Risk factors for occult nodal metastasis in clinical T1N0 lung cancer: a negative impact on survival

Nirmal K. Veeramachaneni, Richard J. Battafarano, Bryan F. Meyers, Jennifer Bell Zoole, G. Alexander Patterson

Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO, United States

Division of Thoracic Surgery, University of Maryland, Baltimore, MD, United States

Received 29 July 2007; received in revised form 18 November 2007; accepted 10 December 2007

Abstract

Background: The application of CT imaging has increased the identification of patients with clinical T1N0 (cT1N0) lung cancer. The optimal management strategy for these early stage lung cancers remains unclear. We analyzed the impact of occult nodal metastasis on cT1N0 lung cancer patients.

Methods: We studied patients with cT1N0 lung cancer enrolled in our database from January 1995 to December 2002. Preoperative staging was confirmed by review of CT and PET scan studies. Pathology specimens were reviewed. Multivariate analysis was performed to determine the risk of occult nodal involvement. Kaplan—Meier method was applied to analyze survival.

Results: Two hundred and ninety-seven patients with cT1N0 disease were identified. Fifty-eight percent of patients were pathological T1N0. Overall, 15% of patients had occult nodal metastasis. Logistic regression analysis demonstrated a three-fold increase in the risk of having pathologic stage II or stage III disease with every 1.0 cm increase in tumor size (odds ratio 3.2; 95% CI: 2.3—4.6). Multivariate analysis demonstrated tumor size to be a significant predictor of nodal metastasis (adjusted odds ratio 3.5; 95% CI: 2.4—5.1). Median survival was different between pathological stage I (96.3 months), stage II (41.4 months), and stage III (36.1 months) disease (p = 0.002).

Conclusion: Clinical T1N0 tumors are often understaged. The risk of occult nodal disease increases with tumor size, and this occult disease negatively impacts survival. Because of the limitations of clinical staging, we believe that lobectomy and lymph node analysis should be offered to cT1N0 lung cancer patients to provide accurate staging and to optimize multimodality adjuvant treatment of lung cancer.

Keywords: Lung cancer; Occult nodal metastasis; Lung cancer survival; Lung cancer resection

1. Introduction

The widespread application of CT imaging has led to an increased identification of patients with small asymptomatic pulmonary lesions. The identification of malignant lesions amongst the many benign radiographic abnormalities remains a clinical challenge, and the optimal treatment of these cancers remains to be defined. While many surgeons have stressed the importance of systematic lymph node dissection and lobectomy [1—4], other investigators have suggested that limited resection with minimally invasive techniques may be done with equal efficacy in these selected patients [5,6].

Investigators utilizing intraoperative frozen section examination of segmental and lobar lymph nodes to exclude occult metastatic disease, have successfully treated small lung cancer tumors with sub-lobar resection [7]. However, previous studies have documented an important rate of N1 or N2 disease in patients with clinical T1N0 tumors [3,8] and survival has been noted to be decreased in stage I tumors with fewer than 15 lymph nodes dissected for pathological evaluation [9,10].

The purpose of this study was to estimate the prevalence of lymph node metastasis in clinical stage IA lung cancer and to assess the impact of occult advanced disease on survival.

2. Methods and materials

This study represents a secondary data analysis of a prospective cohort enrolled in our clinical database from January 1995 to December 2002. Two hundred and ninety-seven patients having undergone attempted resection for preoperative clinical stage of T1N0M0 lung cancer were identified. Available radiographic and preoperative studies were reviewed to confirm preoperative cT1N0M0 status using 1997 AJCC guidelines. Preoperative tissue diagnosis was not
The management of stage I and II NSCLC has evolved over the past two decades. Studies have demonstrated good outcomes following surgical resection of early-stage tumors. The 5-year survival rate following complete resection is approximately 40%, and 5-year disease-free survival is approximately 30%.


table 1

Summary of procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy only</td>
<td>7</td>
</tr>
<tr>
<td>Thoracotomy (no resection)</td>
<td>1</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>31</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>8</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>239</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>4</td>
</tr>
<tr>
<td>Sleeve resection</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2

Pathological staging of resected patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
<td>173 (58%)</td>
</tr>
<tr>
<td>T1N0M1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T1N1M0</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>T1N2M0</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>T1N2M1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>76 (26%)</td>
</tr>
<tr>
<td>T2N1M0</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>T2N2M0</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>T3N1M0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T3N2M0</td>
<td>0</td>
</tr>
<tr>
<td>T4N0M0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T4N1M0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T4N2M0</td>
<td>0</td>
</tr>
</tbody>
</table>

Two hundred and ninety-seven patients presented with clinical T1N0M0 tumors and subsequently underwent resection between January 1995 and December 2002. There were 150 men and 147 women enrolled in our study. The mean age was 66.9 ± 9.4 years. All patients had preoperative CT scan of the chest, and 36% (n = 108) had additional PET scan. Approval for this study was granted from the Washington University School of Medicine Human Studies Committee.

Two hundred and sixty patients (69%) underwent mediastinoscopy. Seven of 206 (3.4%) patients had mediastinal lymph node metastases identified at mediastinoscopy and did not undergo further resection. Anatomic resection was accomplished in 258 patients. Lobectomy was performed in the majority (n = 239) of patients, but more extensive resection by means of bilobectomy (n = 4), sleeve resection (n = 4) and pneumonectomy (n = 3) was performed in a small group of patients to achieve complete resection. Wedge resection (n = 31) and anatomic segment lung resection (n = 8) was performed in a small cohort of patients. Most of these patients had limited pulmonary reserve and could not have tolerated additional resection. (Table 1).

Forty-three patients (15%) were found to have lymph node metastasis upon final pathologic review of the resected specimen. Seventeen patients had metastatic disease in the N2 nodes and 27 patients had metastatic disease in the N1 nodes. Seven patients were excluded from further resection by presence of mediastinal metastasis determined by mediastinoscopy, three additional patients with node negative lung cancer had advanced stage lung cancer by T3 criteria and two patients were classified as having T4 lesions due to the presence of multiple lesions in same lobe (n = 1), or pleural seeding (n = 1) (Table 2).

The final pathologic staging is summarized in Table 2. Adenocarcinoma comprised (n = 153) 53% of specimens, with squamous cell carcinoma representing an additional (n = 94) 32%. Bronchoalveolar carcinoma was found in 7% (n = 20) and 9% (n = 27) had mixed tumor or other histology. Only 58% of clinical T1N0 were determined to be T1N0 on final pathologic review. Analysis of our pathologic T2N0 lesions revealed that 44 of 76 lesions were classified as T2 because of occult visceral pleural involvement not demonstrated by preoperative imaging. Only 20 lesions in our series were classified as T2 because of pathologic size greater than 3 cm. The remaining 12 patients had either bronchial involvement or obstructive pneumonitis demonstrated on pathologic evaluation. Subset analysis of patients who underwent preoperative PET scanning (n = 108) revealed a 10% prevalence...
of occult nodal disease ($n = 6$ N1 disease; $n = 5$ N2 disease). Analysis of patients who did not undergo preoperative PET scanning revealed a 17% (32/189) prevalence of occult nodal disease.

In our series, the median clinical size of the tumors was 2.0 cm (range 0.5–3.0 cm), and the median clinical size of tumors with occult nodal involvement was 2.2 cm ($p = 0.007$; range 1.2–3.0 cm). Logistic regression analysis comparing tumor size and final pathologic staging demonstrated a three-fold increase in the risk of having pathologic stage II or stage III disease with every 1.0 cm increase in tumor size (odds ratio per cm increase equals 3.2; 95% CI: 2.3–4.6). In univariate analysis, neither gender ($p = 0.7$), nor patient age ($p = 0.4$) were predictive of nodal involvement, but tumor histology was predictive ($p = 0.001$). Multivariate analysis demonstrated tumor size to be a significant predictor of nodal metastasis. Gender, age, and tumor histology did not predict nodal metastasis. The adjusted odds ratio for upstaging associated with an increase in size of 1 cm is 3.5 (95% CI: 2.4–5.1) (Table 3).

Although all tumors were clinically T1N0, the final pathologic staging influenced 5-year actuarial survival. Patients were followed for a median of 55.6 months. Median survival was 88.1 months in all studied clinical T1N0 patients. (Fig. 1) Median survival was different between resected pathological stage I (96.3 months; $n = 249$), stage II (41.4 months; $n = 28$), and stage III (36.1 months; $n = 18$) disease ($p = 0.0004$) (Fig. 2). In follow up, 49 of 279 patients undergoing resection had recurrence of disease in the form of locoregional recurrence ($n = 23$) or by distant metastasis ($n = 26$).

4. Discussion

The results of this study highlight the limitations associated with the clinical staging of small lung cancers. Pleural invasion (T2 or T3), occult nodal metastases (N1 or N2), and multifocal disease (T4 or M1) were the most common reasons for more advanced pathologic stage. Increasing tumor size was associated with a significantly greater risk of having a final pathologic stage greater than stage IA, as documented in other studies [11]. However, there were not enough small tumors (less than 1.5 cm) in this study to accurately identify the size at which this risk begins to increase. Other investigators have documented a high prevalence of occult N2 disease in clinical T1 lesions [12–14] with the risk doubling when the tumor size increases from <1 cm to over 2 cm [1,11]. We report a three-fold increase in occult nodal disease, with every 1 cm increase in tumor size.

In this series, patients with clinically occult nodal disease had diminished survival, compared to patients with true T1N0 disease. Nodal involvement of lung cancer clearly impacts patient survival [15–17]. The systematic evaluation of lymph nodes by either sampling or complete dissection will improve the accuracy of staging, but few surgeons routinely perform the procedure [18]. Accurate staging enhances the accuracy of prognosis estimates, as well as directly influencing recommendations for adjuvant therapy. Anatomic studies of lymphatic spread of lung cancer suggest considerable variability in the drainage pattern, and an incidence of skip metastasis of 31–74% [19]. While this suggests the need for lymph node analysis of multiple nodal stations, it is unclear if systematic dissection of lymph nodes has a survival benefit. Lymph node dissection will improve the staging of tumors, and may contribute to the finding of improved survival by means of stage migration [10]. Other investigators have questioned the accuracy of lymph node sampling when comparing the technique to complete lymph node dissection [4], and suggest a survival benefit to complete nodal dissection [20].

Previous studies have documented the importance of anatomic lobectomy in the management of lung cancer, even in stage IA disease [2,12]. Recently, there has been some debate concerning the need for lobectomy in small lung cancers less than 2 cm. Although some investigators have observed no difference in recurrence or survival with non-
anatomic resection of smaller lung cancers, prospective randomized trials specifically examining this question have not been performed [5,7].

The addition of PET imaging has improved the accuracy of clinical staging primarily by identifying occult distant metastases. However, microscopic metastatic disease in the N1 and N2 nodal stations is often below the limits of detection by PET [21,22]. In addition, PET imaging does not provide any advantage over CT imaging in the assessment of pleural invasion. Within the group of patients in this study who had PET imaging as part of their clinical staging, 10% had occult nodal metastases, and additional patients had more advanced disease because of pleural invasion and multifocal disease.

The results from this study demonstrate that clinical staging, even with PET imaging, underestimates the pathologic stage. In our present study, we are unable to draw conclusions as to the extent of lymphadenectomy required to impact survival or recurrence, or the feasibility of non-anatomic resection in clinical T1N0 tumors. As not all of our patients underwent systematic lymph node dissection or sampling, we may underestimate the true prevalence of occult nodal disease in our series of clinical T1N0 tumors. We are able to demonstrate a sizable percentage of patients with occult nodal disease, when lymph nodes were sampled. Given the preponderance of evidence favoring anatomic resection, and the undisputed value in the accurate staging of patients these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125–34.


References


