



## Review

# Prognostic factors for overall survival after lung metastasectomy in renal cell cancer patients: A systematic review and meta-analysis



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## HIGHLIGHTS

- Metastasectomy is a promising treatment for lung metastases of RCC patients.
- A short DFI, LNI of primary RCC are predictors of poor survival.
- Lung metastases features are predictors of over survival for RCC patients.

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## ABSTRACT

**Background:** Pulmonary metastasis of Renal cell carcinomas (RCC) is usually considered as a systemic disease. However, some studies revealed potential survival benefits of pulmonary metastasectomies for such patients. The aim of this study was to conduct a systematic review and meta-analysis to assess the prognostic factors for pulmonary metastasectomy of RCC patients.

**Methods:** An electronic search in MEDLINE, EMBASE, CENTRAL and Chinese BioMedical Literature Database (CBM) were conducted to identify eligible studies. We combined the hazard ratios (HRs) of the identified prognostic factors for overall survival of RCC patients after pulmonary metastasectomy from the eligible studies.

**Results:** Sixteen studies with a total of 1447 patients were included in this meta-analysis. The pooled 1, 3, 5, 10-year overall survival rates for RCC patient after pulmonary metastasectomy were 84%, 59%, 43% and 20%, respectively. The poor prognostic factors were lymph node involvement (LNI) of primary RCC (HR 3.44, 95% confidence interval (CI) 1.78–6.67,  $P = 0.001$ ), incomplete resection of metastases (HR 3.74, 95% CI 2.49–5.61,  $P = 0.000$ ), multiple metastases (HR 1.55, 95% CI 1.18–2.03,  $P = 0.002$ ), larger metastases (HR 1.45, 95% CI 1.26–1.66,  $P = 0.000$ ), LNI of metastases (HR 3.06, 95% CI 1.52–6.19,  $P = 0.002$ ), synchronous metastasis (HR 2.49, 95% CI 1.46–4.24,  $P = 0.001$ ) and short disease free interval (DFI).

**Conclusions:** Surgery may be a promising treatment for pulmonary metastases of RCC patients. A short DFI, LNI of primary RCC, incomplete resection of metastases, multiple metastases, larger metastases, LNI of metastases and synchronous metastasis are predictors of poor survival after pulmonary metastasectomy for RCC patients.

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## 1. Introduction

Renal cell carcinoma (RCC) is the seventh most frequently diagnosed cancer, which was diagnosed in more than 350 000 people worldwide and it is associated with more than 140 000 deaths in 2013 [1]. Distant metastases appear in approximately 30%

of the patients who have primary RCC at the time of diagnosis, and another 25% patients develop metachronous metastases [2–5]. Lung is a common site of metastases in patients who were diagnosed with RCC, with approximately 30%–50% of the metastatic RCC patients found to have metastatic lesions in the lung [6].

Pulmonary metastasis of RCC is usually considered as a systemic disease, so most oncologists didn't approve of surgical procedures for metastatic RCC or consider them just as palliative strategies [7]. Immunotherapies, mainly interferon  $\alpha$  and interleukin-2, are routinely considered for these patients, but durable complete

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responses were achieved in less than 10% of patients and outcomes were only slightly improved [8]. Moreover, post-operative immunotherapy has been associated with severe therapy-related toxic effects [9]. More recently, agents targeting the VEGF/PDGFR/mTOR pathway trended to be the mainstays of treatment. Although improved target specificity has lessened the risk of toxic effects, durable complete responses remain low and there were still some treatment-related adverse events such as fatigue, hypertension, nausea and diarrhea [10,11]. The median survival after targeted therapy remained at about 22 months [10]. So metastatic RCC is still regarded as an incurable disease and the therapy is usually just palliative. Recently, several studies revealed potential survival benefits of pulmonary metastasectomies for metastatic colorectal cancer and breast cancer patients [12,13]. However, whether pulmonary metastasectomies could have favorable effects on survival of metastatic RCC patients is still a controversial issue. With the technological developments in cardiothoracic surgery and anesthesia, pulmonary metastasectomy is associated with a relatively low perioperative morbidity and mortality now. Consequently, pulmonary metastasectomy may be a promising therapy for lung metastases of RCC.

In the current study, we conducted a systematic review and meta-analysis of cohort studies to assess the pooled 1, 3, 5, 10-year overall survival (OS) rates and the potential prognostic factors for pulmonary metastasectomy of RCC.

## 2. Materials and methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement protocol [14].

### 2.1. Search strategy

We searched MEDLINE (via PubMed), EMBASE (via OVID), CENTRAL (via a Cochrane Library) and the Chinese BioMedical Literature Database (CBM) until 10 September 2016 to identify studies relevant to this review. Our search strategy included the following subject headings and/or keywords variably combined by 'renal cell cancer' 'lung metastasis' 'surgery' and 'prognosis'. The detailed search strategy of PubMed is listed here: (((((((((((("surgical procedures, operative"[MeSH Terms]) OR ((Pulmonary Surgical Procedures[MeSH Terms]) OR Pneumonectomy\*[Title/Abstract]))) OR surgical[Title/Abstract]) OR surger\*[Title/Abstract]) OR operate[Title/Abstract]) OR operation[Title/Abstract]) AND (((((((Kidney carcinoma\*[Title/Abstract]) OR Kidney cancer\*[Title/Abstract]) OR Kidney tumor\*[Title/Abstract]) OR Kidney neoplasms [MeSH Terms])) OR carcinoma, renal cell[MeSH Terms]) OR (((renal carcinoma\*[Title/Abstract]) OR renal cancer\*[Title/Abstract]) OR renal tumor\*[Title/Abstract]) OR renal cell carcinoma[Title/Abstract])) AND (((lung metastas\*[Title/Abstract]) OR pulmonary metastas\*[Title/Abstract]) OR "lung neoplasms/secondary"[MeSH Terms])) AND prognos\*[Title/Abstract])). In addition, retrieved articles were reviewed to identify relevant reports. The eligibility of articles retrieved by the search was assessed independently by two of the authors, and the review authors resolved differences of opinion by discussion or by an appeal to a third review author when necessary. The full text of the remaining articles, including the references, was examined to determine whether the articles contained relevant information.

### 2.2. Assessment of study eligibility

The titles and abstracts identified through the search were reviewed. Any article that might meet the eligibility criteria was

included. Disagreement was resolved by consensus. The following inclusion criteria were selected:

- (i) Type of study: cohort study assessing prognostic factors for pulmonary metastasectomy of RCC.
- (ii) Type of participant: patients whose primary RCC had been resected completely proven by histopathology and metastatic disease was limited to the lungs proven by imaging techniques.
- (iii) Type of outcome: overall survival (OS) and prognostic factors for OS were available. OS was defined as the time from pulmonary metastasectomy of RCC until the date of the last follow-up or all-cause death.

Studies were excluded based on any of the following criteria: (i) article type: reviews, letters, laboratory research and animal experiments; (ii) language other than English or Chinese.

### 2.3. Quality assessment

Quality assessment of individual studies was performed independently by two authors, using the Newcastle–Ottawa Scale (NOS) for cohort studies. A quality score of 1–9 was given to patient selection, comparability and outcome measurement of study participants [15]. Studies with NOS scores of  $\geq 8$  were defined as high quality. Any discrepancies were addressed by joint re-evaluation of the original article.

### 2.4. Data extraction

Data were extracted from the selected studies independently by two of the investigators, using a predefined standardized form. Disagreements were resolved by discussion between two review authors or by appealing to a third review author. We extracted data of the eligible articles' basic characteristics, including first author (year), country, study period, study design, number of patients, number of patients evaluated survival and prognostic factors after pulmonary resection, median follow-up, median/mean age at pulmonary metastasectomy, median survival time after pulmonary metastasectomy, 1, 3, 5, 10-year survival rate and prognostic factors. Moreover, the original data included the Kaplan–Meier (KM) survival curves or hazard ratio (HR) and 95% confidence interval (CI) of survival outcomes. Univariate Cox hazard regression analysis data were our priority, but if they were not available, multivariate Cox hazard regression analysis or K–M survival curves with log-rank P-value of survival outcomes were collected instead. The data of K–M survival curves were extracted by Engauge Digitizer4.1 ([http://nchc.dl.sourceforge.net/project/digitizer/Engauge%20Digitizer/digitizer-5.1/digit-exe-windows-5\\_1.zip](http://nchc.dl.sourceforge.net/project/digitizer/Engauge%20Digitizer/digitizer-5.1/digit-exe-windows-5_1.zip)); the HR, which could not be obtained directly from the individual studies, was estimated by the method of Tierney et al. [16].

### 2.5. Data analysis and statistical analysis

Prognostic factors associated with outcome were extracted from all cohorts. A prognostic factor was considered significant if the reported P value was less than 0.05, or the 95% CI of HR did not overlap 1. Only prognostic factors that were assessed via univariate analyses (log-rank test) in at least two cohorts were presented, because in different articles different statistical techniques may be used and choice of covariates used in the individual multivariate models may be different. So the interpretation of data pooled from different multivariate models may be misleading.

To normalize the data, the individual 1, 3, 5, 10-year survival were Arcsin transformed. Then we calculated the pooled 1, 3, 5, 10-

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