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The Impact of Visceral Pleural Invasion in Node-Negative Non-small Cell Lung Cancer

A Systematic Review and Meta-analysis

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BACKGROUND: Visceral pleural invasion (VPI) is considered an aggressive and invasive factor in non-small cell lung cancer (NSCLC). Recent studies found that depending on tumor size, VPI influences T stage, but there is no consensus on whether VPI is important in node-negative NSCLC. In addition, its role in stage IB NSCLC is still uncertain. In this meta-analysis, we assessed the role of VPI in node-negative NSCLC according to various tumor sizes and especially in stage IB disease.

METHODS: A systematic literature search of four databases (EBSCO, PubMed, Ovid, and Springer) was performed to find relevant articles. The primary end point was 5-year overall survival. Pooled ORs were calculated using control as a reference group, and significance was determined by the Z-test.

RESULTS: Thirteen relevant studies in 27,171 patients were included in this study. The number of patients with VPI was 5,821 (21%). VPI was a significant adverse prognostic factor in patients with tumor size ≤ 3 cm (OR, 0.71; 95% CI, 0.64-0.79; $P < .001$), > 3 but ≤ 5 cm (OR, 0.69; 95% CI, 0.56-0.86; $P < .001$), and > 5 but ≤ 7 cm (OR, 0.70; 95% CI, 0.54-0.91; $P = .007$). A further comparison was made with stage IB NSCLC. Tumor size ≤ 3 cm with VPI was associated with a better survival than tumor size > 3 but ≤ 5 cm regardless of VPI (OR, 1.31; 95% CI, 1.19-1.45; $P < .001$). Exploratory analysis found no survival benefit between tumor size ≤ 3 cm with VPI and tumor size > 3 but ≤ 5 cm without VPI (OR, 1.16; 95% CI, 0.95-1.43; $P = .15$); however, the prognosis for tumor size > 3 but ≤ 5 cm with VPI was not as good as that for tumor size ≤ 3 cm with VPI.

CONCLUSIONS: VPI together with tumor size has a synergistic effect on survival in node-negative NSCLC. Patients with stage IB NSCLC and larger tumor size with VPI might be considered for adjuvant chemotherapy after surgical resection and need careful preoperative evaluation and postoperative follow-up. Further randomized clinical trials to determine the impact of adjuvant chemotherapy in patients with stage IB NSCLC with VPI are warranted.

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ABBREVIATIONS: NSCLC = non-small cell lung cancer; VPI = visceral pleural invasion

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Visceral pleural invasion (VPI) has been recognized for the past several decades as an indicator of adverse prognosis in non-small cell lung cancer (NSCLC) and has been included in the TNM staging system as a factor that should upstage the T factor.[1-4] Shimizu et al[5] demonstrated that VPI is a significant and independent predictor of a poor prognosis regardless of tumor size or N status, and as a result, VPI is a good indicator of the degree of invasion and aggressiveness of NSCLC. However, several studies suggested that VPI has no impact on overall survival in small, early stage NSCLC.[6,7] David et al[8] found that the impact of VPI on overall survival in NSCLC varies greatly with tumor size and that VPI is not strongly associated with overall survival or disease-free survival for tumors < 5 cm but shows significant negative effects on disease-free survival for stage T2b and T3 tumors. VPI remains an important, albeit controversial clinical factor for thoracic surgeons, medical oncologists,

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and radiation oncologists when treating patients with NSCLC. The purpose of this study was to review the current literature on node-negative nonmetastatic (N0M0) NSCLC with and without VPI and to compare 5-year overall survival using the available evidence.

Materials and Methods

Literature Search

The electronic search was performed using the EBSCO (through the library of Guangzhou Medical University) and Medline (through PubMed) search engines from inception to August 2014. The Ovid and Springer search engines were also searched for relevant studies. Article language was limited to English. For the search terms, we combined either "visceral pleural," "invasion," "involvement," "PL1," "PL2," "VPI," or "prognostic factor" with "non-small cell lung cancer" or "NSCLC" in all fields. Additionally, the reference lists of relevant publications were subsequently searched as a supplement.

Study Eligibility

Two reviewers (L. J. and W. L.) independently screened article abstracts generated by the search. They first retrieved potentially relevant studies and then determined study eligibility. Eligible studies for the present meta-analysis compared patients given a histologic diagnosis of node-negative nonmetastatic NSCLC with VPI with those without VPI. In this study, we denoted VPI as either PL1 (a tumor extending beyond the elastic layer of the visceral pleural but is not exposed on the pleural surface) or PL2 (a tumor exposed on the pleural surface but does not involve adjacent anatomic structures).[9] In cases of duplicate datasets between studies, only the study with the latest results was included. All publications were limited to human subjects. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded. Studies in < 10 patients with VPI were also excluded.

Data Extraction

The full-text articles were reviewed and data extracted by two independent authors (J. S. and X. S.). Discrepancies were resolved by discussion and consensus with a third author. Extracted data included publication details, sample size, tumor histologic type, tumor size, T stage, 5-year overall survival, surgical procedures, lymph node dissection strategies, adjuvant therapy, and neoadjuvant therapy. For studies that did not numerically present survival outcomes, we measured the survival rates on Kaplan-Meier graphs generated by Engauge Digitizer version 4.1 software (http://digitizer.sourceforge.net).

Statistical Analysis

The meta-analysis was conducted using RevMan 5.1.6 software (Cochrane Collaboration). ORs were calculated for all outcomes. The χ^2 test was used to evaluate the presence of statistically significant heterogeneity across the studies, and the inconsistency index (I^2) was used to quantify the amount of heterogeneity.[10] We predefined heterogeneity as low (25%-49%), moderate (50%-74%), and high (75%-99%). Study-level data were pooled using a random-effects model. The significance of the OR was determined by the Z-test along with 95% CIs. Publication bias was assessed by funnel plot. $P < .05$ was considered statistically significant.

Results

Study Description

A total of 1,928 articles were found after the initial literature search, of which 1,194 were excluded for the following reasons: review articles, comments and editorials, letters to the editor, case reports, expert opinions, and guidelines. After title and abstract screening, 497 additional articles were excluded due to evaluation in animals or a population with types of cancers other than NSCLC. Studies in patients with advanced lung cancer, in which VPI was not classified in detail, and without a comparison between a VPI and no-VPI group were excluded. Thirteen articles were identified as eligible for the final meta-analysis (Fig 1).

The combined population of the 13 included studies was 27,171. All patients included in the present comparisons were given a diagnosis of node-negative nonmetastatic NSCLC. The histologic types were adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others (Table 1). Among the 27,171 patients, 5,821 had VPI (PL1, PL2, or both). Tumor size and VPI were confirmed by pathology after surgery. The surgical procedures included lobectomy, wedge resection, pneumonectomy, segmentectomy, and bilobectomy. David et al[8] and Tao et al[12] performed only lobectomy, and the surgical procedures of Maeda et al[18] and Kawase et al[15] were not reported. Lymph node dissection strategies, the use of neoadjuvant therapy, and follow-up are shown in Table 2. Ten of the included studies presented 5-year overall survival, and

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