Residual disease at the bronchial stump after curative resection for lung cancer

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Summary
The most important surgical goal during potentially curative surgery for non-small cell lung cancer (NSCLC) is a macroscopic and microscopic radical resection (R0-resection). Studies reporting on recurrence and long-term survival mainly comprise patients with completely resected NSCLC (R0-resection). However, there is limited data on incidence, treatment and prognosis of patients with microscopic residual tumour tissue at the bronchial resection margin (R1-resection). Furthermore, the definition of an R1-resection of the bronchial resection margin is not uniform in literature. Based on 19 studies published between 1945 and 2003 with a substantial number of included patients with resected NSCLC, the incidence of an R1-resection of the bronchial resection margin is approximately 4–5% (range 1.2–17%) of all lung resections. Divided into the localisation of the microscopic residual disease, survival of patients with carcinoma in situ (CIS) at the bronchial resection margin is comparable to the survival after a radical resection. The prognosis is negatively influenced in case of microscopic mucosal residual disease. Survival is even worse in patients with peribronchial residual disease; 1- and 5-year survivals range between 20–50% and 0–20%, respectively. This poor prognosis is because peribronchial residual disease, in 75–85% of the patients, is associated with mediastinal lymph node metastasis. According to the stage, survival of patients with stage I and II NSCLC and an R1-resection of the bronchial resection margin is significantly worse as compared to stage-corrected survival after a radical resection. In these patients, survival is limited due to local recurrence. The negative effect of an R1-resection of the bronchial margin in stage III NSCLC is limited, as these patients die due to disseminated disease (distant metastasis) before local recurrence occurs. A conservative approach with frequent bronchoscopic surveillance is justified for CIS. For patients with microscopic residual disease at the bronchial margin and stage I and II NSCLC, further treatment has to be considered. Adjuvant treatment in patients with stage III NSCLC has no proven benefit in terms of survival.

Keywords: Microscopic residual disease; R1-resection; Bronchial resection margin; Non-small cell lung cancer

1. Introduction
Surgical resection remains the treatment of choice, offering the best chance of cure in patients with non-small cell lung cancer (NSCLC). However, only 30% of the patients diagnosed with NSCLC qualify for a potentially curative surgical resection [1]. The most important surgical goal during this procedure is a macroscopic and microscopic radical resection (R0-resection). An R0-resection is established when all resection margins are microscopically tumour free, when there are no extracapsular extension of positive lymph nodes and no lymph node metastasis in the highest mediastinal lymph nodes [2]. Studies reporting on recurrence and long-term survival mainly comprise patients with completely resected (R0-resection) NSCLC. There is, however, limited data on the incidence, treatment and prognosis of patients with microscopic residual tumour (R1-resection) at the bronchial resection margin.

About 60 years ago, Griess and Cotton were the first to describe the occurrence of R1-resections. They reported that even after resections with a macroscopically tumour-free length of the bronchus stump of 2.5 cm, the incidence of R1-resection still was 6% [3,4]. The Dutch evidence-based (CBO) guideline on NSCLC states that microscopic residual disease at the bronchial resection margin affects prognosis negatively and increases the risk of recurrence, both loco-regional and distant recurrence. Furthermore, the risk of bronchopleural fistulas is increased in case of microscopic residual disease at the bronchial resection margin. The CBO guideline recommends adjuvant radiotherapy after an incomplete resection. Furthermore, intraoperative frozen section examination, especially when it concerns a centrally localized tumour, is recommended [5], unless the result of the
examination will not change the further surgical procedure (e.g. due to functional or anatomical limitations).

2. Definition and incidence

The definition of an R1-resection of the bronchial resection margin is not uniform in literature. The localisation of microscopic residual disease is reported according to various classifications, hampering the interpretation and comparability of different studies. Residual tumour cells can infiltrate the entire bronchial wall or can be confined to a specific part of the bronchial wall. The involved part can be classified as mucosal, divided in carcinoma in situ (CIS) and invasive carcinoma, and extra-mucosal. The latter can be subdivided into submucosal residual disease, peribronchial residual disease, tumour cells in lymph nodes and/or lymph vessels or as extra-bronchial residual disease.

In the first study by Griess et al. on this topic, microscopic residual disease at the bronchial resection margin was divided into mucosal, submucosal and residual disease at the outside cover of the bronchus [3]. Cotton was the first to describe the presence of tumour cells in lymph nodes and lymph vessels at the resection margin as well as extra-bronchial tumour expansion [4]. However, different classifications potentially introduce differences in morphological interpretation. Uniform classification to point out the part to which the microscopic residual disease is confined, namely bronchial and extra-bronchial should be applied. Furthermore, bronchial residual disease can be divided into mucosal (subdivided into infiltrative carcinoma or CIS) and peribronchial (outside the cartilage) microscopic residual disease. Additionally, to this classification, for each tumour localisation (e.g. bronchial or extra-bronchial), the presence or absence of lymph vessel involvement at the bronchial resection margin is reported.

The incidence of an R1-resection of the bronchial resection margin is chronologically shown in Table 1. Based on 19 studies published between 1945 and 2003, the incidence is approximately 4–5% (range 1.2–17%) of all lung resections. In spite of better preoperative staging with modern imaging methods, the incidence of R1-resections of the bronchial resection margin has not decreased during the last decades. Considering the limitation that the definition of an R1-resection of the bronchial resection margin is not uniform in literature, the incidence of extra-mucosal, mainly peribronchial microscopic residual disease, is higher as compared to mucosal residual disease [3,6–23].

In studies of both Griess et al. and Cotton, it is concluded that even after resections, in which there is a macroscopic tumour-free margin of 2.5 cm, there is still microscopic residual disease at the bronchial resection margin in 6% of these resections. Subsequently, the authors recommend a minimal macroscopic tumour-free bronchus length of 1.5 cm in case of squamous cell carcinoma and 2.0 cm in case of adenocarcinoma. When these margins are applied to their study population, an R0-resection is obtained in 94% of the cases [3,4]. Kayser et al. found, in 120 resection specimens, microscopic residual disease at the bronchial resection margin in 20 (17%) of them. None of the primary tumours located macroscopically more than 2 cm from the resection margin resulted in R1-resections [16]. In general, 2.5 cm of macroscopically tumour-free bronchial margin is considered as a safe distance. However, Soorae et al. found that 13% of all the R1-resections were seen after a resection with a macroscopic tumour-free resection margin of 2.5 cm or more [17]. Also, Kara et al. studied the proximal microscopic extension of the primary tumour along the bronchus. Thirty percent of all centrally localized tumours extend microscopically along the bronchus with an average length of 7.6 mm. In peripheral tumours, 20% extended proximally, with an average length of 16 mm. According to histological type, squamous cell carcinomas showed proximal microscopic extension more often as compared to adenocarcinomas, 30 and 20%, respectively. In squamous cell carcinoma, the proximal extension mainly consisted of (sub)mucosal extension. In adenocarcinomas, peribronchial extension was seen more often [24–26].

3. Broncho-pleural fistula

The incidence of broncho-pleural fistulas (BPF) in patients after radical surgery ranges between 2.1 and 12.2%. Higher incidences are reported after pneumectomy, especially after right-sided pneumectomy [27–32]. Asamura et al. reported in 2359 patients that the most significant risk factor for a BPF was the type of resection (pneumectomy), followed by the presence of microscopic residual disease at the resection margin (p < 0.01) [27]. Heikkila et al. reported in 1069 patients that the incidence of BPF was significantly higher in patients with microscopic residual disease at the bronchial resection margin (4.2 vs 13.6%, p < 0.01). This increase was significantly more pronounced after lobectomy [18]. Others have also reported high incidences of BPF in patients with an R1-resection of the bronchial resection margin; however, in these studies, no comparison was made with a control group (R0-resections) [9,14,17,33]. Kaiser et al. reported on 45 patients with extra-mucosal residual disease at the resection...
margin. None of these patients developed a BPF. The authors hypothesised that BPF mainly occurs after resections with mucosal residual disease at the bronchial resection margin [34]. Others that report on $R_1$-resection of the bronchial resection margin did not find a higher incidence of BPF [10,12,20,21,29,32].

4. Frozen section examination

Routine frozen section examination of the bronchial resection margin is not common practice in several centres. Especially in peripherally localized tumours with sufficient macroscopic tumour-free length of the bronchus, frozen section examination is omitted because the chance of an $R_1$-resection is considered to be small. Furthermore, frozen section examination is not performed in patients in whom a tumour-positive margin on frozen section examination does not influence the procedure due to anatomical and/or functional restrictions to perform an extended resection [9,10,21,35].

In a study by Maygarden et al. that focussed exclusively on the use of frozen section evaluation of the bronchial resection margin, false-positive and false-negative results of respectively 1.5 and 1.9% were found [36]. However, Weisel et al. reported a higher rate of false-negative results (10%) of frozen section evaluation during sleeve resections of the main bronchus [37]. In a study by Hofmann et al., there was a discrepancy between the frozen section examination and the definitive pathological evaluation in 11 of 21 patients with an $R_1$-resection, especially when it concerned peribronchial residual disease [8]. The difficulty in detecting extra-mucosal residual disease, e.g. peribronchial residual disease during frozen examination is also described by others [9,10,12,34]. Subsequently, in these studies, it is advised to pay more attention to the extra-mucosal parts of the bronchus during frozen section evaluation and to take supplementary samples, if necessary. A possible explanation for the difficulty in detecting extra-mucosal residual disease during frozen section evaluation could be that this tissue is damaged during the preparation of the bronchus. Additionally, pathologists may be more focussed on the mucosa. Finally, there is a limitation to frozen section evaluation due to a sample error and time pressure during the evaluation in general.

5. Survival

According to the localisation of the residual disease, survival of CIS is comparable to survival after a radical resection. If CIS is present at the resection margin, it may be found through the entire bronchial tree. Furthermore, regression of CIS is described [17,20,21,35,38]. However, it is difficult to predict which pre-neoplastic lesions will ultimately go into regression and which will develop into an invasive carcinoma [39].

The prognosis is negatively influenced in patients with peribronchial residual disease; 1- and 5-year survivals of these patients range between 20—50% and 0—20%, respectively [9,14,15,17,20,21,35]. The poor survival is probably due to the association with mediastinal lymph node involvement in 75—85% of the patients with peribronchial residual disease [14,20,34,35]. According to stage, survival of patients with stage I and II NSCLC and an $R_1$-resection of the bronchial resection margin is significantly worse compared to the stage-corrected survival after radical surgery. In the former, survival is limited due to local recurrence [8,10,14,20,21,40,41]. The negative effect of microscopic residual disease at the bronchial resection margin in stage III NSCLC is less pronounced. These patients probably die due to disseminated disease before local recurrence occurs [8,10,20,40,41]. Several studies reported better survival rates in patients with squamous cell carcinoma and after lobectomy as compared to patients with adenocarcinoma and after pneumectomy [10,12,17,34]. However, others have not found such differences [9,11,14,21].

Nonetheless, even after an $R_1$-resection of the bronchial resection margin without adjuvant treatment (e.g. reopera- tion or radiotherapy), long-term survivors have been described. Several publications described patients surviving more than 5 years [6—8,12,15,17—21,23,34].

Law et al. explain that the prolonged survival despite an incomplete resection might be due to the fact that microscopic tumour extends to the point of surgical division of the bronchus but not beyond it. Or that tumour confined to the distal 1—2 mm of the bronchial stump may become necrotic. Furthermore, Law et al. describe an alternative explanation for the relative good survival based on the assumption that a histological report of tumour at the resection margin may reflect an artefact. Two mechanisms are proposed by Law et al. through which a surgical division of the bronchus proximal to the tumour might be reported histologically as having passed through the tumour. The first mechanism is due to the fact that the bronchus is an elastic structure and retracts after resection. Therefore, the distance between the tumour and the resection margin is reduced. When a ring of the bronchus is cut from the bronchus, the distal part may contain tumour because the resected bronchial margin has been brought closer to the tumour. The distal end may later be confused with the proximal end. A second mechanism derives from the fact that the resected lung is kept in formalin which causes shrinkage; this may enhance the first mechanism. Furthermore, normal bronchus tissue may shrink more than the more fixed tumour tissue. Due to the irregular shrinkage, the pathologists must cut more distally to obtain a complete ring of the bronchus. Again the distal end of this ring may contain tumour. Law et al. conclude from the above that the relative good survival curve seen after (mucosal) $R_1$-resections of the bronchial resection margin might be a combination of both the unaffected survival after a radical resection and the poor survival of those with tumour in the bronchus stump [20]. Soorae et al. explain the long survival by an immunological reaction that destroys the residual microscopic disease after the main tumour bulk has been removed [17].

6. Treatment options

Ghiribelli et al. report on 47 patients with an $R_1$-resection of the bronchial resection margin. Five (stage IB) patients
were planned to undergo a reoperation. Three of these patients refused a reoperation and two underwent a pneumectomy after a prior lobectomy. The remaining 42 patients were not suitable for a reoperation because of high stage disease or limited cardio-pulmonary capacity. Ghiroibelli et al. recommend a reoperation in patients with microscopic residual disease and stage I and II NSCLC. However, after prior pneumectomy, a stump amputation is not recommended. For patients with stage III NSCLC and an R1-resection of the bronchial resection margin, radiotherapy could be considered [9]. Kimura et al. describe 38 patients with microscopic residual disease receiving adjuvant radiotherapy, consisting mainly of squamous cell carcinomas, favourable stages and patients with no others ‘none curative factors’. Kimura et al. reported a 5-year survival of 36%, which was the best survival among all forms of irradical resections included in this study. Considering this acceptable 5-year survival rate and the fact that the majority of the recurrences were distant metastasis rather than local recurrence following radiotherapy, Kimura et al. recommend adjuvant radiotherapy to avoid local recurrence and improve survival [19]. Also others report relative good survival rates after radiotherapy and/or a decrease in the number of local recurrences [9,12,18,35]. However, others report no favourable results after adjuvant radiotherapy [13,14,21].

Hofmann et al. reported a trend to a better survival after adjuvant radiotherapy in patients with R1-resections (median survival: 14 vs. 6 months, p = 0.086). However, this trend only applied to N0/N1-disease. In patients with N2-disease, no survival benefit was seen after radiotherapy. Hofmann et al. conclude that in order to prevent local recurrence in patients with an R1-resection and with N0/N1-disease, radiotherapy should be applied. In patients with an R1-resection and N2-diseases, the value of radiotherapy is unclear [8]. Recent randomized studies suggest a survival advantage after radiotherapy in patients with N2-disease after radical surgery (R0-resection). However, whether this also applies to patients with an R1-resection remains unclear.

Liewald et al. compared survival rates of R1-resection of the bronchial resection margin with patients with a radical resection. Median survival for patients with stage III NSCLC was comparable: 9 and 11.6 months, respectively. However, in patients with stage I and II disease, a survival difference was observed: 21 and 64 months (stage I) and 12 and 38 months (stage II), respectively. Furthermore, in stage I and II disease, local recurrence was the predominant form of relapse as compared to more distant metastasis observed in patients with stage III NSCLC. Liewald et al. recommend a reoperation in patients with stage I and II NSCLC, provided that patients are in good physical condition and that a further resection is technically and functionally feasible [10].

Dienemann et al. found that 27% of patients with mucosal residual disease had N2 or N3 lymph node metastasis. In case of submucosal and peribronchial residual disease, this increased to 68 and 88%, respectively [14]. Also Kaiser et al. found that extra-mucosal residual disease was associated with a higher stage NSCLC (stage III) [34]. Law et al. described a poor survival in patients with peribronchial residual disease. Of the eight patients with submucosal or peribronchial residual disease, seven had hilar or mediastinal lymph node metastasis and all died within 2 years [20]. In a study by Massard et al., 87% of the patients with peribronchial residual disease had N2 lymph node metastasis [35]. From the above discussion, it can be concluded that a reoperation will not improve the prognosis in these patients with submucosal or peribronchial residual disease, because these patients will not die as a consequence of residual disease at bronchial margin (i.e. local recurrence). These patients die because of the association with systemic disease and N2/N3 lymph node metastasis. A reoperation for an R1-resection of the bronchial resection margin would only be sensible in patients with stage I/II NSCLC. In patients with an R1-resection and N0/N1-disease in whom a reoperation is not feasible because of various reasons (e.g. anatomical or functional) radiotherapy could be considered in case of a properly defined radiation field. Snijder et al. describe 28 patients with stage I NSCLC and microscopic residual disease at the bronchial resection margin. Five patients underwent a reoperation 3–34 days after the primary operation, and all these reoperations were radical. Five-year survival rate of these patients was 40% as compared to 27% in patients that were not reoperated. None of the patients developed local recurrence after a reoperation. Therefore, Snijder et al. recommend consideration of reoperation in patients with stage I NSCLC and an R1-resection of the bronchial resection margin [21].

The recurrence rate after sleeve resection (10%) seems higher than after standard resections, yet survival seems comparable [42]. A problem in many studies is that the local recurrence is poorly defined. Is the recurrence at the bronchial anastomosis or in loco-regional lymph nodes? Kawahara et al. noted a local recurrence at the bronchial anastomosis in 7 out of 132 sleeve resections. In six patients, the frozen section analyses were negative. Five patients received adjuvant radiotherapy with survival of 6 months to 4 years [43].

There are no studies reporting on the value of adjuvant chemotherapy after an R1-resection of the bronchial resection margin. Probably, in the future, this question will not be evidenced, as the use of adjuvant chemotherapy after radical resection will increase [44,45]. Furthermore, the role of adjuvant chemotherapy after previous neo-adjuvant chemotherapy is unknown. In these patients, the general condition will be important to decide whether or not to give additional adjuvant chemotherapy.

7. Discussion

The incidence of a macroscopically radical resection after which the pathologists report the presence of microscopic residual tumour tissue at the bronchial resection margin (R1-resection) is approximately 4–5% of all lung resections. It is even seen in the more peripheral localized tumours in which there seems to be sufficient macroscopic tumour-free margin. Frozen section evaluation, as advised in some guidelines, especially when it concerns centrally localized tumours, is less reliable in detecting extra-mucosal microscopic disease at the bronchial resection margin. Therefore, in addition to these guidelines, it is advisable to take additional samples from these extra-mucosal parts of the bronchus (especially the peribronchial part). Furthermore,
node metastasis, the indication for radiotherapy is based on resection of the bronchial resection margin with N2 lymph nodes, irrespective of their stage [5]. However, the evidence for this recommendation is limited. The literature only comprises of small retrospective studies collected over many years. Partly due to this, it is difficult to assess a potential beneficial effect of radiotherapy on local recurrence rates. In case of an R1-resection of the bronchial resection margin with N2 lymph node metastasis, the indication for radiotherapy is based on the presence of N2 lymph node metastasis. There is no evidence available concerning adjuvant chemotherapy in patients with an R1-resection of the bronchial resection margin.

Further treatment to prevent local recurrence is not advisable in patients with stage III NSCLC because the prognosis of these patients is limited due to distant metastasis and not due to local recurrence per se. Based on the previous discussion, proposed recommendations for adjuvant treatment of microscopic residual disease at the bronchial margin after lung resection are shown in Table 2. Based on the literature, it is not possible to make an evidence-based recommendation for adjuvant treatment for a local recurrence after sleeve resection. When a local recurrence is becoming evident, it is important to perform a complete work-up of this patient and to judge if a reoperation, mostly a completion pneumonectomy, is possible.

References


