Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins — implications for patient selection for segmentectomy

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Abstract

Objective: Segmentectomy has recently been suggested as alternative to lobectomy for curative treatment of early-stage non-small cell lung cancer (NSCLC). This study was performed to investigate if localisation of the resected segment or width of resection margins influence local recurrence following complete segmentectomy of stage IA NSCLC.

Methods: Between 1987 and 2002, 49 segmentectomies and 150 lobectomies were performed in patients with pT1pN0cM0-NSCLC in our institution. Indications for segmentectomy were a limited pulmonary function or severe comorbidity. The median follow-up duration was 54 months. Local recurrence was distinguished from secondary primary lung cancer and was defined as tumour within the same lung or in the ipsilateral mediastinum. Segment localisation, width of resection margins, tumour size, tumour type, grading and age were analysed concerning their influence on local recurrence.

Results: Local recurrence occurred in 16% of patients with segmentectomy and was significantly more frequent than in patients with lobectomy (5%; \( p = 0.005 \); log-rank test). Segmentectomy in the S1—3 region tended more frequently to local recurrence than segmentectomy in the remaining segments (\( p = 0.08 \); log-rank test): There was no recurrence following segmentectomy in the S7—10 region (\( n = 6 \)) or of S4—5 (\( n = 5 \)). Recurrence occurred in 7 (23%) out of 30 patients with segmentectomy in the S1—3 region and in 1 (12%) out of 8 patients with S6-segmentectomy. Also, resection margins \(< 1 \text{ cm} \) tended to be associated with local recurrence (\( p = 0.06 \); log-rank test). Conclusions: The frequency of local recurrence following segmentectomy might be influenced by segment localisation and width of resection margins. Segmentectomy within the S1—3 region should be avoided whenever possible.

Keywords: Lung neoplasm; Surgery; Prognosis; Survival rate; Local recurrence

1. Introduction

Segmentectomy for the treatment of lung cancer was first described by Jensik et al. [1] in 1973. Nevertheless, lobectomy combined with systematic lymph node dissection has been accepted as the standard treatment for lung cancer even for small primary tumours for a long time. The only randomised trial worldwide, investigating the question whether limited resection is comparable to standard lobectomy has been published in 1995 by the Lung Cancer Study Group (LCSG) [2] demonstrating frequent local recurrences and a tendency towards poorer survival in patients with limited resections.

However, in this trial, wedge resections and segmentectomies were grouped together as limited resections and survival data could not be analysed separately. This was considered a major limitation of the LCSG trial because wedge resections were associated with an increased risk of locoregional recurrence compared to segmentectomies [2].

Recently, it has been reported that segmentectomy for small-sized stage IA lung cancers can yield outcomes equivalent to lobectomy. The studies by Okada et al. and Koike et al. [3—5] showed that survival and local recurrence rate were not compromised following segmentectomy with intraoperative lymph node assessment when the indication was limited to stage IA tumours up to 2 cm. The most convincing advantage of segmentectomy is that it spares pulmonary function compared to lobectomy [6] without compromising survival or local recurrence in stage IA NSCLC [7]. Thus, patients undergoing segmentectomy have a better ability to withstand further pulmonary resection in the future if a second primary lung cancer should develop. Furthermore,
preserving pulmonary function will likely reduce perioperative mortality and morbidity. However, it is repeatedly reported that patient selection for segmentectomy in stage IA NSCLC needs to be performed carefully [5,8—11]. The most common parameter for patients selection is a tumour size of ≤2 cm [3—5] or even ≤1 cm [12]. However, tumour localisation, width of resection margins, tumour histology, tumour differentiation and age might theoretically also impact the further clinical course, and thus be important in patient selection. Therefore, we performed a retrospective study to analyse the influence of these parameters on local recurrence and survival following segmentectomy in stage IA NSCLC.

2. Patients and methods
2.1. Patients

In this retrospective study, we reviewed the clinical and pathology files of 1311 consecutive patients who underwent complete resection (R0) of pT1-4 pN0-2 cM0 NSCLC between 1987 and 2002. Anatomical segmentectomy with systematic lymphadenectomy was performed in 49 and lobectomy with systematic lymphadenectomy in 150 eligible stage IA patients. All patients were operated in the Department of Thoracic Surgery of the Albert-Ludwigs-University Freiburg. Indications for segmentectomy were limited pulmonary function or severe cardiac comorbidity. The standard preoperative evaluation included a careful history and physical examination, full pulmonary function analyses with blood gas analysis, roentgenographic assessment including standard posterolateral chest films and computed tomography of the chest and upper part of the abdomen. No further preoperative staging was performed routinely; however, cranial computed tomography or bone scintigraphy was used selectively to investigate specific preoperative symptoms potentially related to metastatic disease. Mediastinoscopy was not used in preoperative evaluation of stage IA patients. Only patients without suspicion of metastases (cM0) were entered into the study. Furthermore, patients were excluded if they had synchronous or secondary primary lung cancer, had a previous malignant tumour at any site or had received preoperative or postoperative adjuvant therapy.

Postoperative pathologic staging was done after the resected specimen was reviewed histologically and all dissected lymph nodes were assessed. The tumours were classified according to the international union against cancer (UICC) TNM-classification [13]. Furthermore, segment localisation, width of resection margins, tumour size, tumour type, grading and histologic clearance at bronchial, parenchymal and vascular resection margins were recorded. Segment localisations were reported using numbers 1—10 as described previously [14]. The width of resection margins was determined by pathological measurement of the distance between tumour and parenchymal and bronchial resection margins in deflated, formalin-fixed specimens. The closest distance between tumour and resection margins was defined as the width of margin. The surgical and pathologic reports of all patients were carefully reviewed to ensure that no residual tumour was left behind, and that no involved regional nodes (N1 and N2) were present.

Follow-up studies included physical examination, chest X-ray and blood tests in a 3-month interval, and an additional thoracic CT scan, abdominal ultrasound and bronchoscopy in a 6-month interval. Close follow-up was documented by contacting family practitioners with questionnaires concerning local relapse, distant metastasis and death. If possible, a relapse was confirmed at our institution and the patient was admitted for subsequent therapy. Local recurrence was distinguished from secondary primary lung cancer and was defined as tumour within the same lung or in the ipsilateral mediastinum. Criteria for synchronous or secondary primary lung cancer were a different histologic type or an origin from carcinoma in situ, as suggested previously [15]. The median follow-up duration was 54 months (range 3—192 months).

2.2. Operations

The approach to anatomical segmentectomy and lobectomy in this clinical series was standard postero-lateral muscle-sparing thoracotomy being performed as described previously [16]. Both types of resections involved dissecting out the hilar structures and securing the branches of the pulmonary artery, pulmonary vein and segmental bronchus individually as described previously [1]. For segmentectomy, the segmental plane was identified by the use of CPAP after the bronchus was dissected. Subsequently, the segmental plane was prepared by fingerling out and blunt dissection. All patients had a systematic lymphadenectomy as described previously [17,18]. Postoperative care was similar following lobectomy and segmentectomy. The patients were admitted overnight to the surgical intensive care unit for observation. All patients were extubated in the operation room immediately after reversal of anaesthesia.

2.3. Statistical analyses

Statistical analysis was performed using SPSS software version 14.0 for PC (SPSS Inc., Chicago). Continuous variables such as tumour size and width of resection margin were expressed as mean ± standard deviation. Differences between groups with continuous variables were assessed by Students’ t-test. For analysis of follow-up data, life table curves were calculated using the Kaplan—Meier method and were compared by log-rank statistics. For survival analyses, the primary end point was cancer-related death. The survival time was measured from the date of surgery to death and data of patients who were still alive at the end of the study were censored. For analyses of relapse patterns, end points were local recurrence or distant metastasis. Recurrence-free and metastasis-free time was measured from the date of surgery to the first relevant event, and data of patients without relapse at the end of the study were censored. The threshold for statistical significance was p < 0.05.

3. Results
3.1. Clinicopathological parameters

The stage IA patients comprised 141 men and 58 women. Their age range was 34—83 years with a median age of 63
years. The tumour was located in the right lung in 107 (54%) patients and in the left lung in 92 (46%) patients. The histologic type in stage IA was squamous carcinoma in 62 (31%) patients, adenocarcinoma in 77 (39%), large cell carcinoma in 27 (14%) and adeno-squamous, bronchiolo-alveolar or undifferentiated carcinomas in 33 (17%) patients. Eighty-five patients (43%) had tumours of size 2 cm or smaller. The mean tumour size was 2.03 cm. The mean tumour size in the 49 segmentectomies was 1.87 cm and was not statistically different from the mean tumour size in the 150 lobectomies (2.11 cm, p = 0.15, t-test).

Segmentectomies were performed within the S1—3 region in 30 patients, within the S4—5 region in 5 patients, within the S7—10 region in 6 patients and by S6-resection in 8 patients. Segmentectomy resulted in a mean width of resection margins of 9.1 mm ± 9.35 so that we took 10 mm as cut-off value between small and wide resection margins. The width of resection margins following segmentectomy within the S1—3 region (9.9 mm ± 10.5) was not statistically different from the one following segmentectomy within the S4—10 region (8.0 mm ± 7.4; p = 0.49; t-test).

3.2. Local recurrence, metastasis and survival

The median follow-up duration in stage IA was 54 months. Within the observation period, a total of 41 stage IA patients (21%) developed a relapse (Table 1). Local recurrence occurred in 16 patients and distant metastasis in 25 patients (Table 1). All patients with relapse died of cancer-related causes leading to a 5-year survival rate of 79% in stage IA NSCLC. Segmentectomy was associated with a significantly poorer cancer-related 5-year survival than lobectomy in stage IA (67% vs 83%, respectively; p = 0.01, log-rank test) (Fig. 1, Table 1). Occurrence of distant metastasis was equal between segmentectomy and lobectomy; however, segmentectomy was associated with a significantly increased local recurrence rate compared to lobectomy (16% vs 5%, respectively; p = 0.005, log-rank test) (Table 1). Follow-up CT scans showed that 7 (87%) out of the 8 observed local recurrences following segmentectomy developed in the remaining lung parenchyma in the areas of the former resections.

In stage IA tumours of ≤2 cm diameter, 5-year survival rates following segmentectomy or lobectomy did not differ significantly (68% vs 85%, respectively; p = 0.39) (Fig. 2, Table 2), although a significantly increased local recurrence rate following segmentectomy was observed compared to lobectomy (12% vs 2%, respectively; p = 0.04; log-rank test) (Table 2). There was no correlation between tumour size and local recurrence: The mean tumour size in the 16 patients with local recurrence was 1.96 cm and was not statistically different from the mean tumour size in the 183 patients without local recurrence (2.04 cm, p = 0.81 t-test).

To verify possible reasons for the increased local recurrence rate in segmentectomy, localisation of resected segments, width of resection margins, tumour histology, tumour differentiation and age were analysed according to their influence on local recurrence following segmentectomy. Segmentectomy in the S1—3 region tended more frequently to local recurrence than segmentectomy in the remaining segments (p = 0.08; log-rank test, Table 3): There was no recurrence following segmentectomy in the S7—10 region (n = 6) or following bisegmentectomy of left side S4—5.
n = 5) (Table 4). Recurrence occurred in 7 (23%) out of 30 patients with segmentectomy in the S1–3 region and in 1 (12%) out of 8 patients with S6-segmentectomy (Fig. 3, Table 4). The segmentectomies resulted in pathologically determined resection margins of \( < 10 \text{ mm} \) in 35 patients and in margins \( > 10 \text{ mm} \) in 14 patients. No local recurrence was observed in patients with resection margins \( > 10 \text{ mm} \). In contrast, 8 (23%) patients with margins \( < 10 \text{ mm} \) developed a local recurrence (\( p = 0.06; \text{log-rank test} \)) (Table 3). Tumour histology, tumour differentiation and patients age showed no tendency towards a correlation with local recurrence (\( p = 0.71, p = 0.73 \) and \( p = 0.73 \), respectively; log-rank test) (Table 3).

4. Discussion

Here, we demonstrate for the first time an analysis of factors other than tumour size potentially influencing local recurrence following segmentectomy with systematic lymphadenectomy in order to verify criteria for patient selection prior to segmentectomy in stage IA NSCLC. The importance of careful patient selection for segmentectomy has first been shown by Warren et al. [19] who reported a poorer survival associated with segmentectomy in comparison to lobectomy in the total population of his stage IA patients, but an equivalent survival for patients with tumours \( < 2 \text{ cm} \) diameter. However, in this study, local recurrence was increased following segmentectomy even in those small tumours. The Lung Cancer Study Group (LCSG) trial [2]
demonstrated a tendency towards a better survival and less local recurrences following lobectomy, resulting in a widespread adoption of lobectomy as standard procedure for stage IA patients with normal pulmonary reserve. Because of the critical design of the LCSG trial which grouped wedge resections and segmentectomies together, and because of the awareness that patient selection is important for segmentectomy, several thoracic surgeons have continued to perform intentional segmentectomies for the treatment of stage IA lung cancer [3—7].

Besides the most common parameter for patient selection in stage IA— a tumour size of ≤2 cm [3—5] — additional factors are believed to be important for selection to segmentectomy. For example, it has been hypothesized that the width of resection margins is important in segmentectomy for stage IA NSCLC [8,20]. Kodama et al. [20] noted that segmentectomies were only performed for tumours less than 2 cm in diameter with a well-defined tumour extension. In addition, they describe that strong spicula on preoperative computed tomography was a contraindication for segmentectomy in their study [20]. Although they proposed how to prevent small safety margins preoperatively, no standards concerning safety margins in lung cancer segmentectomy have been proposed so far. Although the correlation between width of margin and recurrence was not statistically significant in the present study, it indicates that a safety margin of >10 mm might be reasonable, because none of 14 patients with resection margins >10 mm and in contrast, 8 (23%) patients with margins ≤10 mm developed a local recurrence (Table 3).

Mostly, margins of the segments that need to be resected to completely remove the tumour can only be determined intraoperatively and not on preoperative computed tomography. For cases of intraoperatively detected small safety margins, Martin-Ucar [9] stated in his conference discussion that if he was not intraoperatively certain that he performed a complete excision, then he would convert to a lobectomy—even although all patients in the study of Martin-Ucar et al. had a compromised preoperative pulmonary function (median FEV1 prior to lobectomy 44% of estimated value, range 30—54% and prior to segmentectomy 45% of estimated value, range 19—54%). Since the width of resection margins was important for local recurrence following segmentectomy in the present study, we suggest to consider the ability to keep a safety margin of >10 mm as criterion for preoperative patient selection prior to segmentectomy. A well-defined tumour extension on computed tomography might help to achieve a sufficient safety margin (Table 5) and for cases showing resection margins ≤10 mm on intraoperative frozen section analysis, bisegmentectomy or lobectomy might be recommendable.

Although, Keenan et al. [6] and Martin-Ucar et al. [9] reported the localisations of segments which were resected in their studies demonstrating equal survival following lobectomy and segmentectomy, the influence of the localisation of the resected segments on the further clinical course had not been analysed so far. The present study shows no recurrence following segmentectomy in the S7—10 region or following bisegmentectomy of left side S4—5. In contrast, segmentectomy in the S1—3 region tended more frequently to local recurrence than segmentectomy in the remaining segments (Table 3), suggesting that segmentectomy within the S1—3 region should be avoided whenever possible (Table 5). Since this is the first report describing an increased local recurrence rate following segmentectomy within the S1—3 region, the plan of the present study did not focus on possible reasons for this tendency. Thus, the present study does not allow to draw any conclusions concerning this interesting question. However, there is no hint for smaller resection margins within the S1—3 region: The width of resection margins following segmentectomy within the S1—3 region (9.9 mm ± 10.5) was not statistically different from the one following segmentectomy within the S4—10 region (8.0 mm ± 7.4; p = 0.49; t-test).

The present study shows that cancer-related survival following segmentectomy is not significantly different to lobectomy in stage IA NSCLC of ≤2 cm diameter, but local recurrence is increased even in those small tumours. This observation is comparable to the results of Warren et al. [19], but the causes for local recurrence following segmentectomy in stage IA are only elucidated in the present study considering segment localisation, width of resection margins, tumour size, tumour type, grading and age. It does not seem important that the indications for segmentectomy in Warren et al. [19] and our studies were at the discretion of the surgeon and e.g. dependent on pulmonary function or comorbidity, because similarly, other studies investigating segmentectomy in patients who would have tolerated lobectomy also showed equivalent survival for segmentectomies and lobectomies in patients with stage IA NSCLC of ≤2 cm [3—5].

Although previous well-planned studies showed that careful patient selection may result in adequate postoperative long-term results following limited resection of stage IA NSCLC, [3—5,8,11], controversy remains because of their retrospective designs [10]. Therefore, it has repeatedly been proposed to perform a prospective randomised trial comparing lobectomy to segmentectomy in stage IA NSCLC [10,12]. Such a study would be especially interesting in patients who would tolerate a lobectomy. Since it has already been reported that limited resections in elderly patients ≥75 years of age results in an equal overall survival as lobectomy [11], a prospective randomised trial should include carefully selected patients younger than 75 years.

According to the literature and to the results of the present study, such a patient selection for segmentectomy should consider the following points: First, only patients with tumours of ≤2 cm diameter on computed tomography should be included [3—5] (Table 5). Second, tumour margins should be well defined on computed tomography (Table 5). Third, for

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cases showing resection margins ≤10 mm in intraoperative frozen section analysis, bisegmentectomy or lobectomy might be recommended (Tables 3 and 5). Fourth, systematic pulmonary and mediastinal lymph node dissection with frozen section analysis demonstrating pN0-status should be mandatory as stated previously [3]. A systematic lymph node dissection has been shown to be superior to lymph node sampling [21,22] as, e.g. a 4% increase in number of positive lymph nodes has been observed when lymph node sampling was compared with lymph node dissection in early-stage NSCLC [21]. For preoperative assessment of the lymph node status, fluorodeoxyglucose positron emission tomography (FDG-PET) could be useful [23], but was not evaluated in the present study. Fifth, segmentectomy within the S1–3 region should be avoided when ever possible, as discussed above (Tables 3 and 5).

References


Appendix A. Conference discussion

Dr K. Jeyasingham (Bristol, United Kingdom): When you did your frozen sections, did you have them at the line of resection after inflating the segment that you had removed or was it in a deflated state, and how were you able to measure the separation in terms of millimetres in a deflated segment, or was it in an inflated segment?

Dr Sienel: When frozen sections were performed, the line of resection was examined in deflated lung specimens. As this was a retrospective study, the analysis of the width of resection margins was performed according to the final pathological reports which referred to formalin-fixed lung specimens.

Dr Jeyasingham: The second question, was there a histological examination of the intersegmental lymph nodes to ensure that there was no tumour in any of them?

Dr Sienel: Yes. The pathologist examined all lymph nodes in the resected specimens and also the lymph nodes that were dissected during systematic lymphadenectomy, and only patients were admitted to this study who had pN0 disease.

Dr D. Waller (Leicester, United Kingdom): I would caution you about over-interpreting your data because it’s based on 8 patients. Can you confirm that the local recurrence was confirmed histologically in each of those cases?

Dr Sienel: Sometimes we could not confirm the local recurrence histologically.

Dr Waller: So how can you be sure that all of those 8 patients did have local recurrence, because your analysis is based on a very small number of patients.

Dr Sienel: We are quite sure because the recurrent tumours were growing and all patients with recurrence died of cancer-related causes.

Dr Waller: Was it local changes in the lung or was it nodal disease?

Dr Sienel: We considered everything as local recurrence that was a growing mass in the lung or in the ipsilateral mediastinum, but for this study, so far we have not been able to distinguish between nodal recurrence and recurrence in the lung, but we are working on this topic.

Dr Waller: So of those 8 patients, how many had nodal recurrence and how many had lung recurrence?

Dr Sienel: That remains the question so far.

Dr Waller: But there were how many of those 8 patients that you described?

Dr Sienel: So far we don’t know. We are still working on distinguishing the kind of local recurrence, but we will answer this question in the final report about today’s presentation.

Dr M. Zielinski (Zakopane, Poland): Your results are very interesting. The striking difference in the recurrence rate between the upper and lower lobes is hard for me to understand. You probably have a theory to explain it. Why was the difference so big in the upper and lower lobes? That’s my first question.
Second, could you describe your technique of intrapulmonary lymphadenectomy, how deep you reached the stations 11, 12, or maybe 13? Could you say a few words about that?

Dr Sienel: Concerning the first question, I have asked this question myself many times before, and I found no hint in the literature that could answer this observation. Maybe one can find the answer when the anatomical lymph node drainage is examined, but all the literature I read did not give a concrete answer to this question.

Concerning the second question, we routinely dissect the lymph nodes of stations 11, 10, 9, 8, 7, 5, 4 and 2. Of course, we don’t dissect the intrapulmonary lymph nodes of the lung that is not touched.