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Prognostic Significance of Visceral Pleural Involvement in Early-Stage Lung Cancer

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BACKGROUND: Visceral pleural invasion (VPI) may impact non-small cell lung cancer (NSCLC) survival. However, previous studies are mixed as to whether VPI is an independent prognostic factor in early-stage cancers and whether its effect is size dependent. In the current American Joint Committee on Cancer (AJCC) staging system, VPI leads to upstaging of cancers < 3 cm but not of those 3 to 7 cm in size.

METHODS: Using the Surveillance, Epidemiology, and End Results (SEER) registry, we identified 16,315 patients with stage I-II NSCLC treated with lobectomy. We used the Kaplan-Meier method and Cox regression to assess the association of VPI with lung cancer-specific (primary outcome) and overall survival. Based on these results, we created a revised VPI staging classification.

RESULTS: Overall, 3,389 patients (21%) had VPI. Kaplan-Meier analysis stratified by tumor size showed worse cancer-specific survival in patients with VPI ($P < .0001$). VPI was independently associated with decreased lung cancer-specific survival (hazard ratio, 1.38; 95% CI, 1.29-1.47) after controlling for tumor size and other confounders; this effect was not size dependent. In our revised classification, tumors < 7 cm with VPI were upstaged to the next T category.

CONCLUSIONS: VPI is a prevalent finding associated with worse prognosis in early-stage lung cancer, even among patients with tumors > 3 cm, a factor not captured in the current staging system. Patients with VPI may be considered candidates for more aggressive treatment.

CHEST 2014; 146(6):1619-1626

Manuscript received January 23, 2014; revision accepted June 4, 2014; originally published Online First July 17, 2014.

ABBREVIATIONS: AJCC = American Joint Committee on Cancer; CSE = Collaborative Staging Extension; HR = hazard ratio; LN = lymph node; NSCLC = non-small cell lung cancer; SEER = Surveillance, Epidemiology, and End Results; VPI = visceral pleural involvement

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Part of this article was presented in abstract form at the American Thoracic Society International Conference, May 19, 2014, San Diego, CA.

FUNDING/SUPPORT: The authors report to *CHEST* that no funding or other support was received for this study.

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DOI: 10.1378/chest.14-0204

Accurate staging of lung cancer is critical for optimizing treatment decisions, communicating prognosis, and determining eligibility for clinical trials. Tumor spread to the visceral pleura has been recognized as a poor prognostic factor in non-small cell lung cancer (NSCLC).[1-4] Consequently, visceral pleural involvement (VPI) has been incorporated into the American Joint Committee on Cancer (AJCC) TNM staging system alongside tumor size.[5] According to these criteria, tumors < 3 cm that would otherwise be classified T1a (< 2 cm) or T1b (2-3 cm) disease based on size alone are considered to be equivalent to more advanced tumors (T2a; 3-5 cm) if they extend into the visceral pleura. Conversely, for larger tumors (ie, > 3 cm), VPI does not result in upstaging.[5]

Several studies have evaluated whether VPI is an independent prognostic factor in patients with early-stage NSCLC, with varying results.[2,6-20] Single-center and multicenter series, as well as analyses of patients enrolled in a clinical trial, found that VPI confers worse prognosis among resected tumors < 7 cm.[2,9,12,15,17,18,20] However, the prognostic significance of VPI was not confirmed in adjusted analysis in many of these studies. In contrast, several other studies showed either no impact of VPI on prognosis, or a differential effect based on the size of the tumor.[6,7,11,12,16,19] Thus, the independent prognostic significance of VPI, as well as its proper role in the staging of these cancers, remains unclear. In this population-based study, we used data from a large cohort of patients with surgically resected stage I and II NSCLC to better characterize the prognostic impact of VPI in tumors < 7 cm and to refine the staging of these cancers.

Materials and Methods

We used data from the latest release of the Surveillance, Epidemiology, and End Results (SEER) registry.[21] SEER is a network of cancer registries that covers approximately 28% of the population of the United States and collects data on all new cases of cancer in its coverage regions.[22] From SEER, we identified all incident cases of histologically confirmed NSCLC diagnosed between 2004 and 2010. The study included patients for whom NSCLC was their first and only primary malignancy, who had tumors < 7 cm, without lymph node (LN) involvement (N0) or distant metastasis (M0), and who underwent lobectomy. We excluded patients diagnosed on autopsy or death certificate data, as well as cases with missing tumor size and stage information. We further excluded patients with tumors < 3 cm but classified as having T2 disease due to hilar atelectasis or obstructive pneumonitis, patients with T3 or T4 disease regardless of tumor size, and patients treated with preoperative radiotherapy (due to concerns about possible understaging).

SEER reports data on sociodemographic characteristics, including age, sex, race/ethnicity, and marital status. Cancer information includes year of diagnosis, tumor location (upper lobe, middle lobe, lower lobe, or central), and histology (adenocarcinoma, large-cell carcinoma, squamous cell carcinoma, or other). The registry includes detailed pathologic staging data collected within 4 months of diagnosis or within completion of the first course of treatment.[23,24] Data are available regarding local tumor extension and size, LN involvement, and presence or absence of systemic metastasis. TNM data are also provided according to the AJCC staging system. Based on this classification, cases were grouped according to tumor size into the following categories: < 2 cm, 2 to 3 cm, 3 to 5 cm, and 5 to 7 cm.

The presence of VPI was ascertained using Collaborative Staging Extension (CSE) codes (410, 420, 430, and 450). Of note, VPI cases prior to 2010 were classified using the CSE code 450, which includes both VPI and extension to the pulmonary ligament (ie, the fold of parietal pleura that forms and extends inferiorly from the hilum). In 2010, SEER introduced a distinct CSE code (440) for pulmonary ligament involvement. Of the 25,891 NSCLC cases diagnosed in 2010, 2,074 (8.01%) were coded as having VPI (CSE codes 410, 420, 430) compared with only 9 (0.03%) identified as having pulmonary ligament involvement (CSE code 440). Moreover, all nine of these cases were excluded based on other cohort selection criteria. Therefore, we inferred that the number of pulmonary ligament cases among patients with CSE code 450 prior to 2010 included in the study was negligible, suggesting minimal misclassification.

SEER reports data on surgical treatment and radiation therapy use during the first course of cancer-directed treatment. Patients undergoing lobectomy were identified using SEER surgical codes 30 through 48. Data are also provided regarding the number of LNs sampled during surgery. Radiotherapy and radiation-surgery sequence codes were used to ascertain whether patients underwent postoperative external beam radiotherapy. SEER does not report information about chemotherapy use, due to concerns about misclassification.

The primary study outcome was lung cancer-specific mortality, as the study goal was to assess the impact of VPI on lung cancer prognosis; secondary analyses used overall survival. Survival time was calculated as the number of months from cancer diagnosis until death or last follow-up (December 31, 2010) for censored observations. Cause of death was coded by SEER using information extracted from death certificate data. Patients who died of non-lung cancer causes were classified as censored at the date of death in analyses of lung cancer-specific survival.

Statistical Analysis

Differences in the baseline characteristics of patients with and without VPI were compared using t tests or χ^2 test, as appropriate. The unadjusted association of VPI with survival was assessed using Kaplan-Meier analysis stratifying the sample by tumor size categories (< 2 cm, 2-3 cm, 3-5 cm, and 5-7 cm); tumors > 7 cm or of T3 status were included for comparison. Adjusted analysis was conducted using a Cox proportional hazards model to assess the association between VPI and survival after controlling for age, sex, race/ethnicity, marital status, histology, tumor size, number of LNs examined, and use of adjuvant radiotherapy. The analysis was repeated including interactions between tumor size and VPI to assess if the effect of pleural involvement varied across different tumor size categories. To combine groups with similar prognoses, we fitted a Cox model including one dichotomous indicator for each tumor size category and VPI status (ie, < 2 cm without VPI, < 2 cm with VPI, etc). Based on the findings of this analysis, we grouped cancers with overlapping hazard ratios (HRs), thereby developing a revised prognostic system. Results were deemed significant at a two-sided P value < .05. All statistical analysis was conducted using SAS software, version 9.2 (SAS Institute Inc). The study was determined to be exempt research by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.