Visceral pleural invasion impacts the prognosis of non-small cell lung cancer: A meta-analysis

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Abstract

Background: In the 7th tumor, node, metastasis (TNM) classification, T1 tumors with visceral pleural invasion (VPI) are upgraded to T2a. The objective of this study was to evaluate the prognostic impact of VPI among patients with NSCLC and to propose a method of incorporating VPI into T-status classification in future staging systems.

Methods: A systematic electronic search was conducted from each database's date of inception to October 2015. The included studies were selected according to predefined inclusion criteria. The hazard ratio (HR) was used as the outcome measure for data combining.

Results: A total of 22 studies, published from 2003 to 2015, were included in this meta-analysis. In the subgroup analysis, we identified that VPI was a poor prognostic factor for tumor size ≤2 cm (2.34 [95% confidence interval (CI) 1.55−3.54; P < 0.0001]), 2−3 cm (1.81 [95% CI 1.56−2.10; P < 0.0001]), 3−5 cm (1.61 [95% CI 1.38−1.87; P < 0.0001]) and 5−7 cm (1.50 [95% CI 1.24−1.82; P < 0.0001]). In addition, we also found that there were no significant differences for the following comparisons of OS: tumor size ≤2 cm with VPI versus 3−5 cm without VPI (1.04 [95% CI 0.83−1.31; P = 0.34]); 2−3 cm with VPI versus 3−5 cm without VPI (1.04 [95% CI 0.96−1.13; P = 0.30]); 3−5 cm with VPI versus 5−7 cm without VPI (0.95 [95% CI 0.78−1.17; P = 0.66]); and 5−7 cm with VPI versus T3 status (1.03 [95% CI 0.93−1.14; P = 0.57]).

Conclusions: In addition to the current TNM classification recommendations, consideration should be given to classifying the T2a tumors with VPI as T2b and classifying T2b with VPI as T3 in the next edition of the TNM Classification for Lung cancer.

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Keywords: Visceral pleural invasion; TNM classification; Non-small cell lung cancer

Introduction

Lung cancer is still the leading cause of cancer-related mortality worldwide, according to The World Cancer Report published by the WHO in 2014. Visceral pleural invasion (VPI) of in-patients with NSCLC has been recognized as a poor prognostic factor for the past several decades, ever since it was first described in 1958 by Brewer and colleagues.[1−5] The International Association for the Study of Lung Cancer (IASLC) proposals for the 7th edition of the TNM classification include that tumors of 3 cm or less (T1a and T1b) with VPI are to be upgraded to T2a, whereas tumors larger than 3 cm but less than 7 cm (T2a and T2b) with VPI are to remain unchanged as T2.[6]

Several single-center or multicenter clinical trials have found that VPI confers a poorer prognosis among resected tumors <7 cm in size. However, the prognostic significance of VPI was not confirmed in many of these studies.[2,4,7−10] In addition, several studies even reported that there was no impact of VPI on the prognosis of small tumor sizes or that there was a differential effect according to the size of the tumor.[11−15] Thus, the current independent prognostic significance of VPI, as well as its role in the T factor, remains unclear and controversial. To provide a general idea about the topic, we used a meta-analytical approach to combine the current obtainable data.

The aim of the present meta-analysis of published studies was to identify the impact of VPI on the overall

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survival (OS) of patients with NSCLC and the role of VPI in the T factor. Through this pooled analysis, we hoped to provide a proof for consideration in the next edition of the TNM Classification for Lung Cancer.

Methods

Search strategy for published studies

We established a rigorous study protocol according to the recommendations from the Cochrane Collaboration. To ensure the highest quality for this meta-analysis of literatures, the objective, inclusion and exclusion criteria, major outcomes, and the methods of synthesis were pre-specified before the analyses began. A systematic electronic search was performed by the investigators using PubMed (National Library of Medicine, Bethesda, USA), EMBASE (Elsevier, Amsterdam, the Netherlands) and the Cochrane databases from each database's date of inception up to October 2014. The search and identification process was independently conducted by three authors (Quan Xing Liu, Xu Feng Deng and Dong Zhou), according to a standardized approach, and the selection of each study was reached by discussion. All articles involved patients with NSCLC and dealt with the prognostic implications of VPI in the analysis to achieve the maximum sensitivity of the search strategy and to identify all the potentially relevant studies. The search terms were 'lung cancer', 'NSCLC', 'VPI', 'Visceral pleural invasion', and the Medical Subject Headings (MeSH) headings 'NSCLC' (MeSH), 'VPI' (MeSH), and 'lung cancer' (MeSH) and were used in combination with the Boolean operators AND or OR.

Selection criteria

Eligible studies included those in which the comparative outcomes including OS for patients with NSCLC who were with or without VPI. The search results were compared to the pre-specified inclusion and exclusion criteria. The following inclusion criteria were established before the articles were collected: (1) VPI was classified according to the Japan Lung Cancer Society classification of VPI (including PL1 and PL2), which is identical to the 7th edition of the TNM Classification for Lung and Pleural Tumors: PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; (2) one of the outcomes includes overall survival (OS); (3) articles were published original English language papers, and study subjects were limited to NSCLC patients; (4) median follow-up time exceeded 2 years; and (5) available data for the hazard ratio (HR) and 95% confidence interval (CI), or there were sufficient data for examining HR and 95% CI. The exclusion criteria were described as follows: (1) letters to the editor, articles published in a book, reviews and papers not published in English; (2) when centers published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, only the most informative article was chosen for the meta-analysis for qualitative appraisal; and (3) article did not provide HR and 95% CI and also did not provide the relevant curve for examining HR and 95% CI.

Quality assessment

We assessed the quality of the included studies based on the Newcastle—Ottawa Scale (NOS) for quality of case—control and cohort studies.[16] A star system for the NOS (range, 0—9 stars) was developed for the evaluation. The values for the included studies are shown in Table 1.

Statistical analysis

A meta-analysis was performed by combining the results of the reported OS. The log (hazard ratio) [ln (HR)] and its standard error (SE) were used as the outcome measure for the combined data. Hazard ratio (HR) and associated variance data were obtained or calculated from each selected study using the techniques described by Tierney and Stewart.[17] The SE was obtained as follows: (Upper95%CI-Lower95%CI)/3.92.[18] Because the HR of OS could not obtained in some studies directly, data were extracted from the Kaplan—Meier survival curves of these studies to calculate the HR and SE of OS. Kaplan—Meier curves were read by Engauge Digitizer version 4.1. The calculations were performed independently by two researchers, and discrepancies were discussed to reach consensus.[18—20] The summary statistical analysis was conducted with Review Manager Version 5.1.2. Statistical heterogeneity among the trials was evaluated using the Higgins I^2 statistic to determine the percentage of total variations across studies due to heterogeneity. If the I^2 statistic was $\leq 50\%$, the fixed effect model was used to pool studies. Otherwise, the random effects model was used.

Results

Characteristics of included trials

Twenty-two studies (10,781 patients with VPI and 34,931 patients without VPI) that met the inclusion criteria were identified; all were performed between 2003 and 2014. In all included articles, the VPI statuses of patients were diagnosed by pathological examination after surgical resection. Fig. 1 shows an overview of the literature search performed for the systematic review and meta-analysis according to the PRISMA statement. Our search strategy yielded 323 articles. The full text was reviewed for 32 articles, and finally, 22 comparable studies, which included a total of 45,712 patients, were included in the analysis. Table 1 shows the details for each trial, including the baseline characteristics, the publication year of the study, the