Survival according to the site of bronchial microscopic residual disease after lung resection for non–small cell lung cancer

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Objective: We performed a retrospective study evaluating the effect on survival of different sites of microscopic residual disease at the bronchial resection margin after surgical intervention for non–small cell lung cancer.

Methods: Survival of patients with different sites of residual disease was compared with survival of patients with curative resections, taking the pathologic TNM stage of the tumor into consideration.

Results: There was a trend for patients with stage I and II non–small cell lung cancer with residual disease limited to the epithelium and with peribronchial invasion to behave like patients with complete resections (61% and 41% five-year survival for stage I and II disease, respectively). This contrasts with patients with submucosal invasion and lymphatic infiltration, among whom there were no survivors at 5 years. There was no difference in survival between curative resections and residual disease of any type when the tumor was stage III or IV.

Conclusions: In patients with stage I and II disease, when residual disease consists of submucosal invasion or lymphatic infiltration, specific and aggressive treatments to clear residual margins might be contemplated because of their possible adverse effect on survival. This contrasts with patients with stage III and IV disease, in whom survival is more related to the stage of the primary tumor than to residual disease.

Resection of localized non–small cell lung cancer (NSCLC) is considered complete when all margins involved (ie, bronchial, vascular, and soft tissue) are confirmed to be free of tumor by the pathologist. Such a finding is termed R0 by the American Joint Committee on Cancer.[1] Although macroscopic residues (R2) are clearly associated with grim prognoses,[2] the issue of microscopic residues (R1) is not so clear, and management is still controversial.

Whereas initial studies of R1 resection were obscured by a lack of precise surgical staging, the most recent studies have correlated results with pathologic extent of disease.[3-5] Furthermore, since 1959, it now appears that prognosis might differ according to the pattern of residual disease at the bronchial resection margin.[5-7]

The aim of this study is to establish the survival of patients undergoing operations in a single center according to different patterns of residual disease at the bronchial resection margin with adjustment to pathologic staging.

MATERIALS AND METHODS

The clinical records of 584 consecutive patients who underwent surgical intervention for NSCLC in our center between January 1992 and December 2000 were reviewed. Follow-up ended December 31, 2005. All patients underwent thoracotomy with lobectomy, bilobectomy, or pneumonectomy and mediastinal lymph node dissection. Patients with wedge resections were excluded. The staging system was the International Staging System for NSCLC, which was last revised in 1997.[8] The study was approved by the hospital's ethics committee, and informed consent was obtained from each surviving patient.

Survival curves were calculated by using Kaplan–Meier and life table methods, and R1 types were compared by using the Mantel–Cox log-rank test after stratification for stage (stage I and II vs stage III and IV).

The study comprises 37 patients with microscopic residual disease at the bronchial margin (33 men and 4 women; age 33–75 years; median age, 63 years). Patients with carcinoid tumors (4 patients) or having had induction treatment (1 patient with chemotherapy) were excluded. Pulmonary resections performed were lobectomies in 20 patients (including 4 sleeve resections on the right upper lobe and 4 extended lobectomies, 2 to the thoracic wall and 2 to the adjacent lobe through a wedge resection), bilobectomies in 6 patients, and pneumonectomies in 11 patients (including 2 extended to the thoracic wall).

After pathology review of tumor slides, patients were classified into 4 different types of R1 according to the exact anatomic site of residual disease (Figure 1): (1) disease limited to the epithelium, including carcinoma in situ R1(is) and dysplasia; (2) submucosal invasion; (3) peribronchial invasion; and (4) lymphatic infiltration.

Patients and their characteristics are summarized in Table 1. Because survival is known to be correlated with pathologic TNM stage of the primary tumor,[9] we compared the different types of R1 after stratification to pathologic staging. Patients were then allocated to expectedly favorable and unfavorable outcome groups composed of pathologic stage I and II disease for the first group and stage IIIA, IIIB, and IV disease for the second group, respectively.

We thus identified epithelial limited disease in 5 patients (dysplasia in 2 patients and carcinoma in situ in 3 patients), submucosal invasion in 7 patients, peribronchial invasion in 15 patients, and lymphatic infiltration in 10 patients. Histopathologic examination identified squamous cell carcinoma in 22 patients, adenocarcinoma in 11 patients, and large cell carcinoma in 4 patients.

Thirteen patients received radiotherapy postoperatively, 6 of whom received it after 3 or 4 cycles of platin-based chemotherapy. Radiotherapy was started 30 to 156 days after surgical intervention (median, 40 days) and was aimed at the mediastinum and usually the bronchial stump; doses applied ranged from 12 to 80 Gy (median, 60 Gy) in 6 to 48 daily fractions (median, 31 Gy).

The site of first recurrence was termed *local* when it was intrathoracic and *distant* when it was extrathoracic. The term *not available* was used for patients who did not have extensive research on the site of relapse.

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Received for publication Nov 11, 2007; revisions received Oct 8, 2008; accepted for publication Oct 13, 2008.

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J Thorac Cardiovasc Surg 2009;137:622-6
0022-5223/$36.00

doi:10.1016/j.jtcvs.2008.10.017

Abbreviation and Acronym
NSCLC = non–small cell lung cancer

Follow-up for surviving patients ranged from 5 to 12 years. Twenty-eight patients died during the follow-up, including 6 within the first month of postoperative complication. Postoperative complications included infection in 4 patients (pulmonary in 3 patients and chest wall phlegmon in 1 patient) and heart rhythm disorders in 1 patient; 1 patient died a few hours after pneumonectomy of rupture of the pulmonary artery stump.

It should be kept in mind that given the small sizes of the 4 subgroups considered (between 5 and 15 patients in each), findings observed should be interpreted with some caution and compared with larger series of patients.

Disease Limited to Epithelium

Two types of lesions were considered in this subgroup: dysplasia and carcinoma in situ. *Dysplasia* refers to lesions with cellular abnormalities within the columnar epithelium of the bronchus that do not reach the full thickness of the epithelium, and *carcinoma in situ* refers to proliferation of neoplastic cells in the full thickness of the epithelium, with intact basement membrane and without invasion of surrounding tissues.

Of the 5 patients in this group, all had early-stage NSCLC and did not receive any adjuvant treatment. Four are alive, with survivals varying from 69 to 142 months.

Submucosal Invasion

Of the 7 patients with submucosal invasion, 5 had early-stage NSCLC, and 2 had locoregionally advanced tumors. Three patients had radiotherapy as consolidation therapy after pulmonary resections. One patient was lost to follow-up after 59 months and was censored at that time.

Peribronchial Invasion

Of the 15 patients with peribronchial invasion, 7 had early-stage NSCLC, 6 had locoregionally advanced disease, and 2 had metastatic disease. Both patients with stage IV disease were given diagnoses after surgical intervention: each lesion (a retro-orbital lesion and a skin metastasis) was discovered after surgical intervention but was already present before. In 5 cases tumors relapsed outside the thorax and were treated with radiotherapy. One patient relapsed locally and was treated with chemotherapy.

Lymphatic Infiltration

Of the 10 patients in this subgroup, 7 had locoregionally advanced tumors. Despite adjuvant combined radiochemotherapy in 5 patients, recurrences occurred both inside and outside the thorax, with poor outcomes.

RESULTS

There is a marginally nonsignificant difference in survival between the 4 types of R1 disease after stratification for pathologic staging ($P = .063$) compared with a P value of .007 when no stratification for staging is done.

Figures 2 and 3 detail survivals for each pattern of R1 disease and compare them with survivals achieved by patients with R0 disease, as provided by the Geneva Cancer Registry. Survivals for expectedly favorable, expectedly unfavorable, and R0 groups at 1, 2, and 5 years (with 95% confidence intervals) are summarized in Table 2.

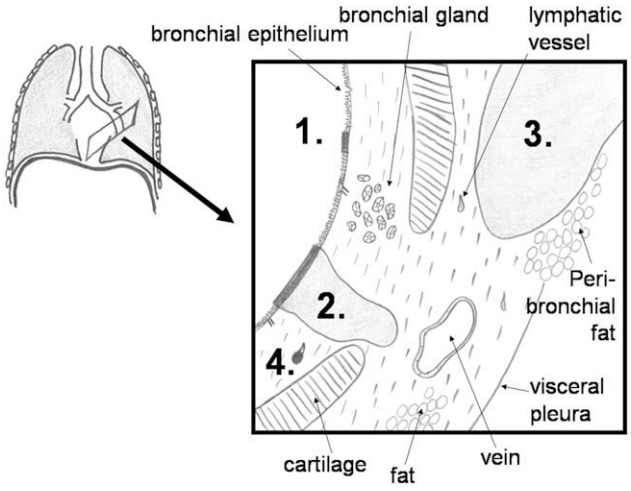

FIGURE 1. The 4 sites of residual tumor at the bronchial resection margin are disease limited to the epithelium *(1)*, submucosal invasion *(2)*, peribronchial invasion *(3)*, and lymphatic infiltration *(4)*.

It appears that within the so-called favorable group (Figure 2 and Table 2), 5-year survival achieved by patients with disease limited to the epithelium (n = 5 [100%]) and peribronchial invasion (n = 7 [43%]) is somewhat better than the 61% and 41% (Figure 2 and Table 2) achieved by control patients with stage I and II disease. In contrast, patients with submucosal invasion (n = 5) and lymphatic infiltration (n = 3) fared much worse than control patients.

As for the unfavorable group, 5-year survival achieved by patients with any pattern of R1 disease is similar to survival of patients with R0 disease (Figure 3 and Table 2).

DISCUSSION

Risk Factors for Positive Bronchial Resection Margins

Positive bronchial resection margins are reported after 1.6% to 14.7%[3,7] of standard lung resections, with a somewhat higher incidence for sleeve lobectomies (6.9% to 13%).[10,11] In the present study, when excluding patients with dysplasia (n = 3), as most authors do, we found 35 (6%) cases of residual disease in a series of 584 consecutive lung resections (including 4 sleeve resections on the right upper lobe). The probability of residual disease is estimated to equal 100% when the bronchial margin is less than 1 mm from the tumor, 30% when the distance is 2 to 5 mm, and zero when the distance is more than 20 mm.[12] It seems neither preoperative medical imaging and endoscopy nor intraoperative frozen sections of the resection margin suffice to prevent incomplete resections, partly because of the high false-negative rate of frozen sections, which is reported to be as high as 41.7%.[3] In this setting frozen sections should be limited to bronchoplastic resections and to elective situations in which the bronchial section is close to the tumor.

TABLE 1. Characteristics of patients with R1

	Patient no.	pTNM staging*	Histology	Adjuvant treatment	Site of first recurrence	Delay from operation (mo)	Treatment	Survival† (mo)
Disease limited to epithelium	1	I (is)	squ	0	L	53	re-op + rt	69+
	2	I (is)	squ	0	L	61	0	63
	3	II (is)	squ	0	0			142+
	4	II (d)	squ	0	0			122+
	5	II (d)	squ	0	0			133+
Submucosal invasion	6	I	squ	0	NA			4
	7	I	squ	rt	L + D	7	ch	8
	8	I	squ	rt	NA			33
	9	I	squ	0	L	16	rt	28
	10	II	squ	rt	L	26	re-op	29
	11	IIIA	adc	0	0			59+*
	12	IIIA	squ	0	0			1
Peribronchial invasion	13	I	adc	0	0			0
	14	I	lac	0	L	21	ch	36
	15	I	squ	0	0			91+
	16	I	lac	rt	0			132+
	17	I	squ	rt	NA			47
	18	II	adc	0	D	15	rt	17
	19	II	squ	0	0			67+
	20	IIIA	lac	rt + ch	0			72+
	21	IIIA	squ	0	0			0
	22	IIIA	squ	ch	D	11	rt	11
	23	IIIA	squ	0	0			0
	24	IIIB	squ	rt	D	10	rt	26
	25	IIIB	squ	0	0			1
	26	IV	squ	0	D	0	rt	3
	27	IV	adc	0	D	1	rt	5
Lymphatic infiltration	28	I	squ	rt	NA			19
	29	I	squ	0	L + D	4	0	4
	30	II	adc	rt + ch	D	11	rt	22
	31	IIIA	adc	rt + ch	L	5	0	9
	32	IIIA	adc	0	0			0
	33	IIIA	adc	rt + ch	L + D	6	rt	6
	34	IIIA	lac	NA	L + D	5	0	19
	35	IIIB	adc	rt + ch	L	3	rt	14
	36	IIIB	adc	rt + ch	L	24	0	42
	37	IIIB	adc	0	D			1

squ, Squamous cell carcinoma; *L*, local; *re-op*, reoperation; *rt*, radiotherapy; *NA*, not available; *D*, distant; *ch*, chemotherapy; *adc*, adenocarcinoma; *lac*, large cell carcinoma. *Type of disease limited to the mucosa: *is*, carcinoma in situ; *d*, dysplasia. †+, Alive at the end of follow-up; +*, lost to follow-up after 59 months.

Survival of the Different Types of Residual Disease at the Bronchial Resection Margin

Favorable group (stage I and II disease). Diseases limited to the epithelium form a heterogenous group, including dysplasia and carcinoma in situ. Such lesions can be found at the bronchial margin but also elsewhere along the bronchial airway; carcinoma in situ, for instance, has been reported in as much as 9.3% of lungs resected for carcinoma (by using fluorescence bronchoscopy).[13]

In the present study disease limited to the epithelium at the bronchial resection margin was found to be associated with a 100% survival at 5 years but decreased to 80% (95% confidence interval, 38% to 96%) 3 months later, which is slightly better than in Dutch[5] and British[7] series (58% and 70%, respectively). Such a finding, which has already been shown in a recent review,[14] likens this subgroup to patients with R0 disease. One explanation for such favorable outcomes is that these lesions are usually found incidentally at the time of pathologic examination and do not represent true residual disease at the bronchial resection margin. Although these are preinvasive lesions (the pathologic sequence goes from hyperplasia to metaplasia to dysplasia to carcinoma in situ and finally to invasive cancer[15]), they do not influence survival. Accordingly, they should probably

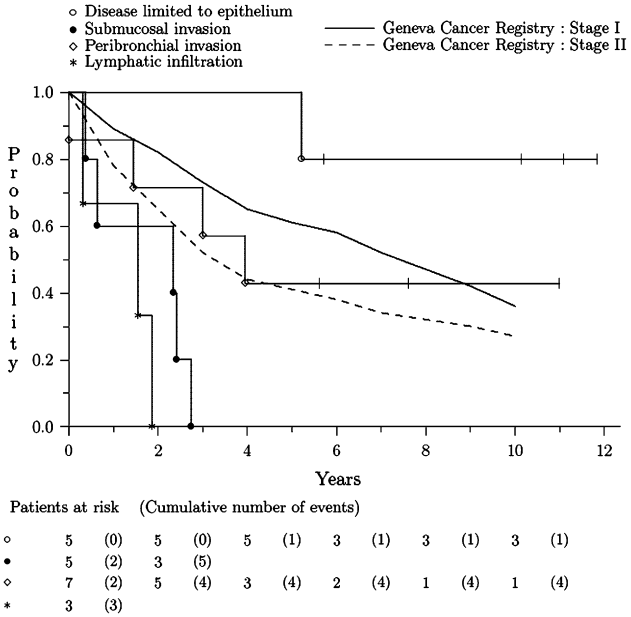

FIGURE 2. Survival for the different sites of residual disease in the expectedly favorable group.

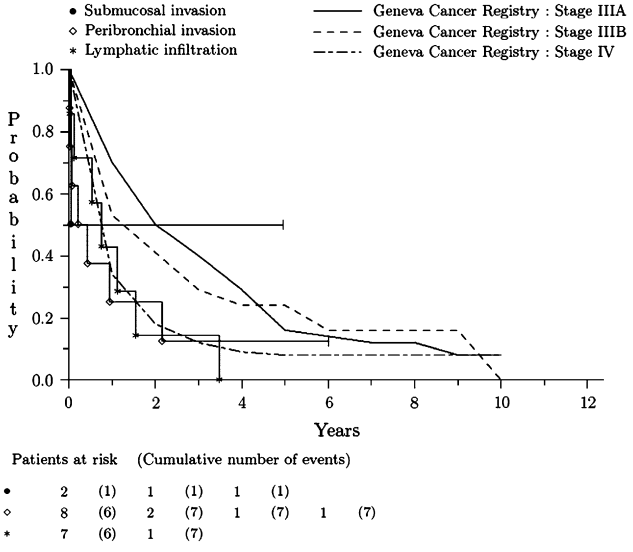

FIGURE 3. Survival for the different sites of residual disease in the expectedly unfavorable group.

not deserve any further therapeutic action when discovered at the bronchial margin.

Although clearly more common in advanced stages, lymphatic infiltration was associated with early stages in 3 of 10 patients; even then, survival was dismal (no patient survived 2 years). This might express early systemic dissemination and argue for chemotherapy (for systemic treatment) and mediastinal radiotherapy (for local control) rather than for reoperation.

The definition of different types of R1 resection in terms of the site of microscopic residual disease is not uniform in the literature.[14] Submucosal and peribronchial invasions are sometimes studied separately[16] or as a whole.[5] Their behavior was somewhat different in the present series. Peribronchial invasion (n = 7) had a 43% (95% confidence interval, 16% to 75%) survival at 5 years (which is similar to our stage II R0 group), whereas survival with submucosal invasion (n = 5) was far worse than that seen in the control group (no survivors at 5 years vs 61% for patients with stage I R0 disease and 41% for patients with stage II R0 disease, respectively). The reason why these somewhat comparable residual tumors do not have the same fate is all but clear because several factors should have favored the submucosal subgroup instead: (1) stage I tumors prevail (4/5 early stages vs 5/7 in the peribronchial subgroup); (2) squamous cell histology is dominant (5/5 vs 3/7, respectively); and (3) absence of postoperative death (vs 1 in the peribronchial subgroup). No doubt a study with larger figures could help assess these findings.

In view of these contrasting behaviors, it is tempting to propose 2 different therapeutic approaches: peribronchial invasion should be treated according to the stage of the primary tumor without taking into account R1 disease. On the contrary, the handling of cases with submucosal invasion is unclear. Adjuvant radiotherapy has been suggested by some in view of relatively good survival rates, decrease in the number of local recurrences, or both.[16-18] Others, however, see no benefit to radiotherapy,[5,19] as in our experience. Reoperation could then be the best option to clear bronchial

TABLE 2. Overall survival at 1, 2, and 5 years

		Overall survival (95% confidence interval)		
	N	1 y	2 y	5 y
Favorable group				
Geneva Tumor Registry stage I	218	89 (85–93)	82 (76–88)	61 (55–67)
Geneva Tumor Registry stage II	77	78 (68–88)	65 (55–75)	41 (29–53)
Disease limited to epithelium	5	100	100	100
Submucosal invasion	5	60 (23–88)	60 (23–88)	0
Peribronchial invasion	7	86 (49–97)	71 (36–92)	43 (16–75)
Lymphatic infiltration	3	67 (21–94)	0	0
Unfavorable group				
Geneva Tumor Registry stage IIIA	71	70 (60–80)	50 (38–62)	
Geneva Tumor Registry stage IIIB	17	53 (29–77)	41 (17–65)	
Geneva Tumor Registry stage IV	91	34 (24–44)	18 (10–26)	
Submucosal invasion	2	50 (10–90)	50 (10–90)	
Peribronchial invasion	8	25 (7–59)	12 (2–47)	
Lymphatic infiltration	7	43 (16–75)	14 (3–51)	

The life-table method was used for the Geneva Tumor Registry, and the Kaplan–Meier method was used for residual tumor groups.

margins in patients with stage I and II disease, as has already been suggested.[17]

Unfavorable group (stage III and IV disease). Patients with R0 disease and the 3 subtypes of R1 disease behave similarly, whatever the exact subtype of residual disease. For patients with advanced disease, the presence of residual disease at the bronchial resection margin is clearly less decisive than N2 and obviously M1 status and thus eliminates the necessity of clearing the bronchial margin with a reoperation. Radiotherapy (as indicated in patients with R0 disease with N2 status) combined with chemotherapy could then be the treatment of choice despite the absence of any study supporting adjuvant chemotherapy after R1 resections.

Residual disease at the bronchial margin is a rare finding. Comparing patients with similar stages and similar sites of residual disease will invariably result in small samples. In such a setting, results and therapeutic suggestions should thus be interpreted with caution. The present study provides a simple microscopic classification for residual bronchial disease.

Taking into account the stage of the primary tumor and the site of the microscopic residual disease leads to interesting prognostic implications. Points of interest, for instance, could include the effect of radiotherapy and reoperation. This deserves further assessment in a larger, prospective, and ideally randomized study.

We thank Mrs Bernadette Mermillod for her help in the statistical analysis of the data.

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