**C**) overall survival (**D**) metastasis-free survival. Abbreviations: **CI** = confidence interval; **IV** = inverse variance; **RNU** = radical nephroureterectomy; **SE** = standard error; **URS** = ureteroscopy



 doi:10.20944/preprints202107.0387.v1

Figure 3. Funnel plot for the evaluation of potential publication bias: (**A**) intravesical recurrence-free survival; (**B**) cancer-specific survival; (**C**) overall survival; (**D**) metastasis-free survival. Abbreviations: **SE** = standard error



3.4.2. Exploratory Subgroup Analyses

Following assessment of primary analyses, pre-specified exploratory subgroup analyses of IVRFS were performed (**Table 3**). Given that CSS, OS, and MFS were reported in very few cohorts, no subgroup analyses were conducted for these oncological outcomes.

Subgroup analysis including patients without biopsy during URS revealed no significant impact of URS on IVRFS (HR = 1.28, 95% CI: 0.90 - 1.80, p = 0.16) in reference to patients who did not undergo URS before RNU. When patients receiving biopsy during URS were separately analysed, results were similar to primary IVRFS analysis (HR = 1.38, 95% CI: 1.20 - 1.60, p < 0.001). Also no association between URS and worse IVRFS was found in the subset of patients with history of bladder tumour. In all other subgroup analyses URS before RNU was significantly associated with worse IVRFS compared to RNU alone, similar as demonstrated in the primary IVRFS analysis.

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Table 3. Results of exploratory subgroup analyses comparing intravesical recurrence-free survival between URS (+) vs. URS (-) groups, stratified by: biopsy status, URS technique, tumour location, bladder cancer history, bladder cuff excision, receipt of perioperative systemic chemotherapy, receipt of intravesical installation post RNU, geographical region.

Stratification variable	Subgroup	No. of studies, n [reference]	No. of patients, n URS (+)/URS (-)	HR [95% CI] URS (+) vs URS (-)	P - value	Heterogeneity, I^2 (%)	Model
Biopsy status	Performed	5 [17,21,24,25,26]	1088/1062	1.38 [1.20 - 1.60]	<0.001	0%	FE
	Not performed	2 [24,25]	146/395	1.28 [0.90 - 1.80]	**0.16**	0%	FE
	Other*	8 [11,13,15,16,18,19,23]	860/1453	1.57 [1.34 - 1.86]	<0.001	45%	FE
URS technique	Rigid	1 [20]	115/281	1.44 [1.00 - 2.08]	0.05	NA	NA
	Flexible	1 [11]	70/23	4.04 [1.37 - 11.9]	0.01	NA	NA
	Other*	11 [13,15,16-21,23-26]	1909/2374	1.42 [1.27 - 1.60]	<0.001	37%	FE
Tumour location	Pelvis	1 [26]	27/158	2.06 [1.16 - 3.64]	0.01	NA	NA
	Ureter	1 [26]	42/160	1.02 [0.62 - 1.67]	**0.95**	NA	NA
	Other*	12 [11,13,15-21,23-25]	2025/2360	1.46 [1.30 - 1.64]	<0.001	41%	FE
Bladder cancer history	Yes	1 [17]	61/87	0.93 [0.65 - 1.33]	**0.69**	NA	NA
	No	10 [11,13,16-19,20,23,24,25]	1553/1861	1.71 [1.48 - 1.97]	<0.001	18%	FE
	Other*	3 [15,20,26]	239/752	1.26 [1.00 - 1.57]	0.05	0%	FE
Bladder cuff excision	Performed	9 [11,13,15,16,17,19,20,25,26]	1199/2328	1.43 [1.26 - 1.63]	<0.001	47%	FE
	Not performed	NA	NA	NA	NA	NA	NA
	Other*	4 [18,21,23,24]	895/260	1.47 [1.16 - 1.85]	0.001	26%	FE
Perioperative systemic CTX	Yes	NA	NA	NA	NA	NA	NA
	No	6 [11,15,18,19,20,26]	464/1388	1.41 [1.18 - 1.69]	<0.001	31%	FE
	Other*	7 [13,16,17,21,23,24,25]	1630/1290	1.46 [1.27 - 1.68]	<0.001	45%	FE
Intravesical installation post RNU	Yes	NA	NA	NA	NA	NA	NA
	No	4 [16,17,20,26]	485/994	1.48 [1.04 - 2.09]	0.03	63%	RE
	Other*	9 [11,13,15,18,19,21,23,24,25]	1609/1654	1.47 [1.29 - 1.68]	<0.001	26%	FE
Geographical region	Asia	9 [13,15,17,18,19,20,21,25,26]	1218/2289	1.38 [1.21 - 1.56]	<0.001	0%	FE
	North America	2 [23,24]	711/267	1.46 [1.14 - 1.86]	0.002	45%	FE

	Europe	2 [11,16]	165/122	3.66 [2.01 - 6.64]	<0.001	0%	FE

* Heterogeneous population in terms of stratification variable or data not reported

Abbreviations: **CTX =** chemotherapy; **FE =** fixed effect**; NA =** not applicable**; RNU =** radical nephroureterectomy; **URS =** ureteroscopy;; **RE =** random effect

 doi:10.20944/preprints202107.0387.v1

4. Discussion

In the present updated systematic review and meta-analysis, we attempted to provide a comprehensive summary of the evidence available for the impact of diagnostic URS prior to RNU on oncological outcomes in patients with UTUC. Our primary analyses confirmed that diagnostic URS before RNU had a significant negative impact on IVRFS after RNU without compromising the other oncological outcomes (CSS, OS, and MFS).

Kulp et al. and Lim et al initially explored the potential role of URS in cancer dissemination [27,28]. The former reported on a series of 13 patients who underwent URS followed by RNU, demonstrating the absence of vascular or lymphatic space tumour cells in their surgical specimens [27], while the latter described a case of suspected lymphatic invasion attribuable to high intrarenal pressures during URS [28]. Subsequently, several theories mainly based on intraluminal tumor seeding or intraepithelial cancer migration hypotheses, have been advanced to explain the observed higher rates of IVR after RNU preceded by URS [29,30]. Audenet et al. showed that the majority of bladder tumours following RNU are clonally related, supporting the hypothesis that IVR occurs through neoplastic cell implantation, rather than representing a second primary tumour [31]. Recent molecular studies demonstrated that UTUC and bladder urothelial carcinoma share mutations in similar genes, but at varying frequencies, which recapitulate with their metachronous recurrences [32]. Such differences in quantitative gene alterations might contribute to the behaviour of these two cancers and imply that they and their metachronous recurrences should be treated as two related yet distinct entities [32].

To the best of our knowledge, this is the first meta-analysis exploring the risk of IVR associated with URS combined with endoscopic biopsy prior to RNU. Although several studies and previous meta-analyses demonstrated that URS combined with tumour biopsy had no influence on IVR when compared to URS alone (only tumour visualization) [5,6,11,15], the direct comparisons of these subgroups (URS biopsy and URS alone) in reference to patients who did not undergo URS before RNU were not found. Herein, in this study, we found that patients not undergoing tumour biopsy during URS had comparable IVRFS to those diagnosed with UTUC based on imaging studies alone. Conversely, those undergoing URS biopsy were significantly associated with worse IVRFS than those not undergoing URS. These findings indicate that increased IVR risk after URS followed by RNU is related mainly to direct tumour manipulation during endoscopic biopsy. Our results thus provide the rationale for immediate administration of intravesical chemotherapy after URS only in those undergoing endoscopic biopsy.

Another potential risk associated with URS being performed prior to RNU raised by several authors is a delay in providing definitive treatment, which could be associated with poorer survival outcomes [33,34]. URS before RNU could significantly prolong the time between presentation and definitive treatment, especially when the histopathological confirmation is expected [33,34]. Recent multi-centre cohort study conducted by Lee et al. showed that delaying RNU for more than three months was associated with poor overall survival, thus, a delay between URS and RNU should not exceed this period [35]. In our meta-analysis we demonstrated that performing URS prior to RNU does not affect long-term oncological outcomes, such as CSS and OS, consistently with previous reports [5,6]. It could be explained by the fact, that reported delay between URS and RNU was not longer than two months in majority of included studies.

Unfortunately, certain technical aspects of URS, such as the duration of the procedure or irrigation pressure, have not been rigorously explored in the included studies. Moreover, only a minority of studies reported on the use of homogenous URS techniques

[11,20]. Results of these studies suggest that both rigid and flexible URS significantly increase the risk of IVR following RNU. Additionally, in a study conducted by Baboudjian et al., the risk of IVR was not decreased even with implementation of technical precautions to avoid contact of bladder mucosa with contaminated urine from the upper urinary tract (use of ureteral sheath, drainage with mono-J and bladder catheter) [11].

As tumour location, bladder cancer history, and bladder cuff management are considered important factors associated with IVR after RNU [2,3,36], we investigated the impact of URS followed by RNU on IVRFS in specific patient cohorts in our exploratory subgroup analyses. However, only one study stratified risk estimates by tumour location and reported that URS biopsy before RNU increased the risk of IVR in patients with renal pelvic tumours, but this was not associated with IVR in patients with ureteral tumours [26]. Study results suggest that the indications for URS combined with endoscopic biopsy should vary according to tumour location. If a ureteral tumour is suspected on other preoperative examinations, URS biopsy should not be spared to allow for pathologic confirmation of the tumour before definitive treatment. Furthermore, even after excluding patients with a previous history of bladder cancer patients undergoing URS were shown to be still at higher risk of IVR than those not undergoing URS. Thus, of the studies included, we subsequently confined our analysis to those involving bladder cuff management and found significantly worse IVRFS in those undergoing URS, a similar finding to that of primary analysis.

Although we demonstrated that URS prior to RNU is associated with significantly worse IVRFS than RNU alone in patients not receiving immediate intravesical installation following RNU or perioperative systemic chemotherapy, we were unable to perform subgroup analyses for populations of patients who received any form of neoadjuvant or adjuvant treatment due to lack of data. Give that single-dose intravesical chemotherapy give for up to postoperative 10 days reduces the risk of IVR within the first post-RNU years and that systemic chemotherapy has a significant beneficial effect on oncological outcomes in patients with UTUC [37,38], further studies including cohorts of patients receiving perioperative chemotherapy are necessary to make preliminary conclusions regarding the impact of URS prior to RNU on IVRFS in such setting.

It must be emphasized that the initial diagnosis of UTUC is still a challenging issue, especially for lower stage or flat growth pattern tumours [39,40]. Although various imaging techniques are available, including computed tomography urography, they fail to detect some proportion of UTUC (e.g. CIS) or to evaluate the superficial extension of the tumour. Given the limitations of imaging studies, URS could prove a valuable tool as a direct visualization method for diagnosis especially when combined with biopsies, as pathological T stage and tumour grade have been established as major prognostic factors for UTUC [2,36]. Thus, a balance should be struck between the risk of misdiagnosis without preoperative URS leading to unnecessary nephrectomy and that of IVR after RNU.

Although the influence of performing URS before RNU has been previously evaluated by other groups [4,5,6], our current study has several strengths. First, we included the latest available studies based on the latest literature search up to 30 June 2021. Second, we did not exclude non-English articles, in contrast to the previous meta-analyses. Third, our meta-analysis included the most detailed exploratory subgroup analyses performed to date. Nonetheless, despite its strengths, this review is not devoid of limitations. First, the strength of the conclusions that can be drawn from our meta-analysis is still limited, given the fact that all included studies were retrospective with their own unavoidable limitations, such as selection bias. Second, the adjustments for confounders in the Cox regression analyses were not uniform in the included trials and some studies provided only univariable data, which might introduce additional bias. Third, the results of

subgroup analyses should be interpreted carefully, as some of them were based on a limited number of patients.

5. Conclusions

The results of this systematic review and meta-analysis confirm that diagnostic URS prior to RNU is significantly associated with worse IVRFS, albeit with no concurrent impact on the other long-term survival outcomes. Our results indicate that URS has a negative impact on IVRFS only when combined with endoscopic biopsy. Future studies are warranted to assess the role of immediate postoperative intravesical chemotherapy in patients undergoing biopsy during URS for suspected UTUC.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, **Table S1**: Technical details of ureteroscopy and radical nephroureterectomy in included studies; **Table S2**: Characteristics of intravesical recurrences in included studies; **Table S3:** Results of sensitivity analyses.

Author Contributions: Conceptualization, Ł.N., W.K. and T.S.; methodology, Ł.N. and K.M.; software, Ł.N. and K.M.; validation, T.S.; formal analysis, W.K. and T.S.; investigation, all authors; resources, all authors; data curation, Ł.N.; writing—original draft preparation, all authors; writing—review and editing, W.K., K.M. and T.S.; visualization, Ł.N. and W.K.; supervision, T.S.; project administration, T.S.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

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