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Review

Lymphovascular invasion as a prognostic factor in the upper urinary tract urothelial carcinoma: A systematic review and meta-analysis

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Abstract ***Background:*** The objective of the present study was to conduct a systematic review and meta-analysis of the published literature investigating lymphovascular invasion (LVI) and its effects on upper urinary tract urothelial carcinoma (UTUC) prognosis.
Methods: To identify relevant studies, PubMed, Cochrane Library, OVID and SCOPUS database were searched from the inception until June 2012.
Results: A total of 17 trials met the eligibility criteria for the meta-analysis. The total number of patients included was 4896, ranging from 60 to 2492 per study. None of the 17 included studies was based on the data of prospective analysis of survival. In 13 of 17 studies, patients had received adjuvant chemotherapy. Despite our attempts to limit the between-study heterogeneity through a strict inclusion criteria, there was a between-study heterogeneity in the effect of LVI on all of the meta-analyses, with a p value of <0.05 and I^2 generally greater than 50%. Thus, the hazard ratio (HR) was calculated using the random-effect model. The pooled HRs were statistically significant for disease-free survival (pooled HR, 1.91; 95% confidence interval [CI], 1.40–2.41), cancer-specific survival (CSS) (pooled HR, 1.72; 95% CI, 1.28–2.71) and overall survival (pooled HR, 4.05; 95% CI, –0.44–8.53). There was no clear evidence of funnel plot asymmetry, and thus, no evidence of publication bias was found.
Conclusions: Our meta-analysis showed that LVI is predictive of mortality in UTUC. However, these findings should be interpreted with caution due to the heterogeneity in the series. These results need to be further confirmed by an adequately designed prospective study to provide a better conclusion on the relationship between LVI and the outcome of patients with UTUC.

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1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) accounts for 10% of all urothelial carcinoma in the literature.[1] Despite advances in the endoscopic and minimally invasive treatments, radical nephroureterectomy (RNU) with excision of a bladder cuff is the standard treatment for the condition. However, the outcome of patients with UTUC is still generally poor,[1] which may be due in part to the difficulty in early detection of the tumour, the thin muscular and submucosal layers and the absence of serosa in the upper urinary tract.[2] Such outcomes indicate the importance of choosing adequate treatment plans and proper adjuvant therapy strategies for patients with higher risks of failure. Improved knowledge of prognostic indicators would help us make better prognostic evaluations, for a more effective approach overall. Numerous studies have been conducted to elucidate significant prognostic factors for UTUC. Although the tumour stage and grade have been used as the major prognostic factors for these patients,[3] little is known regarding the natural history of UTUC. Most of the clinicopathologic characteristics of UTUC are not well known due to its inherent rarity.

Lymphovascular invasion (LVI) is the primary and essential step in the systemic dissemination of cancer cells.[4] LVI has been documented as a poor prognostic factor in many solid organ tumours.[5,6] Within the spectrum of urothelial malignancy, the significance of LVI has been well characterised for the bladder cancer. Several studies have shown an association between the presence of LVI on the bladder biopsy specimen and extravesical disease at the time of cystectomy.[7,8] These reports on the association of LVI with advanced bladder cancer call for further characterisation of the prognostic significance in UTUC. However, because of the rarity of the disease, the significance of LVI has not been clearly established in UTUC. Before a new biomarker such as LVI can be integrated into the clinical decision making process, it needs an external confirmation. The current study evaluated LVI as a prognostic factor for survival. The objective of the present study was to conduct a systematic review and meta-analysis of the published literature investigating LVI and its effects on the UTUC prognosis.

2. Methods

2.1. Search strategy

We conducted a systematic review of the original articles in English which analysed the prognostic role of LVI in patients with UTUC. From inception until June 2012, we searched the electronic database PubMed, OVID, SCOPUS and Cochrane Library to identify relevant studies by using the following separate search criteria: (1) [LVI] AND [upper urinary tract] AND ([cancer] OR [carcinoma]); (2) [LVI] AND [ureter] AND ([cancer] OR [carcinoma]); (3) [LVI] AND [renal pelvis] AND ([cancer] OR [carcinoma]). The deadline for the included articles was June 2012. The references of the retrieved articles were searched in order to identify other potentially eligible studies for inclusion, which were not included in the initial automated search.

2.2. Inclusion and exclusion criteria

As the between-study heterogeneity is a known problem in the meta-analysis of the prognostic marker studies,[9] we used strict inclusion and exclusion criteria to limit heterogeneity across the studies, thus facilitating more clinically meaningful meta-analysis results.

The following criteria for eligibility among studies were set before collecting articles:

(1) Articles were published in English.
(2) LVI was evaluated in the primary upper urinary tract carcinoma tissue.
(3) The histologic type of tumour was urothelial carcinoma.
(4) The authors must offer the size of the sample, hazard ratios (HR) and their 95% confidence intervals (CI), or the information that can help infer the survival results in the papers.

Accordingly, the following exclusion criteria were used:

(1) Reviews and non-original articles were excluded from our review.
(2) Studies on cancer cell lines and animal models were excluded.
(3) Studies which cannot offer sufficient data to acquire HR and its standard error (SE) were excluded.

Studies which did not report an adjusted HR after controlling for the potential confounding variables in multivariate analysis were excluded, since the accuracy of HRs estimated from Kaplan–Meier curves without multivariate analysis is uncertain.[10–12] Where part or all of the same patient series was included in more than one publication, only the most recent or most complete study was included in the analysis in order to avoid duplication of the same survival data.

2.3. End-points

The primary outcome measures were the disease-free (DFS) and cancer-specific survival (CSS). Survival was determined from time of surgery to the time of last follow-up. In assessing DFS, recurrence of disease was defined as local failure or distant metastasis. CSS takes into account deaths due to UTUC, and deaths from causes other than UTUC were censored.