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The impact of tumor location and multifocality on prognosis for patients with upper tract urothelial carcinoma: a meta-analysis

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There is lack of consensus regarding the prognostic significance of primary tumor location of upper tract urothelial carcinoma(UTUC). We performed a meta-analysis to evaluate the impact of primary tumor location on prognosis in patients with UTUC who had undergone radical nephroureterectomy(RNU). We included eligible studies that reported hazard ratios(HRs) estimates with 95% confidence intervals(CIs) for the association between tumor location and recurrence-free survival(RFS) and cancer-specific survival(CSS) of UTUC. The local advanced tumors(pT3/4) and nodal positive(pN+) tumors in patients stratified by tumor location were also estimated. The review contained 17 studies including a total of 12094 patients were identified. Although it was not significant in univariable analysis, meta-analysis demonstrated that ureteral tumors had a worse prognosis than renal pelvic tumors on RFS and CSS in multivariable analysis after adjusted for all covariates. Multifocal tumors also showed a significantly association with both disease progression and cancer-specific mortality in univariable and multivariable analyses. However, no statistically significant differences were found between renal pelvic and ureteral tumors in presentation of pT3/4 and pN+ tumors. Our meta-analysis indicated that ureteral and multifocal tumors are independent prognosticators of disease progression and cancer-specific survival in patients with UTUC treated with RNU.

Upper tract urothelial carcinoma(UTUC) is a rare and heterogeneous disease that accounts for approximately 5% of all urothelial tumors, with an estimated incidence of 2.08 cases per 100000 person-years in the United States[1,2]. The male to female ratio is of approximately 2 : 1[3]. Amongst the known risk factors for the development of UTUC are cigarette smoking, abuse of analgetics, occupational factors, chronic infection and stone disease, as well as antineoplastic agents such as cyclophosphamide[4]. Usually UTUC is a multifocal disease. About 75% UTUC are located in the collecting system of the kidney, whilst 25% occur in the ureter[5]. For invasive, nonmetastatic UTUC radical nephroureterectomy(RNU) with bladder-cuff removal is considered the gold standard treatment of UTUC[6,7].

Several prognostic factors for UTUC have been identified. Widely accepted risk factors consist of the pathological stage of the primary tumor, lymph node status, the presence of distant metastases, lymphovascular invasion and tumor grade[8–12]. However, several other putative factors have been proposed with sometimes conflicting results. The location of the primary tumor (renal pelvis vs ureter) also represents a controversial risk factor. Several investigators reported significantly higher progression and/or cancer specific mortality rates in patients with primary ureteral UTUC[13–15]. Converse results showed significantly higher cancer specific mortality rates in patients with renal pelvis and/or upper ureteral UTUC primaries[16]. Finally other researchers could not demonstrate that tumor location increased or decreased the risk of disease progression and/or mortality[9,17]. Accordingly, here we perform a meta-analysis to testify whether tumor location is a prognostic factor influencing the progression and survival of UTUC.

Results

We identified 121 potentially relevant abstracts in our initial search. Of these, 86 were unrelated or not original research articles. Upon closer examination, 16 studies were excluded for the following reasons: one study was

Table 1 | Characteristics of included studies on tumor location and UTUC

Study	Location	Study period	No. of participants	Tumor location and No. of cases	Median age (range), yr	Study quality[a]	Adjusted variables
Raman 2009	globe	1987–2007	1249	U:426 P:823	68(27–97)	8	age, gender, surgical approach (open vs laparoscopic), prior endoscopic therapy, pT stage, grade, lymph node status
Yafi 2011	globe	1990–2010	673	U:215 P:376 M:46	68(61–75)	8	age, gender, race, presence of lymphovascular invasion, concomitant carcinoma in situ, pathological stage, lymph node dissection and type of surgery (open vs laparoscopic)
Novara 2007	Europe	1989–2005	269	U:92 P:101 M:113	67.7	8	age, gender, history of previous bladder cancer, synchronous muscle-invasive bladder TCC, pT stage, tumor grade, lymph nodes, presence of lymphatic and/or vascular invasion, surgical margin status, tumor site
Isbarn 2009	USA	1988–2004	2824	U:911 P:1913	NR	8	age, race, region, gender, types of surgery, pT stage, pN stage, tumor grade and year of surgery quartiles
Kobayashi 2010	Japan	2000–2004	221	U:111 P:110	72(46–92)	8	age, sex, pT stage, tumor grade, venous invasion, lymphatic invasion, surgical techniques
Dragicevic 2007	Serbia	1998–2005	114	U:30 P:37 M:36	67(38–86)	7	age, sex, BEN or non-endemic area of residence, serum, creatinine levels, Hb, synchronous bladder tumor, tumor size, tumor grade, tumor stage and lymphovascular invasion
Favaretto 2010	USA	1995–2008	253	U:78 P:171	72(64–77)	8	age, gender, race, smoking history, previous non-muscle-invasive bladder tumor, pT stage, pN stage, tumor grade, concomitant carcinoma in situ
Akdogan 2005	Turkey	1987–2003	72	U:21 P:51	58.9	8	age, sex, T stage, grade, bladder tumor history
Park 2004	Korea	1991–2001	86	U:41 P:45	59.5	9	age, grade, T stage, N stage, grade,
Chromecki 2011	globe	1987–2007	2492	U:640 P:1262 M:590	69.2(54.1–84.2)	8	age, gender, T stage, N stage, tumor stage, tumor architecture, lymphovascular invasion, lymph node involvement, receiving adjuvant chemotherapy
Lehmann 2006	Germany	1975–2004	145	U:136 M:19	68(29–85)	8	age, sex, pT stage, tumor grade, N stage, tumor stage, treatinin, alkaline phosphatase, WBC count, blood urea nitrogen, platelet count
Milojevic 2011	Serbia	1999–2009	133	U:45 P:88	NR	7	age, sex, laterality, previous carcinoma not invading bladder muscle, tumor grade, tumor stage, N stage, lymphovascular invasion
Ouzzane 2011	France	1995–2010	609	U:185 P:317 M:107	70(62–76)	8	age, sex, pT stage, tumor grade, N stage, lymphovascular invasion,
Zhang 2012	China	2000–2010	217	U:71 P:146	69(62–81)	8	gender, age, tumor stage, tumor grade, lymphovascular invasion, and lymph node status, preoperative hydronephrosis, type of surgery, follow-up
Park 2009	Korea	1991–2005	224	U:102 P:122	63	9	age, sex, T stage, N stage, grade, adjuvant chemotherapy
Mouracade 2011	Canada	1985–2005	269	U:108 P:161	66.7	8	age, gender, pT stage, pN stage, tumor grade, surgical margin status, adjuvant chemotherapy, period of diagnosis
Cha 2012	globe	1987–2007	2244	U:795 P:1449	69.9	9	age, gender, pT stage, pN stage, tumor grade, lymphovascular invasion, sessile tumor architecture, concomitant CIS, previous bladder cancer

Abbreviation: M, multifocal; NR, not reported; P, pelvis; U, ureter.
[a]: Study quality was judged on the basis of the Newcastle-Ottawa Scale (1–9 stars).

Table 2 | Summary of pooled results of UTUC by pT/pN status and tumor location

	Pooled RR	95%CI	P	I^2(%)
Ureter vs RP				
pT3/4	0.845	0.692–1.033	0.101	82.9
pN+	0.906	0.675–1.215	0.508	38.7

	Univariable analysis				Multivariable analysis			
	Pooled HR	95%CI	P	I^2(%)	Pooled HR	95%CI	P	I^2(%)
Ureter vs RP								
RFS	1.207	0.977–1.491	0.081	46.5	1.473	1.185–1.831	<0.001	61.7
CSS	1.199	0.955–1.505	0.118	74.6	1.456	1.212–1.750	<0.001	53.7
Multifocal tumor vs unifocal tumor								
RFS	1.932	1.336–2.793	<0.001	62.0	1.597	1.004–2.540	0.048	85.2
CSS	1.595	0.972–2.619	0.065	62.4	2.046	1.194–3.506	0.009	84.9

Abbreviation: CI, confidence interval; CSS, cancer specific survival; HR, hazard ratio; RFS, recurrence free survival; RP, renal pelvis; RR, risk ratio.

review; 11 studies did not provide sufficient information to estimate a summary HR and its 95% CI; three studies concerned about the effect of types of surgery; and one study just analysed different tumor location on the ureter, leaving 17 studies for reviewing[11,14,15,17–30].

Study characteristics. The 17 studies including 12094 participants were published in 2003–2012. The demographic characteristics of patients, adjusted variables and study quality of the included trials were summarized in Table 1. Of these 17 studies, four were global trials, six were conducted in Europe, two in north America, and four in Asia. Most studies met high quality criteria(8 to 9 stars) except two conducted in Serbia. All studies provided risk estimates that adjusted for age, gender, pT stage, pN stage and tumor grade; other risk estimates were provided to be adjusted for lymphovascular invasion(9 studies), adjuvant chemotherapy(7 studies), surgical approaches(5 studies), previous or synchronous bladder tumor(6 studies), race(3 studies), tumor architecture(4 studies) and region, marginal status, concomitant carcinoma in situ, smoking(3 studies respectively).

Clinicopathologic characteristics. Table 2 summarized the pooled results of local advanced(pT3/4) tumors and nodal positive(pN+) tumors in patients stratified by tumor location. It revealed that there were no statistically significant differences were found between renal

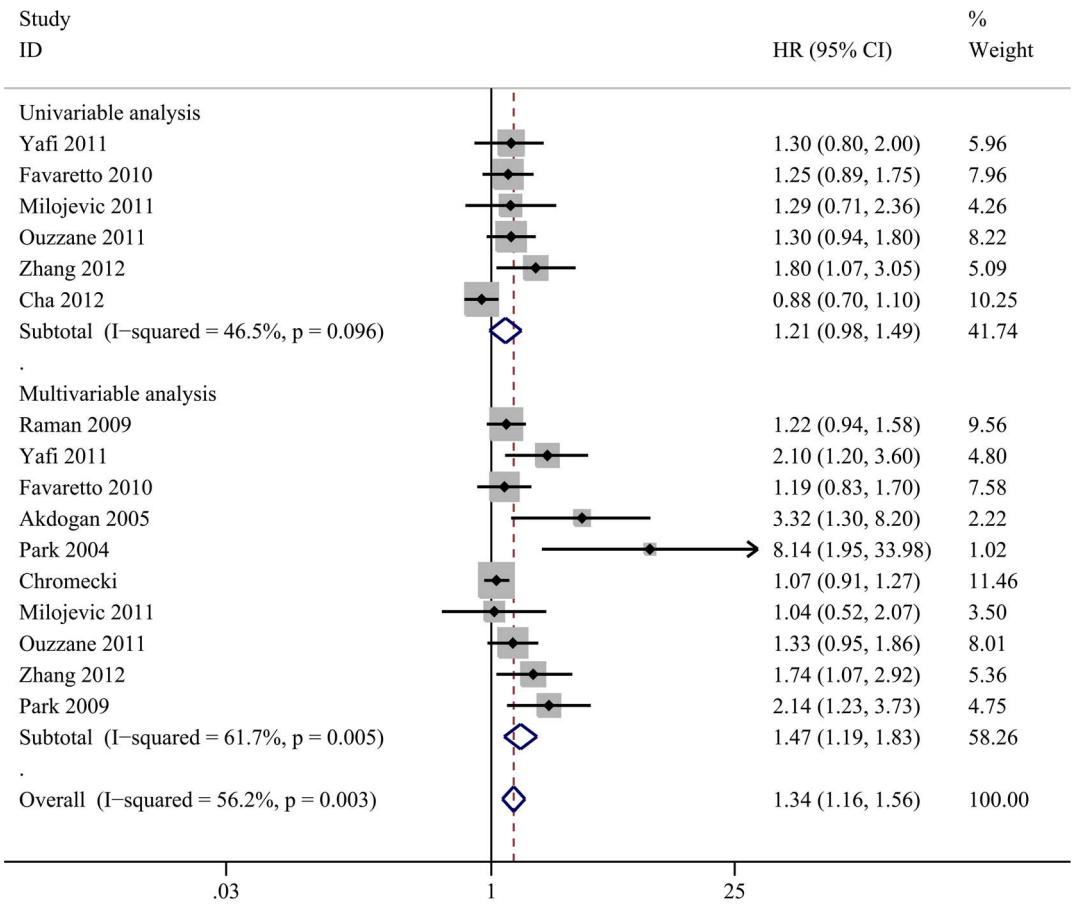

Figure 1 | Meta-analysis of the effect of tumor location on RFS in univariable analysis and in multivariable analysis. The lower and upper confidence interval (CI) values refer to 95% CIs. RFS recurrence-free survival.

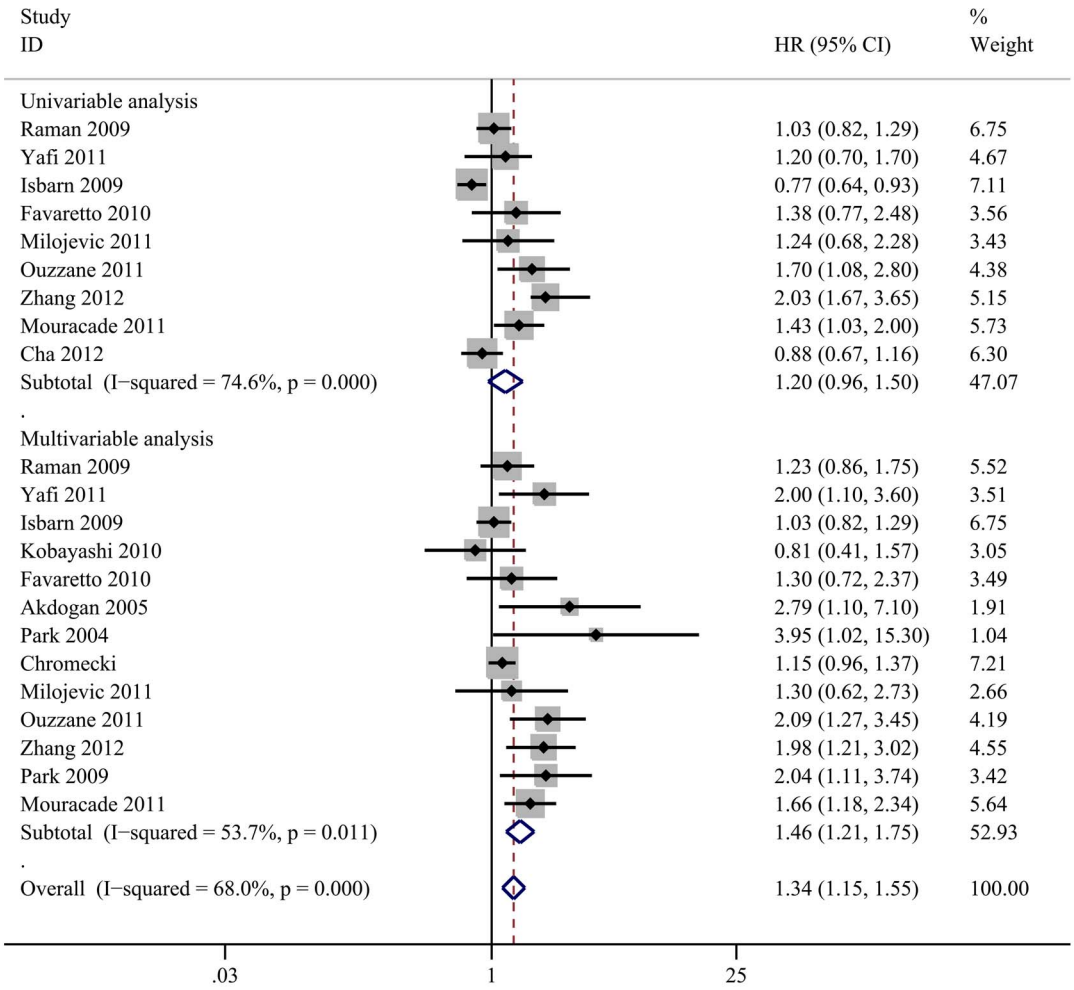

Figure 2 | Meta-analysis of the effect of tumor location on CSS in univariable analysis and in multivariable analysis. The lower and upper confidence interval (CI) values refer to 95% CIs. CSS cancer-specific survival.

pelvic tumors and ureteral tumors in presentation of pT3/4 tumors and pN+ tumors. There was a significant heterogeneity($I^2 = 82.9\%$) between individual trials in the comparison of different tumor location at pT3/4 tumors. Sensitivity analysis showed that the significant heterogeneity of outcome among reported trials could be attributed mainly to the trial reported by Isbarn and colleagues[19].

Ureteral versus renal pelvic tumors. The univariable- and multivariable-adjusted HRs for each study and combination of all studies for the effect of ureteral and renal pelvic tumors on RFS were shown in Figure 1. In univariable analysis, the pooled estimates revealed that tumor location($p = 0.081$) were not associated with recurrence. However, after adjusted for all covariates, tumor location($p < 0.001$) revealed obviously associated with disease recurrence in multivariable analysis (Table 2). The combined results indicated that ureteral urothelial carcinoma was significantly with a higher tumor recurrence than renal pelvic urothelial carcinoma. A statistically significant heterogeneity was detected among studies of effects on RFS stratifying according to tumor location in multivariable analysis. We also performed sensitivity analysis by sequentially excluding one study in each turn to examine the influence of a single study on the overall estimate or in any strata. The results showed that none of the study could considerably affect the summary of risk estimates in our meta-analysis (data not shown). It confirmed the stability of our results.

For the impact of tumor location on CSS of patients with UTUC, no significant differences were found in CSS between ureteral and renal pelvic tumors($p = 0.118$) in univariable analysis. However, the combined results of multivariable analysis revealed that tumor location($p < 0.001$) was independently associated with CSS. The pooled HR was 1.456 for ureteral tumors versus renal pelvic tumors (Figure 2), the tumors originated from the ureter were associated with worse CSS (Table 2). From the results of sensitivity analysis, we concluded the source of heterogeneity among all the included studies probably also came from Isbarn and colleagues[19].

Multifocal versus unifocal tumors. When we stratified the analysis according to multifocal and unifocal upper tract urothelial carcinoma, the pooled HR of FRS(Figure 3) indicated that multifocality was with a higher frequency of tumor recurrence than unifocal tumors either in univariable analysis($p < 0.001$) or in multivariable analysis($p = 0.048$) (Table 2). Sensitivity analysis showed that the significant heterogeneity of outcome among reported trials could be attributed mainly to the trial reported by Chromecki and colleagues[23].

As Figure 4 showed us, the multifocal tumors were associated with increased risk of cancer-specific death. Although the univariable analysis revealed that multifocal tumors were not statistically associated with CSS($p = 0.065$), after adjustment for all covariates the combined HR indicated that multifocality was an independent predictor of CSS($p = 0.009$). Sensitivity analysis identified the study reported by Chromecki and colleagues[23] as the main source of heterogeneity for CSS in multifocal tumors versus unifocal tumors.

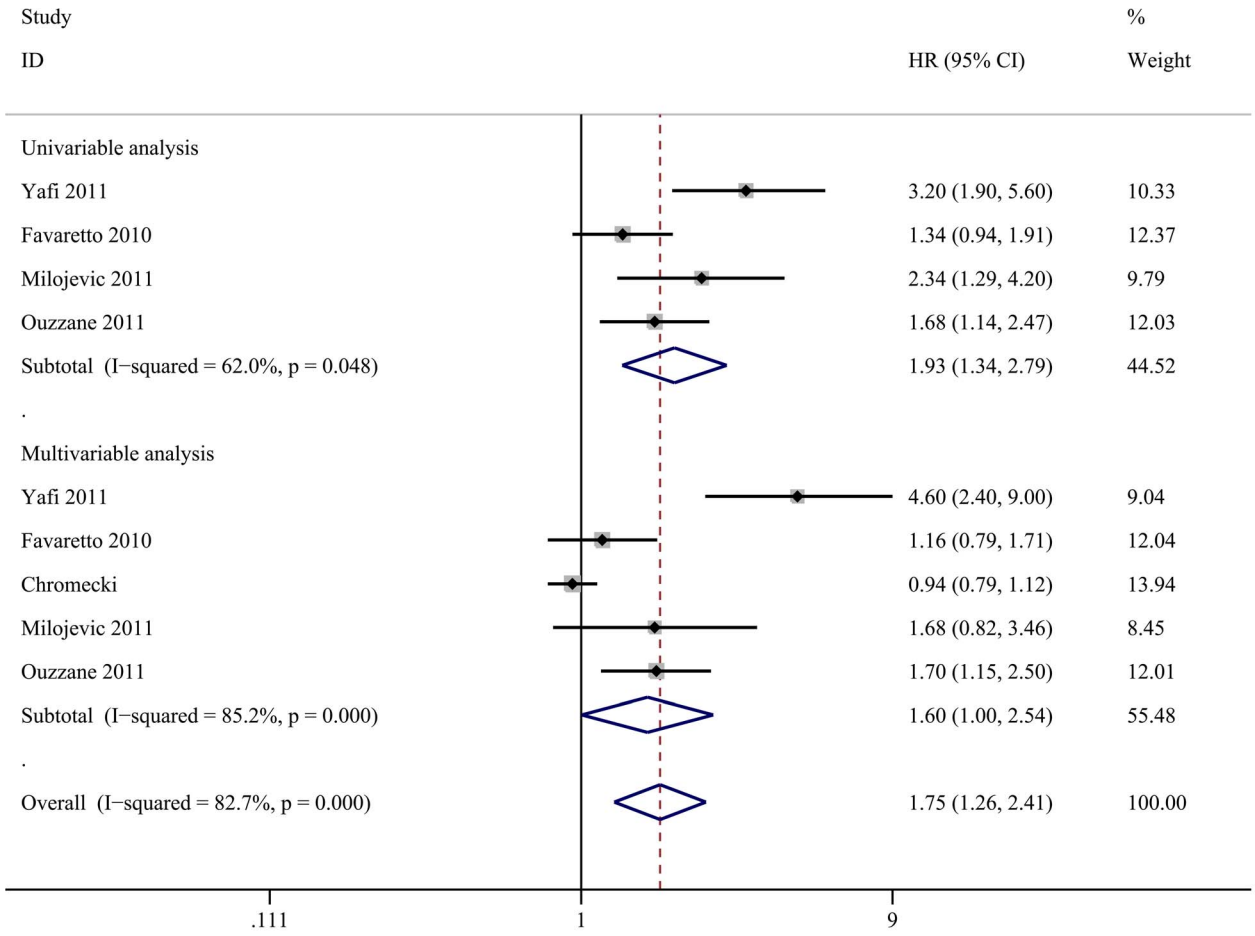

Figure 3 | Meta-analysis of the effect of multifocal tumors on RFS in univariable analysis and in multivariable analysis. The lower and upper confidence interval (CI) values refer to 95% CIs. RFS recurrence-free survival.

Discussion

The impact of tumor location (ureter compared with renal pelvis) on the prognosis of patients with UTUC has been a matter of debate for a long time. Because of lacking of prospective studies, a definitive conclusion regarding the impact of tumor location on UTUC prognosis can not be permitted. In this systematic review we reported evidence from 17 currently retrospective studies about the effect of tumor location on the progression and survival of UTUC tested in a total of 12094 patients. The results of this meta-analysis demonstrated the independent predictor status of tumor location on RFS and CSS, with ureteral tumors showing a worse prognosis than renal pelvic tumors after adjustment for several pathologic variables[15]. In addition, tumor multifocality was also approved to be an independent predictor of progression and survival in patients with UTUC.

Several interesting differences in pathologic characteristics were noted depending on tumor location. We estimated the local advanced tumors and nodal positive tumors in patients stratified by tumor location respectively. Somewhat surprisingly, renal pelvic tumors presented at a more advanced tumor stage than ureteral disease when considering pT3/4 and pN+ cancers in several studies[11,14,18,19,22,25–29]. One explanation for this discrepancy could be that ureteral tumors become symptomatic earlier because of obstruction at lower stages and grades and hence become detectable by endoscopy earlier compared with renal pelvic tumors that may progress before any symptomatic manifestation of disease or obstruction[2]. However, the pooled results of this meta-analysis failed to confirm the interesting findings. The combined RRs showed no statistical differences were detected. In some ways, it could be due to lack of regional lymphadenectomy in most cases. Regional lymphadenectomy was generally performed in patients with enlarged lymph nodes on preoperative axial imaging or with adenopathy detected during intraoperative examination. As such, most of patients in this cohort did not undergo a lymphadenectomy (pNx).

The literature evaluating the impact of tumor location on UTUC outcomes was conflicting. Our researches approved that ureteral tumors were with a worse prognosis compared with renal pelvic tumors. One postulated hypothesis to explain the worse outcome with ureteral tumors is that the presence of a thinner layer of adventitia containing an extensive plexus of blood vessels and lymphatics surrounding the ureter facilitates tumor lymphatic and haematogenous spread. Furthermore, the smooth muscle layer of the ureter is thinner, allowing for higher stage when minimal tumor invasion occurs. Comparatively, the renal pelvis displays a thicker adventitial layer with associated abundant renal parenchyma and perihilar adipose tissue that allows for wider surgical resection margins, which may provide a protective role[28].

Bladder tumors were the most common urothelial cancers. Previous studies showed that 15–50% of patients operated for UTUC had cancer development in the bladder during the follow-up[5,9,31–33]. Zigeuner et al analysed 191 consecutive patients with no history of bladder cancer and operated for UTUC. Bladder tumor development was noted in 39 of 123 (32%), including 18 of 76 (24%) with renal pelvic, 16 of 34 (47%) with ureter and five of 13 with multifocal tumors (P = 0.02 for renal pelvic vs ureter). Zigeuner's research showed that patients with ureteral tumors were more likely to develop subsequent Bladder cancers[34]. van der Poel HG et al investigated the prognostic information of anatomical location of ureter in patients with UTUC. Distally located tumors had a signifi-

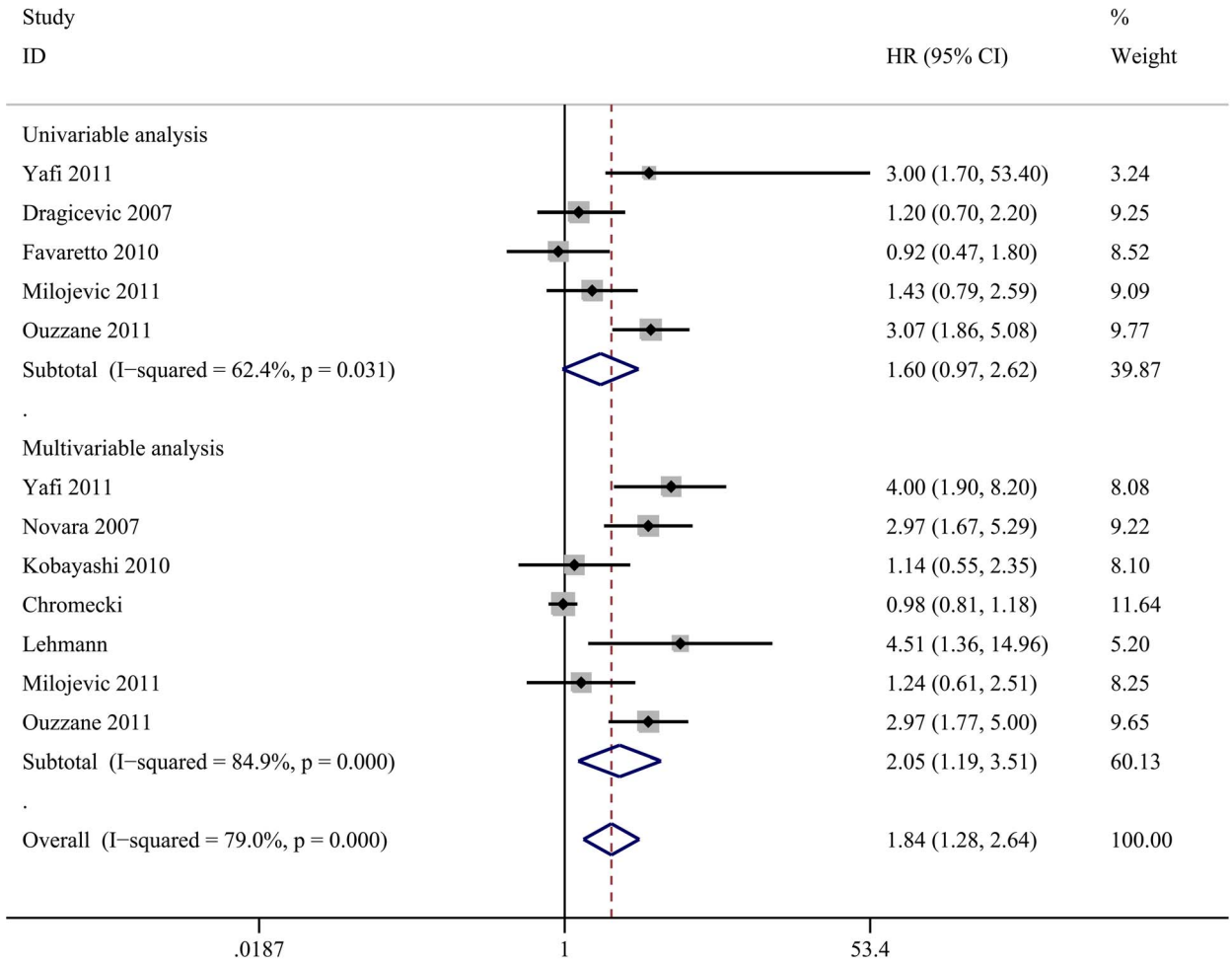

Figure 4 | Meta-analysis of the effect of multifocal tumors on CSS in univariable analysis and in multivariable analysis. The lower and upper confidence interval (CI) values refer to 95% CIs. CSS cancer-specific survival.

cantly better survival than proximally located cancers (median survival 53 months versus 16 months for tumors in the proximal ureter). In a multivariable analysis both tumor stage and location in the upper tract were predictive of disease specific survival after UTUC diagnosis[16].

Multifocal tumors are defined as those tumors with two or more distinct locations within the urinary tract. Keeley et al first reported multifocality as a prognostic factor with a negative impact on RFS[35]. Subsequent studies by Novara et al and Brown et al confirmed the prognostic role of tumor multifocality in UTUC patients[17,36]. Specifically, individuals with a multifocal UTUC showed a threefold higher risk of cancer-specific mortality relative to patients without tumor multifocality. Similar to our research, we found that tumor multifocality was associated with increased risks of disease progression and cancer-specific mortality, and was an independent predictor of both RFS and CSS. Tumor multifocality is a feature of biologically aggressive disease in patients with UTUC. Potential reasons underlying the worse outcomes in patients with tumor multifocality could result from a more aggressive biologic potential of tumors in patients with tumor multifocality or a delay in diagnosis or treatment resulting in more advanced disease. Taken together, it seems that tumor multifocality could help refine clinical decision-making regarding therapy and follow-up of UTUC[23], therefore it should be routinely determined and reported by pathologists.

The heterogeneity of some variables in this study is worthy of comment. Four of ten variables exhibited significant heterogeneity (I^2 more than 70%). Explanations may include the following. First and foremost are the limitations inherent to the biases associated with the retrospective studies included, because of no prospective studies were identified. Second, the studies in our review were done in 3 regions, including Asia, Europe and North America, and some are international multi-institutional studies. The differences in outcomes observed might reflect genetic, environmental or cultural differences among populations. Third, some other risk factors were involved in this meta-analysis which may bring bias. For instance, the surgical approaches were different. Most RNUs were open surgeries, but some were done by laparoscopic approaches. Thus, the performance bias generated. Some studies included patients who had receipt adjuvant chemotherapy, but some studies didn't; similarly some patients with previous or synchronous bladder tumor were included but excluded by other studies. Besides, the definition of RFS was not all the same within the included studies. Most studies defined RFS as local failure in the tumor bed, regional lymph nodes, or distant metastasis[11,14,15,18,23,28,30]. But some studies considered pathologically proven failure in the bladder as disease recurrence[22,25–27], which made some additional patients included. The different inclusion–exclusion criteria and sample sizes brought selection bias. A final source of heterogeneity is that the incorrect classification of multifocality. The multifocal tumor is defined as a tumor with two distinct locations within the upper urinary tract (ie, involving both the renal pelvis and ureter)[26]. Nevertheless, some studies classified the tumors involving both the renal pelvis and the ureter (multifocal) according to the dominant tumor site (based on tumor stage, grade, or size) as renal pelvic or ureteral. Therefore,

some multifocal tumors were missed in some studies, and didn't include in our review, which would produce the selection bias.

With this meta-analysis of articles from the medical literature, we demonstrate that ureteral and multifocal tumors are independent predictors of disease progression and cancer-specific survival in patients with UTUC managed by RNU. Ureteral and multifocal tumors have worse prognoses than renal pelvic tumors. And we postulate that multifocal tumors should be analysed as a distinct entity to avoid misclassification. However, available data are still sparse, and in-depth analyses of the assessed associations in the context of additional longitudinal studies are highly desirable to enable more-precise estimates and a better understanding of the prognostic role of tumor location. Future research should include more high quality, rigorous randomized trials with more stringent uniformity in data reporting to draw firm conclusions.

Methods

Search strategy. The literature search was conducted before March 2014 in the Medline and Embase and The Cochrane Library, reference lists of urology textbooks and review articles, and abstracts of conference proceedings. All the potential articles were required to include the following terms in their titles, abstracts, or key word lists: "urothelial carcinoma", "tumor location", "multifocality", "prognosis" or any combinations of the four words. References in the retrieved publications, as well as those in previous systematic review, were checked for any other pertinent studies. This search strategy was performed iteratively until no new potential citations could be found on review of the reference lists of retrieved articles.

Eligibility criteria. Studies were included in the meta-analysis if they met the following criteria: case-control or cohort study published as an original article; papers reported in English between 1980 and February 2014; papers providing hazard ratio(HR) estimates with corresponding 95% confidence intervals(CIs) or sufficient information allowing us to calculate them. Any study with inconsistent or erroneous data was excluded. Meeting abstracts with insufficient data or unpublished reports were not considered.

Data extraction and quality assessment. Two reviewers (Y.J.W. and Q.D.) independently extracted data and assessed study quality from all potential relevant studies with a predefined data extraction form. Discrepancies were resolved by discussion and arbitration by a third party if necessary. The following variables were recorded: authors, year of publication, geographical region, number of patients, the number of patients with locally advanced pathological stage(pT3/pT4) and positive lymph nodes, and univariate and multivariate models examined the effect of tumor location on recurrence-free survival(RFS) and cancer-specific survival(CSS) rates. When important data were not reported, we tried to contact the authors. Study quality was independently scored by two reviewers using the Newcastle–Ottawa Scale[37]. The Newcastle–Ottawa Scale is frequently used for nonrandom studies such as case-control and cohort studies. The maximum scores of case-control and cohort studies are 9 and 13 respectively. Quality scores of the 17 studies ranged from 7 to 9. All were considered adequate for meta-analysis. We performed all statistical analyses utilizing Stata/SE 12.0 (Stata Corporation, College Station, Texas, USA) commercial software with the most recent updates for meta-analysis commands. Relative risk(RR) values calculated for dichotomous data and study-specific HR estimates were combined using a random-effects model, which considers both within-study and between-study variation[38]. Statistical heterogeneity among studies was evaluated with Q and I^2 statistics. I^2 is a statistic for quantifying inconsistency, it describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error[39]. Sensitivity analysis was performed to evaluate the stability of the results. Each study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled HRs. Heterogeneity was considered statistically significant when a two-sided $P < 0.05$.

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Author contributions

Q.W. and P.H. have contributed to the conception and design of the study, and the critical revision of the article. Y.J.W. and Q.D. searched and selected the studies, analyzed the data, prepared figures and drafted the article. P.H. and L.R.L. participated in the acquisition of data and statistical analysis. Q.D. and Y.J.W. participated in the interpretation of data.

Additional information

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