ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2018) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Review article

A systematic review and meta-analysis of lymphovascular invasion in patients treated with radical cystectomy for bladder cancer

Andrea Mari, M.D.[a,b,1], Shoji Kimura, M.D.[a,c,1], Beat Foerster, M.D.[a,d], Mohammad Abufaraj, M.D.[a,e], David D'Andrea, M.D.[a], Kilian M. Gust, M.D.[a], Shahrokh F. Shariat, M.D.[a,f,g,h,*]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*
[b] *Department of Urology, University of Florence, Careggi Hospital, Florence, Italy*
[c] *Department of Urology, Jikei University School of Medicine, Tokyo, Japan*
[d] *Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland*
[e] *Department of Special Surgery, Jordan University hospital, The University of Jordan, Amman, Jordan*
[f] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria*
[g] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*
[h] *Department of Urology, Weill Cornell Medical College, New York, NY*

Received 17 January 2018; received in revised form 6 March 2018; accepted 26 March 2018

Abstract

Purpose: Lymphovascular invasion (LVI) is an important step in bladder cancer cell dissemination. We aimed to perform a systematic review and meta-analysis of the literature to assess the prognostic value of LVI in radical cystectomy (RC) specimens.

Patients and methods: A systematic review and meta-analysis of the last 10 years was performed using the MEDLINE, EMBASE, and the Cochrane libraries in July 2017. The analyses were performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.

Results: We retrieved 65 studies (including 78,107 patients) evaluating the effect of LVI on oncologic outcomes in patients treated with RC. LVI was reported in 35.4% of patients. LVI was associated with disease recurrence (pooled hazard ratio [HR] = 1.57; 95% CI: 1.45–1.70) and cancer-specific mortality (CSM) (pooled HR = 1.59; 95% CI: 1.48–1.73) in all studies regardless of tumor stage and node status (pT1–4 pN0–2). LVI was associated with recurrence and CSM in patients with node-negative bladder cancer (BC). In patients with node-negative BC, LVI rate increased and was associated with worse oncologic outcome. LVI had a lower but still significant association with disease recurrence and CSM in node-positive BC.

Conclusions: LVI is a strong prognostic factor of worse prognosis in patients treated with RC for bladder cancer. This association is strongest in node-negative BC, but it is also in node-positive BC. LVI should be part of all pathological reporting and could provide additional information for treatment-decision making regarding adjuvant therapy after RC.

Keywords: Lymphovascular invasion; Bladder cancer; Radical cystectomy; Lymph node dissection; Metastasis; Meta-analysis

1. Introduction

Radical cystectomy (RC) and pelvic lymph node (LN) dissection is the standard treatment in patients with muscle-invasive bladder cancer (MIBC) and in patients with very high risk non-MIBC disease [1,2]. Despite adequate surgery, up to 50% patients experience disease recurrence and mortality after RC [3]. Randomized clinical trials failed to demonstrate a benefit to adjuvant chemotherapy (AC). However, most guidelines recommend a discussion regarding AC for patients with pT3–4 or node-positive disease

Conflicts of interest: The author certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript are the following: Shahrokh F. Shariat is advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, and Wolff. He is speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, and Wolff.

[1]Andrea Mari and Shoji Kimura contributed equally to this project and fully share the first authorship.

* Corresponding author. Tel: +43-14040026150; fax: +43-14040023320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

https://doi.org/10.1016/j.urolonc.2018.03.018
1078-1439/

who are able to tolerate cisplatin-based chemotherapy and did not receive neoadjuvant cisplatin-based chemotherapy. Due of challenging adjuvant systemic therapy is to identify the patients who are likely to benefit from it and spare those who are not the side effects from an unnecessary therapy. Current prognostic tools based on TNM staging, however, did not reach sufficient accuracy to change our clinical decision making. Inclusion of easily available pathologic features that are associated with the biological aggressiveness of BC may facilitate clinical decision making regarding adjuvant systemic therapy, patient counseling, and follow up intensity.

Lymphovascular invasion (LVI) is an important step in cancer cell dissemination [4–7]. In BC, the detection of LVI in the RC specimens has been shown to be associated with adverse outcomes in several large retrospective studies. In 2014, a meta-analysis by Kim et al. [8] examined 21 studies and confirmed the significant prognostic role of LVI in RC specimens despite a certain degree of asymmetry between studies. In the recent years, numerous papers added new evidence to the topic [9–14]. These studies add information regarding the prognostic role of LVI in specific subcohorts based on stage and perioperative treatment. We performed a systematic review and meta-analysis to assess the prognostic value of LVI in RC specimens of BC patients focusing on subgroups such as organ confined BC.

1.1. Evidence acquisition

1.1.1. Literature search

A systematic review and meta-analysis of the English-language literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions [15,16]. We systematically searched MEDLINE, EMBASE, and the Cochrane Library to identify studies published between January 2007 and July 2017 (date last search: 30/Jul/2017) that examined the effect of LVI on oncologic outcomes in patients treated with RC for BC. After a first screening based on study title and abstract, all papers were assessed based on full text and excluded with reasons when appropriate. Two reviewers (A.M. and S.K.) carried out this process independently. Disagreement was 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 ("radical cystectomy" OR "cystectomy")) AND ("LVI" OR "lymphovascular invasion" OR "lymphatic invasion" OR "vascular invasion").* Disease recurrence and cancer-specific mortality (CSM) were the primary endpoints of interest.

1.1.2. Eligibility criteria

As proposed by the PRISMA guidelines, we used the Population, Intervention, Comparator, Outcome, and Study design approach to specify the inclusion criteria. Reports were considered relevant when included patients diagnosed with BC (P), recorded LVI (C), and underwent RC (I) to independently determine the prognostic value of LVI on disease recurrence and CSM (O) using multivariable Cox proportional hazard regression analyses (S). If more than 1 report of the same cohort of patients existed, we selected the most recent regarding a specific survival outcome. Review articles, editorials, comments, and meeting abstracts were excluded. References of included manuscripts were scanned for additional studies of interest. The PRISMA 2009 checklist is reported in Supplementary Table 1.

1.1.3. Data extraction

After full text evaluation, data was independently extracted by 2 authors (A.M. and S.K.) for further assessment of qualitative and quantitative analyses. All extracted variables were crosschecked to ensure their reliability. We recorded the baseline characteristics, of the included participants, the use of chemotherapy and the median/mean follow-up duration. Subsequently, the HRs and 95% CIs of LVI associated with each outcome were retrieved. Furthermore, we searched for methods and important confounders to establish comparability. The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies [17]. The NOS assesses the quality of studies using a star system based on 3 domains: selection of cohorts, comparability of cohorts, assessment of outcomes. The NOS ranges from 0 to 9. A threshold ≥ 7 was identified to distinguish studies with higher quality. All discrepancies regarding data extraction were generally resolved by consensus or finally decided by the senior author (S.F.S.).

1.1.4. Statistical analysis

Due to the observational nature of included studies, we extracted adjusted HR and 95% confidence interval for cumulative effect size calculation. Studies with Kaplan-Meier log-rank, univariable Cox proportional hazard regression, or general logistic regression analyses were not considered for meta-analysis. Effect summary estimation methods were not used in these cases; as 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 $P < 0.05$ 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 [18–20]. When these tests were negative for heterogeneity, fixed-effect models were chosen for calculation of pooled hazard ratios through the inverse-variance method. Publication bias including small-study effect were evaluated by visual inspection of funnel plots for all assessed comparisons. Statistical analyses were