The clinicopathological features and prognostic value of lymphovascular invasion in patients with upper tract urinary carcinoma after radical nephroureterectomy: an updated systematic review and meta-analysis.

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Abstract

Background and Purpose: Although the prognostic value of lymphovascular invasion (LVI) for upper tract urinary carcinoma (UTUC) have been described. There is lack of consensus regarding the prognostic factor of LVI in UTUC. The aim of present study was to evaluate the current evidence regarding the contemporary role of LVI through systematic review and meta-analysis according to the updated literatures. **Materials and Methods:** In the light of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, a systematic search of Web of Science, PubMed and EMBASE was performed for all reports published until July 2019 that included detailed results on the predictors of LVI. **Results:** Our meta-analysis included thirty one eligible studies containing 14,653 UTUC patients (81-1,363 per study). According to our final results, there was a significant correlation of LVI with worse cancer-specific survival (CSS) (HR=1.62, 95 % CI: 1.49-1.76, $p < 0.001$), overall survival (OS) (HR=1.55, 95 % CI: 1.41-1.71, $p < 0.001$), recurrence-free survival (RFS) (HR=1.46, 95 % CI: 1.32-1.61, $p < 0.001$), cancer-specific mortality (CSM) (HR=1.25, 95 % CI: 1.00-1.56, $p = 0.047$) and recurrence (HR=1.23, 95 % CI: 1.03-1.48, $p = 0.026$). In addition, LVI was also correlated with advanced TNM stage (III/IV vs. I/II: OR = 7.63, 95% CI: 5.60–10.39, $p < 0.001$), higher tumor grade (3 vs. 1/2: OR = 5.61, 95% CI: 3.71–8.48, $p < 0.001$), lymph node metastasis (yes vs. no: OR = 4.95, 95% CI: 3.66–6.71, $p < 0.001$), carcinoma in situ (yes vs. no: OR = 1.92, 95% CI: 1.36–2.70, $p < 0.001$) and positive surgical margin (yes vs. no: OR = 4.38, 95% CI: 2.71–7.07, $p < 0.001$), but not related to gender (male vs. female: OR = 0.98, 95% CI: 0.80–1.19, $p = 0.825$) and multifocality (multifocal vs. unifocal: OR = 1.10, 95% CI: 0.82–1.47, $p = 0.539$). The funnel plot test indicated that no significant publication bias in the meta-analysis. **Conclusions:** This study demonstrated that LVI was associated with more aggressive clinicopathological features and could serve as a poor prognostic factor for patient with UTUC after radical nephroureterectomy.

Background

Upper tract urothelial carcinoma (UTUC) arises from the urothelium that lines renal pelvis and the ureter, which accounts for approximately 5% of all urothelial carcinoma[1]. Although radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard curative therapy for localized UTUC, about 33% patients with RNU will experience early tumor recurrence within 5 years[2], and the 5-year cancer-specific survival (CSS) is less than 50% for early stage UTUC patients[3]. Owing to the aggressive features of UTUC, comprehensive recognition of potential prognostic factors is important to improve the prediction of oncologic outcomes.

Lymphovascular invasion, which defined as the presence of tumor cells within lymphatic or vascular channels, is a significant and crucial step in tumor distant metastasis[4,5]. The prognostic value of LVI has been established for bladder cancer, and European guidelines recommend the description of LVI in cystectomy specimens as an independent prognostic factor[6]. In 2013, a meta-analysis by Ku et al[7]. examined 17 studies and confirmed the significant prognostic role of LVI in RNU specimens. However, lots raw data were lost from the included literatures in his paper. Besides, no further study was conducted for the relationship between LVI and other clinicopathological features. In recent years, many studies have added the latest relevant reports. These newly reported studies add information regarding the clinicopathological implications of LVI. Therefore, the purpose of the study was to investigate the relationship between LVI and clinical outcome in UTUC patients so that further understanding of prognostic values of LVI and make a clinical decision that is suitable for the individual quickly.

Methods

Literature search strategy

According with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines[8]. A computerized search from PubMed, EMBASE, Web of Science was conducted by two authors (ZLZ, HZ) in July 2019 to identify studies reporting the incidence of LVI in patients with UTUC undergoing RNU. The combination of the following keywords were used: ("upper urinary tract tumor" OR "renal pelvis" OR "ureter") AND ("radical nephroureterectomy") AND

("lymphovascular invasion") AND ("prognosis" OR "clinical outcome" OR "survival"). The language of literatures was restricted to English. At the same time, we also manually screened the reference lists of included papers, including all the relevant studies and reviews. Besides, for the data was got from published studies, no ethical approval and informed consent were required.

Study inclusion and exclusion criteria

The following inclusion criteria were used to select eligible studies: (a) the diagnosis of UTUC and LVI were pathologically confirmed; (b) treatment was limited to radical nephroureterectomy; (c) the prognostic value (hazard ratios (HRs) and 95% confidence intervals (95% CIs)) of LVI for overall survival (OS), CSS, recurrence-free survival (RFS), cancer-specific mortality (CSM) and recurrence risk were reported. Accordingly, the exclusion criteria of the meta-analysis were: (a) studies that were not written in English; (b) meeting abstracts, reviews, review papers or case reports; (c) there are no sufficient data to estimate the HRs and 95% CIs; (d) if more than one articles from one patients cohort were identified, the most complete one was selected.

Data extraction

Two authors (JY and YJF) independently extracted data from the included studies with a predefined data extraction form. Discrepancies were resolved through discussion by a third author (BW) if necessary. The following variables were recorded: patients' characteristics (first author's name, year of publication, geographical region, number of patients, ages, gender, study period, follow-up duration), tumor characteristics (TNM stage, tumor grade, LVI, lymph node metastasis, tumor multifocality, tumor necrosis, positive surgical margin) and the outcomes of interest. Our primary outcome including OS, CSS, RFS, CSM and recurrence. When multivariate analysis and univariate analysis results were both presented in the one study, we choose multivariate analysis result, as it accounts for confounding factors and more accurate.

Quality assessment

The quality of the selected studies was assessed by the Newcastle Ottawa Scale (NOS)[9], which was recommended for the assessment of non-randomized studies. This scale assesses risk in three domains: patient selection, comparability of control and intervention groups and assessment of outcomes. A score of 0-9 stars was allocated to each study. We defined high quality as a score of 6-9 and low quality as a score <6.

Statistical analysis

Effect measures for the outcomes of OS, CSS, RFS, CSM and recurrence were HRs and 95% CIs extracted from published studies. The heterogeneity across studies was tested by performing Cochran's Q test and Higgins I^2 statistic. There was marked heterogeneity if the P value was less than 0.10 and/or $I^2 > 50\%$. A random-effects (RE) model was applied to pool results under significant heterogeneity; otherwise, a fixed-effects (FE) model was applied. A pooled HR greater than 1 indicated a poor survival for the patients with a LVI expression. The source for inter-study heterogeneity were explored by using subgroup analysis. By assessing the asymmetry of funnel plot, publication bias was evaluated. Furthermore, Egger's funnel plots test, which provide quantitative evidence, were employed to search for publication bias between the studies. To examine the stability and reliability of the overall meta-analysis results, we performed the sensitivity analysis by excluding one study in turn. Statistical analyses were conducted with Stata 12.0 software (StatCorp, College Station, TX, USA). All P -values were two sided, and $P < 0.05$ was defined to be statistically significant.

We also studied the associations between LVI and clinicopathological parameters of UTUC. Information about tumor grade (3 vs. 1/2), TNM stage (III/IV vs. I/II), lymph node metastasis (yes vs. no), carcinoma in situ (yes vs. no), positive surgical margin (yes vs. no), multifocality (multifocal vs. unifocal), gender (male vs. female) were dichotomized. The event numbers were obtained from original studies, and the odds ratio (ORs) and corresponding 95% CIs were calculated.

Results

Search results

The initial search yielded 998 references, and 539 studies were excluded because of duplication. After title and/or abstracts screening, 169 articles remained for full-text assessment, and 290 articles were excluded, including reviews, letters, meeting abstracts, and other articles irrelevant to our study. In accordance with the study inclusion criteria, 138 articles were excluded for repeated crowds or without enough extratable data. Finally, thirty-one studies were retrospective design were included in this meta-analysis. A flow diagram about the literature search and study selection process is presented in **Figure 1**.

Features of included studies

Summary characteristics of these studies are shown in **Table 1**. A total of 14,653 UTUC patients (ranged from 81-1363) were included. The median or mean age of patients ranged from 62 to 71 years. The 31 included articles were published from 2009 to 2019. Geographically, 20 studies were conducted in Asia, 7 in Multi-centers, 2 in USA, 1 in France and 1 in Serbia. All patients had received RNU as primary treatment for UTUC. Of this studies, 12 studies reported OS, 24 studies reported CSS, 14 studies reported RFS, 5 studies reported CSM and 6 studies reported recurrence. The characteristics of tumor features and pathologic outcomes are summarized in **Table 2**. LVI was detected in (3,635/14,653) 24.8% in pathological specimens of the included patients. According to the NOS, we assessed the quality of the 31 eligible studies [10-40]. The quality scores of the studies varied from 7 to 9, with a mean of 8.7, which means that all the studies were of high quality. (**Supplementary Table S1**)

Meta-analysis results

The pooled result indicated that the presence of LVI in UTUC specimen was associated with poor CSS (RE model, HR=1.62, 95 % CI: 1.49-1.76, $p < 0.001$; $I^2 = 69.9\%$; **Figure 2**), OS (RE model, HR=1.55, 95 % CI: 1.41-1.71, $p < 0.001$; $I^2 = 73.2\%$; **Figure 3A**), RFS (RE model, HR=1.46, 95 % CI: 1.32-1.61, $p < 0.001$; $I^2 = 78.6\%$; **Figure 3B**), CSM (RE model, HR=1.25, 95 % CI: 1.00-1.56, $p = 0.047$; $p < 0.001$; $I^2 = 91.6\%$; **Figure 3C**) and recurrence (RE model, HR=1.23, 95 % CI: 1.03-1.48, $p = 0.026$; $I^2 = 89\%$; **Figure 3D**). To explore the heterogeneity for CSS, OS, RFS, the prognostic value of LVI was evaluated further via subgroup analysis under the geographical region (Asia vs. non-Asian), year of publication (≥ 2014 vs. < 2014), TNM stage (T3+T4 %) (≥ 40 vs. < 40), tumor grade (G2+G3 %) (≥ 60 vs. < 60), No. of patients (≥ 500 vs. < 500) and median follow-up (≥ 40 months vs. < 40 months) (**Table 3**). Because of too few cohorts in the CSM and recurrence group, no subgroup analysis was conducted. The results in subgroup analyses were consistent with the primary findings, which suggested LVI still as a prognostic factor despite heterogeneity among some groups. Although no significant changes for the inter-study heterogeneity were detected, the observed heterogeneity dropped significantly in some subgroup models, such as No. of patients < 500 , Grade (G3+G4 %) ≥ 60 .

The risk estimate with pooled ORs were used to assess the associations between the LVI and clinicopathological parameters in UTUC patients. As shown in **Table 4**, LVI was significantly related to TNM stage (III/IV vs. I/II: OR = 7.63, 95% CI: 5.60–10.39, $p < 0.001$) (**Supplementary Figure 1A**), higher tumor grade (3 vs. 1/2: OR = 5.61, 95% CI: 3.71–8.48, $p < 0.001$) (**Supplementary Figure 1B**), lymph node metastasis(LNM) (yes vs. no: OR = 4.95, 95% CI: 3.66–6.71, $p < 0.001$) (**Supplementary Figure 1C**), CIS (yes vs. no: OR = 1.92, 95% CI: 1.36–2.70, $p < 0.001$) (**Supplementary Figure 1D**) and positive surgical margin(PSM) (yes vs. no: OR = 4.38, 95% CI: 2.71–7.07, $p < 0.001$) (**Supplementary Figure 1E**), but not related to gender (male vs. female: OR = 0.98, 95% CI: 0.80–1.19, $p = 0.825$) (**Supplementary Figure 2A**) and multifocality (multifocal vs. unifocal: OR = 1.10, 95% CI: 0.82–1.47, $p = 0.539$) (**Supplementary Figure 2B**). No significant heterogeneity were observed in those groups.

In sensitivity analyses omitting enrolled studies in turn, the results showed that the pooled HRs did not alter significantly which suggested that the findings were reliable and robust. (**Supplementary Figure 3**).

Publication bias

We conducted the publication bias assessment of the studies by funnel plots and Egger's test. As shown in **Figure 4**, No obvious asymmetry was founded in all groups. The *P*-values of the Egger's test were all greater than 0.05 in CSS (*p*-Egger = 0.701, **Figure 4A**), OS (*p*-Egger = 0.330, **Figure 4B**), RFS (*p*-Egger = 0.811, **Figure 4C**), CSM (*p*-Egger = 0.984, **Figure 4D**) and recurrence (*p*-Egger = 0.843, **Figure 4E**).

Discussion

UTUC is a rare urothelial carcinoma compared with bladder cancer, however, the incidence of UTUC has increased significantly over the past decade[41]. Although we have done our best to improve the knowledge of UTUC, its management remains challenging. Even after standard surgery of RNU in majority of UTUC patients, there are still some patients with poor postoperative outcomes. Therefore, it is very important to accurately predict the prognosis of patients after RUN, which can better help us to predict the clinical prognosis outcomes in UTUC patients. To date, many studies have been conducted to identify the significant prognostic factors of UTUC. Some traditional prognostic predictors, such as pathologic characteristics of RNU specimens including tumor stage and grade[39], tumor architecture[20], tumour size[23] and CIS[42] had been found as significant prognostic variables for CSS and RFS in different studies.

LVI was considered to be the first step in the metastasis of tumor cells and LNM[29]. Recently, mounting evidences have indicated that LVI is associated with poor prognosis for many kinds of tumors, such as liver, bladder, and prostate cancer[43,6]. Jiang et al.[5] reported that LVI is an independent prognostic factor to predict worse progression in prostate cancer, and they recommended that LVI should be reported in the final pathological diagnosis after radical prostatectomy. Similarly, Canter et al.[44] found that the presence of LVI in the final pathological reports for bladder cancer deliver significant risks for worse CSS and OS. Some studies suggest that LVI can be used as an independent prognostic factor in patients with UTUC after RNU[28,35]. However, some studies suggest that the prognostic value of LVI in assessing survival outcome is meaningless[27,45], which remains the prognostic value of LVI need to be clarified and summarized.

Based on previous researches, the positive rate of LVI in the final pathology report is approximately 15–30 % in patients with UTUC after surgery[29,7,38]. Consistent with previous reports, we found that LVI was appeared in about 24.8% of patients. LVI is an easily accessible pathological parameter, which can be accurately measured among observers. Hurel et al.[35] in their study involving 551 patients, have concluded that the presence of LVI was an independent risk factor for UTUC. Likewise, Lee et al.[29] reported significant association between LVI and tumor grade, tumor stage, and LNM. Although it has been proposed that LVI should be accurately recorded in pathological reports for UTUC specimens, there are still controversial data about the impact of LVI on patient prognosis and survival. For example, Jan et al.[12] recently reported that LVI cm was not associated with OS and CSS on multivariate analysis. Besides, Eich et al.[46] founde that LVI was not associated with tumor progression, total mortality and CSM.

Although the previous studies has largely promoted our knowledge of UTUC, they were limited to small sample sizes and heterogeneous populations. To overcome these shortcomings and better understand the clinical value of LVI, we assessed the LVI and 14,653 patients treated with RNU for UTUC through meta-analysis. In this study, we demonstrated that LVI was an independent prognostic factor for CSS, RFS, OS, CSM and recurrence among patients with UTUC treated with RNU. In some studies, LVI has been related worse tumor differentiation, higher stage and grade, LNM and PSMs. Consistent with previous finds, our results indicated that LVI was associated with the above clinicopathological features, which are all independent poor prognostic factors. All results strongly supported the prognostic value of LVI on poor outcomes in UTUC plays a promoting role in tumor progression. Furthermore, the results of the study may provide a postoperative follow-up protocol for UTUC patients to evaluate the prognostic value of LVI. Interestingly, no obvious association between LVI and multifocality were founded in our study. Although multifocal tumors had a worse oncological ending than renal pelvic tumors, the role of tumor location was not confirmed yet[47]. Hence, multifocal tumors may arise from a more aggressive carcinogenesis pathway.

The results obtained in this study are mainly in line with the previous system review by Ku et al.[7] However, our study presented series of advancement. At first, the Ku's search time was ended in 2013. However, we added 23 extra studies including 10,963 patients, thereby allowing us to perform a subgroup analyses with more exact evaluation for LVI. Besides, the quality of NOS involving in present meta-analysis was greater, which strengthened the persuasiveness of this research. With the stupendous prognostic value of LVI, we suggest that LVI should always be presented in the pathologic report of RNU specimens. Moreover, patients with LVI expression maybe given intensive treatment after RNU. Unfortunately, we are unable to further explore the relationship between LVI and postoperative therapy (radiotherapy or chemotherapy) due to the insufficient data in this study.

Our study had several limitations should be acknowledged. First, literatures were mainly retrospective, with an obviously heterogeneity in our study. The subgroup analysis to identify the source of heterogeneity was conducted in the present study. Although the great heterogeneity among studies had no effect on the pooled result, the heterogeneity should not be neglected completely. Thus, the conclusions yielded in this study may be interpreted with caution. Second, the studies in our paper were mainly done in 4 regions, including Asia, Europe, USA, and multi-institutional studies. The observed differences in statistical results might reflect regional ethnic differences. Third, some other potential risk factors involved in this report may also have affected on the final results. For example, the surgical methods were different. Most RNUs were laparoscopic approaches, but some were done by open surgeries. Thus, the performance bias may generated. Fourth, reporting bias may exist in our research, as some studies with negative results may not are not inclined to been published. However, no significant bias was observed in this research, which indicating that our results were stable and reliable.

Conclusions

In summary, our meta-analysis suggests the fact that LVI is associated with unfavorable prognosis and clinicopathological features in patients with UTUC. Given its convenience and inexpensiveness in clinical application, LVI could be a useful tool for the prediction of prognosis and outcomes of UTUC. However, further prospective multicenter studies should be carried out to confirm our findings, for certain limitations were been observed in our meta-analysis.

Abbreviations

LVI: lymphovascular invasion; UTUC: upper tract urinary carcinoma; RNU: radical nephroureterectomy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS: Newcastle-Ottawa scale; HRs: hazard ratios; ORs: odds ratio; CIs: confidence intervals; CSS: cancer-specific survival; OS: overall survival; RFS: recurrence-free survival; CSM: cancer-specific mortality; CIS: concomitant carcinoma in situ; LNM: lymph node metastasis; PSM: positive surgical margin.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

I give my consent for information about my relative circle to be published in BMC cancer. I understand that the information will be published without my relative's (circle as appropriate) name attached, but that full anonymity cannot be guaranteed. I understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. The pictures, videos and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes. I have been offered the opportunity to read the manuscript.

Availability of materials and data

All data generated or analyzed during this study are included in this published article

Competing interests

We declare that there have no potential competing interests in this research.

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Authors' Contributions

LJ Zhang: Project development and Manuscript writing B Wu: Data Management and Manuscript editing J Yuan: Data Collection YJ Feng: Data Collection ZL Zha: Data analysis, Data Management H Zhao: Data analysis, Data Management

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Tables

Table 1. Clinical characteristics of the included studies in this meta-analysis

Author	Year	Country	Recruitment period	No. of patients	Age (years)	Gender (m/f)	Pelvic/lyceal/ureteral/both	Follow-up (months)	Survival analysis
Liu et al[10]	2019	China	2005-2013	180	Median (range) 67.2 (39-87)	109/71	NA	Median (range) 45.4 (3-180)	RFS, CSS
Li et al[11]	2019	China	1999-2015	885	Mean $\pm$ SD 66.9 $\pm$ 10.6	396/489	474/411	Median (IQR) 61 (38-102)	CSS, OS
Jan et al[12]	2019	China	2007-2017	424	Median (range) 70 (29-96)	189/235	191/138/95	Median (IQR) 35 (14-60)	CSS, OS
Aydin et al[13]	2019	Muti-centers	1990-2008	348	Median (IQR) 70(64-77)	163/185	267/81	Median 36	RFS, CSS, OS
Tan et al[14]	2018	China	2003-2015	620	Mean $\pm$ SD 65.7 $\pm$ 11.3	355/265	350/161/109	Median (range) 51 (1-168)	RFS, CSS, OS
Kohada et al[15]	2018	Japan	1999-2016	148	Median (IQR) 71(64-78)	112/36	82/66	Median (IQR) 35.5(12-66)	RFS, CSS
Abe et al[16]	2018	Japan	2000-2015	214	Median (range) 70.5 (35-93)	151/63	127/82/5	Median (IQR) 41(21-71)	RFS, CSS, OS
Nakagawa et al[17]	2017	Japan	1996-2013	109	Median (IQR) 71(64-77)	67/42	50/23/36	Median (IQR) 46.5(23.2-76.7)	RFS, CSS
Inokuchi et al[18]	2017	Japan	2005-2011	823	Median (IQR) 71(63-77)	578/245	434/375/14	Median (IQR) 59.8(23.3-66.2)	CSS, OS
Ikeda et al[19]	2017	Japan	1985-2013	399	Median (IQR) 67(62-75)	307/92	213/186	Median (IQR) 43(17-89)	RFS, CSS
Fan et al[20]	2017	China	2002-2013	101	Median 69	61/40	55/43/3	Median (range) 41.3 (4.2-106.5)	RFS, CSS
Cho et al[21]	2017	Korea	2004-2015	1,049	Median (IQR) 68.5(60.5-74.3)	759/290	489/462/252	Median (IQR) 40(18.4-64.8)	RFS, CSS, OS
Abufaraj et al[22]	2017	Muti-centers	1990-2008	678	Median (IQR) 69(63-76)	380/298	478/200	Median (IQR) 37.5(20-66)	Recurrence, CSM
Yan et al[23]	2016	China	2002-2012	795	NA	462/333	497/187/111	Median (IQR) 32(17-60)	RFS, CSS, OS
Kobayashi et al[24]	2016	Japan	1990-2011	839	Median (IQR) 70.4(63-78)	610/229	NA	Median (IQR) 34(17-63)	Recurrence, CSS
Kang et al[25]	2016	Korea	2004-2014	566	Median (IQR) 70(62-75)	401/165	258/308	Median 33.8	RFS, CSS, OS
Fukushima et al[26]	2016	Japan	2001-2015	81	Median (range) 71 (41-87)	53/28	36/31/14	Median (range) 41 (4-170)	CSS, OS
Mathieu et al[27]	2015	Muti-centers	1990-2008	732	Median (IQR) 70(63-76)	414/318	518/214	Median(range) 35(16-64)	RFS,CSS
Lee et al[28]	2015	Korea	1986-2013	344	Mean $\pm$ SD 65.1 $\pm$ 10.6	240/104	146/147/51	Median(range) 53.9(1-297)	CSS, OS

Lee et al[29]	2015	China	2004-2010	250	NA	108/142	129/122	Median 41	CSS
Park et al[30]	2014	Korea	1991-2010	392	Median(range) 64(29-86)	299/93	NA	Median(range) 47.6(2-257)	RFS, CSS
Lee et al[31]	2014	Muti-centers	1991-2008	622	Median (IQR) 69(63-76)	346/276	452/170	Median (IQR) 27(12-53)	Recurrence, CSM
Krabbe et al[32]	2014	USA	2000-2012	122	Median(range) 69(35-92)	77/45	88/34	Median(range) 32 (1-149)	CSS
Kluth et al[33]	2014	Muti-centers	1975-2012	242	Median (IQR) 70(63-77)	175/67	145/83/11	Median 9	CSM
Liu et al[34]	2013	China	1999-2010	421	Median (IQR) 62(51-70)	285/136	225/196	NA	CSS
Hurel et al[35]	2013	France	1995-2010	551	Median (IQR) 69.4(61.8-76.4)	365/188	302/169/80	Median (IQR) 26.8(10.3-48.7)	RFS, CSS
Milojevic et al[36]	2012	Serbia	1999-2009	133	Mean $\pm$ SD 66.7 $\pm$ 8.9	77/56	88/45	Median(range) 35(2-113)	Recurrence, CSS
Godfrey et al[37]	2012	USA	1990-2010	222	Mean $\pm$ SD 70 $\pm$ 11.4	124/87	170/41	Median (IQR) 27(11-65.5)	OS
Novara et al[38]	2010	Muti-centers	1987-2008	762	Median (IQR) 68(61-75)	527/235	401/232/48	Median (IQR) 34(15-65)	Recurrence, CSM
Kim et al[39]	2010	Korea	1986-2006	238	Median(range) 64.1(25-91)	164/74	134/104	Median(range) 64.1(25-91)	RFS, CSS
Margulis et al[40]	2009	Muti-centers	1992-2006	1,363	Mean $\pm$ SD 69.7 $\pm$ 11.1	921/442	878/463/22	Median(range) 37.2(1.2-250)	Recurrence, CSM
m/f :male/femal; SD: standard deviation; NA, data not applicable; CSS: cancer-specific survival; OS: overall survival; RFS :recurrence-free survival; CSM: cancer-specific mortality.									

Table 2. Tumor characteristics of the included studies in this meta-analysis

Study	Staging system	Grading system	LVI + / LVI -	Stage 1-2/ 3-4	Grade 1-2/ 3	LN-/ LN+	Unifocal/ Multifocal	Papillary/ Sessile	TN+/ TN-	PSM+/ PSM-
Liu et al[10]	2008 AJCC	2016 WHO/ISUP	28/152	115/65	91/89	169/11	173/7	NA	7/173	NA
Li et al[11]	2002 AJCC	1973 WHO/ISUP	46/839	623/262	518/367	823/62	NA	771/114	114/771	NA
Jan et al[12]	2009 AJCC	2004 WHO/ISUP	115/299	244/180	22/402	399/25	308/116	97/278	86/338	NA
Aydin et al[13]	2002 AJCC	1998 WHO/ISUP	98/250	191/157	NA	314/34	270/78	286/62	62/286	NA
Tan et al[14]	2002 AJCC	WHO/ISUP	100/520	310/310	158/462	554/62	517/103	193/427	NA	50/570
Kohada et al[15]	2002 AJCC	1998 WHO/ISUP	55/93	82/66	60/88	140/8	148/0	NA	NA	12/136
Abe et al[16]	2002 AJCC	1973 WHO/ISUP	96/118	121/83	101/113	195/19	209/5	NA	NA	11/203
Nakagawa et al[17]	2009 AJCC	2004 WHO/ISUP	78/31	0/109	40/69	21/88	73/36	NA	NA	9/100
Inokuchi et al[18]	2002 AJCC	NA	252/52	459/324	444/379	787/26	809/14	NA	NA	34/789
Ikeda et al[19]	2002 AJCC	1973 WHO/ISUP	138/236	237/162	285/109	359/40	399/0	NA	NA	32/358
Fan et al[20]	2002 AJCC	1998 WHO/ISUP	14/87	47/54	25/76	92/9	91/10	60/31	NA	NA
Cho et al[21]	2009 AJCC	1998 WHO/ISUP	202/847	623/426	304/705	965/84	889/160	NA	NA	NA
Abufaraj et al[22]	2002 AJCC	1973 WHO/ISUP	135/543	452/226	174/504	629/49	533/145	558/120	597/81	NA
Yan et al[23]	2010 AJCC	1998 WHO/ISUP	169/626	390/405	212/583	711/84	684/111	256/539	NA	76/719
Kobayashi et al[24]	AJCC	1973 WHO/ISUP	326/513	415/424	347/492	783/56	715/124	NA	NA	NA
Kang et al[25]	AJCC	1998 WHO/ISUP	119/447	346/220	178/388	NA	517/49	NA	NA	NA
Fukushima et al[26]	2002 AJCC	1973 WHO/ISUP	50/31	37/44	31/50	74/7	67/14	NA	NA	NA
Mathieu et al[27]	2002 AJCC	1998 WHO/ISUP	153/579	480/252	187/454	677/55	577/155	601/131	97/635	NA
Lee et al[28]	2010 AJCC	1998 WHO/ISUP	86/258	144/200	53/291	265/79	293/51	NA	NA	NA
Lee et al[29]	AJCC	2004 WHO/ISUP	60/190	166/84	57/193	232/18	191/59	NA	NA	NA
Park et al[30]	1997 AJCC	1973 WHO/ISUP	89/303	248/144	196/196	357/35	NA	265/127	NA	25/367
Lee et al[31]	2002 AJCC	2004 WHO/ISUP	140/482	396/226	164/458	569/53	498/124	518/104	85/537	NA
Krabbe et al[32]	2010 AJCC	NA	28/94	87/35	27/95	113/9	63/59	80/42	NA	NA

Kluth et al[33]	2010 AJCC	2004 WHO/ISUP	131/111	76/166	NA	191/51	139/60	83/47	70/159	NA
Liu et al[34]	2002 AJCC	1998 WHO/ISUP	101/320	248/173	215/206	325/96	288/133	NA	NA	36/385
Hurel et al[35]	2009 AJCC	1973 WHO/ISUP	163/388	266/246	331/415	504/47	471/80	NA	NA	53/498
Milojevic et al[36]	1997 AJCC	1998 WHO/ISUP	78/55	47/86	46/87	128/5	86/47	NA	NA	NA
Godfrey et al[37]	2010 AJCC	1998 WHO/ISUP	68/143	137/74	77/134	197/14	Mean $\pm$ SD 9.03 $\pm$ 5.2	NA	NA	18/193
Novara et al[38]	2002 AJCC	1973 WHO/ISUP	148/614	508/254	320/442	713/49	633/48	NA	NA	NA
Kim et al[39]	1997AJCC	1973 WHO/ISUP	31/207	131/107	95/143	NA	182/56	185/53	NA	10/228
Margulis et al[40]	2002 AJCC	1998 WHO/ISUP	338/1,025	852/511	495/868	455/135	1,341/22	983/380	294/1,069	NA
NA, data not applicable; AJCC: American Joint Committee on Cancer classification; WHO/ ISUP :World Health Organization/International Society of Urological Pathology classification; LVI: Lymphovascular Invasion; LNM: Lymph node metastasis; TN: Tumor necrosis; PSM: Positive surgical margin.										

Table 3. Summary and subgroup analysis of pooled ORs for the eligible studies

Analysis specification	No. of studies	Study heterogeneity		Effects model	Pooled HR(95% CI)	P-Value
		I ² (%)	P _{heterogeneity}			
CSS						
Overall	24	69.9	<0.001	Random	1.62[1.49,1.76]	<0.001
Geographical region						
Asia	19	65.1	<0.001	Random	1.66[1.52,1.81]	<0.001
non-Asian	5	82.5	<0.001	Random	1.51[1.19,1.91]	0.001
Year of publication						
≥ 2014	16	74	<0.001	Random	1.67[1.49,1.86]	<0.001
< 2014	8	59.4	0.016	Random	1.55[1.37,1.76]	<0.001
No. of patients						
≥ 500	9	77.5	<0.001	Random	1.83[1.63,2.06]	<0.001
< 500	15	34.8	0.090	Fixed	1.45[1.33,1.59]	<0.001
Stage (T ₃ +T ₄ %)						
≥ 40	16	68.8	<0.001	Random	1.64[1.49,1.81]	<0.001
< 40	8	74.3	<0.001	Random	1.58[1.34,1.87]	0.001
Grade (G ₂ +G ₃ %)						
≥ 60	15	51.6	0.011	Random	1.60[1.48,1.73]	<0.001
< 60	9	82.9	<0.001	Random	1.70[1.39,2.07]	<0.001
Median follow-up						
≥ 40 months	14	72.1	<0.001	Random	1.65[1.45,1.88]	<0.001
< 40 months	10	69	<0.001	Random	1.59[1.42,1.78]	<0.001
OS						
Overall	12	73.2	<0.001	Random	1.55[1.41,1.71]	<0.001
Geographical region						
Asia	10	76.5	<0.001	Random	1.56[1.40,1.74]	<0.001
non-Asian	2	61.0	0.109	Random	1.49[1.11,2.00]	<0.001
Year of publication						
≥ 2014	10	77.6	<0.001	Random	1.54[1.37,1.73]	<0.001
< 2014	2	0	0.402	Fixed	1.58[1.40,1.77]	<0.001
No. of patients						
≥ 500	4	83.1	<0.001	Random	1.71[1.48,1.97]	<0.001
< 500	8	33.9	0.169	Fixed	1.43[1.29,1.59]	<0.001
Stage (T ₃ +T ₄ %)						
≥ 40	10	71.2	<0.001	Random	1.60[1.45,1.78]	<0.001
< 40	2	80.1	0.025	Random	1.33[0.99,1.80]	0.061
Grade (G ₃ +G ₄ %)						
≥ 60	9	0	0.449	Fixed	1.58[1.50,1.66]	<0.001
< 60	3	93.8	<0.001	Random	1.54[0.92,2.58]	0.098
Median follow-up						
≥ 40 months	7	82.6	<0.001	Random	1.54[1.30,1.81]	<0.001
< 40 months	5	29.4	0.225	Fixed	1.60[1.47,1.75]	<0.001
RFS						
Overall	15	78.6	<0.001	Random	1.46[1.32,1.61]	<0.001
Geographical region						
Asia	12	69.3	<0.001	Random	1.52[1.38,1.67]	<0.001
non-Asian	3	91.8	<0.001	Random	1.28[0.94,1.74]	0.114
Year of publication						
≥ 2014	11	75.8	<0.001	Random	1.50[1.34,1.67]	<0.001
< 2014	4	86.4	<0.001	Random	1.38[1.09,1.74]	0.007
No. of patients						
≥ 500	7	88.2	<0.001	Random	1.57[1.36,1.81]	<0.001
< 500	8	29.6	0.192	Fixed	1.34[1.20,1.49]	<0.001
Stage (T ₃ +T ₄ %)						
≥ 40	11	68.9	0.061	Random	1.57[1.31,1.88]	<0.001
< 40	4	82.7	0.026	Random	1.84[0.95,3.53]	0.068
Grade (G ₃ +G ₄ %)						
≥ 60	4	45.8	<0.001	Random	1.38[1.25,1.51]	<0.001
< 60	2	54.1	0.001	Random	1.71[1.36,2.15]	<0.001
Median follow-up						
≥ 40 months	9	46.8	0.059	Random	1.42[1.30,1.57]	<0.001
< 40 months	6	89.2	<0.001	Random	1.48[1.23,1.79]	<0.001

Table 4. Meta-analysis of LVI and clinicopathological features in UUTC patients.

Variables	Studies	Pooled OR (95% CI)	<i>P</i> _{Value}	Model	Heterogeneity <i>I</i> ² (%)	<i>P</i> _{Heterogeneity}
TNM stage (III/IV vs. I/II)	7	7.63 (5.60-10.39)	< 0.001	RE	44.2	0.097
Tumor grade (3 vs. 1/2)	7	5.61 (3.71-8.48)	< 0.001	RE	45.2	0.090
Lymph node metastasis (yes vs. no)	6	4.95 (3.66-6.71)	< 0.001	FE	0	0.625
Carcinoma in situ (yes vs. no)	4	1.92 (1.36-2.70)	< 0.001	FE	0	0.826
Positive surgical margin (yes vs. no)	3	4.38 (2.71-7.07)	< 0.001	FE	0	0.794
Multifocality (multifocal vs. unifocal)	6	1.10 (0.82-1.47)	0.539	FE	43	0.119
gender (male vs. female)	7	0.98 (0.80-1.19)	0.825	FE	0	0.675

Figures

Figure 1

PRISMA flow chart of literature search and selection process.

Figure 2

Meta-analysis of the effect of LVI on CSS.

Figure 3

Forest plots assessing correlation of LVI and (A)OS, (B)RFS, (C)CSM, (D) recurrence in studies considering patients of UTUC.

Figure 4

Funnel plots evaluating possible publication bias regarding: (A) CSS, (B) OS, (C) RFS, (D) CSM and (E) recurrence.

Supplementary Files

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- [FigureS2.tif](#)
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- [FigureS1.tif](#)
- [TableS1.docx](#)
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