

Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤ 2 cm) non–small cell lung cancer

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Objective: Successful pulmonary wedge resection for early-stage non–small cell lung cancer requires a pathologically confirmed negative margin. To date, however, no clear evidence is available regarding whether an optimal margin distance, defined as the distance from the primary tumor to the closest resection margin, exists. Toward addressing this gap, we investigated the relationship between the margin distance and local recurrence risk.

Methods: We reviewed all adult patients who had undergone wedge resection for small (≤ 2 cm) non–small cell lung cancer from January 2001 to August 2011, with follow-up through to December 31, 2011. The exclusion criteria included other active noncutaneous malignancies, bronchoalveolar carcinomas, lymph node or distant metastases at diagnosis, large cell cancer, adenosquamous cancer, multiple, multifocal, and/or metastatic disease, and previous chemotherapy or radiotherapy. Using Cox regression analysis, we examined the relationship between the margin distance and interval to local recurrence, adjusting for chronic obstructive pulmonary disease, forced expiratory volume in 1 second, smoking, diabetes, tumor size, tumor location, surgeon, open versus video-assisted thoracoscopic surgery, and whether the lymph nodes were sampled.

Results: Of 557 consecutive adult patients, 479 met our inclusion criteria. The overall, unadjusted 1- and 2-year local recurrences rate was 5.7% and 11.0%, respectively. From the adjusted analyses, an increased margin distance was significantly associated with a lower risk of local recurrence ($P = .033$). Patients with a 10-mm margin distance had a 45% lower local recurrence risk than those with a 5-mm distance (hazard ratio, 0.55; 95% confidence interval, 0.35-0.86). Beyond 15 mm, no evidence of additional benefit was associated with an increased margin distance.

Conclusions: In wedge resection for small non–small cell lung cancer, increasing the margin distance ≤ 15 mm significantly decreased the local recurrence risk, with no evidence of additional benefit beyond 15 mm. (*J Thorac Cardiovasc Surg* 2014;147:1169-77)

Lung cancer now represents the leading cause of cancer deaths for men and women.¹ Currently, complete surgical resection is the ideal treatment modality for patients with early-stage non–small cell lung cancer (NSCLC). Among the different surgical options, wedge resection has been the most common limited resection technique used to remove NSCLC,²⁻⁶ although lobectomy and lymph node

dissection are currently the standard treatment for small peripheral resectable NSCLC.⁷ Similarly, many studies on the changing histopathologic patterns of lung cancer have been reported. It has been stated that adenocarcinoma has replaced squamous cell carcinoma as the most frequent histologic subtype for both genders and all races. Recent data have also suggested that the rate of lung cancer incidence is greater in women than in men.⁸ For wedge resection, the status of the margin and the distance of the tumor from the resection margin have been major concerns regarding local recurrence.⁹⁻¹⁵ In an ongoing phase III randomized trial of lobectomy versus sublobar resection for small peripheral NSCLC (Cancer and Leukemia Group B trial 140503), it has been strongly recommended to confirm the absence of disease in the wedge margin using histologic or cytologic frozen section analysis. When performing lung excision for lung cancer, it is mandatory that malignant cells not be left in the residual pulmonary parenchyma. However, several other factors during lung cancer surgery will be important in determining the survival and recurrence outcomes. These have included

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Abbreviations and Acronyms

CI	= confidence interval
HR	= hazard ratio
NSCLC	= non-small cell lung cancer
VATS	= video-assisted thoracoscopic surgery

the degree of histologic differentiation, tumor size, nodal involvement, and visceral pleural invasion.^{9,16,17} Within this framework, however, a paucity of published information is available on the association between margin distance and the risk of local recurrence and what constitutes an optimal margin distance, if such exists, in pulmonary wedge resection. Specifically, no clear guidelines are available in the current data regarding the margin distance from the primary tumor to the closest margin for wedge resection for small, localized tumors. The present study, therefore, aimed to characterize the association between the margin distance in patients who had undergone wedge resection for small (≤ 2 cm) NSCLC and the local recurrence risk. To address this gap, we analyzed detailed follow-up data from a cohort of patients who had undergone successful pulmonary wedge resection for early-stage NSCLC.

METHODS**Study Population**

With institutional review board approval, we reviewed the records for all adult patients who had undergone elective surgical resection for NSCLC tumors ≤ 2 cm at the Brigham and Women's Hospital (Boston, Mass) from January 2001 to August 2011. For the present study, we restricted our attention to pulmonary wedge resections only. All such surgeries were considered, regardless of whether they had been performed by way of thoracotomy or video-assisted thoracoscopic surgery (VATS). To focus our attention on patients with primary NSCLC tumors, we applied the following exclusion criteria: previous major lung resection, distant previous thoracic radiotherapy, neoadjuvant therapy before resection, other active noncutaneous malignancies, pure bronchoalveolar carcinomas, lymph node or distant metastases at diagnosis, multicentric cancers, large cell, adenocarcinoma, and multiple, multifocal, and/or metastatic cancer, and previous chemotherapy and/or radiotherapy. Figure 1 provides an overview of the study population selection and the effect of the various exclusion criteria.

Data Sources

The demographic, clinical, medical and surgical history, and surgical, pathologic, and intra- and postoperative complication data for all patients were abstracted from the hospital clinical records. Using the institutional guidelines, the patients were followed up every 4 months for the first 2 years, every 6 months for years 2 to 5, and annually thereafter. At abstraction, all variables were comprehensively audited. The original imaging (chest radiography and computed tomography) studies were reviewed by a chest radiologist for designation of the location within the hemithorax and the proximity to any major vessels. Vital status as of December 31, 2011 was determined from the hospital records and through the Social Security Death Index.

Local Recurrence

The primary outcome of interest for the present study was local recurrence. In accordance with Martini and Melamed,¹⁸ local recurrence was defined as a tumor of the same histologic type occurring within the same lobe (or draining hilum and/or mediastinum) or a tumor of the same histologic type in a different lobe or lung with carcinoma in the lymphatics common to both, and/or extrapulmonary metastases. Disease recurrence was evaluated by clinical follow-up examination, including chest computed tomography, with the date of the first local recurrence documented. Patients alive on December 31, 2011 who had not experienced local recurrence were administratively censored.

Margin Distance

The margin distance was defined as the distance from the primary tumor to the closest stapled resection margin. The distance was measured by the pathologist, according to a totally deflated lung, and recorded on the final pathology report. Because our interest was in the association between the margin distance and the local recurrence risk, we restricted our analyses to those patients with a confirmed negative margin. Patients with a positive malignant margin were excluded from the analyses, just as were patients with margin distances of < 1 mm and those with missing margin data (Figure 1).

Statistical Analysis

The primary outcome for the present study was the interval to local recurrence, with the margin distance the primary exposure of interest. The distributions of the key covariates were calculated and summarized, stratified by the margin distance (1-5, 6-10, 11-15, and 16-30 mm). Continuous covariates (eg, margin distance, age, and percentage of forced expiratory volume in 1 second) were categorized for the purposes of description but were left in their continuous form for modeling.

Multivariable Cox regression analysis was used to model the interval to local recurrence. We adjusted for covariates that were thought, a priori, to be strong candidates as potential confounders of the association between the margin distance and the interval to local recurrence. These included chronic obstructive pulmonary disease, preoperative percentage of forced expiratory volume in 1 second, smoking status, diabetes, tumor size, tumor lobe location, location with the hemithorax (inner vs outer half), surgery type (thoracotomy vs VATS), and whether the lymph nodes had been sampled. The proximity to a major vessel was not included, because it correlated highly with the location in the hemithorax. All Cox models were adjusted for surgeon by stratification of the baseline hazard function. To ensure a stable estimation of these effects, we restricted attention to operations performed by 8 surgeons who had ≥ 10 observations in our data set; this resulted in the exclusion of 11 surgeries performed by low-volume surgeons (Figure 1). For our analyses, the follow-up period was restricted in the analysis to ≤ 3 years after surgery owing to the scarceness of data after that point, possibly invalidating the proportional hazards assumption of the Cox model. Finally, despite this restriction, a number of patients died during the follow-up period. To investigate the effect of death on our results, we repeated all our modeling using a composite outcome of local recurrence-free survival, in which we considered the interval to the first of death or local recurrence.

In the absence of an a priori hypothesis regarding the form of the margin distance and interval to local recurrence association, we modeled the association using regression splines to allow for a nonlinear association.¹⁹ For the latter, a single knot was used and set to be the midpoint of the observed margin distance distribution. To evaluate the statistical significance of the overall association between the margin distance and local recurrence risk, we used an omnibus Wald test that jointly evaluated all parameters in the spline specification. All analyses were performed using R, version 2.15 (R Foundation for Statistical Computing, Vienna, Austria).²⁰ All reported *P* values are 2-sided.

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