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Systematic or Meta-analysis Studies

A systematic review and meta-analysis of clinicopathologic factors linked to oncologic outcomes for renal cell carcinoma with tumor thrombus treated by radical nephrectomy with thrombectomy

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ABSTRACT

Background: There remain discrepancies over the factors that influence oncologic outcomes after radical nephrectomy with thrombectomy (RNTE). To assess significant predictors of oncologic outcomes after RNTE from a systematic review and meta-analysis.

Methods: A comprehensive search of PubMed, Embase, Cochrane Library and Web of Science was performed to identify eligible studies. The endpoints included cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS). A formal meta-analysis was performed for studies containing non-metastatic and metastatic tumors. Additionally, a sensitivity analysis including the subgroup of studies containing non-metastatic tumors only was conducted. Cumulative analyses of hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were conducted.

Results: Overall, 35 retrospective studies of low to moderate risk of bias including 11,929 patients were included. The results indicated that large tumor size, high Fuhrman grade, tumor necrosis, positive lymph node, and metastasis at surgery were adverse significant predictors for both CSS and OS. Also, IVC tumor thrombus, sarcomatoid differentiation, perinephretic fat invasion, and adrenal gland invasion were associated with poor CSS. In the subset of non-metastatic patients, the significant predictors were clinical symptom, thrombus level, Fuhrman grade and adrenal gland invasion for CSS; thrombus consistency, Fuhrman grade and tumor necrosis for OS; tumor size, Fuhrman grade and perinephretic fat invasion for RFS.

Conclusions: A meta-analysis of available data identified significant prognostic factors of CSS, OS and RFS that should be systematically evaluated to propose a risk-adapted approach to postoperative patient counseling, risk stratification, and therapy selection.

Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers in adults worldwide, and has an annual increase of around 2% in incidence during the past two decades [1]. Improved diagnostics have resulted in the increasing discovery of low stage renal tumors. Involvement of the venous system is a clinical characteristic of advanced RCC, which is observed in 4–10% of all RCC patients [2]. Radical nephrectomy with thrombectomy (RNTE) is the only curative therapeutic modality for these patients [3]. However, despite the aggressive resection was performed, the long-term survival of RCC with tumor thrombus (TT) remains poor compared to localized RCC. According to published studies, the 5-year cancer-specific survival (CSS) rate after surgery is only 25–53% for these cases [4–6].

It seems to be meaningful to study prognosis predictor for RCC with TT, which can guide postoperative patient counseling, risk stratification, and therapy selection. Tilki et al. [6] assessed the association between histologic subtype and CSS for RCC with vena cava TT. Weiss et al. [7] found that friable tumor thrombus is an important inferior prognostic predictor of overall survival in patients absent of nodal and

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distant metastases. Taken that single factor hardly accurately predict the patient survival, many centers have studied the prognostic role of a series of clinicopathological variables in patients with RCC and TT. They identified several significant prognosis predictors, including tumor size, Fuhrman grade, tumor necrosis, sarcomatoid differentiation, perinephretic fat invasion, positive lymph node, and metastasis at surgery [8–13]. In order to obtain accurate prediction of oncologic outcomes for each patient with RCC and TT, several preoperative and postoperative nomograms have been developed [14–17].

However, most studies trying to determine the prognosis predictors for RCC with TT are restricted to small sample size, their single-center design, and inhomogeneous population, embracing patients underwent surgery or not [18–20]. And the proposed nomograms still need to be external validated before clinical application. Moreover, there remain large discrepancies from the publications regarding the prognostic role of clinicopathologic factors for RCC with TT. Hence, we aimed to assess significant prognostic factors of oncologic outcomes after RNTE from a systematic review of the studies and a meta-analysis of the available data.

Materials and methods

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria. The protocol for this study was registered on PROSPERO (CRD42018086218).

Search strategy

We carried out a computerized bibliographic search of PubMed, Embase, Cochrane Library and Web of Science up to November 2017 to identify studies focusing on oncologic outcomes for renal cell carcinoma with tumor thrombus treated by radical nephrectomy with thrombectomy.

Separate searches were performed using diagnosis (renal cell carcinoma, renal cell cancer, renal tumor, kidney cancer, tumor thrombus, venous tumor thrombus), treatment terms (radical nephrectomy, radical surgery, thrombectomy) and oncologic outcomes (prognosis, survival, mortality, recurrence, progression). Furthermore, we examined the references from the relevant studies, embracing all of the identified original articles, reviews, meta-analyses, and comments.

Inclusion criteria and study eligibility

The present study included patients diagnosed with RCC with venous (renal vein and/or inferior vena cava) tumor thrombus and treated by RNTE. Inclusion criteria were literatures that studied the predictors of oncologic outcomes for RCC with TT. The endpoints of oncologic outcomes included cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS). Exclusion criteria included the following items: (1) basic research; (2) studies focusing on non-RCC; (3) non-original articles (eg, letters, editorials, comments, reviews, systematic reviews, meta-analysis); (4) gray literature (e.g., thesis, abstract only); (5) studies that included patients without TT; (6) studies that included non-surgical patients; and (7) studies didn't provide hazard ratios (HRs) from multivariate cox analyses and 95% confidence intervals (CIs). When two or more studies focused on the same variable of the same endpoint, the results were merged. If two or more studies reported the same variable of the same cohort, the most informative study with the largest sample size was selected. Two authors (L.G. and H.L.) independently completed the review of titles and abstracts to separately assess full-text studies. Any disagreement was resolved by discussing with the senior authors (X.M. and X.Z.).

According to the recommendation from the Cochrane Collaboration, the Newcastle-Ottawa Scale were used to evaluate risk of bias [21]. Appling a star system ranging from 0 to 9, each literature was evaluated based on three domains, the inclusion criteria, comparability between the groups, and ascertainment of the outcome of interest. Despite the retrospective design, the included 35 studies were of low to moderate risk of bias (Supplementary material).

Data extraction

Two authors (L.G. and Z.W.) independently extracted data from each included literature. The disagreements were solved through consulting the senior author (X.M.). Firstly, we collected data including the first author's last name, year of publication, study period, country, study design, sample size, patients age, tumor stage, level of tumor thrombus, oncologic outcomes, and median/mean follow-up period for evaluating the overall features of RCC with VTT following RNTE. After that, HRs for clinicopathologic factors associated with oncologic outcomes in multivariate cox models were extracted with relevant 95% CIs to perform cumulative analyses. The oncologic outcomes included CSS, OS and RFS.

A formal meta-analysis was performed for studies containing nonmetastatic and metastatic tumors. Additionally, a sensitivity analysis including the subgroup of studies containing nonmetastatic tumors only was conducted.

Statistical analysis

Appling the predictor effect and their corresponding standard error from available adjusted HRs and its 95% CIs, a meta-analysis was conducted for each possible factor for oncologic outcomes. The inverse variance method was applied to assess cumulative effects of factors of interest. Statistical heterogeneity was evaluated using The Cochrane Q statistic and I^2 statistic. A p value less than 0.05 for the Cochran Q test or an I^2 statistic larger than 50% indicated the presence of significant heterogeneity among literatures, a random-effect model was used. Or else, a fixed-effect model was used. Sensitivity analysis was also performed by omission of each single study to evaluate stability of the findings. For comparison including at least 10 studies, the risk of publication bias was evaluated by visual inspection of funnel plot, the Begg's and Egger's test. All statistical analyses were performed with R software (version 3.2.2).

Results

Data retrieval and study characteristics

The database searching identified 1318 potential studies. After removing duplicated records and excluding literatures by examining the

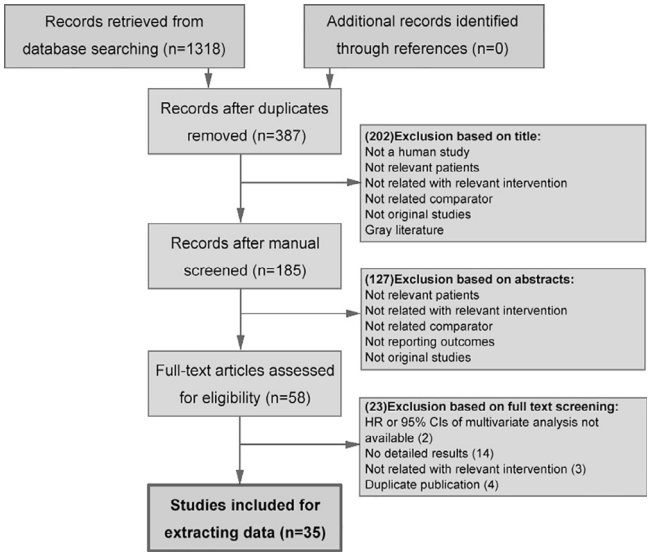

Fig. 1. Flow chart of the selection of publications included in the meta-analysis.