Patterns of Distant Metastases After Surgical Management of Non–Small-cell Lung Cancer

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Abstract

The patterns of distant metastatic progression after surgery for non–small-cell lung cancer (NSCLC) have not been well described. The present analysis of 1719 surgically resected NSCLC patients found that 50% of those who developed metastases did so in ≤ 3 locations, with an improved prognosis compared with those with > 3 metastases. This supports efforts to understand the biology of oligometastases and develop novel treatment paradigms.

Background: Patients with limited metastases, oligometastases (OMs), might have improved outcomes compared with patients with widespread distant metastases (DMs). The incidence and behavior of OMs from non–small-cell lung cancer (NSCLC) need further characterization. **Patients and Methods:** The medical records of patients who had undergone surgery for stage I-III NSCLC from 1995 to 2009 were retrospectively reviewed. All information pertaining to development of the first metastatic progression was recorded and analyzed. Patients with DMs were categorized into OMs (1-3 lesions potentially amenable to local therapy) and DM subgroups. **Results:** Of 1719 patients reviewed, 368 (21%) developed DMs with a median follow-up period of 39 months. A single lesion was diagnosed in 115 patients (31%) and 69 (19%) had 2 to 3 lesions (50% oligometastatic). The median survival from the DM diagnosis for oligometastatic and diffuse DM was 12.4 and 6.1 months, respectively (hazard ratio, 0.54; 95% confidence interval, 0.42-0.68; $P < .001$). Patients with a single metastasis had the longest median survival at 14.7 months. Younger age, OM, the use of chemotherapy for the primary tumor, and DM detection by surveillance imaging were independently associated with improved survival. **Conclusion:** DMs and OMs are common in surgically managed NSCLC. Overall survival appears to be prolonged with OM.

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Introduction

In the United States, an estimated 221,200 new cases of lung cancer and 158,040 lung cancer deaths will have occurred in 2015.[1] Of these cases, approximately 30% will have been clinical stage I-II, for which the 5-year survival ranges from 50% for stage IA disease to 25% for stage IIB disease.[2] Resection of the tumor-containing lobe is the preferred approach for medically operable early-stage non–small-cell lung cancer (NSCLC).[3] Despite the improved clinical outcomes with anatomically based surgery[4] and adjuvant or neoadjuvant chemotherapy,[5] recurrence is common.

The incidence of distant progression in surgically resected NSCLC has been well described. For example, in 1 analysis, the 5-year actuarial risk of any recurrence was 36%,[6] with 75% of recurrences being distant metastases (DMs) alone or combined with locoregional recurrence. However, the distribution of clinically apparent DMs after surgery has not been well described, including the state of limited metastases known as oligometastases (OMs). Although a small analysis of metastatic NSCLC patients reported that 50% of such patients had only 1 to 3 metastases limited to ≤ 3 organs,[7,8] it is not known whether this could be generalizable to definitively treated patients with subsequent distant progression.

An improved understanding of the number and distribution of metastases in NSCLC patients is important for the development of personalized cancer management strategies. Although the standard

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treatment of metastatic NSCLC is systemic therapy, the response rates for nontargeted therapies have been low. Furthermore, the most likely sites of progression after systemic therapy are at known metastatic sites.[7] Given that surgical and radiation series targeting limited NSCLC metastases have demonstrated high rates of treated metastasis control[9] and that a significant fraction of patients with aggressive treatment of metastatic disease will have long disease-free intervals,[10,11] a population of patients might exist for whom metastasis-directed therapy could be beneficial. Therefore, we sought to determine the pattern and number of metastases present at distant progression in a cohort of initially operable, primarily early-stage NSCLC patients. Additionally, we sought to determine whether the number of metastases and method of detection was prognostic.

Patients and Methods

The present institutional review board-approved study was performed by searching the Duke Comprehensive Cancer Center database for patients who had undergone surgery for NSCLC at Duke University from 1995 to 2009. REDCap electronic data capture tools were used for analysis. Patients who had presented with synchronous primary lung tumors or had a history of lung cancer were excluded. The patients' medical records and pertinent radiologic imaging were retrospectively reviewed to characterize the individual demographic information, surgical and pathologic details, use of preoperative or adjuvant therapy, and information pertaining to the development of distant metastatic progression.

Distant metastatic progression was defined as the appearance of new malignant lesions outside the locoregional thorax and/or mediastinum on standard imaging studies. New ipsilateral (in accordance with the American Joint Committee on Cancer Staging 6th edition during the study period) or contralateral pulmonary nodules were considered distant progression, and progression at the wedge resection line or bronchial stump was considered locoregional recurrence. New isolated pulmonary lesions were considered a second primary tumor if the clinicopathologic diagnostic criteria of Martini and Melamed[12] were met. Generally, this was first based on the histologic type (same vs. different). When the histologic type was identical, the interval between cancers, cancer location (different lobe or lung), and clinical situation (carcinoma in the lymphatics or extrapulmonary metastases) were considered. The reason for obtaining the imaging study leading to the diagnosis of DMs was categorized as routine surveillance, symptom workup, or unknown. Malignant lesions were confirmed by biopsy when clinically appropriate and/or by appropriate radiologic and/or metabolic imaging.

All sites of radiographically evident metastases were noted at the first distant progression. The sites of DM were categorized as parenchymal lung, liver, adrenal gland, bone, brain, extrathoracic lymph nodes, pleural/pericardial effusion, or other. Metastases were categorized as oligometastatic (1-3, potentially amenable to local therapy) and diffuse (> 3 or not potentially amenable to metastasis-directed therapy because of findings such as pleural/pericardial effusion). Oligometastatic lesions were further categorized as single versus 2 to 3 lesions. The ability to treat the metastases with metastasis-directed therapy was determined at the discretion of the investigators. However, in general, it was influenced by the sites in which metastasectomy or radiotherapy for palliation or cure have been well described. Information regarding the size of the metastases was recorded if available. Metastasis-free survival was defined as the time from the primary diagnosis to DM. The time to second progression was determined from the diagnosis of DM to subsequent progression, with progression defined as new or enlarging lesions, using the Response Evaluation Criteria In Solid Tumors,[13] when applicable. Overall survival was calculated from both the initial lung cancer diagnosis and the date of diagnosis of metastatic disease until death.

Statistical Analysis

Descriptive statistics were used to characterize the primary patterns of DM. The incidence of DM by site was the number of patients with DM at that site divided by the total number of patients with DMs. Univariate patient characteristics were evaluated with the Wilcoxon signed-rank test and χ^2 analysis for continuous and categorical variables, respectively. Fisher's exact test was used to compare the sites of involvement between oligometastatic and diffuse DM and also to test the effect of chemotherapy on the site of involvement. The Kaplan-Meier product limit method was used to assess metastasis-free survival, the time to second progression, and overall survival. A Cox proportional hazard multivariable model was created for both metastasis-free and overall survival in the DM patients. Two-sided *P* values were reported, unless otherwise stated. All statistical analyses were performed on the SAS platform, version 9.3 (SAS Institute Inc, Cary, NC).

Results

From the database records of 1719 consecutive patients, 368 (21%) developed DM and constituted our study cohort (Tables 1 and 2). DMs were detected by symptoms in 186 (51%), surveillance imaging in 151 (41%), and indeterminate in 31 (8%) patients. The median follow-up period from the initial lung cancer diagnosis for living patients in the entire and study cohorts was 39 months (range, 0-189 months) and 38 months (range, 2-189 months), respectively. Pretreatment positron emission tomography was used in 45% of the patients overall, with no significant difference in usage between groups. On univariate analysis, patients with DM were younger, had less squamous cell but more large cell histologic features, and had larger tumors with more advanced TN stages compared with those without DM (Table 1). Adjuvant chemotherapy and radiation therapy were given more often to patients who ultimately developed DMs.

The predominant mode of recurrence was DMs (Table 3). Local recurrence was significantly associated with metastatic disease, occurring in 174 of DM patients (47%) compared with 109 without DM (8%; $P < .0001$). In patients with both local and distant failure, most of these events were synchronous (124; 71%). The median time to developing DM was 12 months (range, 0-188 months), and the average number of metastatic sites was 1.6 ± 0.8 (range, 1-6).

We next categorized the location and number of DMs. The metastatic sites in order of decreasing frequency were bone (119; 32%), lung (116; 31%), brain (108; 29%), liver (67; 18%), adrenal gland (53; 15%), extrathoracic lymph nodes (45; 12%), pleural/pericardial effusion (28; 8%), and other (37; 10%). The use of neoadjuvant or adjuvant chemotherapy appeared to affect

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