Surgical Resection for Multifocal (T4) Non-Small Cell Lung Cancer: Is the T4 Designation Valid?

Jeffrey L. Port, MD, Robert J. Korst, MD, Paul C. Lee, MD, Amanda L. Kansler, MPH, Yaniv Kerem, BA, and Nasser K. Altorki, MD

Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Weill Medical College of Cornell University, New York

Background. **The current international staging system for lung cancer designates intralobar satellites as T4 disease. In this study, we sought to determine the impact of multifocal, intralobar non-small cell lung cancer (NSCLC) on patient survival and its potential relevance to stage designation.**

Methods. **We conducted a retrospective review of our thoracic surgical cancer registry from 1990 to 2005. Included were 53 patients with a resected lung cancer containing intralobar satellites detected preoperatively (n = 8) or in the resected specimen (n = 45). Patients with multicentric bronchioloalveolar cancer were excluded. All patients had an anatomic resection with mediastinal lymph node dissection. Median follow-up for the entire group was 31 months. Survival was calculated by the Kaplan-Meier method. A Cox proportional hazards regression model was performed to examine simultaneously the effects on overall survival of age, gender, nodal disease, number of satellite lesions, lymphatic invasion, and T status.**

Results. **The median age of the 53 patients with multifocal, intralobar (T4) disease was 68 years and 31 were women. Ten patients had more than one satellite lesion. Overall 5-year survival was 47.6% (95% confidence interval [CI], 27.36% to 65.30%) for all patients with resected intralobar satellites. Patients without nodal metastases had a 5-year survival of 58.4% (95% CI, 28.76% to 79.30%). The Cox regression identified female gender (adjusted hazard ratio [HR], 0.31; 95% CI, 0.10 to 0.96; $p < 0.04$) as a significant prognostic variable but only a trend towards significance for nodal status (adjusted HR, 2.3; 95% CI, .83 to 6.26; $p < 0.11$).**

Conclusions. **Patients with intralobar multifocal NSCLC detected in the resected specimen have a more favorable prognosis after surgical resection than might be predicted by their stage T4 designation. Five-year survival rates, especially in T4N0 patients, more closely approximate those with stages IB or II NSCLC.**

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The staging and treatment of multifocal lung cancer is controversial [1–10], mainly because currently, there is no clear mechanism to establish monoclonality, and the distinction of multiple primary lung carcinomas from intrapulmonary metastases is determined solely by clinical and histopathologic criteria. In 1997, the Union Internationale Contre le Cancer and the American Joint Committee on Cancer revised the TNM staging system and designated multiple lesions within the same lobe as T4 disease and lesions in all other lobes as M1 disease [11].

Although several reports have focused on patients with multifocal bronchioloalveolar carcinoma (BAC), a known favorable subtype, little is known about the ideal management of patients with synchronous, intralobar, multifocal, non-BAC tumors [12–15]. The current analysis was initiated to examine the hypothesis that patients with primary NSCLC and intralobar satellites have a more favorable prognosis after surgical resection than that implied by their T4 designation.

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Address correspondence to Dr Altorki, Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Suite M404, New York Presbyterian Hospital–Weill Medical College of Cornell University, 525 E 68th St, New York, NY 10021; e-mail: nkaltork@med.cornell.edu.

Patients and Methods

We conducted a retrospective review of all patients with multifocal, intralobar NSCLC who were surgically treated at our institution between January 1990 and December 2004. Patients with intralobar (T4) disease that was identified on the preoperative computed tomography (CT) scan report or in the pathology report were included. Intrapulmonary satellites were defined as independent lesions separate from the primary tumor and usually smaller, yet having the same histopathologic features as the primary lesion. Pathologic type, stage, and the presence of lymphovascular invasion were assessed.

Only patients who underwent a complete resection with curative intent were included. Patients with a second primary tumor were excluded. All patients underwent a complete mediastinal lymph node dissection. We excluded patients with multifocal BAC, disparate histologies in the primary versus the satellite lesions, and patients who underwent resection after neoadjuvant therapy. In addition, patients with pure ground glass opacities on preoperative CT scan were excluded. Hospital and office records were examined for demographic and pathologic data, including age, gender, surgical procedure, histology, lymphovascular invasion, tumor size, and multiplicity.

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Table 1. Clinicopathologic Variables

Median age (years)	68
Sex	
Male	31
Female	22
Pathology	
Adenocarcinoma	45
Squamous cell	7
Poorly differentiated NSCLC	1
Number of satellites	
One	43
>One	10
N-status	
N0	36
N1	13
N2	4
Stages (disregarding satellite lesions)	
T1N0	17
T2N0	17
T1N1	3
T2N1	12
T1N2	2
T2N2	2
Types of resection	
Lobectomy	48
Bilobectomy	2
Sleeve lobectomy	1
Lobectomy with chest wall resection	1
Other	1
Lymphovascular invasion	
Yes	36
No	16
N/A	1

N/A = not applicable; NSCLC = non-small cell lung cancer.

Survival was calculated by the Kaplan-Meier method. A Cox proportional hazards regression model was performed to examine simultaneously the effects on overall survival of age, nodal disease, number of satellite lesions, lymphatic invasion, and T status of the index lesion. The effect of each variable in the model was evaluated with the use of the Wald test and expressed by the hazards ratio (HR) with a 95% confidence interval (CI). The study was approved by the Institutional Review Board of Weill Medical College of Cornell University. Individual patient consent was waived.

Results

Fifty-three patients (31 women) with a median age of 68 years were identified from our prospectively assembled thoracic cancer registry (Table 1). Multifocal disease was predicted preoperatively on CT scanning in 8 patients and incidentally noted in the final pathology report in 45. All patients underwent an anatomic resection. The types of resection are summarized in Table 1. An R0 resection was performed in all 53 patients. Almost all of the patients (n = 45) had an adenocarcinoma (Table 1), and 35 had node-negative disease. Median follow-up time was 31 months.

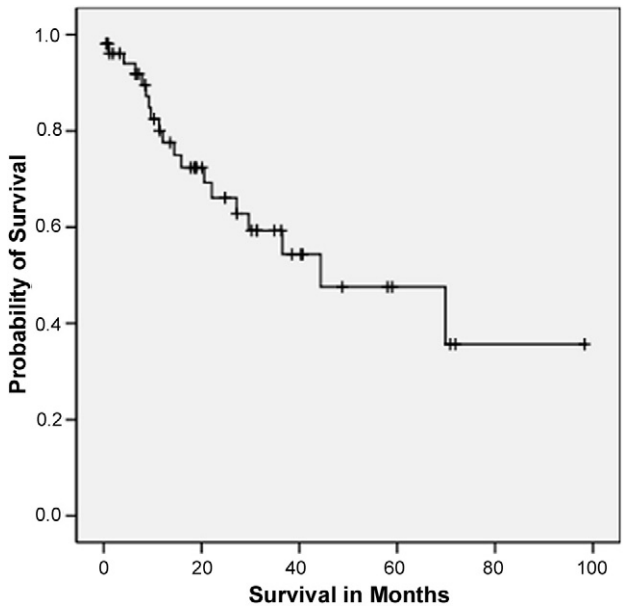

Fig 1. Overall survival in 53 patients.

Overall 5-year survival for all resected patients with intralobar satellites was 47.6% (95% CI, 27.36 to 65.30), with a median survival of 44 months (Fig 1). There was a trend towards an improved 5-year survival for node-negative patients (58.4%; 95% CI, 27.36% to 65.30%; $p = 0.06$; Fig 2). Lymphovascular invasion was identified in 16 patients and did not appear to negatively impact survival (Fig 3). The finding that 43 patients had more than one satellite in the resected lobe did not appear to impact overall survival (Fig 4). When the pathologic stages were

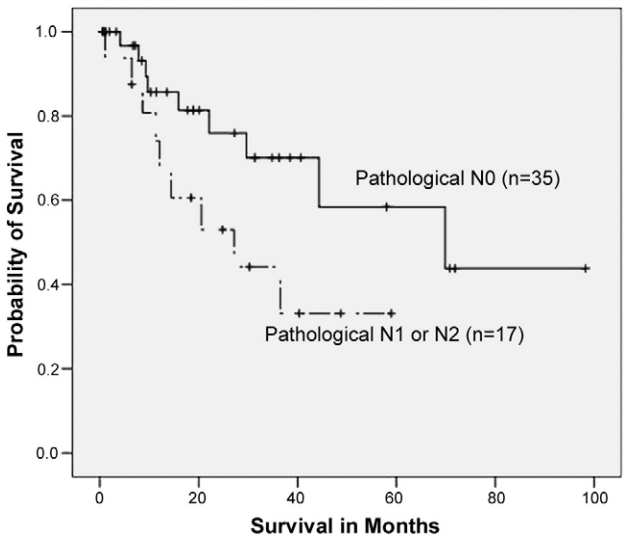

Fig 2. Overall survival for node-positive (N1, N2) versus node-negative (N0) patients.