의학석사 학위논문

방광암에 대한 경요도 절제 검체에서 관찰되는 임파 혈관 침윤의 술 후 종양 병기 상승과 생존과의 관련성: 체계적 문헌 고찰 및 메타 분석

Presence of lymphovascular invasion in urothelial bladder cancer specimens after transurethral resections correlates with risk of upstaging and survival: A systematic review and meta-analysis

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서울대학교 대학원

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이 논문을 의학석사 학위논문으로 제출함

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의학과 비뇨기과학 전공

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김형석의 의학석사 학위논문을 인준함

2016 년 1 월

위 원 장 (인)

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ABSTRACT

Presence of lymphovascular invasion in urothelial bladder cancer specimens after transurethral resections correlates with risk of upstaging and survival: A systematic review and meta-analysis

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Objectives: This study aimed to elucidate the relationship between lymphovascular invasion (LVI) at transurethral resection of bladder tumor (TURBT) and the risk of pathological upstaging as well as the clinical outcomes.

Materials and Methods: PubMed, SCOPUS, Web of Science and Cochrane Library databases were searched from the respective dates of inception until November 11, 2013.

Results: A total of 16 articles met the eligibility criteria for this systematic review, which included a total of 3,905 patients. LVI was detected in 18.6% in TURBT specimens. The significant association was found between LVI at TURBT and pathological

upstaging of bladder cancer (odds ratio 2.21, 95% confidence interval [CI] 1.44–3.39) without heterogeneity (I2 45%, p = 0.14). The pooled hazard ratio (HR) was statistically significant for recurrence–free survival (HR 1.47, 95% CI 1.24–1.74), progression–free survival (HR 2.28, 95% CI 1.45–3.58), and disease–specific survival HR, 1.35; 95% CI, 1.01–1.81), but not overall survival (HR, 1.55; 95% CI, 0.90–2.67). Tests of inconsistency for disease–specific survival (I2 66%, p = 0.007) and overall survival (I2 72%, p = 0.03) could not exclude a significant heterogeneity. The results of Begg's and Egger's test showed that there was evidence of publication bias on pathological upstaging and progression–free survival.

Conclusions: The data obtained in this meta–analysis indicate that the presence of LVI at TURBT portends the increased risk of pathological upstaging and may provide additional prognostic information. However, a large, well–designed, prospective study is needed to investigate potential treatment options for bladder cancer with LVI.

Keywords: Bladder cancer, urothelial carcinoma, meta–analysis, lymphovascular invasion, prognosis, transurethral resection

목 차

표 및 그림 목록

서 론

Urothelial carcinoma of the bladder remains a significant public health cancer worldwide, with 73,510 new cases and 14,880 deaths attributed to bladder cancer in the United States in 2012 [1]. Approximately 70% of newly diagnosed bladder cancer are non-muscle invasive bladder cancer, for which the initial treatment is transurethral resection of bladder tumor (TURBT), while radical cystectomy with pelvic lymph node dissection is the mainstay therapy for high-risk non-muscle invasive and muscle invasive bladder cancer. Identification of patients who are at risk for recurrence and progression is important for clinical decision-making. Improvements in risk stratification may aid in the decision to undertake early cystectomy for patients with disease not invading bladder muscle or neoadjuvant chemotherapy in those with disease invading bladder muscle or who present initially with locally advanced disease. However, recent improvements in the assessment of individual risk calculation using clinicopatholocal parameters, predictive accuracies for recurrence and progression of bladder cancer are still limited.

Lymphovascular invasion (LVI) is an essential and important step in the systemic dissemination of cancer cells [2]. Previously, we have demonstrated an association between poor prognosis and the

presence of LVI of urothelial carcinoma in final pathologic specimens (radical nephroureterectomy [3] and radical cystectomy [4]. In fact, LVI has been strongly associated with poor clinical outcomes, leading investigators to propose that the presence of LVI at radical cystectomy specimen be incorporated into staging system.

LVI found at TURBT is also associated with increased risk of advanced pathological stage and lymph node metastases [5]. Pathological upstaging at cystectomy is associated with poor outcomes in urothelial carcinoma of the bladder [6]. Based on the M.D. Anderson Cancer Center criteria, LVI at TURBT is one of the high risk features and the presence of high risk features identifies patients with a poor prognosis who are most likely to benefit from neoadjuvant chemotherapy [7]. However, the prognostic significance of the presence of LVI at TURBT is still controversial.

The present study aimed to elucidate the relationship between LVI at TURBT and the risk of pathological upstaging as well as the clinical outcomes.

실험 재료 및 방법

Search strategy

We conducted and reported this systematic review and meta-analysis following the Preferred Reporting Items for Systematic reviews and Mata-Analyses (PRISMA) statement [8]. PubMed, SCOPUS, Web of Science and Cochrane Library were searched on November 11, 2013 and no lower date limit was used. However, since the first article was published in February 1, 1994, literatures published from February 1994 to November 2013 were included. The search strategy included the following keywords variably combined by “bladder cancer” and “lymphovascular invasion”. We only performed the review of the studies published in English language. Conference abstracts were not in the scope of this analysis owing to the insufficient data provided by the authors.

Study selection

Two reviewers (HSK and MK) primarily examined the titles and abstracts of all literature. The full articles were then screened separately by two reviewers (CWJ and CK) to determine whether they met the inclusion criteria or not. Disagreements were resolved through the consensus with a third reviewer. Inclusion criteria were: (1) urothelial carcinoma of the bladder; (2) LVI examined in TURBT specimens; (3) evaluation of the relationship between LVI and pathological features or prognosis; and (4) sufficient information provided to estimate the odds ratio (OR) or hazard ratio (HR) and their 95% confidence intervals (CIs). Exclusion criteria were: (1) letters, commentaries, case reports, reviews, and conference abstracts; (2) non-English articles; (3) articles from

which the relevant data could not be extracted; and (4) overlapping articles or ones with duplicate data. When there were multiple articles by the same group based on similar patients, only the largest or the most recently article was included.

Data extraction and management

Two reviewers (MK and CWJ) independently extracted the required information from all eligible studies. Separate data tables were independently made to extract all relevant data from tests, tables and figures of each included studies encompassing author's name, year of publication, region, stage of disease, number of patients and follow-up. Completed databases were compared and discussed by both reviewers to find if required a consensus.

Methodological assessments

For the methodological evaluation of the studies, three reviewers (MK, HHK and JHK) read through each publication independently, and assessed and scored them according to Reporting recommendations for tumor marker prognostic studies (REMARK) guidelines and quality scale [9,10]. The quality scale has seven criteria, and a study with a total score of 8 was considered to have the highest study quality, whereas a score of zero indicated the lowest quality. The three reviewers provided the quality scores and compared them, and then reach a consensus value for each item.

Statistical analysis

The random-effects models were used to pool the effect size based on the DerSimonian and Laird method [11]. ORs with 95% CIs were used to evaluate the association between LVI and pathological upstaging. HRs and their 95% CIs were used to assess the impact of

LVI at TURBT on survival of bladder cancer patients. Survival data were extracted or calculated according to the methods described by Parmar et al [12]. An observed OR or HR >1 implied the significant association between LVI and pathological upstaging or a worse survival for the group with LVI, respectively, if the 95% CI did not overlap 1.

Chi-square-based Q statistic test was performed to test the heterogeneity among the studies included in meta-analysis. A $p>0.10$ for the Q-test indicated a lack of heterogeneity among the studies. I-squared statistic was also used to assess the between-studies heterogeneity. I-squared values of >50% indicate heterogeneity among studies [13]. Subgroup analysis with meta-regression analysis was further performed to explore the source of existed heterogeneity. The inverted funnel plots, Begg's test (rank correlation analysis) and Egger's test (linear regression analysis) were used to evaluate the publication bias [14,15]. Publication bias was indicated when the p value from Begg's test and Egger's test was <0.05. All the p values were two-sided and p values <0.05 denoted statistical significance. We pooled ORs and HRs of the studies by using software RevMan 5.0 (the Cochrane Collaboration, Copenhagen). The analysis of meta-regression and publication bias was performed by using R 2.13.0 (R development Core Team, Vienna, http://www.R-project.org).

결 과

Study selection and characteristics

The database searches identified 683 articles for initial evaluation (Figure 1). Of these, 368 articles were excluded because of duplicate publications, 170 were excluded through reading title and abstract, 108 were excluded because LVI was not assessed for TURBT specimens, 11 were excluded because there were studies irrelevant to the current analysis, five articles were excluded because there was no result of urothelial carcinoma, three were excluded because the estimation of HRs in the studies was not allowed because of insufficient data provided by the authors, and two were excluded because data overlapped with another study. Therefore, 16 studies meeting the inclusion criteria were finally enrolled in this systematic review and meta-analysis [16-31] (Figure 1).

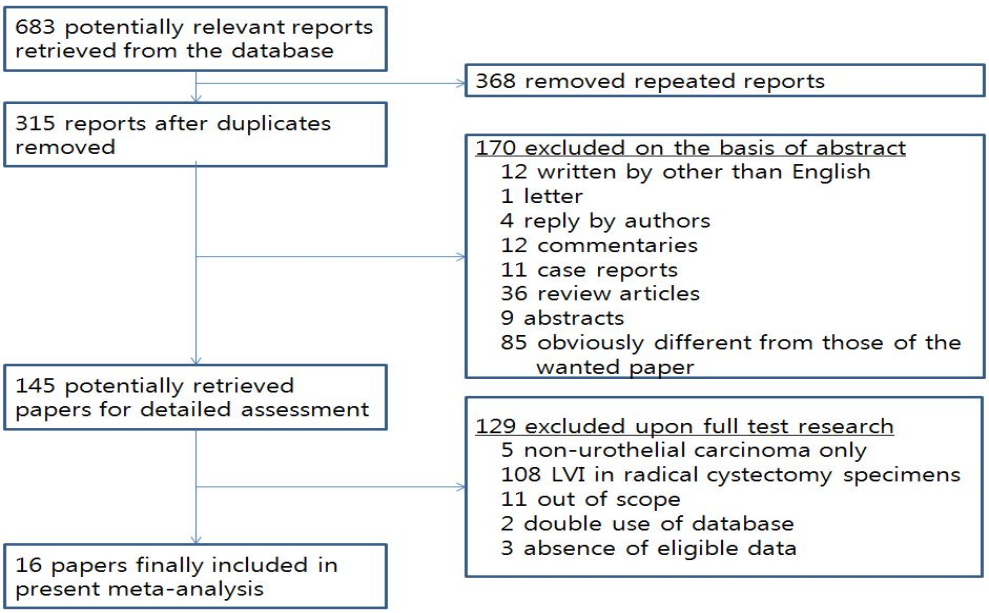

Figure 1. Flow chart of the literature search used in this meta-

analysis

The characteristics of the 16 eligible studies are extracted and summarized in Tables 1−3. These eligible studies were published from 2007 to 2013 and all the studies were retrospective in design. Eight studies assessed the patients from North America, four from Europe, and five from Asia. The total sample size was 3,905 with a mean of 230 (range, 80−948 patients). Ten datasets included <200 patients, and seven dataset had enrolled ≥200 patients. LVI was found in TURBT specimens in 18.6% (663 of 3,567 patients) of total bladder cancer patients. In most studies, data comparing clinico−pathological parameters in the context of LVI at TURBT were not reported or extractable (data not shown). Some studies did not perform multivariate analysis (Supplemental Tables 1−5).

LVI was not defined in seven studies [16,18,20,22,23,25,27,30]. In other studies, LVI was defined as tumor cells that were unequivocally noted within or attached to the wall of a vascular or lymphatic space (with a single−cell endothelial lining)on hematoxylin−and−eosin−stained sections[17,19,21,24,26,28,29,31]. If there was suspicion of LVI but the reporting pathologist was unable to unequivocally document its presence, immunohistochemistry was performed for CD31, CD34 or factor 8 in some studies [21,29,31].

To estimate the quality of studies included into our meta−analysis, we calculated a quality score for each study. Overall, none of the studies examined in this review fulfilled all evaluation criteria. Only six of the included studies obtained scores of 4 or more in methodological assessment, indicating that they were of not high quality (Table 1).

Table 1. Main characteristics of the eligible studies.

Study	Year	Country	Recruitment period	Study design	Inclusion and exclusion criteria	Definition of survival	Definition of LVI	Interpretation of LVI	Quality scale
Kassouf [16]	2007	USA	1990-2005	Retrospective	No	No	No	NA	3
Cho [17]	2009	Korea	2001-2007	Retrospective	Yes	Yes	Yes	NA	6
Park [18]	2009	Korea	1989-2005	Retrospective	Yes	No	No	NA	3
Streeper [19]	2009	USA	1995-2005	Retrospective	Yes	No	Yes	NA	2
Miyake [20]	2011	Japan	1998-2009	Retrospective	Yes	Yes	No	NA	3
Resnick [21]	2011	USA	1987-2008	Retrospective	Yes	Yes	Yes	NA	5
Rodriguez Faba [22]	2011	Spain	1978-2002	Retrospective	No	No	No	NA	2
Badalato (1990-1999) [23]	2012	USA	1990-1999	Retrospective	Yes	No	No	NA	3
Badalato (2000-2010) [23]	2012	USA	2000-2010	Retrospective	Yes	No	No	NA	3
Green [24]	2012	USA	NA	Retrospective	Yes	NA	Yes	NA	4
Kwon [25]	2012	Korea	1999-2010	Retrospective	Yes	No	No	NA	3
Olsson [25]	2012	Sweden	1992-2001	Retrospective	Yes	Yes	Yes	NA	5
Xie [27]	2012	China	2003-2011	Retrospective	Yes	NA	Yes	NA	3
Bolenz [28]	2013	Germany	2000-2006	Retrospective	No	Yes	Yes	NA	5
Brimo [29]	2013	Canada	2004-2012	Retrospective	No	Yes	Yes	NA	3
Mitra [30]	2013	USA	1971-2008	Retrospective	Yes	Yes	No	NA	4
Levidou [31]	2013	Greece	1985-1995	Retrospective	No	No	Yes	NA	2

LVI: lymphovascular invasion, NA: not available

Table 2. Patient characteristics of the eligible studies.

Study	No. of patients	Median age, range (years)	Gender (male/female)	Main therapy	Other therapy	Median Follow-up, range (months)
Kassouf [16]	120	64 (34-82)	97/23	RC (n = 120)	Neoadjuvant chemotherapy (n = 77)	32 (1-177)
Cho [17]	118	67 (39-91)	101/17	TUR (n = 118)	Intravesical therapy (n = 100), systemic chemotherapy (n = 11), RC (n = 4)	35 (12-89)
Park [18]	144	60.5	121/23	TUR (n = 144)	Intravasical therapy (n = 119)	52.5
Streeper [19]	103	NA	83/20	TUR (n = 103)	Neoadjuvant chemotherapy (n = 12), adjuvant chemotherapy (n = 17), Cystectomy (n = 66)	NA
Miyake [20]	130	NA	114/16	TUR (n = 130)	Intravesical therapy (n = 75)	36 (1-140)
Resnick [21]	474	65.7 (mean)	372/110	RC (n = 474)	Adjuvant chemotherapy (n = 75)	NA
Rodriguez Faba [22]	141	63 (47-80)	11/25	RC (n = 142)	Neoadjuvant chemotherapy (n = 15) adjuvant chemotherapy (n = 8), adjuvant radiation therapy (n = 2)	42.5 (mean) (1.3-246)
Badalato (1990-1999) [23]	90	NA	NA	TUR (n = 36), RC (n = 54)	NA	NA
Badalato (2000-2010) [23]	259	NA	NA	TUR (n = 200), RC (n = 59)	NA	NA
Green [24]	201	72.9 (41-92)	165/36	Cystectomy (n = 201)	NA	NA
Kwon [25]	406	64.4 (mean)	339/67	TUR (n = 406)	Intravesical therapy (n = 406)	76.9 (12-167)
Olsson [26]	211	74	175/36	TUR (n = 211)	None	60 (3-192)
Xie [27]	248	60 (25-87)	205/43	RC (n = 248)	NA	NA
Bolenz [28]	111	69 (39-92)	83/28	TUR (n = 111)	Intravesical therapy (n = 21)	30 (0-105)
Brimo [29]	86	71 (mean)	NA	TUR (n = 86)	NA	29 (mean)
Mitra [30]	948	67.2 (23.4-93)	729/219	RC (n = 948)	Adjuvant chemotherapy (n = 249)	14.2 yr (1.1-35.6 yr)
Levidou [31]	115	NA	100/15	TUR (n = NA), RC (n = NA)	Adjuvant chemotherapy (n = 46)	NA

FU: follow-up, RC: radical cystectomy, TUR: transurethral resection, NA: not available

Table 3. Tumor characteristics of the eligible studies.

Study		Clinical stage			Pathologic stage		
	No. (%) of positive LVI	Tumor grade (LG/HG) or (G1/2/3)	Clinical T stage (cTis/a/1/2/3/4)	Clinical N stage (cN-/+)	Tumor grade (G0/LG/HG)	Pathologic T stage (pT0/is/a/1/2/3/4)	Pathologic N stage (pN-/+)
Kassouf [16]	38/120 (31.7%)	6/114	0/0/21/65/20/14	113/7	120/0/0	120/0/0/0/0/0/0	120/0
Cho [17]	33/118 (28.0%)	3/60/55	0/0118/0/0/0	NA	NA	NA	NA
Park [18]	9/144 (6.3%)	0/0/144	0/0/144/0/0/0	144/0	NA	NA	NA
Streeper [19]	69/103 (67.0%)	NA	0/0/6/67/5/25	NA	NA	0/0/11/8/9/14/25	NA
Miyake [20]	20/130 (15.4%)	84/33*	0/104/26/0/0/0	NA	NA	NA	NA
Resnick [21]	60/474 (12.7%)	NA	39/13/49/259/64/35	NA	NA	34/73/10/39/93/161/77	339/134
Rodriguez Faba [22]	28/141(19.9%)	9/132	12/10/34/55/30/0	NA	141/0/0	141/0/0/0/0/0/0/	134/7
Badalato (1990-1999) [23]	22/90 (24.4%)	0/90	0/0/90/0/0/0	NA	NA	NA	NA
Badalato (2000-2010) [23]	26/259 (10.0%)	0/259	0/0/259/0/0/0	NA	NA	NA	NA
Green [24]	21/193 (10.9%)†	3/198	15/19/67/100/0/0	NA	NA	20/37/13/24/36/52/19	163/38
Kwon [25]	12/406 (3.0%)	165/241	0/274/132	406/0	NA	NA	NA
Olsson [26]	16/166 (9.6%)‡	0/26/175	0/0/211/0/0/0	NA	NA	NA	NA
Xie [27]	44/248 (17.7%)	34/54/160	117(<T1)/131/0/0/0	NA	NA	NA	NA
Bolenz [28]	20/111 (18.0%)	21/56/34	0/38/38/35/0/0/0	NA	NA	NA	NA
Brimo [29]	11/86 (12.8%)	NA	0/0/86/0/0/0	NA	NA	NA	NA
Mitra [30]	208/663 (31.4%)††	50/898	0/0/0/948/0/0	948/0	NA	NA	NA
Levidou [31]	26/115 (22.6%)	28/35**	73(<T1)/42(T2-3)/0	NA	NA	NA	NA

*PUNLMP (n = 13), **PUNLMP (n = 32), †missing (n = 8), ‡suspected (n = 45), ††missing (n = 285).

LVI: lymphovascular invasion, LG: low grade, HG: high grade, NA: not available

Study results and meta-analysis

Correlation of LVI at TURBT and pathological upstaging

Four studies that referred to the correlation between LVI at TURBT and pathological upstaging were pooled to calculate the pooled ORs. As indicated in Figure 2, a significant association was found between LVI at TURBT and pathological upstaging of bladder cancer (pooled OR 2.21, 95% CI 1.44-3.39) without heterogeneity (I2 45%, p = 0.14).

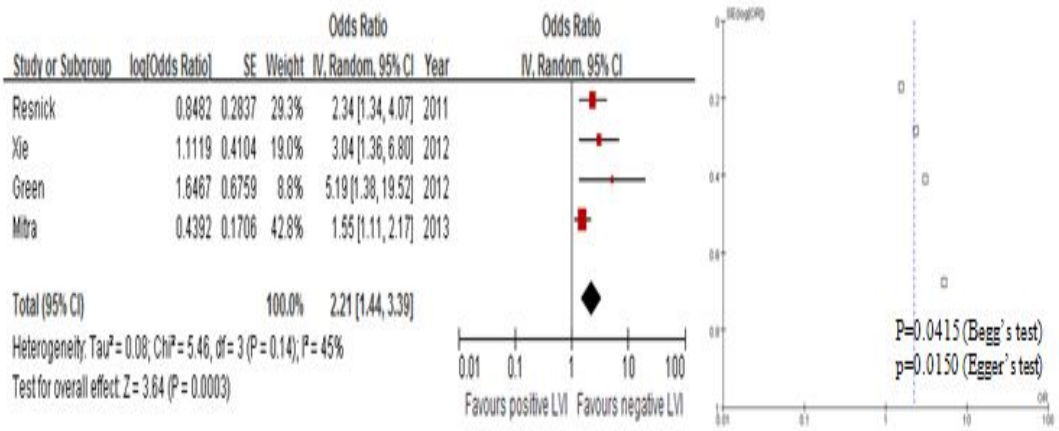

Figure 2. Forest plots of odds ratio of pathological upstaging according to lymphovascular invasion in transurethral resection specimens (Left). The horizontal lines correspond to the study-specific hazard ration and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of hazard ratio and 95% confidence interval. Begg's Funnel plots for publication bias test (Right). Each point represents a separate study for the indicated association. Vertical line represents the mean effects size.

Association of LVI at TURBT and survival of bladder cancer

The pooled analysis of recurrence-free survival (RFS) was based on eight publications including 2,517 patients. A significant association of LVI at TURBT and RFS was observed in bladder cancer patients (pooled HR 1.47, 95% CI 1.24-1.74) (Figure 3A). As for progression-free survival (PFS), seven studies involving 1,206 patients were included in the analysis, indicative of the significant correlation between LVI at TURBT and PFS (pooled HR 2.28, 95% CI 1.45-3.58) (Figure 3B). Six studies (seven datasets) and three studies investigated disease-specific survival (DSS) and overall survival (OS) in a total of 1,393 and 1,542 patients, respectively. The pooled HRs (95% CI) of included studies for DSS and OS were 1.35 (1.10-1.81) (Figure 3C) and 1.55 (0.90-2.67) (Figure 3D), respectively. Tests of inconsistency for DSS (I2 66%, p = 0.007) and OS (I2 72%, p = 0.03) could not exclude a significant heterogeneity.

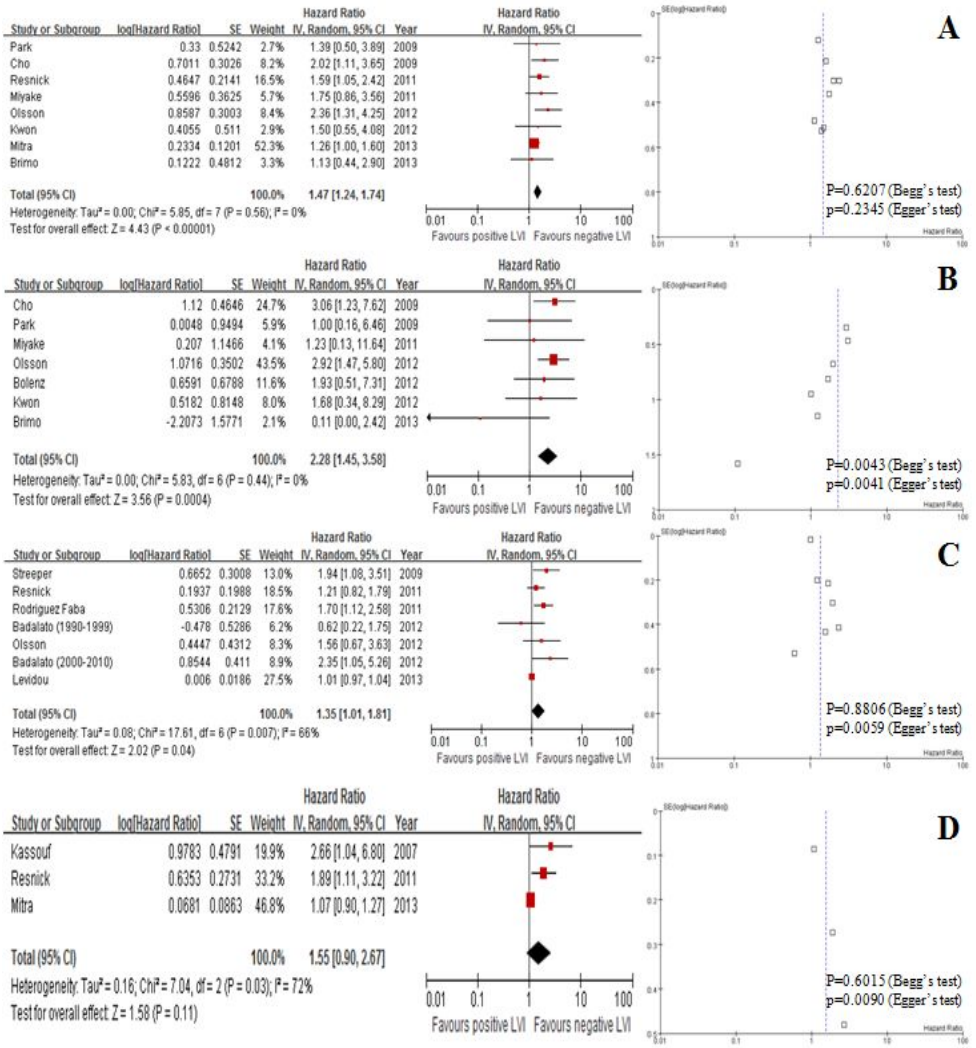

Figure 3. Forest plots of prognosis of lymphovascular invasion in transurethral resection specimens. (Left) The horizontal lines correspond to the study-specific hazard ration and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of hazard ratio and 95% confidence interval. Begg's Funnel plots for publication bias test (Right). Each point represents a separate study for the indicated association. Vertical line represents the mean effects size. (A) Recurrence-free survival. (B) Progression-free survival. (C) Disease-specific survival. (D) Overall survival.

Subgroup analysis

Similar analysis was performed between LVI at TURBT and the prognosis of patients with non-muscle invasive bladder cancer. Six, seven, and two studies (three datasets) investigated RFS, PFS, and DSS in a total of 1,095, 1,206, and 560 patients, respectively. Meta-analysis of patients with non-muscle invasive bladder demonstrated the significant association of LVI at TURBT and RFS (pooled HR 1.28, 95% CI 1.34-2.46) and PFS (pooled HR 2.28, 95% CI 1.45-3.58), while the analysis did not demonstrate the significant correlation in a random-effects model (pooled HR 1.40, 95% CI 0.68-2.88). Overall test for heterogeneity recorded a I2 value of 50% for DSS, suggesting the presence of inter-study heterogeneity (Figure 4).

Owing to heterogeneity across studies reporting DSS and OS of patients with bladder cancer, we analyzed the source of the heterogeneity using meta-regression by publication year, region, number of patients, median follow-up. HR estimation, analysis results, and quality scale (Supplements 6-9). If there was only one article, we gave its HR and 95% CI instead. Meta-regression analysis revealed that 'analysis result' might account for part of the inter-study heterogeneity for DSS ($p = 0.0002$). In addition, 'duration of follow-up' and 'analysis result' were observed to significantly affect the relationship between LVI at TURBT and OS (all $p = 0.0099$). Notably, others of these subgroup analyses did not reveal heterogeneities of data.

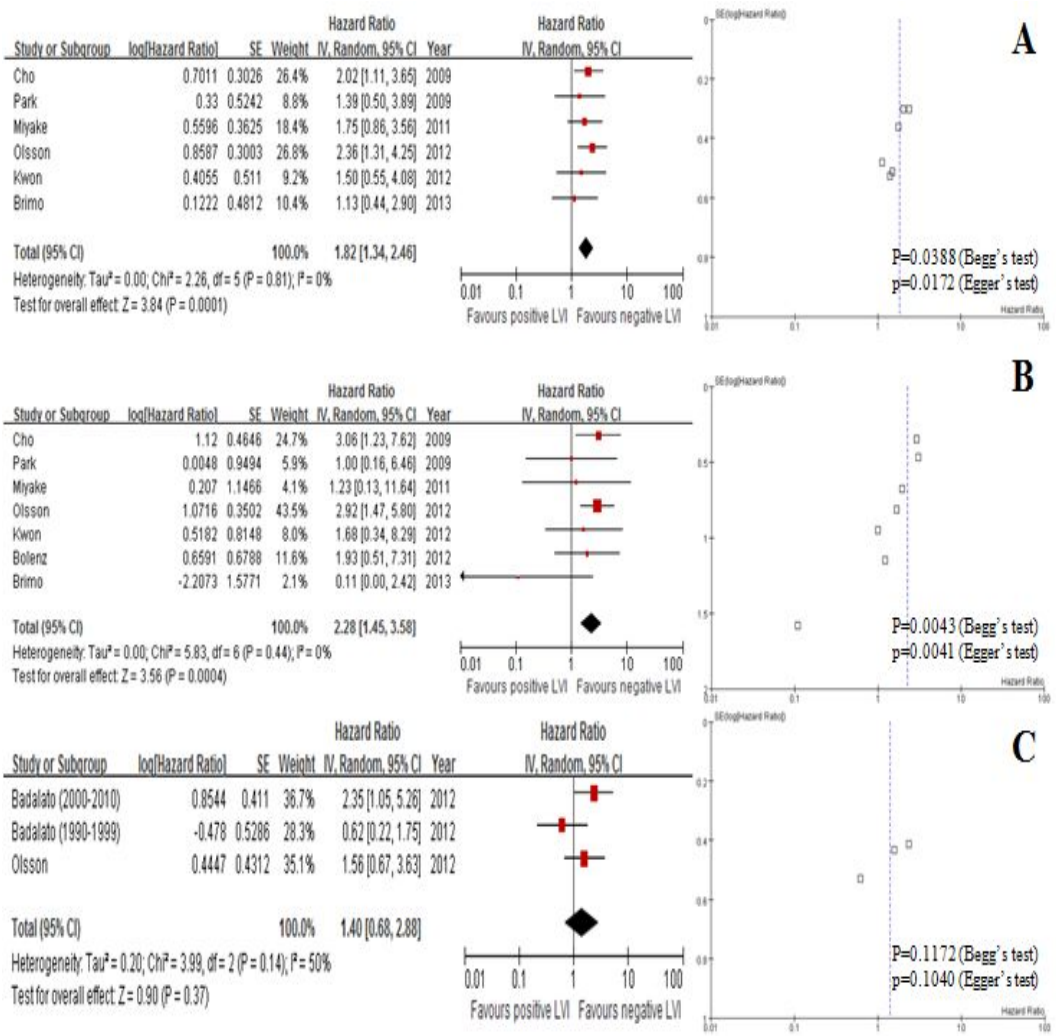

Figure 4. Forest plots of prognosis of lymphovascular invasion in transurethral resection specimens in patients with non-muscle invasive bladder cancer. The horizontal lines correspond to the study-specific hazard ration and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of hazard ratio and 95% confidence interval. Begg's Funnel plots for publication bias test (Right). Each point represents a separate study for the indicated association. Vertical line represents the mean effects size. (A) Recurrence-free survival. (B) Progression-free survival. (C) Disease-specific survival.

Publication bias

Begg's funnel plot for publication bias of the association between LVI at TURBT and pathological upstaging demonstrated a certain degree of asymmetry (Figure 2). The evaluation of publication bias indicated that both Begg's test (p = 0.0415) and Egger's test (p = 0.0150) reached the significance.

Assessment of publication bias revealed that Begg's test (p = 0.0043) and Egger's test (p = 0.0041) for PFS were significant, and the funnel plots for PFS revealed a certain degree of asymmetry. According to DSS and OS, Begg's test indicated no publication bias among these studies regarding risk ratio (p = 0.8806 for DSS and p = 0.6015 for OS), but Egger's test indicated publication bias (p = 0.0059 for DSS and p = 0.0090 for OS) (Figure 3).

When the analysis was limited to studies with non-muscle invasive bladder cancer, there was evidence for significant publication bias in RFS (Begg's test, p = 0.0388; Egger's test, p = 0.017) and PFS (Begg's test, p = 0.0043; Egger's test, p = 0.0041) (Figure 4).

Table S1. Estimation of the odds ratio for pathological upstaging.

Study	OR estimation	Co-factors	Analysis results
Resnick [21]	event no. (univariate)	-	Significant
Green [24]	OR, 95% CI	TURT stage, abnormal imaging	Significant
Xie [27]	OR, 95% CI	Age, recurrence frequency, tumor size, hydronephrosis, TUR T stage, tumor grade	Significant
Mitra [30]	event no. (univariate)	-	Significant

OR: odds ratio, CI: confidence interval, TUR: transurethral resection.

Table S2. Estimation of the hazard ratio for recurrence-free survival.

Study	HR estimation	Co-factors	Analysis results
Cho [17]	HR, 95% CI	Bladder tumor history, tumor size, no. of tumors, intravesical therapy	Significant
Park [18]	P value, event no. (univariate)	-	Not significant
Miyake [20]	HR, 95% CI (univariate)	-	Not significant
Resnick [21]	P value, event no. (univariate)	-	Significant
Kwon [25]	HR, 95% CI	Age, sex, diabetes hypertension, clinical stage, grade, size, multiplicity, resection weight	Not significant
Olsson [26]	HR, 95% CI	Tumor size, tumor grade, multiplicity, tumor volume proportion, CIS	Significant
Brimo [29]	HR, 95% CI	Maximum tumor depth, maximum tumor diameter, muscularis mucosa invasion, no. of chips containing invasion, total diameter of invasive carcinoma, CIS, adverse histologic subtype	Not significant
Mitra [30]	P value, event no. (univariate)	-	Not significant

HR: hazard ratio, CI: confidence interval, CIS: carcinoma in situ

Table S3. Estimation of the hazard ratio for progression-free survival.

Study	HR estimation	Co-factors	Analysis results
Cho [17]	HR, 95% CI	Tumor size	Significant
Park [18]	P value, event no. (univariate)	-	Not significant
Miyake [20]	HR, 95% CI (univariate)	-	Not significant
Kwon [25]	HR, 95% CI	Age, sex, diabetes hypertension, clinical stage, grade, size, multiplicity, resection weight	Not significant
Olsson [26]	HR, 95% CI	Tumor size, tumor grade, multiplicity, tumor volume proportion, CIS	Significant
Bolenz [28]	HR, 95% CI	Tumor architecture, concomitant CIS, tumor stage, suburothelial D2-40 positivity, tumor grade, nontumoral lymphatic vessel density	Not significant
Brimo [29]	HR, 95% CI	Maximum tumor depth, maximum tumor diameter, muscularis mucosa invasion, no. of chips containing invasion, total diameter of invasive carcinoma, CIS, adverse histologic subtype	Not significant

HR: hazard ratio, CI: confidence interval,CIS: carcinoma in situ

Table S4. Estimation of the hazard ratio for disease-specific survival.

Study	HR estimation	Co-factors	Analysis results
Streeper [19]	P value, event no. (univariate)	-	Not significant
Resnick [21]	P value, event no. (univariate)	-	Not significant
Rodriguez Faba [22]	HR, 95% CI	Previous bladder tumor, 5 or greater recurrences, N+, TUR stage, CIS, induction chemotherapy	Significant
Badalato (1990-1999) [23]	HR, 95% CI	Age, race, urethral involvement, immediate radical cystectomy	Not significant
Badalato (2000-2010) [23]	HR, 95% CI	Age, race, urethral involvement, immediate radical cystectomy	Significant
Olsson [26]	HR, 95% CI	Tumor size, tumor grade, multiplicity, tumor volume proportion, CIS	Not significant
Levidou [31]	HR, 95% CI	Osteoprotegerin expression, histological grade, tumor T category, tumor configuration, FGFR3 expression, recurrence	Not significant

HR: hazard ratio, CI: confidence interval,TUR: transurethral resection, CIS: carcinoma in situ

Table S5. Estimation of the hazard ratio for overall survival.

Study	HR estimation	Co-factors	Analysis results
Kassouf [16]	HR, 95% CI	Age, prior tumors, clinical stage, concomitant variant histology, concomitant CIS, hydronephrosis, total no. of nodes, neoadjuvant chemotherapy, distant metastasis	Significant
Resnick [21]	P value, event no. (univariate)	-	Significant
Mitra [30]	P value, event no. (univariate)	-	Not significant

HR: hazard ratio, CI: confidence interval,CIS: carcinoma in situ

Table S6. Subgroup analysis for recurrence-free survival.

	No. of included articles	No. of cases	Pooled HR (95% CI)	Chi^2 (p value)	I^2	P_h^*
Publication year						0.3665
2007-2010	2	262	1.84 (1.10-3.07)	0.38 (0.54)	0%	
2011-2013	6	2,255	1.43 (1.19-1.71)	4.66 (0.46)	0%	
Region						0.4678
Asia	4	798	1.76 (1.20-2.58)	0.50 (0.92)	0%	
Others	4	1,719	1.48 (1.13-1.93)	4.32 (0.23)	30%	
No. of patients						0.6433
<200	4	478	1.67 (1.14-2.45)	1.18 (0.76)	0%	
≥200	4	2,039	1.50 (1.16-1.95)	4.11 (0.25)	27%	
Median follow-up						0.8476
<60 months	5	952	1.64 (1.23-2.17)	1.21 (0.88)	0%	
≥60 months	3	1,565	1.56 (1.02-2.38)	3.76 (0.15)	47%	
HR estimation						0.0994
Univariate	5	2,102	1.37 (1.13-1.66)	1.44 (0.84)	0%	
Multivariate	3	415	1.96 (1.34-2.87)	1.70 (0.43)	0%	
Analysis results						0.0539
Not significant	5	1,714	1.31 (1.06-1.61)	0.91 (0.92)	0%	
Significant	3	8.03	1.87 (1.39-2.51)	1.23 (0.54)	0%	
Quality scale						0.7549
<4	4	766	1.48 (0.95-2.30)	0.54 (0.91)	0%	
≥4	3	1,277	1.69 (1.10-2.59)	5.14 (0.08)	61%	

HR: hazard ratio, CI: confidence interval, NMIBC: non-muscle invasive bladder cancer.

P_h^* for heterogeneity between subgroups with meta-regression analysis.

Table S7. Subgroup analysis for progression-free survival.

	No. of included articles	No. of cases	Pooled HR (95% CI)	Chi^2 (p value)	I^2	P_h^*
Publication year						0.7587
2007-2010	2	262	2.39 (0.96-5.94)	1.11 (0.29)	10%	
2011-2013	5	944	2.00 (1.04-3.86)	4.67 (0.32)	14%	
Region						0.7468
Asia	4	798	2.15 (1.08-4.30)	1.55 (0.67)	0%	
Others	3	408	1.72 (0.53-5.53)	4.24 (0.12)	53%	
No. of patients						0.3818
<200	5	589	1.71 (0.79-3.73)	4.92 (0.30)	19%	
≥200	2	617	2.68 (1.43-5.03)	0.39 (0.53)	0%	
Median follow-up						0.3818
<60 months	5	589	1.71 (0.79-3.73)	4.92 (0.30)	19%	
≥60 months	2	617	2.68 (1.43-5.03)	0.39 (0.53)	0%	
HR estimation						0.4239
Univariate	2	550	1.35 (0.40-4.54)	0.17 (0.68)	0%	
Multivariate	5	656	2.34 (1.30-4.20)	0.48 (0.30)	17%	
Analysis results						0.0908
Not significant	5	877	1.28 (0.57-2.87)	2.97 (0.56)	0%	
Significant	2	329	2.97 (1.72-5.14)	0.01 (0.93)	0%	
Quality scale						0.0788
<4	4	766	1.01 (0.37-2.78)	2.40 (0.49)	0%	
≥4	3	440	2.79 (1.68-4.63)	0.35 (0.84)	0%	

HR: hazard ratio, CI: confidence interval, NMIBC: non-muscle invasive bladder cancer.

P_h^* for heterogeneity between subgroups with meta-regression analysis.

Table S8. Subgroup analysis for disease-specific survival.

	No. of included articles	No. of cases	Pooled HR (95% CI)	Chi^2 (p value)	I^2	P_h*
Publication year						0.2041
2007-2010	1	103	1.94 (1.08-3.51)	Not applicable	Not applicable	
2011-2013	5 (6 dataset)	1,290	1.27 (0.95-1.70)	12.93 (0.02)	61%	
Region						Not applicable
Asia	0	0	Not applicable	Not applicable	Not applicable	
Others	6 (7 dataset)	1,393	1.35 (1.01-1.81)	17.61 (0.007)	66%	
No. of patients						0.6871
<200	4	478	1.27 (0.84-1.94)	11.61 (0.009)	74%	
≥200	3	944	1.42 (1.00-2.03)	2.17 (0.34)	8%	
Median follow-up						0.7376
<60 months	5 (6 dataset)	1,182	1.34 (0.98-1.83)	16.62 (0.005)	70%	
≥60 months	1	211	1.56 (0.67-3.63)	Not applicable	Not applicable	
HR estimation						0.7347
Univariate	2	577	1.46 (0.93-2.28)	1.71 (0.19)	42%	
Multivariate	4 (5 dataset)	816	1.31 (0.89-1.94)	12.10 (0.02)	67%	
Analysis results						0.0002
Not significant	4	890	1.01 (0.97-1.05)	2.76 (0.43)	0%	
Significant	3	503	1.85 (1.36-2.54)	0.52 (0.77)	0%	
Quality scale						0.7396
<4	4 (5 dataset)	708	1.39 (0.92-2.10)	15.81 (0.003)	75%	
≥4	2	698	1.27 (0.89-1.81)	0.28 (0.60)	0%	

HR: hazard ratio, CI: confidence interval, NMIBC: non-muscle invasive bladder cancer.

Table S9. Subgroup analysis for overall survival.

	No. of included articles	No. of cases	Pooled HR (95% CI)	Chi^2 (p value)	I^2	P_h^*
Publication year						0.2154
2007-2010	1	120	2.66 (1.04-8.80)	Not applicable	Not applicable	
2011-2013	2	1,442	1.34 (0.78-2.31)	3.92 (0.05)	75%	
Region						Not applicable
Asia	0	0	Not applicable	Not applicable	Not applicable	
Others	3	1,542	1.55 (0.90-2.67)	7.04 (0.03)	72%	
No. of patients						0.2154
<200	1	120	2.66 (1.04-8.80)	Not applicable	Not applicable	
≥200	2	1,442	1.34 (0.78-2.31)	3.92 (0.05)	75%	
Median follow-up						0.0099
<60 months	2	1,442	1.34 (0.78-2.31)	3.92 (0.05)	75%	
≥60 months	1	120	2.66 (1.04-8.80)	Not applicable	Not applicable	
HR estimation						0.2154
Univariate	2	594	2.05 (1.29-3.27)	0.39 (0.53)	0%	
Multivariate	1	948	1.07 (0.90-1.27)	Not applicable	Not applicable	
Analysis results						0.0099
Not significant	1	948	1.07 (0.90-1.27)	Not applicable	Not applicable	
Significant	2	594	2.05 (1.29-3.27)	0.39 (0.53)	0%	
Quality scale						0.2154
<4	1	120	2.66 (1.04-6.80)	Not applicable	Not applicable	
≥4	2	1,422	1.34 (0.78-2.31)	3.92 (0.05)	75%	

HR: hazard ratio, CI: confidence interval, NMIBC: non-muscle invasive bladder cancer.

P_h^* for heterogeneity between subgroups with meta-regression analysis.

고 찰

Although the exact mechanisms of lymphatic metastases are still poorly understood, infiltration of microscopic lymphovascular spaces by tumor cells is probably the initial entry of neoplastic cells into the circulation, prior to the development of fulminant lymph node metastasis [24]. Therefore, LVI represents tumor invasion into lymphatic and vascular channels, and is considered to be a sentinel step in metastatic dissemination and, thus, may be reflective of a disease state where the malignant cells have attained a metastatic phase [32].

The presence of LVI has been associated with poor clinical prognosis in numerous solid tumors [33-36]. Our previous studies also indicated LVI as an important histological marker in the final pathologic specimens of urothelial cancer [3,4]. Since LVI could predict tumor behavior, it may guide treatment decisions. Based on the assumption that undetectable micrometastasis may be present in patients with LVI, it might be a reasonable option to consider systemic chemotherapy. For example, in the M.D. Anderson Cancer Center, neoadjuvant chemotherapy is routinely offered for patients with LVI at TURBT [16].

We conducted this systematic review and meta-analysis to assess whether LVI at TURBT could predict the pathologic upstaging and prognosis of bladder cancer patients. This study aggregated the outcomes of 3,905 bladder cancer patients. To our knowledge, this systematic review and meta-analysis is the first study to systematically assess the association between LVI at TURBT and the risk of pathologic upstaging as well as prognosis of bladder cancer. This systematic review and meta-analysis supports the use

of LVI at TURBT as a prognostic marker. The significant associations were exhibited between LVI at TURBT and pathological upstaging and LVI at TURBT is a significant predictor for poor RFS, PFS and DSS of bladder cancer patients.

However, to get a convincing conclusion on the value of LVI at TURBT for the prognosis of bladder cancer, some issues should also be addressed. It is not clear that the detection of LVI in TURBT specimens would directly correlate with the detection of LVI in cystectomy specimens. Only a small fraction of cT1 cancers have detectable LVI in the TURBT specimen, demonstrating low sensitivity for predicting LVI in cystectomy specimen [5]. Another equally problematic issue is false positive results since false positive results are possible and retraction artifact can mimic LVI of urothelial cancer [37,38]. This underscores the need to standardize the detection of LVI, perhaps with immunohistochemical studies such as CD31 or CD34 staining [34]. Standard diagnostic criteria for LVI are required and the potential usefulness of subsidiary immunohistochemical staining studies be examined in this context. In this way, LVI will be able to be introduced as an additional factor of the therapeutic approach for evaluation of bladder cancer [39].

This systematic review has some limitations. First, the combined HR >2 was considered as useful practical value [40]. In our systematic review and meta-analysis, the pooled HR of LVI at TURBT for RFS (pooled HR 1.47, 95% CI 1.23-1.74) and DSS (pooled HR 1.35, 95% CI 1.01-1.81) were not greater than 2 and did not influence OS (pooled HR 1.55, 95% CI 0.90-2.67). Additionally, in patients with non-muscle invasive bladder cancer, LVI at TURBT was not correlated with poor DSS (pooled HR 1.40, 95% CI 0.68-2.88). Furthermore, subgroup analysis by several factors did alter the prognostic significance of LVI at TURBT regarding prognosis of bladder cancer. Second, significant

heterogeneity was found in the systematic review and meta-analysis for DSS and OS of the prognostic role of LVI at TURBT. The source of inter-study heterogeneity present in this analysis was analyzed using meta-regression and subgroup analysis. We found that the heterogeneity mainly came from the 'analysis results' (for DSS and OS) or 'duration of follow-up' (for OS). Though the random-effects model takes heterogeneity into account and was used to analyze the studies with heterogeneities, the conclusion drawn in this systematic review and meta-analysis should be approached with caution. Third, one weakness of our study was publication bias, which could be seen from our publication bias evaluation (especially in pathological upstaging and PFS studies); A tendency for journals to only publish positive results leads to the larger magnitude of an association seen in a pooled analysis than it actually is. Fourth, the results of this systematic review and meta-analysis were based on unadjusted estimates because some studies did not provide detailed information. Furthermore, we have to admit that a possible bias may be the fact that all studies were of retrospective nature, whereas, to the best of our knowledge, high quality randomized, controlled trials investigating the association of LVI at TURBT with clinicopathological parameters or prognosis have not been published. Finally, we cannot exclude that we introduced a language bias by including only English written articles, which might favor positive results [41].

결 론

The data obtained in the present systematic review and meta-analysis indicate that the presence of LVI at TURBT portends and increased risk of pathological upstaging and may provide additional prognostic information. However, strict criteria are required to unify the reproducibility of diagnosis of LVI and a large, well-designed, prospective study is needed to investigate potential treatment options for bladder cancer with LVI, especially non-muscle invasive bladder cancer.

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국문초록

방광암에 대한 경요도 절제 검체에서 관찰되는 임파 혈관 침윤의 술 후 종양 병기 상승과 생존과의 관련성: 체계적 문헌 고찰 및 메타 분석

김형석

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서론: 본 연구의 목적은 방광암으로 경요도 방광종양 절제술을 시행 받은 환자에서 관찰된 임파혈관 침윤이 근치적 방광 적출술 후 종양 병기 상승 및 임상적인 예후와 어떠한 관련성을 가지는지를 체계적 문헌 고찰 및 메타 분석을 통해 평가하는데 있다.

대상 및 방법: PRISMA statement에 따라, PubMed, Cochrane Library, SCOPUS, Web of science database에서 2013년 11월 까지 발표된 논문을 대상으로 논문 검색을 시행하였다.

결과: 총 16개의 논문이 이 체계적 문헌 고찰을 시행할 수 있는 기준에 적합하였다. 총 3,905명의 환자를 포함하였고 이들 중 약 18.6%의 환자에서 경요도 방광 종양절제술 검체 표본에서 임파혈관 침윤 소견이 관찰되었다. 경요도 방광 종양 절제술 검체 표본에서 관찰된 임파 혈관 침윤은 포함된 논문들 사이의 이질성 없이 근치적 방광 적출술 후 종양의 병리학적 병기 상승과 유의한 관련성 (pooled

OR 2.21, 95% 신뢰구간 [CI], 1.44-3.99) 을 보였다. 생존 결과와의 관련성에 대한 분석 결과 경요도 방광 종양 절제술에서의 임파혈관 침윤은 전체 생존 (pooled HR 1.55; 95% CI, 0.90−2.67)을 제외한 무재발 생존률 (pooled HR, 1.47; 95% CI, 1.24-1.74), 무진행 생존률 (pooled HR, 2.28; 95% CI, 1.45-3.58) 및 종양 특이 생존률 (pooled HR, 1.35; 95% CI, 1.01-1.81)의 유의한 예측인자였다. Begg's and Egger's test로 평가한 publication bias는 술 후 병리학적 병기 상승 및 무진행 생존과 관련된 메타분석에 대해서만 관찰되었다.

결론: 본 체계적 문헌 고찰 및 메타 분석 결과 방광암에 대한 경요도 절제 검체 표본에서 관찰되는 임파혈관 침윤은 근치적 방광 적출술 후 병리학적 병기 상승과 밀접한 연관성이 있으며 술 후 생존 결과를 예측할 수 있는 유의한 예후 인자가 될 수 있음을 알 수 있었다. 향후 임파혈관 침윤을 동반한 방광암 환자에 대한 적절한 치료 방법 선택에 대한 적절하게 설계된 전향적 연구들이 필요할 것으로 생각된다.

주요어: 방광암, 요로상피암, 임파혈관 침윤, 경요도 방광 종양 절제술, 근치적 방광절제술, 생존, 예후