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Original article

Prognostic roles of lymph node micrometastasis in non-small cell lung cancer

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ABSTRACT

Objective: This study aimed to confirm the prognostic roles of lymph node (LN) micrometastasis (LNMM) in non-small cell lung cancer (NSCLC) through a meta-analysis.
Methods: This study included 2026 NSCLC cases without detection of LN metastasis in histologic examination. We investigated the detection rate of LNMM in early-stage NSCLC and analyzed the correlation between LNMM and the rates of recurrence and survival.
Results: The range of detection rates of LNMM was 3.8–68.8% in the eligible studies. The detection rate of LNMM in early-stage NSCLC was 25.3% (95% confidence interval [CI] 19.8–31.6%). In subgroup analysis based on detection method, polymerase chain reaction method had higher detection rate than immunohistochemistry (33.7%, 95% CI 25.5–43.0% vs. 23.1%, 95% CI 18.0–29.0%). The presence of LNMM was significantly correlated with a higher recurrence rate (odds ratio 3.913, 95% CI 1.595–9.600, P = 0.003). In addition, there were significant correlations between LNMM and worse overall and disease-free survival rates (hazard ratio [HR] 2.345, 95% CI 1.863–2.951, and HR 1.606, 95% CI 1.170–2.206, respectively).
Conclusion: Taken together, our results showed that LNMM was detected in 25.3% of NSCLCs without nodal disease through ancillary test. In addition, the presence of LNMM was significantly correlated with a higher recurrence rate and worse survival rates in early-stage NSCLC.

1. Introduction

Lung cancer can be classified as either small cell lung cancer or non-small cell lung cancer (NSCLC). Among all lung cancers, approximately 80% are NSCLC [1,2]. In early-stage NSCLC, surgical resection is the first-line therapy. A previous study reported that recurrence was found in approximately 30% of stage I NSCLCs [3]. The possibility of lymph node (LN) micrometastasis (LNMM), which is not detected in routine pathologic examination, might be considered as a cause of recurrence in early-stage NSCLC. The accurate assessment of LNMM may be important for deciding whether to treat patients with adjuvant therapy after surgical resection. According to the American Joint Committee on Cancer (AJCC), LNMM includes isolated tumor cells (a single or small number of tumor cells) and micrometastases (< 0.2 mm) [4,5]. LNMM can be detected by observing the expression of markers of tumor cells using immunohistochemistry (IHC). In addition, other non-morphologic methods, such as flow cytometry and reverse transcriptase polymerase chain reaction (RT-PCR), can use for detection of LNMM. Regardless of the detection method, LNMM is coded with the suffix mi, and is not classified as N1, N2, or N3 in the current staging system [4,5]. However, the correlation between LNMM and the prognosis of NSCLC has not been fully elucidated. In addition, the methods and biomarkers for the detection of LNMM have not yet been standardized.

Regional node involvement is an adverse prognostic factor in malignant tumors. In NSCLC, node (N) stage is defined by the location, but not the number, of the involved lymph nodes. The prognostic roles of the upstaging after detection of LNMM are not fully understood in early-stage NSCLC. The present study aimed to evaluate the impact of detection of LNMM in NSCLC without nodal disease through a meta-analysis. In addition, the correlations between LNMM and recurrence and survival of patients with early-stage NSCLC were analyzed.

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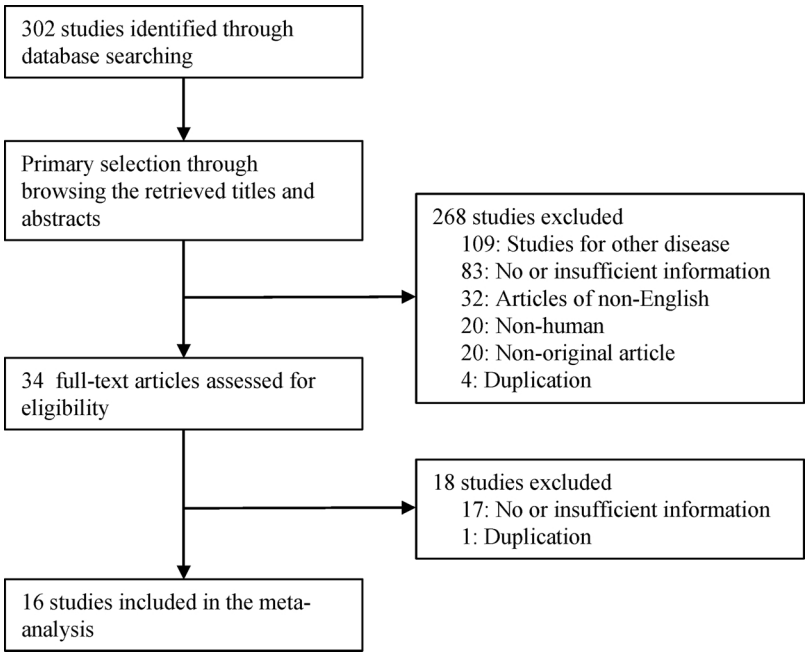

Fig. 1. Flow chart of study search and selection methods.

2. Materials and methods

2.1. Published studies search and selection criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through December 31, 2016. These databases were searched using the following key words: "lung cancer or non-small cell lung cancer," "lymph node," "isolated tumor cell," and "micrometastasis." The titles and abstracts of all searched articles were screened for exclusion. Review articles were also screened to find additional eligible studies. Articles were included if the study was performed in human NSCLCs and if there was information about the correlation between LNMM and recurrence or survival rate. Articles were excluded if they were case reports or non-original articles; or if the article was not written in English.

2.2. Data extraction

Data from all eligible studies were extracted by two independent authors. The following data were extracted from each of the eligible studies [6–21]: the first author's name, year of publication, study location, number of patients analyzed, tumor stage, histologic type, detection method of LNMM, and information on the correlations between LNMM and rates of recurrence and survival. For quantitative aggregation of survival results, the correlation between LNMM and overall or disease-free survival rate was analyzed according to the hazard ratio (HR) using one of three methods. In studies not quoting the HR or its confidence interval (CI), these variables were calculated from the presented data using the HR point estimate, log-rank statistic or its *P*-value, and the O-E statistic (difference between the number of observed and expected events) or its variance. If those data were unavailable, HR was estimated using the total number of events, number of patients at risk in each group, and the log-rank statistic or its *P*-value. Finally, if the only useful data were in the form of graphical representations of survival distributions, survival rates were extracted at specified times to reconstruct the HR estimate and its variance under the assumption that patients were censored at a constant rate during the time intervals [22]. The published survival curves were read independently by two authors in order to reduce reading variability. The HRs were then combined into an overall HR using Peto's method [23].

2.3. Statistical analyses

To perform the meta-analysis, all data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA). We investigated the detection rate of LNMM and the correlation between LNMM and recurrence and survival rate in early-stage NSCLC. Heterogeneity between the studies was checked by the Q and I^2 statistics and expressed as *P*-values. Additionally, sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. In the current meta-analysis, because eligible studies used various detection methods and populations, the application of a random-effect model rather than a fixed-effect model was more suitable. For the assessment of publication bias, Begg's funnel plot and Egger's test were primarily used. If significant publication bias was found, fail-safe N and trim-fill tests were performed to confirm the degree of publication bias. The results were considered statistically significant at $P < 0.05$.

3. Results

3.1. Selection and characteristics of the studies

The current meta-analysis discovered 302 reports from the database search. Among these, 109 reports were excluded owing to studies for other diseases. In addition, 100 studies were excluded because of insufficient or no information. Other studies were excluded because they were published in a language other than English (n = 32), used animals or cell lines (n = 20), or were non-original articles (n = 20). Five studies were excluded due to duplication of population. Finally, 16 studies were included in this meta-analysis (Fig. 1 and Table 1). These studies included 2026 NSCLC patients without nodal disease.

3.2. Meta-analysis

First, the detection rate of LNMM in patients with early-stage NSCLC was investigated. The detection rate was 25.3% (95% CI 19.8–31.6%) in patients in NSCLC without nodal disease (Table 2). The detection rates of eligible studies ranged from 3.8% to 68.8%. In subgroup analysis based on detection method, there was no significant difference in direction between IHC and PCR (23.1%, 95% CI 18.0–29.0% vs. 33.7%,