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Prognostic Significance of Lymphovascular Invasion in Bladder Cancer after Surgical Resection: A Meta-analysis*

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Summary: Bladder cancer remains a commonly diagnosed malignancy worldwide, bringing huge economic burden and high morbidity for patients. Assessment of prognostic significance of lymphovascular invasion (LVI) is a critical issue in the surgical management of bladder cancer after transurethral resection or radical cystectomy. A systematic search of PubMed, Embase and Cochrane Library was performed up to Oct 10, 2014 to identify eligible studies. Outcomes of interest were collected from studies comparing overall survival (OS), cancer specific survival (CSS) and recurrence free survival (RFS) in patients with the LVI. Results of studies were pooled, and combined hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for survival were used as the effect size estimation. Funnel plots were done to show the publication bias, while the forest plots and subgroup analyses were used to limit the heterogeneity. A total of 20 studies (10663 patients) met the eligibility criteria and were included for this meta-analysis. Our pooled results showed that there were significant differences in OS (pooled HR, 1.71; 95%CI, 1.52–1.92; P<0.00001), CSS (pooled HR, 2.25; 95% CI, 1.80–2.81; P<0.00001) and RFS (pooled HR, 1.91; 95% CI, 1.57–2.32; P<0.00001) between the patients with LVI and the patients without LVI. There were significant heterogeneities observed in the studies concerning the relationship between LVI and CSS, RFS. There was no clear evidence of publication bias. When tumor stage was beyond T3, LVI lost its predictive value for CSS and RFS. For the patients who had negative lymph nodes, LVI was still an adverse predictor. Our pooled results demonstrate that LVI indicates poor prognosis of patients with bladder cancer after surgical procedures, and it can be of particular importance in clinical practice. However, these results need to be further confirmed by more adequately designed prospective studies.

Key words: lymphovascular invasion; survival; bladder cancer; meta-analysis

Bladder cancer remains a commonly diagnosed malignancy, with more than 350 000 new cases worldwide each year[1]. Approximately 70% of newly diagnosed bladder tumors are nonmuscle invasive bladder cancer (NMIBC) at diagnosis and patients diagnosed with bladder cancer in early stage present excellent prognosis, in contrast to the dismal outcomes of those with muscle invasive disease[2]. Contemporarily, radical cystectomy (RC) (with pelvic lymphadenectomy and urinary diversion) remains the mainstay of treatment for muscle-invasive diseases, while transurethral resection of the bladder in combination with intravesical chemotherapy or immunotherapy is considered as the standard treatment for NMIBC[3, 4]. There is also a growing body of evidence supporting the use of extended lymphadenectomy in accurate staging or in improving patient survival[5]. Besides, the role of systemic chemotherapy, neoadjuvant therapy and other adjuvant therapies can also reduce the morbidity and recurrence in urothelial urinary bladder cancer[6].

Urinary bladder cancer is a highly heterogeneous disease with diverse genetic and environmental risk factors that can influence disease risk or clinical course of recurrence, progression, and survival[7]. Despite of many improvements in diagnosis and management of bladder tumors, the risk of both recurrence and progression remains significant and elusive. Thus, it is of particular value to identify certain predictors that can give accurate assessment of tumor prognosis. Some molecular biomarkers and clinicopathologic features can provide much information for us to adjust our prediction of prognosis and our therapies for specific patient[8–10]. So far, effective predictive tools or nomograms are absent for bladder cancer after surgical procedures, thus more studies are needed to better evaluate the existing predictors and discover the promising ones.

The definition of lymphovascular invasion (LVI) is the presence of tumor cells inside an endothelial lined space without underlying muscular walls adjacent to the lymph node capsule. The invasion of the space near an

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arteriole, the unequivocal involvement of the endothelial lining with more than one tumor cell and the presence of a complete free thrombus consisting of tightly cohesive cells with smooth border within an endothelial-lined space were considered to be typical diagnostic features of LVI[11]. The reported incidence of LVI in patients who underwent cystectomy varies much and the pathological standards may also be different. Generally speaking, LVI is seen as an independent factor for bladder cancer after resection; however, the poor diagnosis reproducibility restricts the use of LVI for prognostic prediction. Now that more well-designed studies are completed and the detection of LVI is more accurate, we can analyze the prognosis role of LVI in bladder cancer with more confidence in this article.

1 METHODS

1.1 Literature Search Strategy

A systematic review of original articles of the electronic databases, including PubMed, Embase and Cochrane Library, was conducted to identify literatures published up to Oct. 10, 2014 focusing on the prognostic impact of LVI on bladder cancer after surgical resection. The following search terms were used to identify the relevant studies: [bladder cancer] AND [lymphovascular invasion] AND [survival] AND [transurethral resection] OR [radical cystectomy]. Then the articles concerned with the predictive values of LVI were selected. All of the eligible literatures were written by English language in full-text. The references of the retrieved articles which seemed to be eligible were searched in order to identify other potentially suitable studies, which were not included in the initial automated search.

1.2 Inclusion and Exclusion Criteria

In order to limit the inter-study heterogeneity, we used rigorous inclusion and exclusion criteria to increase the reliability of this meta-analysis. Studies were considered eligible if they met the following criteria: (1) articles were published in English; (2) LVI was evaluated in the bladder cancer patients after transurethral resection of bladder tumor (TURBT) or RC; (3) the histological type of tumor was bladder cancer; (4) the authors must offer the sample size, hazard ratios (HR) and their 95% confidence intervals (CIs), or the survival results can be analyzed from the given information in the papers (e.g. Kaplan-Meier curves). Articles were excluded based on the following criteria: (1) review articles or letters, (2) non-English articles, (3) laboratory studies on cancer cell lines and animal models, or other non-human research and (4) studies which cannot offer sufficient data to acquire HR and its standard error (SE) .

1.3 Data Extraction and Survival End-points

To minimize the bias and improve the reliability of the results, two reviewers investigated all the potentially relevant studies, respectively. The information extracted from the eligible studies consisted of data as follows: (1) baseline characteristics of eligible studies: last name of first author, publication year, country, period of recruitment, type of study design, inclusion and exclusion criteria (yes or no), consecutiveness of patients, definition of survival, sample size of patients, age, gender, operative procedures, adjuvant therapies, definition of LVI, number and percentage of LVI, histological subtype, stage, grade, lymph node condition, duration of follow-up; (2) HR corresponding 95% CIs and *P* value of Cox's proportional hazards regression models, the Kaplan-Meier curves. If the above information was not mentioned or could not be extracted in the original study, the item was treated as "Not Available (NA)". Two inquirers extracted data from the suitable studies independently and discussed the discrepancies, thus the disagreements could be resolved by consensus smoothly. Our outcomes of interest were overall survival (OS), cancer specific survival (CSS) and recurrence free survival (RFS).

1.4 HR Pooled and Statistical analysis

HRs and 95% CIs were used to estimate the predictive significance of LVI on OS, CSS or RFS of the bladder cancer patients. A combined HR>1 implied a worse survival of the positive LVI group as compared with the negative one, and it was considered statistically significant if 95% CI for the combined HR did not overlap 1, in other words, $P<0.05$. If the HRs and 95% CIs results of trials could not be obtained directly from the text or tables of the papers but the Kaplan-Meier curves were available, the specific curves were extracted and read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). This work was performed by two independent persons to reduce inaccuracy in the extracted survival rates.

We performed the meta-analysis by using the Review Manager Software (RevMan 5.1, Cochrane Collaboration, Oxford, UK). We used HRs and their 95% CI to evaluate the association between the pathological factors and prognosis of bladder cancer patients after surgery. The respective analysis of OS, CSS and RFS was conducted using results of HRs and 95% CI. The statistical assessment was performed using a Chi^2-based test of homogeneity and evaluation of the inconsistency index (I^2) statistic. The I^2 statistic is defined as the percentage of variability due to heterogeneity rather than chance, and the values >50% represents the possibility for substantial heterogeneity[12]. By heterogeneity test, if $P>0.05$, we selected the fixed-effect model, and if not, a random-effect model was used. The heterogeneity of respective combined HRs was also evaluated by graphical examination of the Forrest plots, while funnel plots were used to manifest any possible publication bias.

1.5 Subgroup Analysis

In order to rule out other confounding factors, we also conducted analysis of the subgroup which was categorized by surgical procedures (RC *vs*. TURBT), tumor stage (≤T2 *vs*. ≥T3), lymph node status (negative *vs*. overall), area (eastern *vs*. western), year of publication (≥2010 *vs*. <2010) and sample size (>250 *vs*. ≤250). The pooled HRs and 95% CIs were calculated, respectively, and compared in subgroups. Then the between-study heterogeneity might be explained and managed better.

2 RESULTS

2.1 Study Selection and Characteristics

According to the searching strategies, a total of 493 studies were identified from electronic databases. Totally, 253 studies of PubMed, 237 from Embase and 3 from Cochrane were identified through initial searches. We removed 137 articles for duplicating and 356 studies remained. After the titles and abstracts of all identified

studies were carefully reviewed, we abnegated 238 articles which were reviews, editorials, comments, non-English articles or irrelevant topics. Based on the inclusion/exclusion criteria mentioned above, 20 studies were eventually eligible for the meta-analysis[13–32]. More details can be seen from the flow chart in fig. 1.

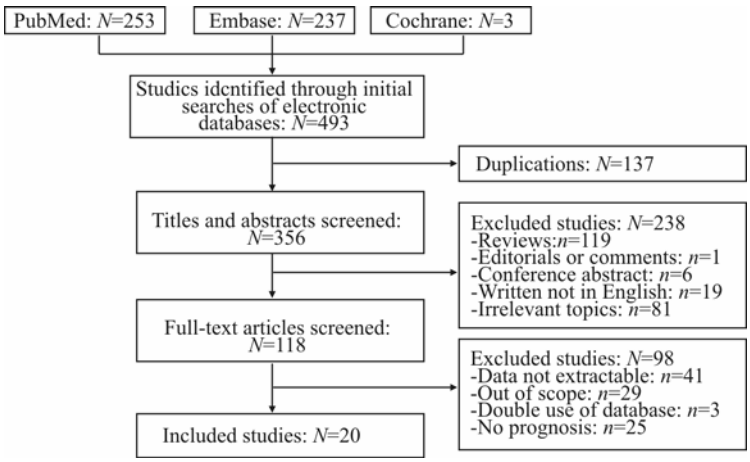

Fig. 1 The flow diagram of the literature selection process

A total of 10 663 patients were included in the meta-analysis. The pathology analyses were done on the specimens from needle-biopsy or pathological sections of resected tumors. The studies were conducted between 1971 and 2010, and the sample size of the studies ranged from 101 to 4257. There were 3494 persons who had been diagnosed with LVI, and the percentage of LVI in each trail was from 3.9% to 96.8% (the overall proportion of LVI was 32.8%). Almost all the studies were retrospective design, except for one prospective study[17]. All the patients enrolled in all trials must accord with specific inclusion/exclusion criteria. The included patients all received surgical procedures, such as RC, transurethral resection, lymphoadenectomy, urinary diversion or intravesical therapy. Some high risk patients received chemotherapy, radiotherapy or other adjuvant therapies, and then all the subjects were evaluated and followed up according to study designs. Age, gender, histological subtype, stage, grade, lymph node status and follow-up time data of patients were presented by most investigators, so we could display them in this article. The details of design and clinicopathological features in each study can be seen in tables 1 and 2. Outcomes of interest including OS, CSS and RFS were calculated and pooled HRs and corresponding 95% CIs are shown in fig. 2A–2C.

2.2 Prognostic Values of Lymphovascular Invasion in Bladder Cancer after Surgery

HRs and 95% CIs of Cox proportional hazard regression models of literatures were listed, the other HRs and 95% CIs were extracted from Kaplan-Meier survival curve (table 3). Our pooled results showed that there were significant differences in OS, CSS and RFS between the patients with LVI and the patients without LVI, and the analysis results were as follows: OS (pooled HR, 1.71; 95% CI, 1.52–1.92; P<0.00001; fig. 2A), CSS (pooled HR, 2.25; 95% CI, 1.80–2.81; P< 0.00001; fig. 2B) and DFS (pooled HR, 1.91; 95% CI, 1.57–2.32; P<0.00001; fig. 2C).

The study heterogeneities were evaluated mainly by forest plots and I^2 statistics. Inspection of Forrest plots did not reveal substantial heterogeneity; however, as for CSS (I^2=62%) and RFS (I^2=54%), there were significant heterogeneities observed in the studies (fig. 2A–C). In our meta-analysis, investigation of publication bias by funnel plots showed no substantial funnel plot asymmetry for prognosis of LVI, suggesting no presence of significant publication or selection bias (fig. 3A–C).

2.3 Subgroup Analysis

We also underwent the subgroup analyses and listed the respective pooled HRs and 95% CIs in table 4. There was no obvious difference between the two surgical procedures (table 5), while LVI lost its predictive value for CSS and RFS when the tumors were extravesical (stage≥T3) (table 6). For the patients who had negative lymph nodes, LVI could still predict the dismal outcomes of survival (table 7). The prognostic values were all statistically significant between eastern and western countries, between different years of publication and between the different sample sizes of studies.

3 DISCUSSION

Urinary bladder cancer is a common carcinoma of urinary tract, despite improvements in management and treatment of bladder tumors, the risk of recurrence, disease progression and death still needs to be paid attention to. Identifying the prognostic predictors of bladder cancer after surgical procedures is paramount for disease prevention and optimal clinical management. Many clinicopathological features such as sex, age, grade, stage, multifocality, history of previous recurrence, carcinoma in situ in the prostatic urethra and early recurrence were proven to be prognostic factors for recurrence, progression and death in bladder cancer[33]. What's more, several novel markers (p53, ki-67, p21 or survivin) which were identified to be associated with the biologic and clinical behavior of bladder cancer may help improve the staging, prognosis, and selection of therapeutic strategies[34]. However, the sample sizes of these biomarker studies were in general too small, and/or the performance of the single biomarker was moderate. The results suggested that single biomarker might be insufficient for effective monitoring and management of the disease, thus estab-

lishment of comprehensive panels of validate biomarkers was necessary for clinical application[8]. In consideration of the weak predictive value of basic characteristics like age and the insufficient reliability of many biomarkers, we made great efforts to look into the predictive value of LVI in bladder cancer.

Table 1 Baseline characteristics of eligible studies

References	Country	Period	Study design	Inclusion/ exclusion	Consecutive patients	Definition of LVI	No. of patients	Age of patients (years)	Gender (M/F) (% M)	Operative procedure	Adjuvant therapy
Bolenz, 2009	Germany	1985–2008	R	yes	NA	yes	1099	64.9±12.9 (29–92) †	906/193 (82.4%)	RC, LA, UD	5.8% chem
Branchereau, 2013	France	1994–2009	R	yes	NA	yes	108	69.1±13.1†	87/21 (81%)	TURBT	55.6% BCG
Canter, 2008	USA	1998–2006	R	yes	yes	NA	356	65.6±10.0†	285/71 (80%)	RC, UD	No
Cho, 2009	Korea	2001–2007	R	yes	NA	yes	118	67 (39–91)*	101/17 (85.6%)	TURBT	9.3% chem
Fritsche, 2013	Germany	2006–2010	P	yes	NA	yes	158	69 (61.8–76)*	121/37 (76.6%)	RC	No
Gondo, 2012	Japan	2000–2009	R	yes	yes	yes	194	68±0.7†; 70 (38–85)*	162/32 (83.5%)	RC	24.7% chem
Karam, 2007	Germany	1986–2005	R	yes	NA	NA	614	67 (31–82)*	480/134 (78.2%)	RC, LA, UD	No
Herrmann, 2008	USA	1987–2002	R	yes	yes	NA	226	66.2 (58.0–74.7)*	180/46 (79.6%)	RC, LA	27% chem, 9% radio
Lotan, 2005	Canada	1984–2003	R	yes	NA	yes	750	64.8±16.8†	612/138	RC, LA	7% radio, 31.6% chem
Ma, 2013	China	2000–2010	R	yes	NA	yes	101	65.8±12.2; 69 (24–84)*	83/18 (83%)	RC, UR	29% chem
Manoharan, 2010	USA	1992–2008	R	yes	NA	yes	357	NA	285/72 (80%)	RC, LA	No
Palmieri, 2010	Italy	1995–2007	R	yes	yes	NA	265	69 (46–93)*	218/47 (82.3%)	RC, LA, UD	No
Park, 2007	Korea	1989–2004	R	yes	NA	yes	260	61.5±8.6†	237/23 (91.2%)	RC, LA, UD	23.1% chem
Quek, 2005	USA	1971–2004	R	yes	NA	NA	702	68 (30–93)*	543/153 (77%)	RC, LA	No
Resnick, 2010	USA	1987–2008	R	yes	NA	NA	487	65.7†	376/111 (77.2%)	TURBT/ RC	No
Seo, 2010	Korea	2001–2006	R	yes	NA	NA	129	4.2 (38–88)*	104/25 (80.6%)	TURBT	6.2% BCG
Shariat, 2010	USA	1979–2008	R	yes	NA	yes	4257	67*	3373/864 (79.6%)	RC, LA	22.4% chem
Streeper, 2008	USA	1995–2005	R	yes	NA	NA	229	64.8 (35–88)*	180/49 (78.6%)	TURBT/ RC	22.3% chem
Tilki, 2012	Germany	1989–2003	R	yes	yes	yes	101	64.5 (38–87*)	86/15 (85%)	RC	No
Youssef, 2011	USA	1997–2003	R	yes	NA	yes	152	51 (36–74)*	99/53 (65.1%)	RC, LA	No

LVI: lymphovascular invision; UD: urinary diversion; TURBT: transurethral resection of bladder cancer; BCG: Bacille Calmette Guerin therapy; RC: radical cystectomy; DC: delayed cystectomy; LA: lymphoadenectomy; UR: uretheral reimplantation; chem: chemtherpy; radio: radiotherapy; R: retrospective; P: prospective; NA: not available; *: Data in median (range); †: Data in $\bar{x}\pm s$

Table 2 Characteristics of patients

References	No. of LVI	Patients (%)	Histological subtype	Stage (≤T1/T2/T3/T4)	Grade (G1/G2/G3)	Lymph node status	No. of re-sected nodes	Follow-up (months)
Bolenz, 2009	295	26.8	98.1% UC	621/438 (≤T2/≥T3)	G3:475 (43.8%)	All LN (–)	NA	NA
Branchereau, 2013	39	36.1	All UC	pT1a:64%; pT1b:36%	All G3	NA	NA	47.8±41.2†
Canter, 2008	114	32	All UC	27/87 (≤T2/≥T3)	NA	LN (+) 28%	NA	45.6†
Cho, 2009	33	28	All UC	all T1	3/60/55	NA	NA	35 (12–89)*
Fritsche, 2013	153	96.8	All UC	31/127 (≤T2/≥T3)	All G3	All LN(+)	14 (9–19)*	20 (11–38)*
Gondo, 2012	79	40.7	75.8% UC	108/86/58/28	46/148 (G1+G2/G3)	LN (+) 10.8%	NA	36.6±2.1†
Herrmann, 2008	NA	NA	86.3% UC	147/118/269/61	11/188/376	LN (+) 27.9%	NA	44 (0.1–220)*
Karam, 2007	101	44.7	All UC	42/65/83/36	17/209 (G1+G2/G3)	LN (+) 28.8%	17 (14–23)*	36.9 (13.3–19.6)*
Lotan, 2005	273	36.4	All UC	180/261/122/89	1/39/710	LN (+) 22.5%	NA	37.2 (0.4–16)/15.6 (0.1–171.6)*
Ma, 2013	25	24.7	All UC	pT2:69/pT3:32	23/78 (G1+G2/G3)	All LN(–)	NA	53.0 (9–120)*
Manoharan, 2010	105	29.4	All UC	140/84/98/35	49/15/293	LN (+) 20.4%	NA	NA
Palmieri, 2010	77	29.1	All UC	85/55/82/43	15/35/215	LN (+) 23.0%	NA	108 (1–216)*
Park, 2007	125	48.1	All UC	48/79/93/40	2/29/229	LN (+) 29.3%	14.6±8.2†	33.6 (3–180)*
Quek, 2005	249	35.5	All UC	374/328 (≤T2/≥T3)	44/658 (G1+G2/G3)	LN (+) 22.2%	NA	132 (0.3–278.4)*
Resnick, 2010	221	45.4	All UC	156/93/161/77	NA	LN (+) 27.5%	NA	NA
Seo, 2010	5	3.9	All UC	Ta:81/T1:46	31/76/22	NA	NA	48.6 (6.1–96.0)*
Shariat, 2010	1407	33.1	All UC	1361/1012/1322/55	78/1761/2167	LN (+) 26.7%	M18	43 (0.1–324)*
Streeper, 2008	163	71.2	All UC	11/158/13/36	NA	NA	NA	NA
Tilki, 2012	6	5.9	All UC	T0:17/Ta:6/TIS:21/T1:57	10/91 (G1+G2/G3)	All LN (–)	19 (9–80)*	38 (0.4–177)*
Youssef, 2011	24	15.8	All SCC	10/76/57/9	81/61/10	LN (+) 30.5%	20 (0–70)*	63.2 (1–100)*

UC: urothelial carcinoma; SCC: squamous cell carcinoma; LN (–): negative lymph node; LN(+): positive lymph node; NA: not available; *Data in median (range); †Data in $\bar{x}$±s

Table 3 Estimation of the HR

References	OS	CSS	RFS
Bolenz, 2009	2.117 (1.449–3.093)	2.611 (1.589–4.292)	3.502 (2.184–5.617)
Branchereau, 2013	*1.74 (1.21–2.51)*	NA	NA
Canter, 2008	1.63 (1.06–2.51)	1.81 (1.06–3.08)	1.59 (0.93–2.71)
Cho, 2009	NA	NA	1.686 (0.901–3.022)
Fritsche, 2013	NA	2.47 (1.37–4.43)	NA
Gondo, 2012	NA	2.162 (1.086–4.292)	NA
Karam, 2007	NA	NA	1.38 (0.84–2.27)
Herrmann, 2008	*1.704 (1.24–2.34)*	NA	NA
Lotan, 2005	1.84 (1.33–2.55)	2.07 (1.33–3.23)	2.02 (1.38–2.95)
Ma, 2013	2.902 (1.515–5.559)	3.010 (1.386–6.538)	2.055 (1.121–3.765)
Manoharan, 2010	NA	1.34 (0.85–2.1)	NA
Palmieri, 2010	NA	3.96 (2.53–6.21)	NA
Park, 2007	NA	3.566 (1.522–8.357)	NA
Quek, 2005	*1.47 (1.19–1.82)*	NA	*1.75 (1.28–2.38)*
Resnick, 2010	*1.68 (1.23–2.29)*	*2.18 (1.37–3.47)*	*2.06 (1.34–3.17)*
Seo, 2010	NA	1.28 (0.31–5.24)	4.59 (1.02–20.79)
Shariat, 2010	NA	1.453 (1.272–1.659)	1.427 (1.264–1.612)
Streeper, 2008	NA	2.68 (1.55–4.63)	NA
Tilki, 2012	NA	6.7 (1.5–30.3)	4.9 (1.4–16.5)
Youssef, 2011	NA	2.54 (0.92–7.00)	2.22 (0.97–5.12)

LVI: lymphovascular invasion; OS: overall survival; CSS: cancer specific survival; RFS: recurrence free survival; NA: not available
Data of HR estimated through Kaplan-Meier curves is indicated in italic, and remaining data is as reported by investigators.

Table 4 Subgroup analysis

	OS	CSS	RFS
Overall	1.71 [1.52, 1.92]	1.79 [1.61, 1.98]	1.62 [1.47, 1.77]
OP			
RC	1.70 [1.51, 1.93]	2.17 [1.75, 2.71]	1.90 [1.55, 2.34]
TURBT	1.74 [1.20, 2.53]	1.55 [1.05, 2.31]	2.17 [0.92, 5.10]
Stage			
T≤T2	1.52 [1.22, 1.91]	2.30 [1.59, 3.33]	1.86 [1.35, 2.57]
T≥T3	2.56 [1.08, 6.10]	1.88 [0.41, 8.58]	2.99 [0.88, 10.22]
LN(–)	2.29 [1.65, 3.18]	2.18 [1.62, 2.94]	2.99 [2.10, 4.28]
Area			
Eastern	2.90 [1.52, 5.54]	2.31 [1.42, 3.75]	1.99 [1.32, 3.01]
Western	1.68 [1.49, 1.89]	2.26 [1.76, 2.90]	1.90 [1.52, 2.37]
Year of publication			
≥2010	1.82 [1.45, 2.28]	2.20 [1.62, 3.00]	1.52 [1.36, 1.69]
<2010	1.67 [1.45, 1.91]	2.34 [1.84, 2.97]	1.90 [1.60, 2.27]
Sample number			
>250	1.66 [1.45, 1.91]	2.12 [1.59, 2.83]	1.82 [1.46, 2.28]
≤250	1.83 [1.46, 2.29]	2.56 [1.92, 3.43]	2.19 [1.54, 3.12]

OS: overall survival; CSS: cancer specific survival; RFS: recurrence free survival; OP: operative procedure; RC: radical cystectomy; TURBT: transurethral resection of bladder tumor; LN (–): lymph node negative

Table 5 Subgroup estimation of the HR by operative procedure

OP	References	OS	CSS	RFS
LA, RC, UD	Bolenz, 2009	2.117 (1.449–3.093)	2.611 (1.589-4.292)	3.502 (2.184–5.617)
RC, UD	Canter, 2008	1.63 (1.06–2.51)	1.81 (1.06–3.08)	1.59 (0.93–2.71)
RC	Fritsche, 2013	NA	2.47 (1.37–4.43)	NA
RC	Gondo, 2012	NA	2.162 (1.086–4.292)	NA
LA, RC, UD	Karam, 2007	NA	NA	1.38(0.84–2.27)
LA, RC	Herrmann, 2008	*1.704 (1.24–2.34)*	NA	NA
LA, RC	Lotan, 2005	1.84 (1.33–2.55)	2.07 (1.33–3.23)	2.02 (1.38–2.95)
RC, UR	Ma, 2013	2.902 (1.515–5.559)	3.010 (1.386–6.538)	2.055 (1.121–3.765)
LA, RC	Manoharan, 2010	NA	1.34 (0.85–2.1)	NA
LA, RC, UD	Palmieri, 2010	NA	3.96 (2.53–6.21)	NA
LA, RC, UD	Park, 2007	NA	3.566 (1.522–8.357)	NA
LA, RC	Quek, 2005	*1.47 (1.19–1.82)*	NA	*1.75 (1.28–2.38)*
RC	Resnick, 2010	*1.68 (1.23–2.29)*	*2.18 (1.37–3.47)*	*2.06 (1.34–3.17)*
LA, RC	Shariat, 2010	NA	1.453 (1.272–1.659)	1.427 (1.264–1.612)
RC	Streeper, 2008	NA	*2.01 (1.13–3.57)*	NA
RC	Tilki, 2012	NA	6.7 (1.5–30.3)	4.9 (1.4–16.5)
LA, RC	Youssef, 2011	NA	2.54 (0.92–7.00)	2.22 (0.97-5.12)
TURBT	Branchereau, 2013	*1.74 (1.21–2.51)*	NA	NA
TURBT	Cho, 2009	NA	NA	1.686 (0.901–3.022)
TURBT	Resnick, 2010	NA	NA	NA
TURBT	Seo, 2010	NA	1.28 (0.31–5.24)	4.59 (1.02–20.79)
TURBT	Streeper, 2008	NA	*1.58 (1.05–2.37)*	NA

OP: operative procedure; UD: urinary diversion of bladder cancer; TURBT: transurethral resection of bladder cancer; RC: radical cystectomy; DC: delayed cystectomy; LA: lymphoadenectomy; UR: uretheral reimplantation; OS: overall survival; CSS: cancer specific survival; RFS: recurrence free survival; NA: not available. Data of HR estimated through Kaplan-Meier curves is indicated in italic, and remaining data are as reported by investigators.

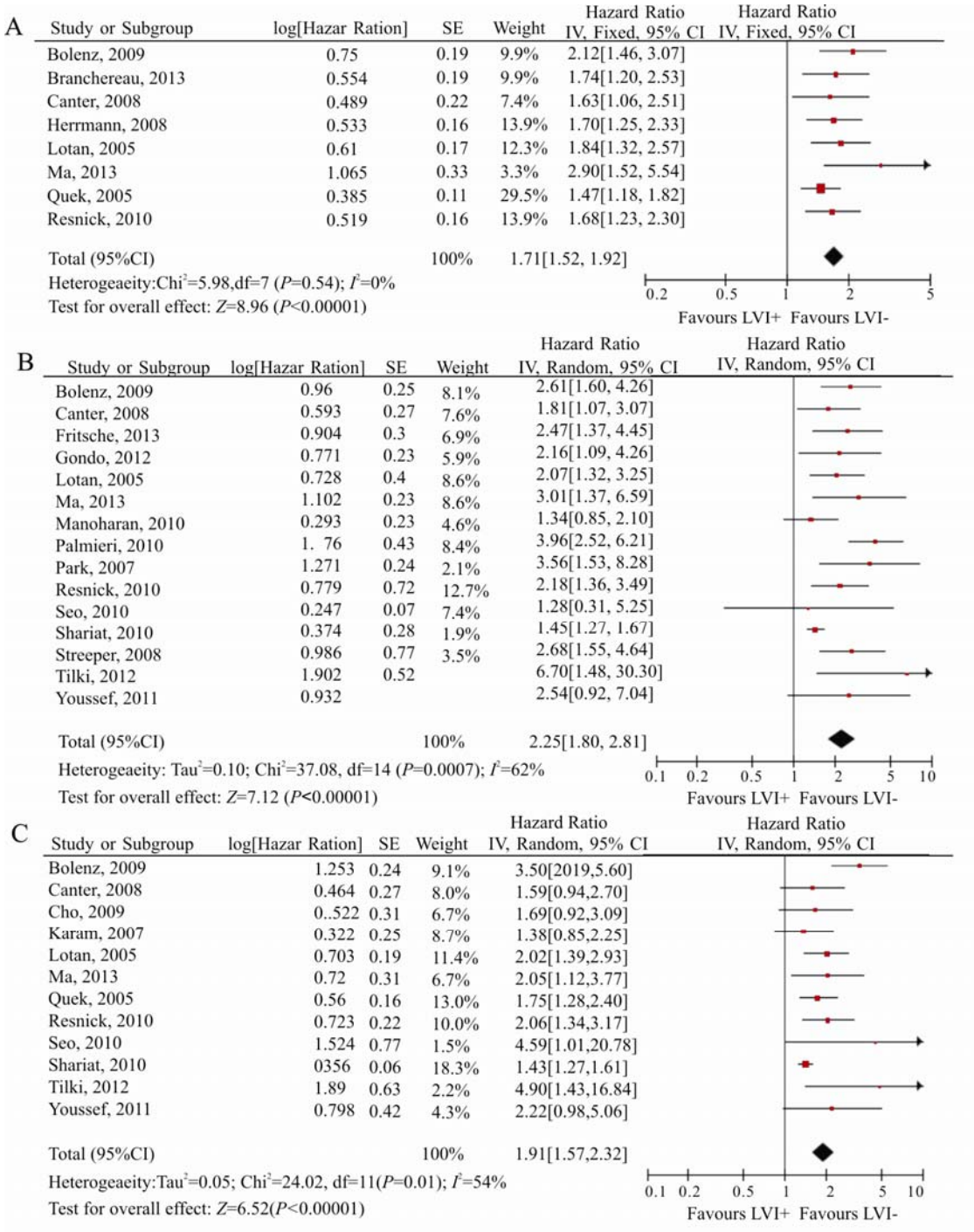

Fig. 2 Forrest plots of studies evaluating HRs of LVI for OS (A), CSS (B) and RFS (C)

Table 6 Subgroup estimation of the HR by pathological stage

Stage	Reference	OS	CSS	RFS
T≤T2				
T1T2	Bolenz, 2009	1.405 (1.055–1.872)	1.968 (1.281–3.023)	1.824 (1.226–2.712)
Ta	Seo, 2010	NA	1.28 (0.31–5.24)	4.59 (1.02–20.79)
T1a	Branchereau, 2013	*1.74 (1.21–2.51)*	NA	NA
T1	Cho, 2009	NA	NA	1.686 (0.901–3.022)
T0TaT1	Tilki, 2012	NA	6.7 (1.530–30.3)	4.9 (1.4–16.5)
T1T2	Streeper, 2008	NA	2.68 (1.55–4.63)	NA
T≥T3				
T3T4	Bolenz, 2009	3.951 (2.781–5.613)	6.870 (4.267–11.06)	5.569 (3.491–8.885)
T3T4	Canter, 2008	1.63 (1.06–2.51)	1.81 (1.06–3.08)	1.59 (0.93–2.71)
T3T4	Streeper, 2008	NA	0.54 (0.72–1.69)	NA

OS: overall survival; CSS: cancer specific survival; RFS: recurrence free survival; NA: not available.

Table 7 Subgroup estimation of the HR in lymph node negative patients

LN	Reference	OS	CSS	RFS
LN (–)	Bolenz, 2009	2.117 (1.449–3.093)	2.611 (1.589–4.292)	3.502 (2.184–5.617)
MIBC, LN (–)	Ma, 2013	2.902 (1.515–5.559)	3.010 (1.386–6.538)	2.055 (1.121–3.765)
LN (–)	Tilki, 2012	NA	6.7 (1.5–30.3)	4.9 (1.4–16.5)
LN (–)	Palmieri, 2010	NA	1.69 (0.86–3.32)	NA
LN (–)	Manoharan, 2010	NA	1.4 (0.76–2.57)	NA

LN (–): lymph node negative; OS: overall survival; CSS: cancer specific survival; RFS: recurrence free survival; NA: not available. MIBC: muscle invasive bladder cancer. Data of HR estimated through Kaplan-Meier curves is indicated in italic, and remaining data is as reported by investigators.

The objective of our meta-analysis was to examine the association between LVI and survival of bladder cancer after surgical operations. This meta-analysis combined the results from 20 studies of 10663 patients and revealed that detection of LVI significantly predicted poor OS, CSS and DFS of bladder cancer patients (HR=1.68, 95%CI 1.09–2.59, *P*=0.02). The included articles in this meta-analysis also proved that LVI was a useful prognostic factor and it should be incorporated into disease evaluation and clinical decision-making. With progression of detection of LVI by medical imaging methods and pathological assessment, the significance of LVI may be elucidated better. If LVI can be integrated into more accurate, flexible and easily accessible prognostic models, the practical task of predicting the prognosis of bladder cancer will be simplified particularly.

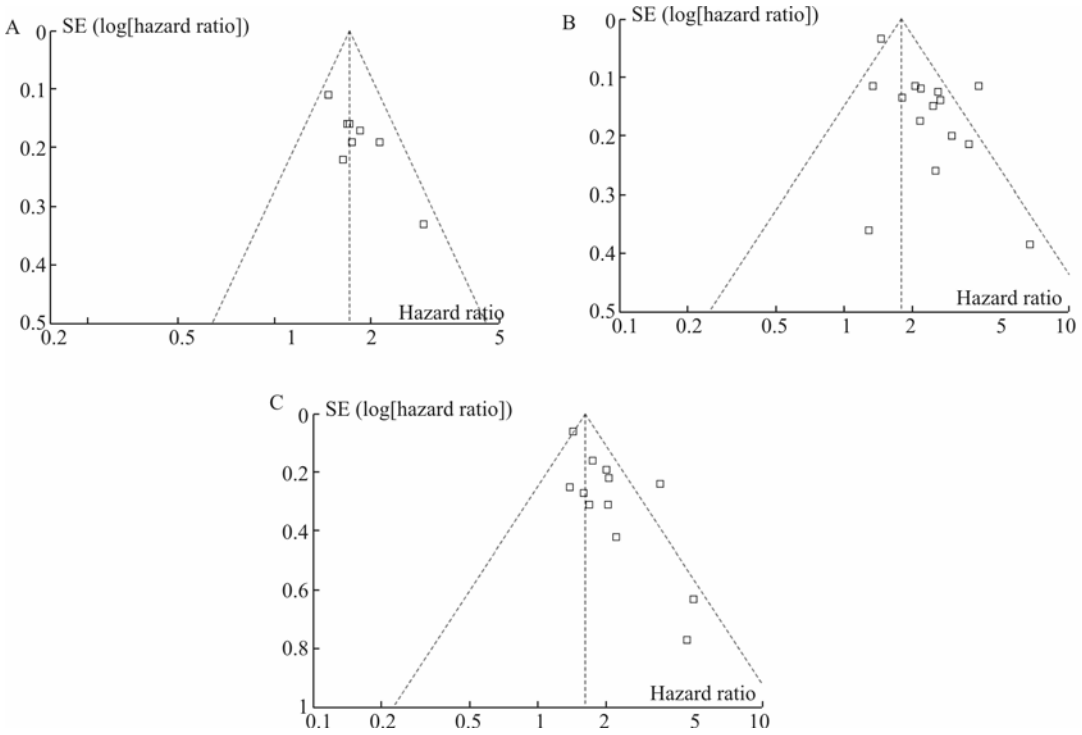

Fig. 3 Funnel plots of studies evaluating the HRs of LVI for OS (A), CSS (B) and RFS (C)

Our meta-analysis was consistent with previous studies which suggested that LVI was a dismal predictor of prognosis of cancer patients. Several studies have evaluated the prognostic significance of LVI, and then laid the foundation of LVI as an independent risk factor for bladder cancer after surgery. Algaba looked into the predictive value of LVI in locally advanced bladder cancer, and pointed out the necessity to reach a consensus on strict diagnostic criteria to incorporate this prognostic factor in clinical practice[11]. Mazzucchelli *et al* confirmed the clinicopathological significance of LVI in the assessment of urothelial carcinoma, and thought LVI should routinely be reported upon in the pathological report[35].

Our research results were of great significance in clinical practice. First, detection of LVI prior or after surgery could significantly predict poor prognosis of bladder cancer patients. The LVI, together with other well accepted predictors, could jointly show a clearer picture of prognosis for cancer patients. Second, our results could provide supports for incorporation of LVI into future bladder cancer staging systems, and the prognostic information could be incorporated into disease evaluation and clinical decision-making. Third, the detection of LVI could help the doctors identify the high risk population and then adjust the follow-up schedule, and the identified patients could receive adjuvant therapies timely. Besides, with the progression of detection of LVI by medical imaging methods and pathological assessment, the importance of LVI may be elucidated better. If the LVI can be integrated into more accurate, flexible and easily accessible prognostic models, and then be vali-

dated in large prospective studies, the practical task of predicting the prognosis of bladder cancer will be simplified; the patients can also get truly informed consent and make better decision together with their clinician.

We should admit that there existed certain inherent limitations in the trials included in our meta-analysis, but we could overcome these through analyzing the valid data. The major limitation is that our findings are based on the limitations of lower evidence level of the included studies which were mainly retrospective studies. And sample sizes of some studies were really small. Therefore, more high-quality prospective studies with sufficient information need to be conducted, and they contribute to a more significant meta-analysis. Secondly, the inner-study heterogeneity of eligible studies could not be ignored, which decreased the reliability of our meta-analysis. There was also difference between inner subgroup, so the relative risk of LVI might come from internal discrepancy.

However, despite these limitations about statistics, our study applied a rigorous inclusion/exclusion criterion, divided different subgroups to identify studies, adopted large sample size with a total of 10 663 patients, and advanced meta-analysis of HR for survival. Hence, with the help of sufficient data available from extraction by resourceful electronic databases, we successfully provided a comprehensive meta-analysis concerning the prognostic role of LVI in predicting survival in patients with surgical resected bladder cancer.

In conclusion, our pooled results demonstrate that LVI can denote poor prognosis of patients with bladder cancer after RC or TURBT. Our meta-analysis has provided a better understanding of the association between the presence of LVI and bladder cancer survival. Besides, our study also sheds new light on practical management of patients as LVI can be of particular value for prognostic prediction of people and for guidance of proper adjuvant therapies to high risk groups. However, these findings should be interpreted with caution due to the heterogeneity in the eligible studies. Therefore, these results need to be further confirmed by adequately designed prospective studies to provide a better conclusion on the association between LVI and the prognosis of patients with bladder cancer.

Author contributions: Yuan-feng TIAN, Hui ZHOU and Hua XU conceived and designed the experiments. Yuan-feng TIAN, Gan YU, Heng LI, Ding XIA and Hai-bing XIAO performed the experiments. Hui ZHOU and Ji WANG analyzed the data. Ji-hong Liu, Zhang-qun YE, Hua XU and Qian-yuan ZHUANG contributed reagents/materials/analysis tools. Yuan-feng TIAN, Hui ZHOU and Qian-yuan ZHUANG wrote the paper.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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