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Prognosis of synchronous and metachronous multiple primary lung cancers: Systematic review and meta-analysis

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ABSTRACT

Background: With the development of imaging technology, an increasing number of multiple primary lung cancers (MPLC) are diagnosed in recent years. However, there is still ambiguity in the stage classification rules for patients with MPLC. Our purpose was to access the prognosis of synchronous and metachronous MPLC.

Methods: A systematic literature search was performed on four databases (EBSCO, Pubmed, OVID and Springer) to obtain relevant articles. We used published hazard ratios (HRs) of overall survival (OS) if available or estimates from the published survival data.

Results: There were 1796 patients with MPLC in 22 relevant studies, who were eligible for analysis. We found that the OS of patients with synchronous MPLC was inferior to the one of metachronous MPLC patients when starting from the diagnosis of the first metachronous tumor (HR 3.36, 95% CI 2.39–4.74; $p < 0.001$). However, there was no difference when starting from the diagnosis of the second metachronous tumor (HR 1.19, 95% CI 0.86–1.66; $p = 0.29$). From further analysis we found the OS of patients with MPLC was superior to that of patients with intrapulmonary metastasis (HR 2.66, 95% CI 1.30–5.44; $p = 0.007$). Besides, we found no difference in OS between synchronous (HR 1.39, 95% CI 0.98–1.96; $p = 0.06$) and metachronous (HR 1.05, 95% CI 0.75–1.47; $p = 0.77$) patients, in spite of the histology. In terms of unilateral and bilateral MPLC patients, the OS had no difference either (HR 1.30, 95% CI 1.00–1.69; $p = 0.05$).

Conclusion: We found that MPLC had better OS than the lung cancer patients with intrapulmonary metastasis. And despite the tumor-free interval, the OS for metachronous MPLC was as good as that for synchronous MPLC. Furthermore, there was no difference of OS in different subgroups, including histology and position.

1. Introduction

MPLC (multiple primary lung cancer) is classified as synchronous (occurring at the same time) and metachronous (occurring at different times). In 1924, Beyreuther et al. [1] first identified and reported two separate pulmonary lung cancers in one patient with tuberculosis, after that the incidence and diagnostic criteria for this condition were reported by others. The most commonly accepted criteria was outlined by Martini and Melamed [2] and modified by Antakli [3] (Table 1). In 2007, the American College of Chest Physicians [4] updated the diagnostic criteria, by adding additional clinical assessments such as lymph node and systemic metastasis, and revising the proposed interval between metachronous MPLC as at least 4 years.

Unfortunately the classification of MPLC has not reached consensus amongst three major lung cancer research institutes (American Joint Committee On Cancer (AJCC), Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC)). The IASLC states that "multiple synchronous primary tumors should be staged separately" [5]. However, the following guideline documents present that, "The highest T category and stage of disease should be assigned and the multiplicity of the number of tumors should be indicated in parenthesis, e.g. T2(m) or T2(5)" [5]. Therefore the guideline in

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Table 1
Criteria for diagnosis of second primary lung cancer.

Martini and Melamed criteria
Synchronous MPLC
A. Tumors physically distinct and separate
B. Histological type
1. Different
2. Same, but in different segments, lobes, or lungs, if
a. Origin from carcinoma in situ
b. No carcinoma in common lymphatics
c. No extrapulmonary metastases at the time of diagnosis
Metachronous MPLC
A. Histologically different
B. Histologically identical, if
1. Free interval between cancers > =2 years, or
2. Origin from carcinoma in situ
3. Second cancer in different lobe or lung, but:
a. No carcinoma in common lymphatics
b. No extrapulmonary metastases at time of diagnosis
Antakli et al. modifications
A. Different histological conditions
B. Same histological condition with two or more of the following
1. Anatomically distinct
2. Associated premalignant lesion
3. No systemic metastases
4. No mediastinal spread
5. Different DNA ploidy

regards to whether staging should be based on a combination of all tumors with one TMN designation, or each tumor separately is ambiguous [6]. The IASLC guideline implies that the TNM classification can be applied to both same and different histology between primary and secondary tumors, but the AJCC guideline only fits for tumors with the same histological subtype [7]. The 2012 manual of UICC suggests, "A tumor in the same organ with a different histologic type is counted as a new tumor" [8]. As there is no consensus between these three major institutes, the official rules for the stage classification of MPLC are still controversial.

The present meta-analysis aimed to investigate the overall survival (OS) starting from the diagnosis of the first and the second tumor of metachronous MPLC and compare the prognosis between synchronous and metachronous MPLC. OS of intrapulmonary metastasis was also analyzed. The subgroup analysis of histology and position were performed simultaneously.

2. Method

The methods of literature search strategy, inclusion and exclusion criteria for eligible studies, outcome measures, and methods of statistical analysis followed the Preferred Items for Systematic Reviews and Meta-Analysis [9] and Meta-Analysis of Observational Studies in Epidemiology recommendations for study reporting [10].

2.1. Literature search

Four electronic databases (EBSCO, Medline, Ovid and Springer) were searched for relevant studies from inception to June 2014 (Fig. 1). Language was limited to English. In order to comprehensively collect as many studied as possible, we used "multiple primary lung cancer", "metachronous", "synchronous", "second primary lung cancer" or "MPLC" with "lung cancer" in different combinations in all fields. The reference lists of relevant publications were subsequently searched for supplement studies.

2.2. Study eligibility

The inclusion criteria was as follows: (i) the articles contained either synchronous or metachronous MPLC or both; (ii) the definition of MPLC must be clarified in the study; (iii) surgical resection should be the main treatment with no metastasis found during postoperative pathologic examination; (iv) the main outcome of overall survival (OS) should be included; (v) information was stated in the article on which the hazard ratios (HR) of OS can be calculated; (vi) no less than 10 patients in both comparable groups of each study; (vii) in the case of studies containing the same datasets as studies that had been published before, only the study with the latest results was included. All publications were limited to human subjects. Abstracts, case reports, conference presentations, editorials and reviews were excluded.

2.3. Data extraction and quality assessment

The full-text articles were reviewed and data was extracted by two independent authors (Xiaoshun Shi and Jianfei Shen). Any discrepancies were resolved by discussion and came to consensus with a third author. Extracted data included: publication details, sample size, tumor histological type, tumor stage, median survival time, and 3-year and 5-year survival rates. The quality of studies was modified by criteria suggested by the Newcastle–Ottawa quality assessment tool [11]. The details were listed in the appendix.

2.4. Statistical analysis

The log (hazard ratio) [ln (HR)] and its standard error (SE) were used as the outcome measure for data combination [12]. The SE could be calculated as:

$$\frac{\text{Upper95\% CI} - \text{lower95\% CI}}{3.92}$$

When possible, the HR and associated variance were obtained directly from each publication. If HRs were not reported, we calculated by the Parmar et al's methods [12]. The ln (HR) and its SE of OS were calculated from the reported data directly by HR and its 95% CI or indirectly by log-rank P value with number of events, or data reading from Kaplan–Meier survival curve using Engauge Digitizer, respectively.

The publication heterogeneity among studies was accessed by using chi-squared (χ^2) test. We predefined heterogeneity as low (25–49%), moderate (50–74%) and high (75–99%). The random effect model was used in the present meta-analysis. Publication bias was analyzed by Egger's method and graphically using performing Begg's funnel plot. Statistical analysis was performed with Review Manager Software 5.1.6 (Cochrane Collaboration, Oxford, UK) and STATA version 11 (StataCorp LP, College Station, TX 77845, USA). A p value <0.05 was considered statistically significant.

3. Results

3.1. Description of studies

A total of 210 articles were obtained from the initial literature search. After applying inclusion and exclusion criteria, 22 retrospective studies published from 1975 to 2013 were eligible for further investigation. The total number of MPLC patients was 1796, including 913 synchronous MPLC and 883 metachronous MPLC. In metachronous MPLC, the median tumor-free interval between the first and second tumor of all studies ranged from 24 to 71 months. The TNM classification of single nodule of MPLC in the studies relevant to this meta-analysis was mainly concentrated in stages I and II. Excluding surgical contraindications, surgical resection was the