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Systematic Review and Meta-Analysis

A systematic review and meta-analysis of the impact of lymphovascular invasion in bladder cancer transurethral resection specimens

Andrea Mari*†, Shoji Kimura*‡, Beat Foerster*§, Mohammad Abufaraj*¶, David D'Andrea*, Melanie Hassler*, Andrea Minervini†, Morgan Rouprêt**, Marko Babjuk†† and Shahrokh F. Shariat*‡‡§§¶¶

*Department of Urology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria, †Department of Urology, Careggi Hospital, University of Florence, Florence, Italy, ‡Department of Urology, Jikei University School of Medicine, Tokyo, Japan, §Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland, ¶Department of Special Surgery, Jordan University Hospital, University of Jordan, Amman, Jordan, **GRC no 5, ONCOTYPE-URO, AP-HP, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France, ††Department of Urology, Second Faculty of Medicine, Hospital Motol, Charles University, Praha, Czech Republic, ‡‡Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria, §§Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA, and ¶¶Department of Urology, Weill Cornell Medical College, New York, NY, USA

A.M. and S.K. contributed equally to this project and share first authorship.

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The aim of the present review was to assess the prognostic impact of lymphovascular invasion (LVI) in transurethral resection (TUR) of bladder cancer (BCa) specimens on clinical outcomes. A systematic review and meta-analysis of the available literature from the past 10 years was performed using MEDLINE, EMBASE and Cochrane library in August 2017. The protocol for this systematic review was registered on PROSPERO (Central Registration Depository: CRD42018084876) and is available in full on the University of York website. Overall, 33 studies (including 6194 patients) evaluating the presence of LVI at TUR were retrieved. LVI was detected in 17.3% of TUR specimens. In 19 studies, including 2941 patients with ≤cT1 stage only, LVI was detected in 15% of specimens. In patients with ≤cT1 stage, LVI at TUR of the bladder tumour (TURBT) was a significant prognostic factor for disease recurrence (pooled hazard ratio [HR] 1.97, 95% CI: 1.47–2.62) and progression (pooled HR 2.95, 95% CI: 2.11–4.13), without heterogeneity ($I^2 = 0.0\%$, $P = 0.84$ and $I^2 = 0.0\%$, $P = 0.93$, respectively). For patients with cT1–2 disease, LVI was significantly associated with upstaging at time of radical cystectomy (pooled odds ratio 2.39, 95% CI: 1.45–3.96), with heterogeneity among studies ($I^2 = 53.6\%$, $P = 0.044$). LVI at TURBT is a robust prognostic factor of disease recurrence and progression in non-muscle invasive BCa. Furthermore, LVI has a strong impact on upstaging in patients with organ-confined disease. The assessment of LVI should be standardized, reported, and considered for inclusion in the TNM classification system, helping clinicians in decision-making and patient counselling.

Keywords

lymphovascular invasion, transurethral resection, recurrence, progression, upstaging, meta-analysis, #blcsm, #BladderCancer

Introduction

Bladder cancer (BCa) is the fourth most commonly diagnosed malignancy in men, with significant morbidity and mortality worldwide [1]. In western countries, ~70% of patients with BCa are diagnosed with non-muscle-invasive BCa (NMIBC) [2]. Transurethral resection of the bladder tumour (TURBT) is necessary for the diagnosis, risk stratification and treatment of patients with NMIBC; however, up to 61% and 17% of patients who undergo TURBT and adjuvant treatment with BCG, respectively, for high-risk cT1 BCa experience disease recurrence or progression to carcinoma invading the bladder muscle (MIBC) within the first year [2,3]. Identification of patients with NMIBC who are at high risk of experiencing

BJU International | doi:10.1111/bju.14417
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progression to MIBC would allow selection for intensified therapy such as early radical cystectomy (RC) or inclusion in clinical trials of new therapies.

Lymphovascular invasion (LVI) is a crucial step in the initiation of tumour dissemination and metastasis [4]. Although LVI has been established as a feature of biologically and clinically aggressive disease in patients treated with RC [5–8], its role at TUR is not yet clear. The results from a previous meta-analysis suggested an increased risk of pathological upstaging and poor clinical outcomes in patients with LVI at TURBT [9]; however, the selection criteria included all studies regardless of the patients' tumour stage. Moreover, new studies have added further data with which to analyse the prognostic impact of LVI at TUR in patients with organ-confined BCa [10–18].

The aim of the present study was to perform a systematic review and meta-analysis to assess the role of LVI in TUR specimens, regardless of tumour stage, to investigate its prognostic impact on disease recurrence and progression in patients with NMIBC, and to assess its predictive value for upstaging at RC in patients with clinically organ-confined (cT1–2) disease.

Evidence Acquisition

Table S1 shows a completed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2015 checklist, which clearly describes the methodology of the review [19]. The protocol has also been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018084876).

Literature Search

A systematic review and meta-analysis of the English-language literature was performed according to the PRISMA statement and the Cochrane Handbook for Systematic Reviews of Interventions [20,21]. The MEDLINE, EMBASE and Cochrane Library were systematically searched on 9 August 2017 to identify studies published between January 2007 and August 2017 that investigated the impact of LVI in TUR specimens on oncological outcomes in patients with urothelial BCa. After a first screening based on study title and abstract, all papers were assessed based on full text and excluded with reasons when inappropriate. A further check of the appropriateness of the papers based on full-text revision was performed after data extraction. Two reviewers (A.M. and S.K.) carried out this process independently. Disagreements were solved by a third party (B.F.). The following string terms were used: ((('bladder') AND ('cancer' OR 'urothelial carcinoma' OR 'urothelial neoplasm' OR 'carcinoma' OR 'transitional cell carcinoma')) AND ('TUR' OR 'TURB' OR 'TRANSURETHRAL RESECTION')) AND ('LVI' OR 'lymphovascular invasion' OR 'lymphatic invasion' OR 'vascular invasion'). The process used to identify articles is summarized in Fig. 1. Disease recurrence, disease progression and upstaging were the primary outcomes of interest.

Eligibility Criteria

As proposed by the PRISMA guidelines, we used the Population, Intervention, Comparator, Outcome and Study design approach to specify the eligibility criteria: studies were considered eligible if patients with LVI in BCa (population) treated with TUR with or without RC (intervention) were compared with patients without LVI (comparator) to investigate the prognostic value of LVI on disease recurrence, progression and upstaging (outcomes) in non-randomized observation or cohort studies.

Inclusion and Exclusion Criteria for the Systematic Review

After article selection according to the eligibility criteria, the following types of study were excluded: review articles; editorials; commentaries; papers written in languages other than English; meeting abstracts; replies from authors; and case reports. If multiple articles published by the same author or group and based on similar patient cohorts were found, only the paper with the largest cohort was included. For the purposes of the present study, all eligible studies were included in the systematic review, regardless of the clinical stage involved.

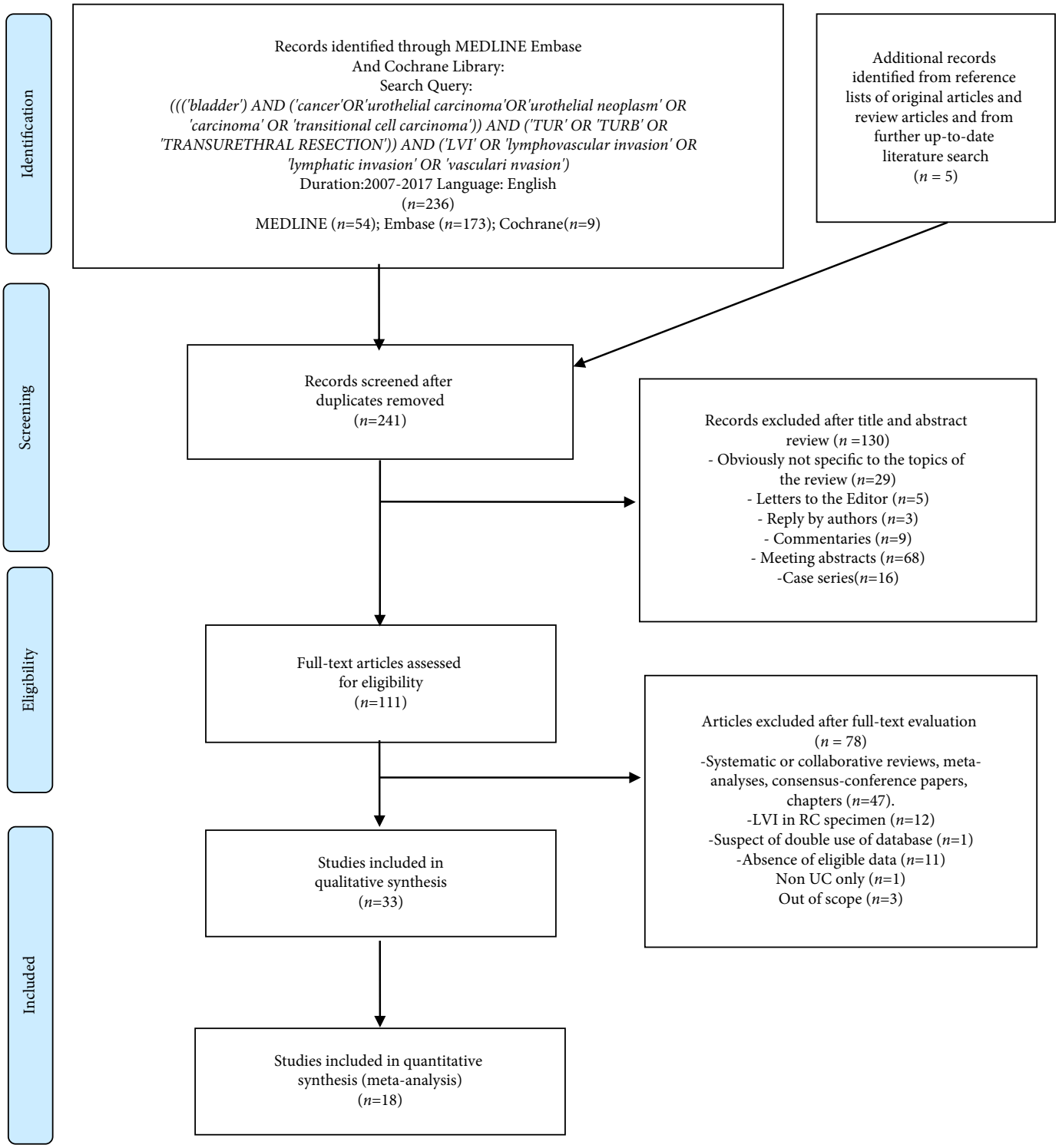
Inclusion and Exclusion Criteria for the Meta-Analysis

The studies selected for the systematic review were then screened for the quantitative analysis. Of these, studies analysing patients with ≤cT1 (cTa-Tis-T1) stage disease were included in the meta-analysis of the prognostic impact of LVI at TUR on disease recurrence and progression. Studies analysing patients with organ-confined (≤cT2) disease and subsequently treated with RC were included in a meta-analysis of the prognostic impact of LVI at TUR on upstaging at RC.

Data Extraction

After full-text evaluation, data were independently extracted by two authors (A.M. and S.K.) for further assessment of qualitative and quantitative evidence synthesis. All extracted variables were crosschecked to ensure their reliability. We recorded the baseline characteristics of the included participants, the use of peri-operative chemotherapy and the median/mean follow-up duration. Subsequently, the hazard

Fig. 1 Flow chart for the article selection process. LVI, lymphovascular invasion; RC, radical cystectomy; UC, urothelial carcinoma.



ratios (HRs) and 95% confidence intervals (CIs) of LVI associated with each outcome were retrieved. Furthermore, we searched for methods and important confounders to establish comparability. All discrepancies regarding data extraction were resolved by consensus or finally decided on by the senior author (S.F.S.).

Statistical Analysis

Because of the observational nature of the included studies, we extracted the adjusted HR and odds ratio with 95% CI for cumulative effect size calculation from multivariable Cox regression analysis (for recurrence and progression outcomes) and logistic regression analysis (for upstaging outcome), respectively. Studies reporting only Kaplan–Meier log-rank or univariable analyses were not considered for the meta-analysis. Effect summary estimation methods were not used in these cases as a high level of additional selection bias would have been introduced. Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed with the Cochrane Q test and I^2 statistic. Significant heterogeneity was indicated by a P value <0.05 in Cochrane Q tests and a ratio >50% in I^2 statistics, which led to the use of random-effect models according to the DerSimonian and Laird method [22–24]. When these tests were negative for heterogeneity, fixed-effect models were chosen for calculation of pooled HRs through the inverse-variance method. Publication biases including small-study effect were evaluated by visual inspection of funnel plots for all assessed comparisons. Statistical analyses were performed using STATA/MP 14.2 (Stata Corp., College Station, TX, USA).

Risk of Bias

The risk-of-bias assessment is reported in Tables S2, S3, S4. The risk-of-bias evaluation of included studies was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions for including non-randomized studies [25,26]. Because of the inclusion of only non-randomized comparative studies, risk of bias was determined by examining the risk of preassigned confounders. The main confounding factors were identified as the most important prognostic factors affecting disease recurrence, progression and upstaging. For this purpose, the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) was used for evaluating risk of bias in estimates of the comparative effectiveness of interventions from studies that did not use randomization to allocate units to comparison groups [27]. The ROBINS-I tool was used for each of the three outcomes analysed. The presence of confounders was determined by consensus between A.M. and B.F.

Evidence Synthesis

Study Selection

We identified a total of 236 articles from the search query and five from the reference lists. Overall 130 articles were excluded after title and abstract screening and 78 after full-text evaluation. The remaining 33 articles were included in the systematic review. The flow chart of the study selection process is shown in Fig. 1.

Study Population

Study characteristics are reported in Table 1 [10–18,28–51]. The 33 studies included 6194 patients treated with TUR with or without RC. The population examined was from the USA/Canada in 13 studies, Europe in 10 studies and Asia in 10 studies. All the studies had a retrospective design. LVI definition was provided in 16 studies (48.5%) and was found in 1 069 of 6194 patients (17.3%). Pathological characteristics are reported in Table 2 [10–18,28–51]. Overall, 62% of patients had NMIBC, 32% had cT2 stage and 6% had cT3–4 stage. In 19 studies, only patients with NMIBC were analysed (n = 2 941) and LVI was detected in 15% of these patients. Extravesical disease and node involvement were reported in 633/1715 (36.9%) and 371/1537 patients (24.2%) subsequently treated after RC, respectively.

Meta-Analysis

Association of LVI in cT1 TUR Specimens with Disease Recurrence

The impact of LVI on disease recurrence was investigated in six studies including 1412 patients treated with TURBT for cT1 BCa. The forest plot (Fig. 2) shows that LVI was significantly associated with disease recurrence (pooled HR 1.97, 95% CI: 1.47–2.62; z = 4.61). The Cochrane Q test (χ^2 = 2.06; P = 0.841) and I^2 test (I^2 = 0.0%) did not show any significant heterogeneity. The funnel plot did not identify any study over the pseudo 95% CI (Fig. S1).

Association of LVI in cT1 TUR Specimens with Disease Progression

The impact of LVI on disease progression was investigated in nine studies including 1334 patients treated with TURBT for cT1 BCa. The forest plot (Fig. 3) shows that LVI was significantly associated with disease progression (pooled HR 2.95, 95% CI: 2.11–4.13; z = 6.30). The Cochrane Q test (χ^2 = 3.15; P = 0.925) and I^2 test (I^2 = 0.0%) did not show any significant heterogeneity. The funnel plot did not identify any study over the pseudo 95% CI (Fig. S2).

Association of LVI in cT1–2 TUR Specimens with Upstaging at RC

The impact of LVI on upstaging after RC was investigated in seven studies including 1710 patients treated with TURBT for cT1–T2 BCa. The forest plot (Fig. 4) shows that LVI was significantly associated with upstaging after RC (pooled HR 2.39, 95% CI: 1.45–3.96; z = 3.40) in all of the seven studies. Subgroup analysis showed that LVI was not significantly associated with

Table 1 Characteristics of the eligible studies included in the systematic review.

First author of study and year	Country	Recruitment period	No. of patients	LVI, %	Definition of LVI	NOS	Main treatment
Andius P (2007) [28]	Sweden	1987–1989	121	9.9	Yes	5	TUR
Kassouf W (2007) [29]	USA	1990–2005	120	31.7	No	6	RC
Herr HW (2008) [30]	USA	1995–2001	63	55.6	No	8	TUR
Weizer AZ (2009) [31]	USA	1995–2007	95	12.6	No	6	RC
Cho KS (2009) [32]	Korea	2001–2007	118	28.0	Yes	7	TUR
Streeper N (2009) [33]	USA	1995–2005	103	67.0	Yes	4	RC
Seo HK (2010) [34]	Korea	2001–2006	129	3.9	No	4	TUR
Font A (2011) [35]	Spain	1994–2007	98	14.3	No	6	RC
Faba OR (2011) [36]	Spain	1978–2002	141	19.9	No	5	RC
Badalato G (2012) [37]*	USA	1990–1999	90	24.4	No	6	RC
Badalato G (2012) [37]*	USA	2000–2010	259	10.0	No	6	RC
Green DA (2012) [38]	USA	NR	201	10.4	Yes	6	RC
Xie HY (2012) [39]	China	2003–2011	248	17.7	Yes	5	RC
Kwon D (2012) [40]	Korea	1999–2010	406	3.0	No	7	TUR
Branchereau J (2013) [41]	France	1994–2009	108	36.1	Yes	5	TUR
Brimo F (2013) [42]	Canada/USA	2004–2012	86	12.8	Yes	6	TUR
Bolenz C (2013) [43]	EU	2000–2006	111	18.0	Yes	6	TUR
Levidou G (2013) [44]	Greece	1985–1995	115	22.6	No	5	NR
Olsson H (2013) [45]	Sweden	1992–2001	211	7.6	Yes	6	TUR
Kaimakliotis HZ (2014) [46]	USA	2008–2013	308	9.1	No	5	RC
Prelevic R (2014) [47]	Serbia	2002–2012	233	69.5	Yes	4	RC
Svatek RS (2014) [48]	USA	2000–2008	545	9.0	No	4	RC
Goldsmith B (2014) [49]	USA	1987–2010	315	12.7	No	6	RC
Go H (2015) [10]	Korea	1996–2006	274	2.9	Yes	6	TUR
Pietzak EJ (2015) [50]	USA	1990–2009	275	12.0	No	5	RC
Miyake M (2015) [11]	Japan	1998–2013	106	38.7	No	6	TUR
Patschan O (2015) [12]	Sweden	1997–2003	156	24.2	No	7	TUR
Weiss BE (2015) [13]	USA	1977–2009	120	4.2	No	6	TUR
Fukumoto K (2016) [14]	Japan	1994–2013	116	25.9	Yes	6	TUR
Haas CR (2016) [15]	USA	1990–2012	117	8.5	No	7	RC
Li G (2016) [16]	China	2003–2014	206	27.7	Yes	7	RC
Sha N (2016) [17]	China	2006–2010	155	21.9	Yes	6	TUR
Lucca I (2016) [51]	EU	2001–2014	350	9.7	Yes	6	RC
Ukai R (2017) [18]	Japan	2000–2012	86	17.4	Yes	4	TUR

*EU, European Union; LVI, lymphovascular invasion; NOS, Newcastle–Ottawa score; NR, not reported; RC, radical cystectomy; TUR, transurethral resection. *Two different cohorts of patients treated from 1990 to 1999 and from 2000 to 2010 analysed in a single study.*

upstaging after RC in studies evaluating cT2 patients alone (pooled HR 1.25, 95% CI: 0.35–4.44; $z = 0.35$), but it was significantly associated in studies evaluating patients with cT1–2 disease together (pooled HR 3.08, 95% CI: 1.99–4.78; $z = 3.67$). The Cochrane Q test ($\chi^2 = 12.93$; $P = 0.044$) and I^2 test ($I^2 = 53.6\%$) showed significant heterogeneity. The funnel plot identified one study over the pseudo 95% CI (Fig. S3).

Discussion

Non-muscle invasive BCa is a disease with highly variable behaviour and outcome. Patients with high-risk T1 BCa have a greater risk of disease recurrence and progression compared with patients with T1 BCa without high-risk features [3]. The inherently heterogeneous course of T1 high grade/G3 disease makes this entity of NMIBC challenging to treat. An accurate risk stratification would allow the identification of those patients who should receive intensified therapies, such as early RC and preoperative systemic therapy, with the attempt to control micrometastatic disease. LVI is a histological feature of biologically and clinically aggressive BCa; it is associated with poor oncological outcomes if detected in RC specimens [5–8] as well as in patients with upper tract urothelial carcinoma [52]. In non-seminomatous testicular germ cell cancer, LVI presence upstages the tumour according to the TNM classification [53].

In the present study, a systematic review and meta-analysis was conducted to assess the role of LVI in TUR specimens, to investigate its prognostic impact on disease recurrence and progression in patients with NMIBC and to evaluate its predictive value for upstaging at RC in patients with organ-confined disease. We identified 6194 patients treated with TUR, for whom LVI status was evaluated in 33 studies. Overall, LVI was reported in 17.3% of cases and in 15% of patients in studies analysing only patients with ≤cT1 stage. We found that, in patients with NMIBC, the presence of LVI at TUR doubled the risk of developing disease recurrence (pooled HR 1.97, 95% CI: 1.47–2.62) and increased the risk of disease progression to MIBC threefold (pooled HR 2.95, 95% CI: 2.11–4.13) compared with patients without LVI.

Table 2 Pathological characteristics of the eligible studies included in the systematic review.

Study and year	cT stage (%)			High grade or G2–3 (%)	Muscle in TUR specimen (%)	Re-staging TUR (%)	Intravesical adjuvant treatment			NAC	AC	Upstaging (pT3–4 at RC) (%)	pN stage at RC (%)	Median follow-up (months)
	cTa-Tis-T1	cT2	cT3–4				BCG	Chemotherapy	Immediate					
Andius P (2007) [28]	100	0	0	96.0	88	17	1	3	NR	NR	NR	NR	NR	NR
Kassouf W (2007) [29]	17.0	54.0	29	100	NR	NR	NR	NR	NR	64	NR	NR	NR	32
Herr HW (2008) [30]	0	57.0	43	NR	100	100	NR	NR	NR	100	0	NR	NR	86
Weizer AZ (2009) [31]	100	0	0	NR	100	24.2	NR	NR	NR	excl	NR	13.7	8.4	45.6
Cho KS (2009) [32]	100	0	0	97.4	NR	26.3	62	23	NR	NR	NR	NR	NR	35
Streeper N (2009) [33]	5.8	65.0	29	NR	NR	NR	NR	NR	NR	excl	11.3	37.9	NR	NR
Seo HK (2010) [34]	100	0	0	76.0	100	NR	100	0	NR	NR	NR	NR	NR	48.6
Font A (2011) [35]	0	3.0	97	NR	100	NR	NR	NR	NR	100	NR	NR	NR	45
Faba OR (2011) [36]	40.0	39.0	21	93.6	NR	NR	NR	NR	NR	NR	5.7	NR	13.4	42.5
Badalato G (2012) [37]	100	0	0	NR	31	NR	NR	NR	NR	NR	NR	NR	NR	NR
Badalato G (2012) [37]	100	0	0	NR	47.5	NR	NR	NR	NR	NR	NR	NR	NR	NR
Green DA (2012) [38]	50.2	49.8	0	98.5	NR	NR	35.3	NR	excl	NR	35.4	18.9	NR	
Xie HY (2012) [39]	47.0	53.0	0	87.0	NR	NR	NR	NR	NR	excl	NR	NR	NR	NR
Kwon D (2012) [40]	100	0	0	59.4	NR	NR	NR	100	0.2	excl	NR	NR	NR	76.9
Branchereau J (2013) [41]	100	0	0	100	100	72.2	0.1	100	0.1	NR	NR	NR	NR	47.8
Brimo F (2013) [42]	100	0	0	NR	74	0	NR	NR	NR	NR	NR	NR	NR	29
Bolenz C (2013) [43]	68.4	31.5	0	81.1	NR	NR	5.3	22.4	27.6	NR	NR	NR	NR	30
Levidou G (2013) [44]	63.5	T2–3: 36.5	47.8	NR	NR	33.6	NR	excl	NR	NR	NR	NR		
Olsson H (2013) [45]	100	0	0	100	NR	14.7	NR	18.5	0	excl	NR	NR	NR	60
Kaimakliotis HZ (2014) [46]	0	100	0	NR	NR	NR	NR	NR	NR	22.1	14.6	43.5	29.2	30
Prelevic R (2014) [47]	24.9	75.1	0	100	NR	NR	NR	NR	NR	excl	NR	56.6	NR	NR
Svatek RS (2014) [48]	40.9	41.7	17	NR	NR	NR	NR	NR	NR	36.9	NR	NR	15.8	49.3
Goldsmith B (2014) [49]	13.0	64.1	23	NR	NR	NR	NR	NR	NR	excl	NR	45.6	25.7	NR
Go H (2015) [10]	100	0	0	50.4	NR	NR	5.9	38.3	NR	NR	NR	NR	NR	NR
Pietzak EJ (2015) [50]	0	100	0	NR	100	NR	NR	NR	NR	8.7	NR	45.6	30.2	23.2
Miyake M (2015) [11]	100	0	0	100	100	12	13.0	54.0	NR	NR	NR	NR	NR	23
Patschan O (2015) [12]	100	0	0	100	NR	60.3	3.2	25.6	NR	NR	NR	NR	NR	78
Weiss BE (2015) [13]	100	0	0	100	NR	NR	19.2	80.8	NR	NR	NR	NR	NR	53
Fukumoto, K (2016) [14]	100	0	0	100	NR	NR	13.8	73.3	0	NR	NR	NR	NR	53
Haas CR (2016) [15]	100	0	0	NR	NR	42.7	0.0	100	NR	NR	NR	12.8	18.8	60.7
Li G (2016) [16]	100	0	0	41.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sha N (2016) [17]	100	0	0	39.4	NR	NR	97.4	NR	NR	NR	NR	NR	78.4	
Lucca I (2016) [51]	29.0	71.0	0	79.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ukai R (2017) [18]	100	0	0	100	91	NR	4.7	46.5	NR	NR	NR	NR	NR	49

AC, adjuvant chemotherapy; adj: adjuvant; CT: chemotherapy, excl: excluded, NAC: neoAC, NR: not reported, RC: radical cystectomy, TUR: transurethral resection.

Fig. 2 Forest plot showing the association between lymphovascular invasion and disease recurrence in studies including patients treated with transurethral resection for non-muscle-invasive bladder cancer. HR, hazard ratio; RFS, recurrence-free survival.

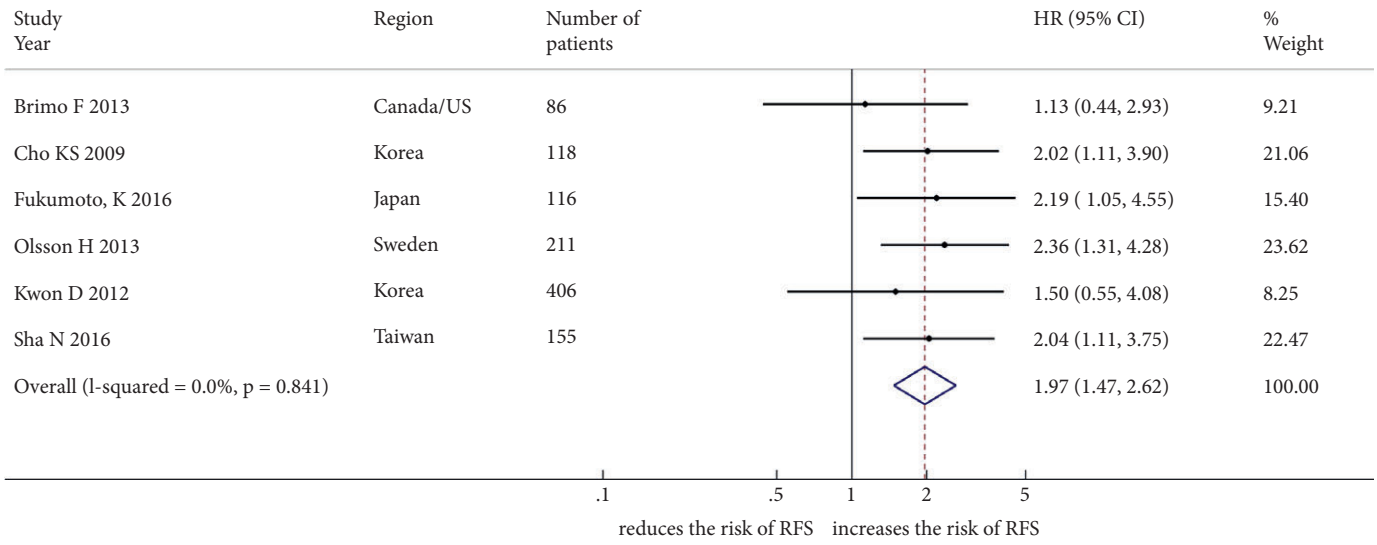
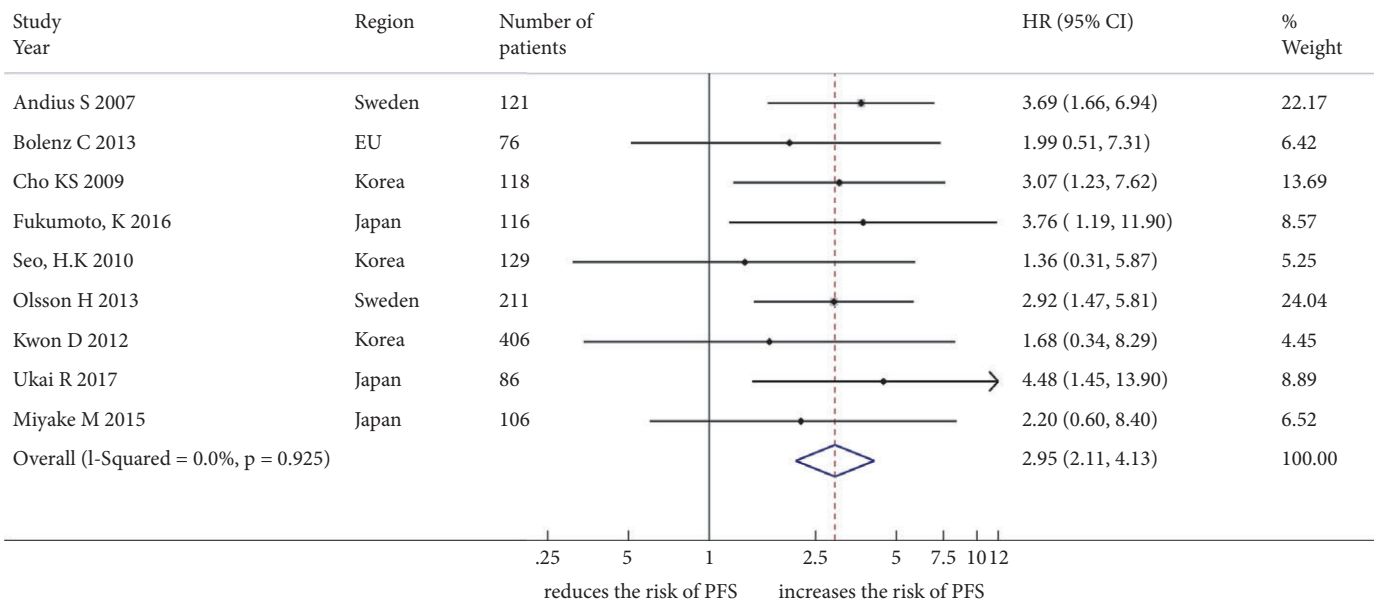
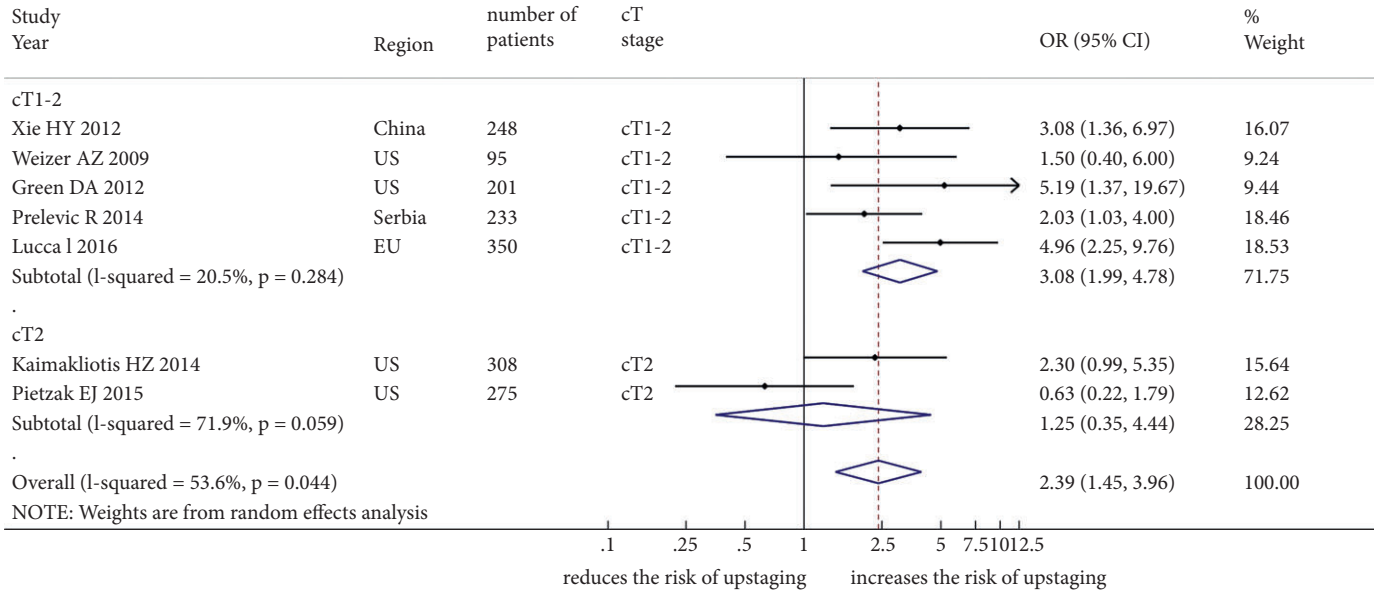


Fig. 3 Forest plot showing the association between lymphovascular invasion and disease progression in studies including patients treated with transurethral resection for non-muscle-invasive bladder cancer. HR, hazard ratio; PFS, progression-free survival.



The currently recommended scoring models for individualized prediction of disease recurrence and progression are the European Organization for Research and Treatment of Cancer (EORTC) [3] and the Spanish Urological Club for Oncological Treatment (CUETO) [54] risk tables. The two scoring models are based on the most relevant clinical and pathological predictors, sex, age, tumour stage and grade, number of tumours, size, carcinoma *in situ* and prior recurrence rate. These tools aim to help in personalized risk assessment, thereby guiding clinical decision-making regarding follow-up and therapy; however, an external validation of these scores exhibited poor discrimination of both tools regarding disease recurrence and progression [55]. Additional factors not included in the EORTC or the CUETO models might enhance their usefulness. Hydronephrosis as well as micropapillary or neuroendocrine variant histology could help identify patients who are likely to need multimodal intensified therapy [56].

Fig. 4 Forest plot showing the association between lymphovascular invasion and disease upstaging in studies including patients treated with transurethral resection and subsequently radical cystectomy for organ-confined (≤cT2) bladder cancer. OR, odds ratio.



An additional key feature with which to identify patients with aggressive biology and poor outcomes is LVI. The invasion of the numerous blood and lymphatic vessels in the lamina propria allow early haematogenous and lymphatic cancer cell dissemination [57]. In this context, LVI might indicate a histological pattern associated with a higher propensity to muscle-invasive, non-organ-confined disease and micrometastases. We found that LVI was associated with a more than double risk of upstaging after RC. Unfortunately, we could not identify any study analysing the impact of LVI on upstaging in NMIBC at TURBT; however, subgroup analysis showed that the association between LVI and upstaging was even higher in cT1–2 patients, while it was not significant in patients with cT2 disease. These results suggest that the presence of LVI is an independent prognostic factor of upstaging in cT1 disease, while it lost its significance in cT2 stage disease because of the greater aggressiveness of the cT2 disease itself. Thus, cT1 disease with LVI should be considered as an intermediate stage between cT1 and cT2 disease in terms of prognosis, thereby prognostically upstaging cT1. Whether this is because of the micrometastatic potential conferred by LVI remains to be determined. Further prospective studies could assess the indication to perform neoadjuvant systemic therapy prior to RC in patients with LVI in cT1 BCa. In patients with cT2 LVI, this has been already widely suggested [58,59].

Critical for LVI assessment is the quality of the specimen. The rate of muscle presence in the specimen, which could be seen as a surrogate of quality of resection, ranged from 31% to 100% in the studies included in the review. Similarly, the rate of re-staging TUR was often not reported and varied considerably among one-third of studies included in the review. The depth of resection, the specimen size as well as the experience of the surgeon might influence the detection of LVI in the TUR specimen, the therapeutic decision-making process and, therefore, the course of the disease.

The present meta-analysis has some limitations. Only non-randomized observational studies were included and all of them had a retrospective design. Furthermore, patients could not be controlled for the quality of the TUR, effect of repeat TUR and follow-up schedules. In addition, a limitation was the different type of drug used for adjuvant therapy (BCG, mitomycin C, doxorubicin, epirubicin, etc.), the different treatment schedule and maintenance drug adopted. In addition, some studies did not provide a definition of LVI, usually described as the unequivocal presence of tumour cells within an endothelium-lined space, with no underlying muscular walls [60]. Studies separately analysing the combination of vascular and lymphatic invasion by tumour cells were excluded from the analysis as they may represent another disease entity, leading to heterogeneity. Pathology was performed by various pathologists and no study provided a centralized pathology assessment. Most of the studies did not report the long-term oncological outcomes; this could have significantly influenced the results of the present meta-analysis. Studies that did not identify independent predictors of outcomes are less likely to be published. All these limitations introduce a selection bias, as shown in the risk-of-bias assessments. Finally, in the analysis of the impact of LVI

on upstaging (Figs 4 and S3) a significant heterogeneity was detected. This could be related to the different surgical indication to perform RC related to centres' and surgeons' preference according to the clinical features of each patient and to treatments other than RC not considered in this analysis, such as partial cystectomy and trimodality therapy.

In conclusion, despite the limitations inherent to the retrospective nature of studies included, the results of the present meta-analysis suggest that LVI at TUR is a significant prognostic factor for disease recurrence and progression in patients with NMIBC. Furthermore, LVI seems to have a strong impact on upstaging. The assessment of LVI should be standardized and included in the TNM system. This readily accessible histological feature, together with other factors, may help clinicians to design more personalized management strategies helping in the decision-making regarding intensified therapy, counselling and follow-up for patients with NMIBC.

Conflict of Interest

Prof. Shahrokh F. Shariat owns or co-owns the following patents: Methods to determine prognosis after therapy for prostate cancer, granted 2002-09-06; Methods to determine prognosis after therapy for bladder cancer, granted 2003-06-19; Prognostic methods for patients with prostatic disease, granted 2004-08-05; Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma, granted 2010-07-20. He is also an advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi and Wolff and a speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi and Wolff. The remaining authors have no conflicts of interest to declare.

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Correspondence: Shahrokh F. Shariat, Department of Urology and Comprehensive Cancer Centre, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

e-mail: sfshariat@gmail.com

Abbreviations: BCa, bladder cancer; CUETO, Spanish Urological Club for Oncological Treatment; EORTC, European Organization for Research and Treatment of Cancer () [3]; HR, hazard ratio; LVI, lymphovascular invasion; MIBC, carcinoma invading the bladder muscle; NMIBC, non-muscle invasive bladder cancer; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-

Analyses; RC, radical cystectomy; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions; TURBT, transurethral resection of the bladder tumour; TUR, transurethral resection.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Funnel plot showing the effect estimates of individual studies for the analysis of the impact of lymphovascular invasion on disease recurrence in patients treated with transurethral resection for non-muscle-invasive bladder cancer.
Fig. S2 Funnel plot showing the effect estimates of individual studies for the analysis of the impact of lymphovascular invasion on disease progression in patients treated with transurethral resection for non-muscle-invasive bladder cancer.
Fig. S3 Funnel plot showing the effect estimates of individual studies for the analysis of the impact of lymphovascular invasion on disease upstaging in patients treated with transurethral resection and consequently to radical cystectomy for organ-confined (≤cT2) bladder cancer.
Table S1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.
Table S2 The Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment of individual studies for the analysis of the impact of lymphovascular invasion on disease recurrence in patients treated with transurethral resection for non-muscle-invasive bladder cancer.
Table S3 The Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment of individual studies for the analysis of the impact of lymphovascular invasion on disease progression in patients treated with transurethral resection for non-muscle-invasive bladder cancer.
Table S4 The Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment of individual studies for the analysis of the impact of lymphovascular invasion on disease upstaging in patients treated with transurethral resection for non-muscle-invasive bladder cancer.