Prognostic implications of a positive bronchial resection margin

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Abstract

Objective: This retrospective study evaluates probability of survival and mode of recurrence in patients with a microscopically positive bronchial resection margin following resection for primary bronchogenic carcinoma, as well as influence of radiotherapy on survival.

Methods: From January 1986 to July 1997, 40 patients had a microscopically positive bronchial resection margin following a macroscopically complete resection (17 lobectomies, three bilobectomies, four sleeve-lobectomies, and 16 pneumonectomies). Tissue diagnosis was squamous cell carcinoma in 32 patients, adenocarcinoma in four, adenosquamous carcinoma in two and neuroendocrine carcinoma in two.

Lung neoplasm; Surgery; Resection margin; Incomplete resection; Radiotherapy; Carcinoma in situ; Photodynamic therapy

Keywords: Lung neoplasm; Surgery; Resection margin; Incomplete resection; Radiotherapy; Carcinoma in situ; Photodynamic therapy

1. Introduction

Surgical resection remains the basis of curative treatment for non-small cell lung cancer, provided that a complete resection of the tumor may be performed on anatomic and functional grounds. A complete resection of the primary tumor is confirmed by pathology when all resection margins are free from tumor. The pathologist should specify in his report that transection lines of vessels and bronchus, visceral pleura and hilar fat have been adequately investigated.

In case of lymph node involvement, North American authors qualify the resection as complete when the most cephalad lymph node is free from disease [1].

A gross incomplete resection does not offer any positive impact, neither on survival, nor on local control of disease [2]. For example, 5-year survival of operated mediastinal T3 tumors was 35\% following complete resection, and 18\% when tumor was left in place [2]. Similar results were observed with superior sulcus tumors, with respective 5-year survivals of 40 and 9\% [3]. On the other hand, pioneering work has underscored that patients with microscopic residual disease had a less adverse prognosis [4]. In the
latter subset, the resection usually appears macroscopically complete, whereas microscopic examination reveals residual tumor at the bronchial transection margin. This category is classified R1 in the TNM system and forms the substance of the present study. Several articles dealing with this annoying topic are currently available. Whereas initial studies were obscured by lack of precise surgical staging, the most recent studies have correlated results with pathologic extent of disease [5–7]. Cotton suggested a different prognosis according to the type of residual disease, which he classified into extramucosal tumor and mucosal tumor [8]. Soorae et al. further subdivided this classification into four categories defined as follows. Extramucosal tumor was described as either direct peribronchial invasion by tumor and lymph nodes, or submucosal lymphangitic spread; mucosal tumor included both invasive carcinoma and carcinoma in situ. As expected, comparison of these four categories showed different prognoses [9]. Snijder et al. similarly demonstrated the worse prognosis of peribronchial disease, and underlined the relatively favorable outcome of residual carcinoma in situ [7]. However, none of these studies has set up guideline for optimal management of patients with residual disease. Classic options are simple observation, reoperation, and radiation therapy.

The main purpose of this study was to estimate survival and to specify mode of recurrence following bronchial R1 resection, and to evaluate the impact of adjuvant radiotherapy on survival. Secondary objectives were to define situations at risk for incomplete resection, and the most appropriate management.

2. Patients and methods

2.1. Patients

Patient files coded ‘bronchial R1 resection’ were selected in a database enrolling prospectively all patients admitted to our department since 1979. Bronchial R1 was determined by routine pathologic assessment of the most proximal part of the bronchus on the resected specimen. To homogenize for operating surgeons and adjuvant treatment options, we have limited the study to a period lasting from January 1986 to July 1997. A total of 40 charts were identified, corresponding to 36 males and four females with a mean age of 59.7 ± 8.8 years (median: 61.5 years).

Mucosal involvement was not anticipated by perioperative endoscopy. Intraoperative frozen section analysis was not performed routinely, since many patients would not have sustained further extension of the resection on functional grounds.

2.2. Methods

Patients were classified into 3 categories according to the type of R1 disease [7]:

• mucosal carcinoma in situ;
• mucosal invasive carcinoma;
• peribronchial infiltration, usually associated with N + disease.

During the duration of the study, a positive resection margin implicated adjuvant radiotherapy, as we routinely perform for N2 disease; only the three most recent patients with carcinoma in situ did not undergo radiation therapy.

Survival data were updated for January 1st, 1999. Cause of death was identified whenever possible. Recurrent malignant disease diagnosed during follow-up was specifically coded for local recurrence, metastatic progression, metachronous primary lung cancer, and primary head and neck cancer.

2.3. Statistics

Quantitative data were expressed as mean ± standard deviation. Comparison was made with Student’s t-test for quantitative data, and with the χ²-test for qualitative data. Survival estimates were made with the Kaplan–Meier model, survival curves were compared with the log-rank test. Any value of P below 0.05 was considered as statistically significant.

3. Results

3.1. Demographics

The 40 cases of R1 resection performed from January 1986 to July 1997 account for less than 2% of patients operated on for primary non-small cell lung cancer. Seven patients had a history of previous malignancy. Four of them had been operated on for a stage I bronchial squamous cell carcinoma; three had undergone lobectomy and one bilobectomy. Disease-free intervals were 6, 11, 53, and 113 months, respectively. Three patients had been operated on for laryngeal cancer.

Preoperative chest films were considered abnormal in 36 patients: 16 had a rounded opacity, eight a lobar atelectasis, ten a hilar mass, and two a pneumonic infiltrate. The tumor was discovered by endoscopy in the four patients with normal chest films.

Location of tumors was as follows: right upper lobe, 13; right middle lobe, 2; right lower lobe, 13; left upper lobe, 10; left lower lobe, 2. Preoperative endoscopy was normal in six patients. In all other patients, feasibility of a curative resection by conventional resection was anticipated.

3.2. Type of surgery and pathology

Resections included 17 lobectomies, three bilobectomies, 14 standard pneumonectomies, two completion pneumonectomies, and four sleeve lobectomies. Pathology disclosed 32 squamous cell carcinomas, four adenocarcinomas, two adenosquamous carcinomas and two neuroendocrine carci-
nomas. Lymph node involvement was classified N0 in 14 patients, N1 in ten, and N2 in 16. According to the 1997 revision, eight patients were classified in stage I, four in stage IIa, ten in stage IIb, and 18 in stage IIIa. Type of R1 resection was as follows: carcinoma in situ, 20; invasive mucosal carcinoma, five; peribronchial infiltration, 15.

3.3. Rough survival data

During follow-up, 24 patients developed relapse of malignant disease (60%). Nineteen suffered from recurrence of their initial disease (47.5%): 12 had metastatic spread (30%), four isolated local recurrence (10%), and three association of metastases and local recurrence (7.5%). A second primary cancer appeared in five patients: four had a second bronchial cancer (10%), and one patient a laryngeal cancer (2.5%) (Table 1). The median delay between treatment and relapsing disease was 26.5 months for local recurrence, 10 months for metastatic progression, 21 months for association of recurrence and metastases, and 28 months for second primary cancers.

At the conclusion of the study (January 31st, 1999), nine patients were alive, one patient was lost to follow-up, and 30 were deceased. Among the nine survivors, three had undergone treatment for a second primary bronchial cancer, one for laryngeal cancer, and one for local recurrence. The causes of the 30 deaths were as follows. Two patients died post-operatively: one of them died of postpneumonectomy pulmonary edema on post-operative day 8, and the second died of malignant hypercalcemia 32 days after completion pneumonectomy. Recurrent cancer was the cause of 17 long-term deaths: 12 had metastatic disease, one had an isolated locoregional recurrence, three had combined recurrence and metastases, and one had a second primary bronchial cancer. The ten remaining deaths occurred without relation to initial disease: one pulmonary embolism, one bowel obstruction, two myocardial infarctions, one radiation induced broncho-esophageal fistula, three respiratory failures and two extensive pneumonias. The six latter cases were believed to be long term complications of radiation therapy, because extensive radiation pneumonitis was shown by medical imaging.

3.4. Carcinoma in situ

Six out of this group of 20 patients had a history of previous primary cancer (30%): two had been treated for laryngeal cancer and four for primary bronchial cancer.

Resection of the present disease was made by lobectomy in eight patients, bilobectomy in two, pneumonectomy in five, completion pneumonectomy in one, and bronchoplastic lobectomy in four. All 20 patients had squamous cell carcinoma. Lymph node staging was N0 in 13 patients, N1 in six, and N2 in one. Seventeen patients underwent adjuvant radiation therapy.

At the conclusion of the study, one patient was lost to follow-up, seven were alive and 12 were deceased. Among the seven survivors, three developed a second primary cancer, located in the bronchus in two and in the larynx in one patient. The causes of death were related to disease in five patients (three metastatic progressions, one second primary cancer, one combined recurrence and metastases). Five out of seven independent deaths could be favored by an adverse effect of radiation therapy. Most patients developing a new primary cancer during follow-up were in this group. Finally, ten out of these 20 patients had multiple primary cancers: six before the current resection, and four following the current resection.

Five-year survival of all 20 patients was estimated 38.7 ± 13.7% (median 31 months) (Fig. 1). Estimates

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 40)</th>
<th>Cancer in situ (n = 20)</th>
<th>Invasive cancer (n = 5)</th>
<th>Peribronchial cancer (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>16</td>
<td>10</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Metastases</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Recurrence + metastases</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Metachronous bronchial cancer</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metachronous head and neck cancer</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 1. Survival (Kaplan–Meier) of patients with residual carcinoma in situ: Global result with 20 patients. N.B. Comparison of estimation with all deaths considered as events (dotted line) to estimation considering only cancer-related deaths as events (dark line) showed no significant difference.
rose to 55.0 ± 16.6% (median not reached) when only cancer-related deaths were considered as events. Comparison of the latter two curves was marginal to signification (\( \chi^2 = 3.939; P = 0.0472 \)) (Fig. 2).

3.5. Peribronchial infiltration

Fifteen patients (12 males, three females) had peribronchial infiltration associated with lymph node metastases. One of them had a history of laryngeal cancer. The tissue diagnosis was squamous cell carcinoma in nine patients, adenocarcinoma in four, adenosquamous and neuroendocrine carcinoma in each one. N-status was classified N2 in 13 patients, and N1 in two. There were eight pneumonectomies, six lobectomies and one bilobectomy.

Most patients presenting recurrent disease during follow-up in this group had distant metastatic spread (Table 1).

At the conclusion date, 13 patients had died. One death occurred post-operatively, ten were due to cancer recurrence, and two occurred without evidence of disease. Each one patient survived following treatment for local recurrence and for a second primary cancer, respectively.

Estimated 5-year survival for all 15 patients was 20.0 ± 10.3% (median 18 months). Estimated survival of the 13 N2 patients was 15.4 ± 10.0% (median 17 months). When restricting definition of events to cancer-related deaths, 5-year survival was 23.3 ± 11.8% (median 23 months) (Fig. 3).

3.6. Invasive mucosal carcinoma

Five patients had residual invasive mucosal carcinoma at the bronchial transection margin. The resections included three lobectomies, one standard pneumonectomy and one completion pneumonectomy. Tissue diagnosis was squamous cell carcinoma in three patients, adenosquamous carcinoma in one, and neuroendocrine carcinoma in one. Lymph node status was classified N0 in a single patient, N1 in two, and N2 in two. One patient died postoperatively. Two died from metastatic progression, and two died without evidence of disease. One of the two latter deaths is interpreted as a long-term complication of radiation therapy: this patient presented with a benign esophagobronchial fistula discovered 15 months after radiation therapy. The patient succumbed following bipolar exclusion from diffuse pneumonia. No malignant disease was seen during autopsy. None of the five patients survived for longer than 17 months.

3.7. Type of resection

Table 2 displays patient demographics according to a stratification by the type of resection: lobectomy, 17 patients; bilobectomy or bronchoplastic lobectomy, seven patients; pneumonectomy, 16 patients. Patients undergoing pneumonectomy had preferentially lymph node metastases, whereas previous history of squamous cell carcinoma was mainly observed in patients submitted to lobectomy.

Mode of recurrence of malignant disease did not differ between the three groups. However, most independent late deaths were observed in lobectomy patients; both postoperative deaths occurred following pneumonectomy.

Survival estimates show less favorable outcome for pneumonectomy patients, which is explained by a high prevalence of N2 disease in this subset (Fig. 4). Survival estimates confirm that most patients dying without evidence of disease had undergone lobectomy (Table 3).

![Fig. 2. Survival (Kaplan–Meier) of patients with residual carcinoma in situ: Result with 13 patients classified N0. N.B. Comparison of estimation with all deaths considered as events (dotted line) to estimation considering only cancer-related deaths as events (dark line) showed a significant difference.](https://academic.oup.com/ejcts/article-abstract/17/5/557/446753)

![Fig. 3. Survival (Kaplan–Meier) of patients with peribronchial infiltration: Global result with 15 patients. N.B. Comparison of estimation with all deaths considered as events (dotted line) to estimation considering only cancer-related deaths as events (dark line) showed similar outcome.](https://academic.oup.com/ejcts/article-abstract/17/5/557/446753)
4. Discussion

4.1. Population at risk for R1 resection

Available preoperative evaluation with high resolution CT scan and endoscopy performed by an experienced observer should keep down the prevalence of R1 resection close to 2% or lower following standard lobectomy or pneumonectomy [5±7]. However, the reported prevalence of a positive resection margin varies from 1.6 to 14.7% [5,9]. It is therefore tempting to define a population at risk, which would benefit from an intensified preoperative work-up. Autofluorescence endoscopy is credited a high sensitivity to detect occult carcinoma in situ, but carries a cost which makes this tool unsuitable for mass screening [10]. Besides, it would fail to recognize the one half of R1 resections which are characterized by peribronchial invasion. Attempts to correlate risk of R1 resection to the type of standard resection, lobectomy or pneumonectomy, have failed [5]. Sleeve lobectomies however seem to carry an increased risk of R1 resections with reported rates ranging from 6.9 to 13% [11,12]. This estimation also applies to tracheal sleeve pneumonectomy [13]. Advanced tumor stage heralds an increased prevalence of peribronchial residual disease, which is virtually always associated with lymph node involvement [5]. In opposition, stage distribution is even in patients with mucosal residual disease [6,9]. A study by the Heidelberg group further demonstrated the influence of the distance separating gross tumor from bronchial transection. When this distance was less than 1 mm, 100% of section margins contained microscopic residual tumor. For distances ranging from 2 to 5 mm, there were 30% of R1 resections. The prevalence decreased to 15% between 5 and 10 mm, and to 5% between 10 and 20 mm. There was no positive resection margin in case of a distance exceeding 20 mm [14].

It is striking that 12 out of 32 patients operated on with squamous cell carcinoma had multiple primary squamous cell cancers; a history of a previous bronchial or laryngeal carcinoma was reported in seven patients, and five others developed a second primary squamous cell cancer during follow-up. Half of the patients with residual carcinoma in situ had multiple primary cancers. Our hypothesis is that a subset of patients with squamous cell carcinoma have diffuse abnormalities of the mucosa of the upper air-ways and bronchi and may show multicentric areas of severe dysplasia or carcinoma in situ together with a peripheral tumor. Patients with a history of previous head and neck cancers, or previous squamous cell carcinoma of the bronchus presenting with a new primary lung cancer should be considered as a high risk population. The progression from metaplasia via moderate and severe dysplasia to carcinoma in situ is well documented and claims for an intensive endoscopic surveillance program in such patients. Association with mutations of the p53 oncogene have been demonstrated on an individual basis [15].

Adequate planning of the operation by medical imaging and endoscopy obviously is not a guarantee against incomplete resection. Similarly, intraoperative frozen section

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**Table 2**

Patient demographics according to the type of resection

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy (n = 17)</th>
<th>Misc. (n = 7)</th>
<th>Pneumonectomy (n = 16)</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial cancer</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>(\chi^2 = 6.616) (P = 0.036^*)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Adenocancer</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>(\chi^2 = 2.399) (P = 0.66, \text{ ns})</td>
</tr>
<tr>
<td>Neuroendocrine cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>N status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>(\chi^2 = 9.678) (P = 0.046^*)</td>
</tr>
<tr>
<td>N2</td>
<td>4</td>
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<td>11</td>
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<tr>
<td>R1-type</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Carcinoma in situ</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>(\chi^2 = 5.245) (P = 0.26, \text{ ns})</td>
</tr>
<tr>
<td>Peribronchial</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* Misc: miscellaneous, i.e. bilobectomy and sleeve lobectomy. * Statistically significant; ns, not significant.

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![Fig. 4. Survival (Kaplan–Meier) following R1 resection: Estimates correlated to type of resection. N.B. Less favorable outcome of pneumonectomies is correlated to a higher incidence of N2 disease.](https://academic.oup.com/wjcts/article-abstract/17/5/557/446753)
4.2. Long term prognosis of R1 resection

Despite the intuitive feeling that incomplete resection is detrimental, most recent studies surprisingly conclude that long term survival is not affected per se. Controversial publications underscore the lack of a large scale prospective study. During former years, Soorae et al. concluded that any kind of R1 resection adversely affects survival [9], but this study was obscured by inaccurate pathologic staging. Subsequently, Kaiser et al. focused a study on extramucosal residual disease in stage III patients. The observed median survival of 15 months was sensibly lower when compared to a non randomized control group with completely resected N2 disease, but this comparison cannot be statistically validated [5]. More recently, Liewald et al. argued that prognosis is not affected by the R1 status in stage III disease: reported median survival was 9 months for R1 vs. 11.6 months for R0 resections. On the other hand, they obviated an adverse effect of R1 resection in low-stage disease: respective median survival for R1 and R0 was 21 and 64 months in stage I, and 12 and 38 months in stage II. However, most patients included in their study had extramucosal disease which could explain an ominous effect on survival [6]. Snijder et al. reviewed a series of patients with stage I disease. Patients with residual carcinoma in situ achieved a 5-year survival of 58% without any adjuvant treatment. Comparatively, the 5-year survival in completely resected patients was 54%. Survival dropped significantly ($P = 0.03$) to 27.3% in patients with residual invasive mucosal carcinoma [7]. The latter data are contradicted by Gebitekin et al.: a short sample of seven stage I patients with residual invasive tumor achieved 5-year survival of 40.8% [16]. A previous study by our group evaluating adjuvant radiation therapy in a multivariate model credited no significant influence on survival to the R1 status [17]. Our present data tend to confirm that residual carcinoma in situ does not affect survival per se; further, peribronchial infiltration is associated with a poor prognosis because most of these patients are N2. Law suggested that the overall satisfactory results of R1 resections might be due to an overestimation of invasion of the bronchial section margin by the pathologist owing to shrinking artifacts of the operative specimen [18].

4.3. Local recurrence

Thoracic oncologists may anticipate that survival is not directly influenced by the R1 status, since cause of death in cancer patients is usually distant metastatic recurrence, which depends on the N status rather more than on the total clearance of endobronchial tumor. On the other hand, residual disease may trigger local recurrence. Local recurrence signs failure of treatment and adversely affects quality of life, which is a substantial goal in cancer patients.

Our policy of routine adjuvant radiation therapy resulted in a cumulated local recurrence rate of 17.5%, which can be broken down to 15% for carcinoma in situ, 0% for invasive mucosal carcinoma, and 26.6% for peribronchial infiltration. These figures contrast with a local recurrence rate of 54.5% reported by Snijder et al.: in their series only 17% of patients underwent radiation therapy [7]. Similarly, Gebitekin et al. reported a local recurrence rate of 57% [16]. Despite use of adjuvant radiation therapy, Kaiser et al. observed a local recurrence rate of 32% with extramucosal residual disease, occurring at a median delay of 8 months [5]. Histology did influence the prevalence of local recurrence: the respective rates for squamous cell carcinoma and adenocarcinoma were 40 and 28%. Furthermore, 60% of recurrent disease was local in N0 patients, and 23% only in N2 patients [5]. These numbers suggest that risk of local recurrence is higher with R1 resection. However, such intuitive thoughts about local recurrence in R1 patients, argued with retrospective single arm studies, have recently been frustrated. Lacasse et al. demonstrated with a multivariate analysis that neither a positive resection margin, nor involvement of the highest resected lymph node predicted recurrence at a 3-year follow-up [1], and hence challenged the classic definition of complete resection. Their numbers (a total of 20 patients with positive bronchial section margin) did not allow for subgroup analysis by type of bronchial involvement. The only criticism one might oppose to

Table 3

<table>
<thead>
<tr>
<th>Survival analysis according to type of resection</th>
<th>Lobectomy</th>
<th>Misc. $^a$</th>
<th>Pneumonectomy</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rough survival (% at 5 years)</td>
<td>35.9 ± 12.8</td>
<td>26.8 ± 21.4</td>
<td>16.5 ± 10.4</td>
<td>$\chi^2 = 1.139$</td>
</tr>
<tr>
<td>Median (months)</td>
<td>30</td>
<td>34</td>
<td>17</td>
<td>$P = 0.5658$</td>
</tr>
<tr>
<td>Corrected survivalb (% at 5 years)</td>
<td>53.3 ± 15.5</td>
<td>32.1 ± 15.3</td>
<td>25.8 ± 15.3</td>
<td>$\chi^2 = 1.827$</td>
</tr>
<tr>
<td>Median (months)</td>
<td>Not reached</td>
<td>34</td>
<td>30</td>
<td>$P = 0.4012$</td>
</tr>
</tbody>
</table>

$^a$ Misc., miscellaneous, i.e. bilobectomy or sleeve lobectomy.

b Only death from disease is considered as an event.
Lacasse and colleagues is that a 3-year follow-up is probably too short to detect the real trend of local recurrence, since the median delay of occurrence in our study for example was 26.5 months.

4.4. Management of patients with R1 status

Based on the paradoxical conclusion that R1 status does not affect neither survival, nor mode of recurrence, the following question is how to manage patients with microscopic residual disease. The different options include a 'wait and see' policy, reoperation, radiation therapy, and endobronchial treatments. The answer should be stratified along two different prognostic settings, i.e. intramucosal and peribronchial residual disease.

Patients with intramucosal disease have fair chances to achieve long term survival. According to Snijder et al. [7], a 'wait and see' attitude is a viable option in lower stages, provided that the patient will adhere to a close follow-up program. Furthermore, spontaneous regression of severe dysplasia and even carcinoma in situ may occur owing to cessation of smoking, local scarring phenomena and unknown immunologic pathways [15]. Treatment with derivatives of retinoid acid could favor apoptosis of dysplastic and even neoplastic cells [19]. A 'wait and see' policy leaves open all treatment possibilities in case of gross local recurrence. On the opposite, reoperation for recurrence following radiation therapy is hazardous [20].

Immediate reoperation to extend resection may be offered to patients with suitable cardiorespiratory function. However, in case of carcinoma in situ, this strategy implicates an increased operative risk in patients who have real chances of spontaneous long-term survival. Completion pneumonectomy carries a mortality rate close to 10% [21]; bronchoplastic operations after reiterative bronchial dissection have not been evaluated as such, but the risk for anastomotic dehiscence is probably increased. A more aggressive approach could be justified in patients with invasive mucosal carcinoma and N0 status, who have a lower spontaneous life expectancy.

Although radiation therapy may contribute to a satisfactory prevention of local recurrence, our results suggest a deleterious effect on long term survival. We observed an unexpectedly high rate of deaths without evidence of disease in the group of patients with the most favorable spontaneous prognosis. Six out of ten deaths occurring without evidence of disease could be attributed to long term adverse effects of radiation therapy such as radiation pneumonitis, hilar fibrosis, and even tracheo-esophageal necrosis. These findings are in line with the results of the PORT-metaanalysis which demonstrated an adverse effect of radiation therapy on survival in stages I and II [22]. Adjuvant radiotherapy should probably be withheld in patients with residual carcinoma in situ.

Endoscopic treatments include mainly photodynamic therapy and brachytherapy. Brachytherapy is not readily available in many centers because it requires a specific high-technical environment. The feasibility is questionable in patients without a residual stump to block the brachytherapy catheters. The technique is further plagued by frequent radiation bronchitis and subsequent stenosis [23].
scopic photodynamic therapy with intravenously injected photosensitizers is a promising way to destroy selectively intramucosal cancer. The complete remission rate after a single treatment is estimated close to 85%; a 5-year survival rate of 93% has been reported for patients with endobronchial stage I disease [24,25]. Our current management plan in patients with residual carcinoma in situ is based on repeated endoscopy and CT scan at 3-month intervals (Fig. 5). The first examination is scheduled no earlier than 2–3 months postoperatively, in order to leave time for spontaneous regression of dysplasia or in situ carcinoma. In case microscopic cancer is evidenced on biopsies, the patient is offered photodynamic therapy. Discussion about reoperation or radiation therapy is initiated if cancer persists despite photodynamic therapy, or in case of gross recurrence. This plan started in 1998 is under prospective evaluation. In the event of peribronchial involvement, a ‘wait and see’ policy is hardly acceptable on an ethical basis. Reoperation conveys a high operative risk without proven survival benefit in N2 patients. Similarly, radiation therapy did not prevent local recurrence in Kaiser’s series [5]. However, these authors used suboptimal doses ranging from 30 to 52 Gy. On the contrary, we have reported acceptable results in a single arm study with less than 14% of local recurrence in stage III disease [18]. The present series confirms a satisfactory local control in case of residual peribronchial cancer, although long term survival remains unaffected in stage III [23]. Endoscopic treatments have little value besides palliation of bronchial obstruction.

4.5. Conclusion

Our data lead us to a two-tailed conclusion. The prognosis of peribronchial infiltration is set by the associated N2 status; a satisfactory local control of disease may be favored with adjuvant radiotherapy. Residual in situ carcinoma does not influence survival per se; local control of disease is probably in part improved by radiotherapy. However, the high prevalence of unrelated late deaths suggests an adverse impact of radiotherapy on survival, and hence we have stopped to irradiate such patients.

References

Appendix A. Conference discussion

Mr K. Moghissi (East Yorkshire, UK): Before coming to this meeting, I had the pleasure of reviewing a number of papers concerned with bronchial margin microinvasion. The incidence stated is anything between 4% to nearly 18%. So the first question is what is the incidence of positive bronchial resection margins.

Also, I don’t know whether you are aware of fluorescence bronchoscopy, which, uses a low energy laser light which can potentially discriminate between normal and abnormal tissue. Secondly, in the work of the Japanese, the prime indication of photodynamic therapy is for early or mucosal cancer. It is shown that one can actually achieve a 5-year survival rate of nearly 18%. So the first question is what is the incidence of positive bronchial resection margins.

Dr G. Massard: The incidence of positive resection margin over the study period was about 2%, which is surprisingly low. But we have to be aware that it is very difficult for our colleagues from pathology to really state whether the bronchial margin is free from disease or not. This is perhaps best illustrated by a study done by Kaiser and Martini from Sloan Kettering Memorial Cancer Center, were they observed a false negative rate of 40% on intraoperative frozen section analysis. And then, of course, even experienced pathologists may come into terrible doubts when they have to decide whether the bronchial margin contains either severe dysplasia or carcinoma in situ. The latter may be a very difficult decision.

Dr L. Gasiorowski (Poznan, Poland): I have a question. I saw, I guess, 17 lobectomies. In how many cases was the completion pneumonectomy in the majority, of the study group.

Dr Massard: We have an anecdotal experience with endoscopic brachytherapy for technical reasons. However, a high proportion of these patients had severe radiation-induced bronchitis and even stenosis. This led us to stop this kind of treatment. If there is any endobronchial treatment to apply at this time, we would go for photodynamic therapy, which naturally has to go through the proof of time and to be evaluated prospectively.

Mr S. Barnard (Bradford, UK): We’ve heard early this afternoon that the PORT Meta-analysis study shows that radiotherapy after surgery is not a good idea, or perhaps not a good idea, conversely, the Rome study suggested it may be a good idea. You have a high incidence of carcinoma in situ which was N0, so they’re comparable studies. You gave them radiotherapy, but they did badly. Do you have an explanation for this?

In your study, the carcinoma in situ was also mainly N0, but you showed, in keeping with the PORT study, that there is a lot of postoperative morbidity and mortality when the radiotherapy is given, which is in contradiction to the paper earlier today from Rome showing that radiotherapy in N0 was useful.

Dr Massard: Exactly. We are drawing conclusions similar to the PORT study, with a very small of patients of course. But in these N0 patients, without any doubt, irradiation of the bronchial stump will flush the hilum with a high dose radiation therapy, and burn everything that is on its way to the hilum. As a consequence, these patients will have some respiratory insufficiency. And if they get infected, the risk of fatality is high.

Mr Barnard: Which is the feelings of the PORT study. Are you in agreement?

Dr Massard: We have never performed any routine radiotherapy for stage I or stage II disease, we applied it just to those who had a positive resection margin. Knowing now the detrimental effect, we will be reluctant to do that again.

Mr P. Goldstraw (London, UK): I think you’ve been unnecessarily hard on yourself to include carcinoma in situ as R1 disease. We know so little of the natural history of carcinoma in situ. We know that it can be multifocal. And so I think we should not count it as R1 disease. You’ve shown us quite happy for bronchoscopists to shine their light on it and monitor it; but if they start treating it with photodynamic therapy, we will never learn the natural history of carcinoma in situ. So I would leave it alone.

Dr Massard: If I may just underline once more that our actual policy is to do nothing, at least during a 3-month period, and then we go in with a bronchoscope and we do biopsies again and then we think it over. But we would rather become nervous if the carcinoma in situ persists.

Mr Goldstraw: Why?

Dr Massard: Because we would fear for progression.

Mr Goldstraw: But it hasn’t progressed, it’s persisting.

Dr Massard: It is clear that perhaps it will not progress. Perhaps many patients operated on had occult carcinoma in situ on the opposite side, and we did not know about it. There would be some place to develop prospective trials using retinoids and similar medications, as we do for carcinoma in situ of the head and neck.