Lymphovascular Invasion in Non–Small-Cell Lung Cancer

Implications for Staging and Adjuvant Therapy

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Background: Lymphovascular space invasion (LVI) is an established negative prognostic factor and an indication for postoperative radiation therapy in many malignancies. The purpose of this study was to evaluate LVI in patients with early-stage non–small-cell lung cancer, undergoing surgical resection.

Methods: All patients who underwent initial surgery for pT1-3N0-2 non–small-cell lung cancer at Duke University Medical Center from 1995 to 2008 were identified. A multivariate ordinal regression was used to assess the relationship between LVI and pathologic hilar and/or mediastinal lymph node (LN) involvement. A multivariate Cox regression analysis was used to evaluate the relationship of LVI and other clinical and pathologic factors on local failure (LF), freedom from distant metastasis (FFDM), and overall survival (OS). Kaplan-Meier methods were used to generate estimates of LF, FFDM, and OS in patients with and without LVI.

Results: One thousand five hundred and fifty-nine patients were identified. LVI was independently associated with the presence of regional LN involvement ($p < 0.001$) along with lobar (versus sublobar) resections ($p < 0.001$), and an open thoracotomy (versus video-assisted thoracoscopic surgery). LVI was not independently associated with LF on multivariate analysis (hazard ratio [HR] = 1.23, $p = 0.25$), but was associated with a lower FFDM (HR 1.52, $p = 0.005$) and OS (HR 1.26, $p = 0.015$). In addition, multivariate analysis showed that LVI was strongly associated with increased risk of developing distant metastases (HR = 1.75, $p = 0.006$) and death (HR = 1.53, $p = 0.003$) in adenocarcinomas but not in squamous carcinomas.

Conclusions: LVI is associated with an increased risk of harboring regional LN involvement. LVI is also an adverse prognostic factor for the development of distant metastases and long-term survival.

Key Words: Lymphovascular invasion, Lung cancer, Local failure.

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Stage is currently the dominant factor affecting adjuvant-treatment recommendations in resected non–small-cell lung cancer (NSCLC).[1] Practice guidelines have been profoundly influenced by three recent randomized trials demonstrating a survival benefit with the addition of adjuvant chemotherapy.[2–4] This benefit has been largely confined to N1 to N2 disease,[5] although subset analyses have suggested that chemotherapy is also advantageous for patients with larger stage I tumors.[4,6] The role of postoperative radiation therapy is less well defined, but is generally recommended for patients with involved mediastinal lymph nodes (LNs) (N2) or positive surgical margins.

Elucidation of high-risk pathologic features in resected NSCLC may help to further stratify patients into risk groups, allowing for further refinement of adjuvant treatment recommendations. For example, lymphovascular space invasion (LVI) is an adverse prognostic factor for numerous solid tumors. Furthermore, the presence of LVI is an independent indication for postoperative radiation therapy in several epithelial malignancies, including cervix,[7] endometrial,[8] vulvar,[9] and head and neck cancers.[10]

Several studies have demonstrated that LVI is also a poor prognostic factor for recurrence-free and overall survival (OS) in NSCLC.[11–15] One recent study has demonstrated that presence of LVI in a biopsy specimen is an independent risk factor for death and metastatic progression for patients treated with definitive chemoradiotherapy.[16] However, the influence of LVI on adjuvant-treatment recommendations after resection is unclear. Current NCCN guidelines are somewhat ambiguous, stating that the presence of LVI is considered "high-risk".[17] Whether LVI increases the risk of local or distant recurrence (or both) is unknown. In addition to this question, we also sought to investigate the association between the presence of LVI in the primary tumor and the risk of harboring disease in hilar and/or mediastinal LNs.

METHODS

This Institutional Review Board-approved study identified all patients who underwent surgery for T1-3N0-2 NSCLC at Duke University between 1995 and 2008. Patients were excluded if they received preoperative chemotherapy and/or preoperative radiation therapy, or had a prior history of lung cancer. Medical records and pertinent radiological imaging were reviewed to characterize each patient's demographic information, obtain surgical and pathological details, and

score patterns of failure after surgery. The pathologic staging of patients in this cohort reflects the updated tumor, node, metastasis staging for NSCLC.[1]

Between 1995 and 1997, lung tumor specimens were interpreted by multiple pathologists at Duke University Medical Center. After 1998, all specimens were interpreted by a single pathologist with a special interest in pulmonary pathology (TAS). Hematoxylin and eosin stains were performed on all specimens. LVI was reported when tumor cells were demonstrated on histologic examination within lymphatic channels, veins/venules, and/or arteries/arterioles.

Patterns of failure were assessed by means of follow-up imaging studies and information obtained from procedures such as computed-tomography (CT)–guided transthoracic biopsies, bronchoscopy, endobronchial ultrasound, and mediastinoscopy, etc. A local failure (LF) was scored when disease recurred at the surgical resection margin or regional LNs (ipsilateral hilum and/or mediastinum). Nodal failures in the ipsilateral hilum or mediastinum were defined as a new or enlarging LN of 1 cm or more on short axis on CT, and/or hypermetabolic on positron emission tomography imaging, which in the patient's subsequent clinical follow-up was consistent with disease progression. All cases of possible local and distant recurrence were reviewed by two authors (CK and JB/KH) to ensure accuracy. All patients had routine postsurgical surveillance with imaging studies, including chest CT, but the frequency and choice of imaging modality was not standardized.

Statistical Analysis

The Mann-Whitney *U* test was used to test for an association between LVI and the presence of involved regional LNs. Primary tumor size, type of surgery (wedge/segmentectomy versus lobectomy/pneumonectomy), thoractomy versus a video-assisted thoracoscopic surgical (VATS) approach, histology, visceral pleural invasion, grade, and primary tumor location (right versus left, upper/middle versus lower) were also included in this assessment. Factors with a p value of 0.1 or less were included in a multivariate ordinal regression. Patients without regional LN sampling/dissection were excluded from this part of the analysis.

Univariate and multivariate analyses were also performed to examine clinical and pathological factors associated with LF, development of distant metastases (DM), and OS, including LVI, type of surgical resection (thoracotomy versus VATS), size of primary tumor, number of hilar LNs sampled, number of hilar LNs involved, number of mediastinal LN stations sampled, number of mediastinal LNs involved, tumor histology (squamous/large-cell versus others),[18] tumor grade, visceral pleural invasion, stage, adjuvant chemotherapy, age, and sex. Factors with a p value of 0.1 or less on univariate analysis were included in the multivariate model. For the LF analysis, patients with positive margins and/or those receiving postoperative radiation were excluded. Univariate and multivariate analyses were also performed based on histology, with LF, DM, and OS examined separately in squamous-cell carcinomas and adenocarcinomas.

The Kaplan-Meier product-limit method[19,20] was used to estimate 5-year recurrence probabilities and confidence intervals, and comparisons were made via the log-rank test. When generating survival curves for patients with LVI versus no LVI, the patients with unknown LVI status were grouped into the "no LVI" category. Progression-free survival was calculated from the date of surgery to date of treatment failure (defined as local and/or distant recurrence, development of a second primary lung cancer, or death from any cause). Time to LF and time to distant failure (DF) were calculated from the date of surgery to date of local or distant recurrence, respectively. For these analyses, patients developing what was felt to be a second primary lung cancer were censored on the date the second primary malignancy was diagnosed. Local and distant recurrences were scored independently (i.e., patients developing a distant recurrence were not censored for LF, but were assessed for LF until the date of last follow-up or death).

RESULTS

Between 1995 and 2008, 1559 patients met the inclusion criteria. Median follow-up for all patients was 34 months and for survivors it was 40 months. Patient characteristics are reported in Table 1. The majority (98%) had hilar and/or mediastinal LN sampling/dissection at the time of surgery. The majority of patients were stage I, with 41% of patients with pathologic stage IA disease and 26% of patients with stage IB disease. Presence of LVI was noted in 23% of the patients.

LVI and Regional LN Involvement

Patients with no regional LN sampling were excluded from this analysis (n = 33). Of the remaining 1526 patients, 1219 were pathologic N0, 235 patients were pathologic N1, and 72 patients were pathologic N2.

Factors associated with regional LN involvement on univariate analysis included LVI, increasing size of the primary tumor, lobar versus sublobar resection, thoracotomy versus VATS approach, visceral pleural invasion, and squamous/large-cell histology. On multivariate ordinal regression, the presence of LVI ($p < 0.001$), thoracotomy ($p < 0.001$), and lobar resections ($p < 0.001$) continued to be significant predictors of harboring pathologically involved regional LNs (Table 2).

In patients who underwent lobectomy or pneumonectomy (n = 696), the risk of harboring ipsilateral hilar LN disease was 36% versus 21% ($p < 0.001$) and the risk of harboring mediastinal LN disease was 12% versus 5% ($p < 0.001$), for patients with and without LVI, respectively. Furthermore, LVI was associated with increasing number of positive LNs ($p < 0.001$), with the median number of positive LNs equal to one (interquartile range 1–2) for patients without LVI and two (interquartile range 1–4) for patients with LVI.

LVI and Risk of Local Recurrence

For this analysis, patients with positive surgical margins and those receiving postoperative radiation were excluded, leaving 1458 evaluable patients. On univariate analysis, LVI was associated with statistically significant increased risk of LF with Kaplan-Meier estimates of 5-year local control of 79% versus 71% (p = 0.001) (Fig. 1). However, on multivariate analysis this association was lost (Table 4).