Detection of Recurrence Patterns After Wedge Resection for Early Stage Lung Cancer: Rationale for Radiologic Follow-Up

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Background. **Wedge resection for selected patients with early stage non-small cell lung cancer is considered to be a valid treatment option. The aim of this study was to evaluate the recurrence patterns after wedge resection, to analyze the survival of patients under routine follow-up, and to recommend a follow-up regimen.**

Methods. **A retrospective analysis was done of 446 consecutive patients between May 2000 and December 2012 who underwent a wedge resection for clinical stage I non-small cell lung cancer. All patients were followed up with a computed tomography scan with or without contrast. The recurrence was recorded as local (involving the same lobe of wedge resection), regional (involving mediastinal or hilar lymph nodes or a different lobe), or distant (including distant metastasis and pleural disease).**

Results. **Median follow-up for survivors (n = 283) was 44.6 months. In all, 163 patients died; median overall survival was 82.6 months. Thirty-six patients were diagnosed with new primary non-small cell lung cancer, and 152 with recurrence (79 local, 45 regional, and 28 distant). There was no difference in the incidence of recurrence detection detected by computed tomography scans with versus without contrast ($p = 0.18$). The cumulative incidence of local recurrences at 1, 2, and 3 years was higher than the cumulative incidence for local, regional, and distant recurrences: 5.2%, 11.1%, and 14.9% versus 3.7%, 6.6%, and 9.5% versus 2.3%, 4.7%, and 6.4%, respectively. Primary tumor diameter was associated with local recurrence in univariate analysis.**

Conclusions. **Wedge resection for early stage non-small cell lung cancer is associated with a significant risk for local and regional recurrence. Long-term follow-up using noncontrast computed tomography scans at consistent intervals is appropriate to monitor for these recurrences.**

(Ann Thorac Surg 2016;■:■–■)

A lobectomy is considered to be the optimal treatment for patients with clinical stage I non-small cell lung cancer (NSCLC) [1]. In these patients, there is a 20% to 30% risk for disease recurrence, and recurrences usually present as distant disease in the first couple of years after surgery, rarely presenting at an earlier stage [2, 3]. Given the preponderance of distant recurrences and the lack of curative treatments, some have questioned the benefit of close surveillance after surgical treatment [4]. Nonetheless, the National Comprehensive Cancer Network guidelines recommend close follow-up after surgery with eventual transition to yearly screening [5].

Treatment of clinical stage I NSCLC with a wedge resection, however, has been mostly reserved for patients with poor lung function, multiple comorbidities, or previous lung surgery [6]. The reluctance to use this approach in fitter patients has been due to concerns about a higher risk of local and local-regional failure. Yet with the increasing use of computed tomography (CT) screening, there will be an expected tripling in the detection of early stage NSCLC [2, 7]; this has ignited a renewed interest for the broader use of sublobar resections as a possible treatment option. This interest has resulted in an ongoing prospective randomized trial (Cancer and Leukemia Group B 140503) that will compare the results of sublobar resections to lobectomy in early stage lung cancer.

The timing and benefit of postoperative surveillance in patients who undergo more limited resections is unknown; the expectation, however, would be that if there is a higher incidence of curable disease detected radiographically after surgery, the potential benefit of screening should be greater [8]. Although some studies in these patients have shown that follow-up CT scans can be useful in detecting a new primary lung cancer, the data are less clear regarding detection of recurrences and the impact on overall survival [9, 10]. Indeed, some studies report that routine CT surveillance failed to detect asymptomatic recurrences or improve survival [11, 12].

The primary aim of this study was to evaluate the patterns of recurrence among patients with early clinical

Accepted for publication April 20, 2016.

Presented at the Fifty-second Annual Meeting of The Society of Thoracic Surgeons, Phoenix, AZ, Jan 23–27, 2016.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.04.056

stage NSCLC who were treated with a wedge resection, to analyze the survival of patients under routine follow-up, and to provide a rational CT scan surveillance regimen based on these patterns.

Material and Methods

Patient Population

We performed a retrospective analysis of all patients between May 2000 and December 2012 who underwent a wedge resection for clinical stage I NSCLC. Patients with tumor completely excised and with negative margin were included in the analysis. Lymph nodes were not routinely sampled: 56% had no lymph node station sampled; 21% had one station sampled; 20% had two to three stations sampled; and 3% had four to six stations removed.

Indications for a wedge resection included patients with peripheral lesions less than 2 cm (n = 364), previous anatomic lung resection (n = 115), and poor pulmonary function (n = 24), cardiac function (n = 80), or chronic renal failure (n = 19). Staging was performed in accordance with the cancer staging manual, seventh edition, of the American Joint Commission on Cancer [13]. Patients with previous surgically resected NSCLC were considered to have a new primary and were included in the study if the interval was more than 2 years and if there was no pathologic correlation between these two cancers [14]. Reasons for exclusion included the following: recurrent lung cancers (n = 49); synchronous cancers (n = 154); any neoadjuvant treatment (n = 16); any adjuvant treatment (n = 31); completion lobectomy (n = 15); satellite nodule in the same lobe (n = 46) or in other lobes (n = 40); incomplete resection, defined as microscopic or macroscopic residual tumor or margins involved by the tumor (n = 135); carcinoid (n = 69); and pure ground glass lesions with no solid component (n = 38). In addition, patients who had scans done at an outside facility (n = 44) were excluded if we were unable to review the images. Follow-up was conducted until April 2015. The study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board.

Computed Tomography Follow-Up Protocol

All patients were regularly followed up with a CT scan either with or without contrast (by physician choice). Scans were performed every 3 to 6 months for the first 2 years, also according to physician preference, and then every 12 months. Other modalities of surveillance, such as positron emission tomography, bronchoscopy, or bone scans, were not routinely performed. Each patient received also a physical examination and interval history at the time of each scan.

Recurrence and New Primary Lung Cancer

The type of recurrence, date of recurrence, imaging modality, and presence of symptoms were collected. Recurrence was classified as local if limited to the same lobe of the resection, regional if involving the mediastinal or hilar lymph nodes or a different ipsilateral lobe from the location of the wedge resection, or distant if including distant metastasis to other organs and diffuse pleural disease. Second primary tumors were recorded using the previously described criteria by Martini and Melamed [14]. Recurrences were documented with a biopsy and compared with the previous surgical specimen. A positron emission tomography scan and brain magnetic resonance imaging were used to complete the assessment of any recurrence.

Statistical Analysis

Descriptive statistics such as frequencies, medians, and ranges were utilized for patient and tumor characteristics. The primary endpoint was recurrence, which was analyzed using competing risks methods. New primary and death without recurrence or new primary were considered competing events. Time was calculated from date of surgery until recurrence, new primary, or death (whichever came first). Patients who were alive without recurrence or new primary were censored at the date of last available follow-up. Gray's test was used to compare the cumulative incidence functions of subgroups in univariate analyses. The univariate associations of patient and tumor characteristics with local recurrence were also analyzed using competing risks methods. In addition to new primary and death without recurrence or new primary, regional recurrence and distant recurrence were also competing events.

Overall survival for the whole cohort was estimated from date of surgery until death using the Kaplan-Meier method. Overall survival for the comparisons of patients who had a recurrence or had a second primary lung cancer were calculated from date of documented recurrence or second primary lung cancer until death. Patients who did not die during the study period were censored at date of last available follow-up.

All p values were two-sided, and p less than 0.05 was considered significant. All statistical analyses were done in R (version 3.2.0; The R Foundation for Statistical Computing, Vienna, Austria), including the "survival" and "cmprsk" packages [15, 16].

Results

Demographics

Four hundred and forty-six patients were included in the analysis. Median age was 70 years, and female patients represented 57% of the study population. One hundred ten patients had a previous NSCLC that was treated surgically and presented at this time with a biopsy-proven new primary NSCLC, and were consequently considered for limited surgical resection. Patient characteristics are summarized in Table 1. Median follow-up for survivors (n = 283) was 44.6 months (range, 0.8 to 145.4); 163 patients died, with median overall survival of 82.6 months. Most follow-up CT scans were performed without contrast (n = 318, 71%). During the first 2 years