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Unsuspected residual disease at the resection margin after surgery for lung cancer: fate of patients after long-term follow-up☆

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Abstract

Objective: This retrospective study evaluates the survival impact of the residual margin disease after bronchial resection for cancer and suggests tactics in cases of microresidual disease. **Methods**: Between March 1988 and 1998, 4530 consecutive patients underwent surgery for non-small cell lung cancer at our institution. Only incomplete resections after microscopic evaluation (R1) were included in the study. Residual tumour cells were found on the bronchial resection margins of 39 lobectomies, 12 pneumonectomies, 4 segmental resections and one bilobectomy. Histological findings were: squamous cell carcinoma in 38 cases, adenocarcinoma in 15 and large cell carcinoma in three. In all 56 cases, invasive mucosal carcinoma was found exclusively on the bronchial resection margin. Nineteen tumours were stage I; 12, stage II; 17, stage IIIa; 5, stage IIIb; and three, stage IV. Nineteen patients (59.3%) with early stage tumours (I and II) received adjuvant radiation therapy and only three chemotherapy. **Results**: The prognosis in these cases was disease-stage related (21 and 38.4% of deaths due to the disease). Forty-one percent of the stage IIIa patients received radiation therapy and 17.6% chemotherapy: 70.6% died of tumour relapse. Forty percent of the stage IIIb patients received radiation therapy and 20% chemotherapy: 60% died of disease progression. All of the stage IV patients died within 3 months from surgical resection. At the end of the study, 21 patients were alive after an interval of 22–142 months (18 in stage I or II). The 10-year actuarial survival rate was 44%. The percentage survival for stage IIIa was 16.8, after 10 years, and fell to 45 months for stage IIIb. **Conclusions**: The prognosis of our stage I or II patients with microresidual tumour on the bronchial resection margin (R1) was similar to that of the patients in the same disease stage, whose resection was microscopically radical (R0) and the same was true of the patients in stage III. In patients with residual tumour cells on the bronchial stump we did not observe worsened long-term survivals.

Keywords: Lung cancer; Surgery; Resection margin; Incomplete resection; Survival

1. Introduction

Radical resection is universally recognised to be the primary aim of surgical treatment for all solid malignant neoplasms and the first goal of lung cancer treatment. A resection is considered radical when the pathologist confirms that all of the resection margins are tumour free, i.e. when the upper limit in positive nodes is not infiltrated [1]. A macroscopically incomplete resection does not assure a good prognosis in terms of local disease control or survival [2]. The first studies of microresidual disease (R1) indicated a bad prognosis [3]. Cotton [4] showed that prognoses differed depending on whether the residual disease was inside the mucosa or not. Soorae and Stevenson [5] divided residual disease into four categories: extra-mucosal tumour with direct peribronchial invasion by tumour and lymph nodes, or submucosal lymphangitic invasion; mucosal tumour including carcinoma; and in situ carcinoma.

The main aim of this study was to estimate the long-term survival of patients with R1 disease. The secondary aim was to define the conditions for a simple 'wait and see' approach, a new surgical procedure, or radiation therapy.

2. Materials and methods

We examined the clinical records of 4530 consecutive non-small cell lung cancer patients who underwent resection in the Oncological Thoracic Surgery Department of the Istituto Nazionale Tumori of Milan between March 1988 and 1998. The follow-up ended in September 2000. The

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Table 1
Relapse sites related to histology

Histology	Stage IA/IB			Stage IIA/IIB			Stage IIIA			Stage IIIB			Total
Relapse site	T	N	M	T	N	M	T	N	M	T	N	M	
Epidermoid	3	2		1	1	1	2		4			2	16
Adenoca	1	1			1		2	1	1				7
Large cells			1							1			2

patients with radical or macroscopically incomplete resections at any disease stage were excluded, and the study only considered the 56 patients (48 males and eight females aged 48–80 years) with microscopically revealed residual tumour at the bronchial stump (R1).

All of the patients underwent thoracotomy with mediastinal lymph node dissection. We chose the kind of resection to be performed following oncological criteria, and performed segmentectomies in only four cases, as all of them had peripheral tumours smaller than 3 cm and a preoperative forced expiratory volume in 1 s (FEV_1) less than 800 ml, therefore we decided to perform a limited resection. The risk of microresidual disease was not always unsuspected.

The pulmonary resections performed were: 39 lobectomies, 12 pneumonectomies, 4 segmentectomies for peripheral tumours and one bilobectomy; none of the patients underwent bronchus sleeve resection.

The pathological analysis identified 38 squamous carcinomas, 15 adenocarcinomas and three large cell tumours. The bronchial margin was infiltrated in all of the cases. No patient with in situ carcinoma was included in the study. Fifty-five percent of the patients were in an early disease pathological stage (19, stage Ia–b and 12, stage IIa–b), 17 were in stage IIIa, 5 in stage IIIb, and three in stage IV. All the patients classified at stage IIIa had clinical T3 N1 disease that could be surgically resected, only three of them were demonstrated to have mediastinal lymph nodal involvement at histological post-operative examination. Stage IIIb patients were classified at this stage because of post-operative finding of multifocal disease in the same lobe; according to the last TNM classification of Mountain the presence of multiple nodules in the same lobe represents T4 disease. Stage IV patients have been operated on because of concomitant brain single metastases treated with stereotactic radiotherapy in the perioperative period.

Each patient had been informed, after operation about the presence of a microscopic disease, the possible choices of treatment and the side effects related to each of these. So each patient decided by themselves for 'wait and see' or for adjuvant therapy.

Chemotherapy was carried on in the presence of mediastinal lymph nodes involvement independently from R1 disease.

Of the 31 patients who had stage I and II disease, only 2 (6.5%), underwent chemotherapy, because of the presence of particularly aggressive histological type with low grade of differentiation (G3). Eighteen patients (58%) were submitted to radiation therapy; two of these patients underwent surgical resection for local relapse 11 and 17 months after the first procedure. The first patient underwent left completion pneumonectomy, the second one had a left wedge main steam bronchial resection. The remaining 21 cases did not receive any adjuvant therapy.

Seventeen patients were pathologically classified at stage IIIa: three of these (18%) had mediastinal lymph nodal involvement (N2) and underwent adjuvant radio-chemotherapy; four (23%) had only radiation, the remaining ten (59%) had only 'wait and see'.

Five patients belonged to stage IIIb because of intraoperative finding of multifocal disease in the same lobe; one of them received radio-chemotherapy and another only radiation.

All the stage IV subjects had already started post-operative chemotherapy prior to the time of death.

Twenty-five patients developed a disease relapse. Sixteen patients showed a loco-regional relapse and nine distant metastases. The loco-regional relapse was in ten cases at T level and in six at N level. The features of histotypes and of relapse stage-related modalities are summarised in Table 1.

3. Results

We compared the effects of long-term survival of radiotherapy vs. redo surgery vs. 'wait and see' in presence of R1 disease on the bronchial resection margin.

Most of the patients with early stage disease (93.5%) did not receive post-surgical chemotherapy; 58% underwent radiation therapy. In these cases, the prognosis was mainly related to limited disease. Forty-one per cent of the stage IIIa patients underwent radiation therapy and only 17% received chemotherapy; their prognosis was much worse and 59% died because of disease progression. Three stage IIIb cases (60%) died because of disease progression 9–38 months after surgical resection. None of the stage IV disease patients was alive at the end of the follow-up.

Of the original 56 patients, 20 were alive at the end of study, including 17 in stage I and II (two of whom were T1N0 and were reoperated on without receiving any other treatment). The therapies applied and the fate of the series have been summarised in Table 2.

Twenty-five patients (44.6%) developed a disease

Table 2
Fate of patients with residual disease by pStage and adjuvant therapies[a]

		RT		CT		Fate					
		y	n	y	n	an	ar	dd	nt	do	lf
Stage I R1	19	11	8	1	18	8	3	5	–	1	2
Stage II R1	12	7	5	1	11	5	1	3	–	2	1
Stage IIIa R1	17	7	10	3	14	3	–	10	–	–	4
Stage IIIb R1	5	2	3	1	4	–	–	3	1	–	1
Stage IV R1	3	–	–	3	–	–	–	3	–	–	–

[a] Abbreviations used: y, yes; n, no; an, alive no disease; ar, alive with recurrence; dd, death due to disease; nt, new tumour; do, death due to other causes; lf, loss of follow-up.

relapse. Sixteen patients (28.6%) showed a loco-regional relapse and nine (16.1%) distant metastases. The loco-regional relapse was in ten (17.9%) cases at T level and in six (10.7%) at N level (Table 2). Only four patients with recurrence and all of whom had early stage disease at the time of resection were alive at the end of the study.

The survival rate was calculated using the Kaplan–Meier life table method, and the curves were compared by means of the log–rank test. The minimum follow-up was 22 months. The overall survival rate was 44% after 5 years and remained similar after 10 years. Five and 10 years survival rate was 64.5% for stage I, 63.5% for stage II, 16.8% for stage IIIa, 0 for stage IIIb and for stage IV. Survivals seem to be related to the pathological stage and the presence of microresidual disease did not influence them. We did not find any real difference between the percentage survival of the early stage patients with and without residual disease (66.1 vs. 64.5% in stage I, and 63.5 vs. 62.5% in stage II) (Fig. 1). Our stage IIIa patients had better long-term survival rates in comparison to literature data; maybe the presence of N2 disease only, in three cases, was the influencing factor.

The stage IIIa survival rate was 16.8% after 5 years and remained same after 10 years. The survival curves of the stage IIIb patients (R0 or R1) fell to zero within 5 years from surgery.

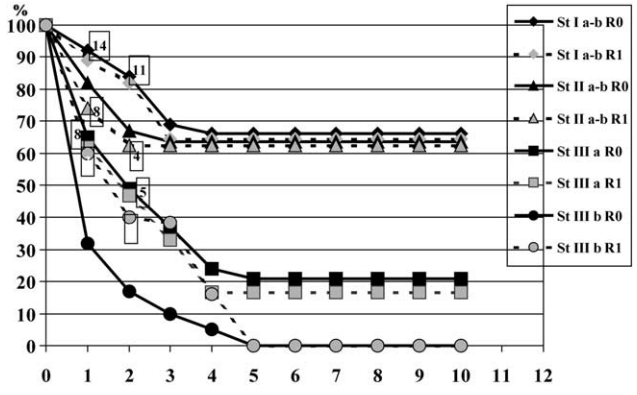

Fig. 1. Probability of survival according to pathologic stages and complete resection (R0) vs. microresidual disease (R1). The patients still alive at two and three time points of analysis were: 14 and 11 for Stage Ia-bR1; eight and four for Stage IIa-b R1; eight and five for Stage IIIa R1; three and two for stage IIIb R1.

4. Discussion

Post-resection residual disease has been classified in many different ways. Intramucosal, extramucosal and peribronchial infiltration with in situ carcinoma have been related to prognosis [6,7]. Some authors have reported similar results in patients with residual tumour at the resected bronchial stump in comparison to radical margins [10,11], but others have reported a worse prognosis than in the case of R0 patients [6,8,9]. Some authors reported the percentage of infiltrated resection margins to range from 1.6 to 14.7% [5]. This pathological finding appeared only in 1.2% of our cases. There is more incidence of microresidual disease after tracheo-bronchoplasty than after standard procedures. The probability of residual disease is 100% if the margin is less than 1 mm from the tumour, and decreases to 30% if the distance is 2–5 mm. The risk is zero when the distance is more than 20 mm. Preoperative investigations and even frozen intra-operative examinations may have a high percentage of false results (42%) [9]. However, technical artefacts may make it difficult to recognize extramucosal disease and separate the high-grade dysplasia and carcinoma in situ. We restricted the frozen section indication to bronchoplastic resection and to the close vicinity of the tumour.

Disease relapse was more frequent in the squamous cell carcinoma than in the adenocarcinoma patients (64 vs. 28%). The relapses were considered loco-regional if at T level or if they involved the ipsilateral endothoracic N. There were 16 loco-regional relapses (28.6%) and only nine distant metastases.

Each patient had been informed after the operation about the presence of a microscopic disease, the possible choices of treatment and the side effects related to each of these. So each patient decided by themselves for ‘wait and see’ or for adjuvant therapy.

The outcome of the untreated stage I patients was: alive and disease free in seven cases, and alive with relapse in the remaining one.

The outcome of all early stage untreated patients (I–II) was: alive and disease free in 11 cases, one alive with relapse and one dead for lung metastases.

We locally treated more, early stage, patients with microresidual tumour with conventional external or stereotactic radiation therapy: 18 patients out of 31. Among the 11 stage I treated cases, there were seven loco-regional relapses: five patients died because of the disease and two were alive at the end of the follow-up. Of the remaining four cases: three were alive and disease free and the last one was lost to follow-up after 17 months from surgery.

Among the 12 stage II patients seven were treated with radiation therapy: three were alive and disease free, one

alive with disease, two dead due to relapse (one loco-regional and one distant metastasis).

Survival among the untreated patients in stages I–II was similar.

The same result of radiation therapy was observed among the nine out of 22 patients with extended disease: five in stage IIIa and two in stage IIIb experienced local relapse, and all died because of disease progression. Once again, the results observed in the untreated patients were similar.

Some authors consider R1 disease itself as an unfavourable prognostic factor [5], whereas others have found a direct relationship between disease stage and prognosis in R1 patients. Our data indicate a similar prognosis in stages Ia–b and IIa–b, with the radical and incomplete resection survival curves: 66.1–63.5% vs. 64.5–62.5%. When we analysed the patients with stage III disease, percentage survival was 21 in R0 and 16.8 in R1 stage IIIa, whereas the survival curves in stage IIIb overlap at 45 months and fall to zero.

The choice of radiation therapy for its apparent and presumed better efficacy in controlling loco-regional relapse was not supported by our study. Some authors suggest that it might be preferable to reoperate on R1 patients with stage I or II disease whenever possible [7], keeping radiation therapy for patients in more advanced stages or with N2 disease.

The paradoxical finding of our study that microresidual disease does not modify survival or the type of recurrence, raises the question of how to treat patients with microresidual disease at the bronchial margin. The various options include a 'wait and see' policy, reoperation, radiation therapy or endobronchial treatment. On the basis of our and others' experiences [8], careful monitoring and a strict follow-up could be the best choice in the early stages because it also leaves open the possibility of treatment in the case of a macroscopic local relapse. On the contrary, a reoperation in case of a recurrence after radiation therapy could be considered dangerous [12].

5. Conclusions

In this study, stage I and II patients with microscopic residual disease and a squamous histotype had a similar prognosis to that of patients with radically resected tumours.

However, in the case of unsuspected residual disease at the bronchial stump of resected stage III tumours, no therapeutic parameter seemed to play a favourable role in improving the prognosis.

Our results suggest that the need for post-surgical adjuvant treatment in such patients may be questionable, although it is still unclear what treatment provides the best long-term results.

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