Treatment and survival after lung resection for non-small cell lung cancer in patients with microscopic residual disease at the bronchial stump

C. Ghiribelli, L. Voltolini, P. Paladini, L. Luzzi, M. Di Bisceglie, G. Gotti*

Thoracic Surgery Unit, University of Siena, Viale Bracci 1, 53100 Siena, Italy

Received 26 April 1999; received in revised form 2 August 1999; accepted 1 September 1999

Abstract

Objective: The aim of this study is a retrospective evaluation of survival in patients who had undergone lung resection for non-small cell lung cancer and in whose microscopic residual disease at the bronchial resection margin was found, according to the type of infiltration, histology, lymph node involvement and postoperative treatment. Methods: A total of 1384 patients underwent lung resection for non-small cell lung cancer at the Thoracic Surgery Unit of the University of Siena from 1983 through 1998. All patients underwent complete mediastinal lymphadenectomy and this guaranteed an accurate stadiation. Staging was done according to the TNM and UICC classifications. Residual microscopic disease at the bronchial resection margin was divided in mucosal microscopic residual disease and extramucosal microscopic residual disease. Patients dying within 30 days from operation were excluded from survival analyses. Survival was analysed by the product limit method of Kaplan and Meier and curves were compared using the log-rank test. Results: Microscopic residual disease was found postoperatively at the bronchial margin in 3.39% (47/1384) of all patients undergoing lung resection for non-small cell lung cancer. Thirty patients (2.16%) had extramucosal microscopic residual disease and 17 (1.22%) had mucosal microscopic residual disease. Seventeen patients received adjuvant radiotherapy after operation, two patients underwent completion pneumonectomy; no chemotherapy was given. Median survival for the whole group was 22 months. The probability of survival was not significantly (P > 0.05) correlated with the type of infiltration, nor with lymph node disease, neither with histology, although patients with squamous cell carcinoma had a median survival of 30 versus 12 months of patients with adenocarcinoma. The probability of survival could not be correlated with the administration of adjuvant radiotherapy. Conclusions: A frozen-section analysis of the bronchial resection margin and peribronchial tissue should be made in all patients with endobronchial tumour. We suggest that patients with microscopic residual tumour and stage I or II disease should undergo re-operation, if possible. In patients with documented N2 disease we don’t recommend re-operation; extending the magnitude of the resection is unlikely to alter their outcome. Choice treatment for these patients is radiotherapy. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Non-small cell lung cancer; Surgery; Prognostic factors; Survival

1. Introduction

Surgical treatment of non-small cell lung cancer (NSCLC) mandates surgical resection of the primary tumour in association with mediastinal lymphadenectomy for staging. Incomplete resection can result from the finding of microscopic residual disease at the bronchial resection margin. This depends on the presence of mucosal microscopic residual disease (MMRD) spreading from endobronchial tumour or on extramucosal microscopic residual disease (EMRD) involving peribronchial lymphatics or soft tissues [1–3].

The aim of this study was a retrospective evaluation of survival in patients who had undergone lung resection and in whom microscopic residual disease at the bronchial stump was found, according to the type of infiltration, histology, lymph node involvement and postoperative treatment.

2. Materials and methods

A total of 1384 patients underwent lung resection for NSCLC at the Thoracic Surgery Unit of the University of Siena from 1983 through 1998. Of these patients, 289 were in stage I, 226 in stage I, 103 in stage II, 322 in stage II, 397 in stage III and 47 in stage IIIB. Fifty-four exploratory thoracotomies, 388 pneumonectomies, 810 lobectomies, 87 segmentectomies and 45 sleeve-resections (in patients undergoing lobectomy) were performed. Microscopic residual disease at the bronchial resection margin
was found in 47 patients (3.4%), 41 men and 6 women, with a median age of 63 years (range from 47 to 78 years). Twenty-five patients underwent lobectomy, 14 pneumonectomy and 8 sleeve-resection (Table 1).

Histologic classification and tumour staging are listed in Tables 2 and 3. Staging was done according to the TNM and UICC classifications (1987).

Patients were studied with CT of chest, abdomen and brain, bone scintigraphy and bronchoscopy (only in the ‘coin lesions’ bronchoscopy was performed just before surgical resection in the operating room). Cervical mediastinoscopy, with biptic samples of stations 2, 4 (both left and right) and 7, was performed only in patients with bulky nodes or to exclude a N3 disease detected by CT scan.

All patients underwent complete mediastinal lymphadenectomy and this guaranteed accurate staging; 11 patients were N0, 15 patients N1 and 21 patients N2. Recurrent disease was described as local or distant. Local recurrence was defined as tumour recurring within the ipsilateral lung, bronchial stump or hemithorax. Distant recurrences were those occurring outside the thorax.

Follow-up data were obtained from telephone calls to referring physicians, or the patient’s family or by direct clinical examination. Patients dying within 30 days from operation were excluded from survival analyses.

Follow-up data were 97.8% complete, with only one patient lost to follow-up. Survival was analysed by the product limit method of Kaplan and Meier [4] and curves were compared using the log-rank test [5].

### 3. Results

Microscopic residual disease was found postoperatively at the bronchial margin in 3.4% (47/1384) of all patients undergoing lung resection for NSCLC. Thirty patients (2.2%) had EMRD and 17 patients (1.2%) had MMRD. Intraoperative frozen section were performed in nine patients when the resection line wasn’t considered to be at a safe distance away from the tumour. A false negative result was diagnosed in four cases, because extramucosal infiltration had been overlooked during the first histologic examination; in the other five patients we made a new resection of the bronchus at 0.5 cm from the first, but even this margin resulted infiltrated on postoperative routine histologic examination. In the other patients the resection was thought to be at a safe distance away from the tumour and therefore no frozen section of the bronchial margin was examined intraoperatively. Four patients died in the immediate postoperative period for respiratory failure and two for bronchopleural fistula.

Complications that required treatment developed in six patients (15%) among the 41 operative survivors. The most frequent complication was prolonged air leak (three patients) and bronchopleural fistula with empyema (four patients). We observed also pulmonary embolus in one patient.

Two patients (in stage IB), who had had resection of the lower right lobe and of the upper left lobe, underwent completion pneumonectomy. Seventeen patients received adjuvant radiotherapy after recovery from operation; of these patients, three in stage IB have refused re-operation, the others were excluded from re-operation because of a more advanced stage or because of their bad cardiorespiratory function. Total radiation doses ranged from 50 to 60 Gy. The other patients didn’t receive some form of therapy for their bad clinical conditions or because they refused it.

Our oncologists never proposed chemotherapy in the treatment of microscopic residual disease.

Recurrent disease developed in 21 of the 40 valuable patients (52%) and details of site of recurrence are known for 19.

There were 11 local recurrences (27.5%). Median time from operation to diagnosis of local recurrence was 10 months; four patients received radiotherapy, three patients underwent completion pneumonectomy, the other four patients refused any form of treatment. From the diagnosis

![Table 1](https://academic.oup.com/ejcts/article-abstract/16/5/555/472637)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>MMRD No. (%)</th>
<th>EMRD No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>7 (15)</td>
<td>18 (38)</td>
<td>25 (53)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>6 (13)</td>
<td>8 (17)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Sleeve resection</td>
<td>3 (6)</td>
<td>5 (11)</td>
<td>8 (17)</td>
</tr>
</tbody>
</table>

![Table 2](https://academic.oup.com/ejcts/article-abstract/16/5/555/472637)

<table>
<thead>
<tr>
<th>Histologic classification</th>
<th>MMRD No. (%)</th>
<th>EMRD No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>12</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>29</td>
<td>47</td>
</tr>
</tbody>
</table>

![Table 3](https://academic.oup.com/ejcts/article-abstract/16/5/555/472637)

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Classification</th>
<th>MMRD</th>
<th>EMRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>II A</td>
<td>T1N1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>II B</td>
<td>T2N1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>III A</td>
<td>T3N1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>III B</td>
<td>T2N2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>I IIB</td>
<td>T3N2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>I IIB</td>
<td>T4 N0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>I IIIB</td>
<td>T4 N1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>I IIB</td>
<td>T4 N2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
of recurrence, despite treatment, survival was poor except for two patients who had recurrence in the bronchial stump and who underwent completion pneumonectomy. These two patients are alive and free of disease at 28 and 49 months, respectively from the diagnosis of recurrence. Another patient (pT2N1M0) with recurrence at the bronchial stump 4 months after operation, is alive 17 months after the recurrence was diagnosed and radiotherapy was given.

Eight patients presented distant metastases as recurrent disease with median interval from operation to first recurrence of 11 months; five of these patients received different regimes of chemotherapy without results, the others refused chemotherapy. Of these patients, one (pT2N2) is alive with liver metastasis at 40 months following surgical treatment and adjuvant therapy.

Fourteen patients are alive and free of disease (range from 9 to 132 months after surgical treatment). Nineteen patients have died as result of lung cancer and five others died of causes not directly attributable to their disease.

Median survival for the whole group was 22 months with a survival of 61, 42 and 40% at 12, 24 and 36 months, respectively.

The probability of survival was not significantly \((P > 0.05)\) correlated with the type of infiltration (Fig. 1), nor with lymph node disease (Fig. 2), neither with histology (Fig. 3), although patients with squamous cell carcinoma had a median survival of 30 months versus 12 months of patients with adenocarcinoma.

The probability of survival could not be correlated with the administration of adjuvant radiotherapy, although we observed a trend toward improved survival in patients treated with postoperative radiotherapy.

4. Discussion

Many authors have studied the problem of microscopic residual tumour at the bronchial resection margin, differentiating various types of residual disease. The classification of microscopic residual disease into two distinct patterns, EMRD and MMRD, was first described by Cotton [1].

As many other authors [2,3,6,7] we observed that survival rate in patients with microscopic residual tumour at the bronchial resection margin is worse than that in patients who undergo complete resection. This is true even when the comparison is made stage by stage. The 5-year survival rate for patients with stage I NSCLC with a complete resection is of 68.5% compared with a 50% rate for patients with microscopic residual tumour; for patients in stage II 42 versus 39% and for patients in stage III 16.3 versus 16%. According to Snijder and colleagues [7] only the presence of CIS at the bronchial resection margin does not affect the 5-year survival rate in patients with resected stage I NSCLC.

Recurrent disease, specially local recurrence, develops significantly more often in patients with microscopic residual disease. Gebitekin and colleagues [8] found local recurrences in 56% of their patients. Kaiser [6] noted 60% of local recurrent disease in their patients with N0 disease and peribronchial tumour at the resection margin. We found
11 local recurrence in our patients with microscopic residual disease; recurrence at the bronchial stump was 55% of all the cases of local recurrence. We found no stump recurrences in patients who underwent completion pneumonectomy.

Shields [2] reported that patients with gross tumour remaining at the site of resection had the same poor prognosis as those with residual mediastinal lymph node disease. In contrast patients with microscopic tumour residues survived longer. Soorae and Stevenson [3] have found that patients with tumour in the peribronchial lymphatics had the worst prognosis. Liewald [9] reported that patients with EMRD had a poorer prognosis than patients with MMRD.

In our study we have not found significant difference in survival between patients with EMRD and those with MMRD, even if patients with MMRD seem to have a better survival. The non statistically significance was probably due to the small number of patients.

Six patients of 47 (13%), developed bronchopleural fistula, while its incidence in patients with complete resection was of 6% (varying from 2.1 to 10% in literature [10,11]). This confirms that residual disease at the bronchial stump is one of the technical factors predisposing to bronchopleural fistula.

Frozen-section analysis of the bronchial resection margin usually reveals mucosal microscopic residual disease if present, but can miss extravascular disease. A frozen-section diagnosis of tumour in peribronchial soft tissue should not be ignored. So, it is very important that intraoperative frozen section covers not only the bronchial margin but even the peribronchial tissue; only in this way the surgeon can be certain that a complete resection has been performed. The four false negative results reported, probably are due to the fact that not the whole circumference of the bronchus has been dispatched to histopathology laboratory. It is obvious that, when we speak of peribronchial infiltration, we must relate it to that lymph nodes which surround the resected bronchus and which are often radically removed only apparently, during lobectomy. In these cases, the certainty of lymphatic infiltration should induce the surgeon to a more demolishing approach (pneumonectomy or sleeve-resection) because the prevention of local recurrence is preferable to the other current treatment options and once the diagnosis of recurrence is made, the survival is very poor.

The problem arises in those cases in which the resection line is at an apparently safe distance away from the gross tumour itself; as our analysis revealed, microscopic tumour infiltration was overlooked at the time of operation in 38 patients, because the distance of the resection line from the tumour was considered ‘safe’ and therefore no intraoperative frozen-section tissue of the bronchial stump was examined.

A frozen-section analysis of the bronchial resection margin and of peribronchial soft tissue should be made in all the patients with endobronchial tumour. From this and other papers we can assure that patients with microscopic residual disease at the bronchial resection margin have poorer prognosis than patients without residual disease. Moreover, once the recurrence develops, median survival is very poor, despite whatever treatment.

Reports in literature differ concerning a possible correlation between pathologic tumour classification of non-small cell carcinoma and patients survival. Liewald and colleagues [9] have found that patients with residual disease of the squamous cell type did have a better prognosis than when residues of an adenocarcinoma were detected. Instead Kaiser [6] and Snijder [7] have not found a correlation between the probability of survival and histology. We have found that patients with residual disease of the squamous cell type have a better prognosis than patients with residual disease of adenocarcinoma, but the difference in survival between the two histotypes was not statistically significant. Prolonged survival with documented microscopic residual disease at the bronchial resection margin has been reported. Soraae and Stevenson [3] had 15 5-year survivors of 64 patients, Jeffery [12] reported six 5-year survivors of 18 patients with residual tumour on the bronchial stump, and Shields [2] reported nine such survivors of 54 patients with microscopic residual tumour on the bronchial stump.

It is interesting that all 5-year survivors had squamous cell tumours. We had four 5-year survivors, three of whose with squamous cell type residual disease and one with adenocarcinoma.

The value of adjuvant radiotherapy is unclear. Snijder [7] reported that patients with a positive resection margin derived no benefit from radiotherapy administration, neither in terms of survival advantage nor in a lower incidence of local recurrence. Kaiser [6] reported that adjuvant radiotherapy had no effect on the development of recurrence disease in patients with microscopic residual disease. Also Gebitekin [8] reported that administration of RT did not affect the survival of patients with a positive bronchial stump. However, at the moment it is assumed that radiotherapy does improve survival in patients with tumour of squamous cell type [9]; effectually 87% of patients alive had a squamous cell type tumour and 50% of them received postoperative radiotherapy.

Our therapeutic attitude, in case of microscopic residual disease at the bronchial margin, changes according to the stage disease. We take in consideration a more extended resection (pneumonectomy) only in patients with stage I or II disease with a good cardiorespiratory function; if N2 lymph nodes are infiltrated (stage III), we do not recommend reoperation because distant disease is likely [13,14]. In pneumonectomies, we rarely consider amputation of the stump, because of the high risk and the poor probability of success, specially in extravascular infiltration.

Choice treatment for patients in which we do not recommend reoperation is radiotherapy. In all cases we perform a close follow-up with serial bronchoscopy and CT (every 4
months for the first 2 years, every 6 months the third postoperative year and once a year thereafter), just to diagnose a recurrence at an early stage when it’s rational to propose some forms of therapy.

References