Original Article

Clinical and bronchoscopic aspects of bronchial healing after sleeve resection for lung cancer: a multivariate analysis on 541 cases

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Contributions: (I) Conception and design: A Lopez-Pastorini, C Eckermann, E Stoelben; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: A Lopez-Pastorini, C Eckermann; (V) Data analysis and interpretation: A Lopez-Pastorini, C Eckermann; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Anastomotic insufficiency is a feared complication after sleeve lobectomy. Bronchoscopy can help to identify anastomoses at risk. We evaluated negative predictors of anastomotic healing using a bronchoscopic grading system in a large collective of lung cancer patients.

Methods: From 2006 to 2019, 541 sleeve lobectomies for lung cancer were performed. Anastomotic healing was documented by bronchoscopy on the seventh postoperative day using a standardized classification system for anastomotic grading (grade 1, perfect healing to 5, insufficiency). Grade 1 and 2 were considered satisfactory and the patients were discharged. Grade 3 or higher was considered critical. These patients received systemic antibiotic treatment and re-bronchoscopy was performed 4 days later.

Results: In 18.5% of the patients, the anastomosis was assessed as critical. 19% of patients with critical anastomosis on the 7th postoperative day developed anastomotic insufficiency during the postoperative course, compared to 0.2% in patients with satisfactory anastomotic healing. Bilobectomies, low preoperative forced expiratory volume in 1 second (FEV1) values, high preoperative levels of C-reactive protein and neoadjuvant radiation were identified as independent risk factors for critical anastomotic healing.

Conclusions: Bronchoscopic assessment of anastomotic healing is an effective tool to identify critical anastomoses. Neoadjuvant radiation, bilobectomies and acute or chronic inflammation were independent risk factors for bronchial healing disorders and should be considered at the planning stage of surgery.

Keywords: Sleeve lobectomy; anastomotic insufficiency; bronchoscopy

Submitted Oct 22, 2021. Accepted for publication Jan 07, 2022.
doi: 10.21037/jtd-21-1627
View this article at: https://dx.doi.org/10.21037/jtd-21-1627

Introduction

The purpose of sleeve lobectomy is to avoid pneumonectomy and thus to preserve functional lung tissue. In specialized centers, the systematic application of sleeve resection can reduce the rate of pneumonectomies below 10% (1). Patients benefit from lower postoperative morbidity, better quality of life and higher long-term survival (2,3).

Anastomotic insufficiency is a severe complication following sleeve resection. Completion pneumonectomy performed due to anastomotic complications is associated

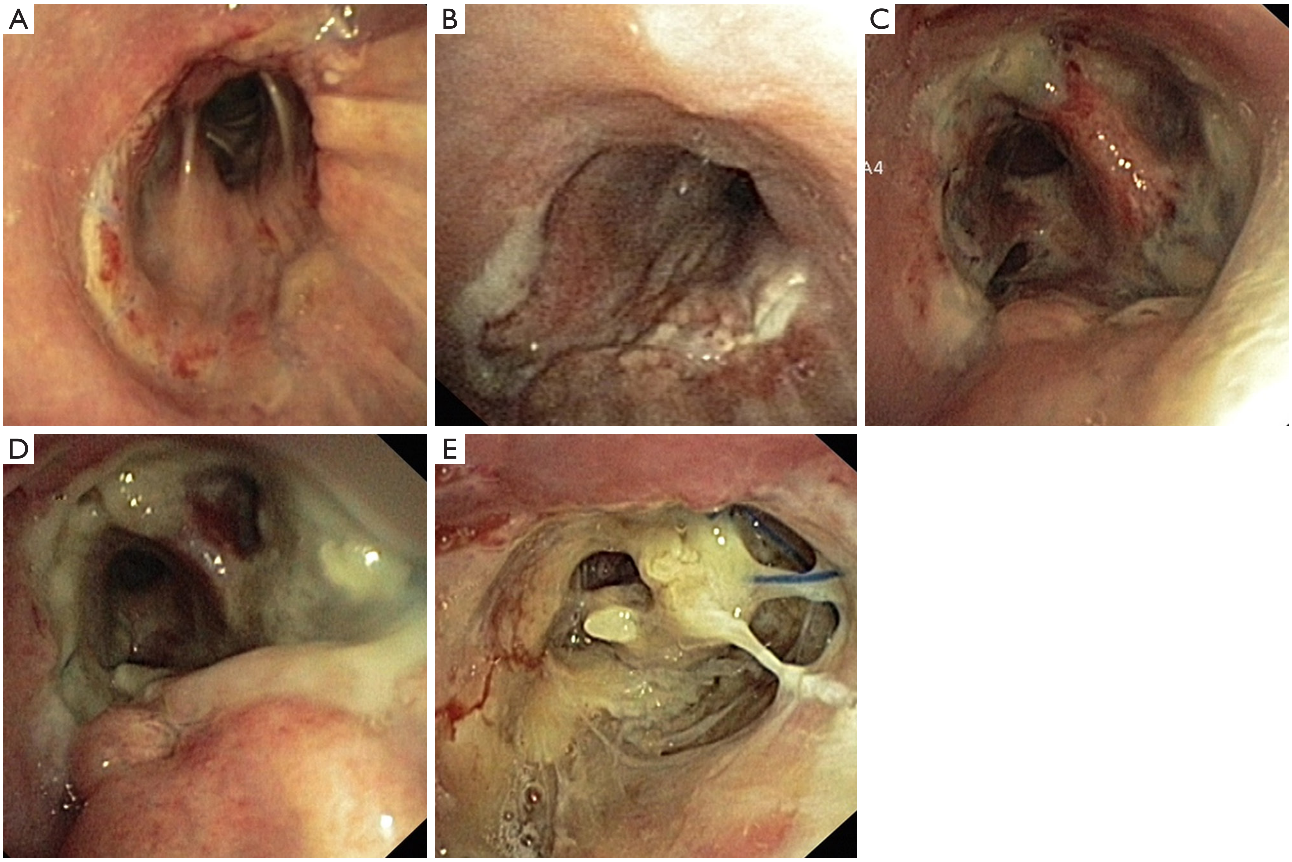


Figure 1 Bronchoscopic classification of anastomotic healing. (A) grade 1, good healing without signs of ischemia or necrosis; (B) grade 2, focal mucosal necrosis without ischemia; (C) grade 3, circular mucosal necrosis and/or ischemia in the distal bronchus of the anastomosis; (D) grade 4, bronchial wall necrosis with instability; (E) grade 5, bronchial wall necrosis with perforation, insufficiency (1).

with high morbidity and mortality (4,5). Previously, various factors influencing anastomotic healing have been listed, among these neoadjuvant mediastinal radiation, non-radical resection and postoperative infection (6-10). However, systematic investigations were carried out only for preoperative irradiation, where a negative influence on anastomotic healing could be demonstrated (1,8,10).

In our institution, a five-level bronchoscopic classification was developed to assess anastomotic healing on the seventh postoperative day (*Figure 1*). The classification is based on the degree of ischemic changes in the mucosa of the distal part of the anastomosis. From circular endobronchial signs of mucosal ischemia onwards (grade 3 or higher), the anastomosis is considered to be at high risk for the development of insufficiency (1). Based on the grading of the anastomosis, patients are discharged (grade 1 and 2) or are kept in hospital for systemic antibiotics and re-bronchoscopy 4 days later (grade 3 or higher). This procedure was based on clinical experience and has not yet been systematically validated.

Therefore the aims of this study were first, to investigate the predictive power of our anastomosis classification for the development of insufficiencies and second, to identify negative predictors of anastomotic healing based on this classification. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1627/rc).

Methods

The study was approved by the ethics committee of the University of Witten Herdecke (Nr. 51/2017). All participants gave informed consent before taking part in the study. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

From January 2006 to December 2019 3883 anatomic

Table 1 Anastomosis grading on postoperative day 7 (n=541)

Anastomosis grading	n (%)
Grade 1	234 (43.3)
Grade 2	207 (38.3)
Grade 3	75 (13.9)
Grade 4	21 (3.9)
Grade 5	4 (0.7)

resections (including lobectomies, bilobectomies, segmentectomies and pneumonectomies) for the treatment of lung cancer were performed in our hospital. Of these, 621 (16%) were performed as sleeve resections. To focus on a homogenous group of patients, sleeve pneumonectomies (n=16), isolated bronchial sleeve resections (n=21), carinal resections (n=20) and segmentectomies (n=1) were not included in the analysis. For the same reason, patients with carcinoid tumors (n=26) were excluded because they differ from other lung cancer patients in terms of age, pretreatment, smoking habits and prognosis. Finally, 541 consecutive patients who underwent sleeve lobectomy or sleeve bilobectomy for lung cancer between January 2006 and December 2019 were included in this study and retrospectively analyzed.

Patients' characteristics and perioperative data were collected prospectively using a standardized data entry form. Patients consented preoperatively for anonymous data collection.

Preoperative staging consisted in whole body MRI or PET-CT, brain MRI and mediastinal staging by mediastinoscopy or EBUS bronchoscopy.

Neoadjuvant chemotherapy was based on a platinum-containing treatment combined with vinorelbine or pemetrexed. In case of neoadjuvant chemoradiation two cycles of chemotherapy were applied simultaneously to radiotherapy. Depending on histology, tumor size and location two cycles of induction chemotherapy were optional.

Radiotherapy was applied using a fractionated radiation therapy with a single daily dose of 1.8 to 2 Gy with 5 fractions per week up to a total dose of 60–66 Gy.

Preoperative pulmonary function testing (FEV1) and C-reactive protein (CRP) levels were obtained prior to resection.

The surgical procedures included lobectomies and bilobectomies with complete bronchus sleeve resection and radical lymphadenectomy. Angioplastic or intrapericardial resections were performed when necessary. The bronchial anastomosis was performed by a continuous suture with 4-0 polydioxanone (PDS). In the case of neoadjuvant radiotherapy, the anastomosis was routinely covered with vital pedicled tissue. In addition to pedicled thymic flaps, which are standard practice at our hospital, flaps from intercostal muscle, pectoralis major, latissimus dorsi, and pericardium were used. Covering of the anastomosis in non-pretreated patients was performed at the surgeon's preference.

In all patients the healing of the anastomosis was assessed by bronchoscopy at the 7th postoperative day, using our classification from grade 1 to 5 (*Figure 1*). Anastomotic insufficiency was defined as grade 5 anastomosis (bronchial wall necrosis with perforation, insufficiency).

Bronchoscopy was performed by the surgeon who performed the operation or by a member of the surgical team. Intraoperative bronchoscopy to examine the anastomosis was not performed as a standard procedure. Bronchoscopies before postoperative day seven were performed when clinically necessary.

Grade 1 and 2 healing were considered satisfactory and the patients were discharged. An anastomosis healing of grade 3 or higher was considered critical. These patients received systemic antibiotic treatment and re-bronchoscopy was performed 4 days later to monitor bronchial healing.

Anastomotic insufficiencies were treated conservatively with antibiotics or surgically. The decision regarding the approach was made on an individual basis.

Statistical analysis

Statistical evaluation was conducted with MedCalc 20.013 (MedCalc Software Ltd., Belgium). Categorical data between groups was compared made using the χ^2-test. Comparison of means was performed by the unpaired t-test. In order to evaluate the independence of factors on anastomotic healing (grade <3 *vs.* grade ≥3), all variables showing statistical significance (P<0.05) were included in a logistic regression analysis. The classifying cut-off value was set to 0.5. P values <0.05 were considered significant.

Results

Anastomosis grading on the seventh postoperative day is shown in *Table 1*. Clinicopathological characteristics are summarized in *Table 2*. Anastomotic healing was satisfactory (grade 1 or 2) in 441 patients (81.5%). In 100 patients

Table 2 Clinicopathological characteristics (univariate analysis)

Variables	Anastomosis grade <3 (n=441)	Anastomosis grade ≥3 (n=100)	P value
Male sex	290 (65.8%)	75 (75.0%)	0.08
Age ≥70 years	124 (28.1%)	32 (32.0%)	0.44
Preop. CRP			
>3 mg/L	402 (91.2%)	95 (95.0%)	0.21
>20 mg/L	153 (34.7%)	48 (48.0%)	0.013
>40 mg/L	103 (23.4%)	40 (40.0%)	<0.001
FEV1 <80%	276 (62.6%)	83 (83.0%)	<0.001
Neoadjuvant therapy			
No neoadjuvant therapy	330 (74.8%)	64 (64.0%)	0.03
Chemotherapy	38 (8.6%)	6 (6%)	0.39
Radiation/chemoradiation	73 (16.6%)	30 (30%)	0.002
Current or former smoker	410 (93%)	97 (97.0%)	0.14
Tumour size, cm	4.52±2.56	4.71±2.82	0.53
Nodal stage (postoperative)			
N0	156 (35.4%)	41 (41.0%)	0.29
N1	163 (37.0%)	27 (27.0%)	0.06
N2/N3	122 (27.7%)	32 (32.0%)	0.39
Stage (postoperative)			
Ia/Ib	30 (6.8%)	3 (3.0%)	0.15
IIa/IIb	178 (40.3%)	35 (35.0%)	0.33
IIIa/IIIb	215 (48.8%)	58 (58.0%)	0.1
IVa/IVb	18 (4.1%)	4 (4.0%)	0.96
Histology			
Adenocarcinoma	150 (34.0%)	29 (29.0%)	0.34
Squamous cell carcinoma	237 (53.7%)	65 (65.0%)	0.04
Other	47 (10.7%)	6 (6.0%)	0.16
Type of resection			
Lobectomy	412 (93.4%)	78 (78.0%)	<0.0001
Right upper lobe	161 (36.5%)	28 (28.0%)	0.11
Left upper lobe	125 (28.3%)	17 (17.0%)	0.02
Right lower lobe	47 (10.7%)	14 (14.0%)	0.35
Left lower lobe	75 (17%)	19 (19.0%)	0.63
Middle lobe	4 (0.9%)	0	0.34

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Anastomosis grade <3 (n=441)	Anastomosis grade ≥3 (n=100)	P value
Bilobectomy	29 (6.6%)	22 (22.0%)	<0.0001
Upper	23 (5.2%)	13 (13.0%)	0.005
Lower	6 (1.4%)	9 (9.0%)	<0.0001
Thoracoscopic resection	9 (2.0%)	2 (2.0%)	0.98
Angioplasty	166 (37.6%)	47 (47.0%)	0.08
R1/R2 resection	59 (13.4%)	18 (18.0%)	0.24
Discharge on postoperative day	12.0±7.77	16.7±10.54	<0.0001
Postoperative complications	179 (40.1%)	61 (61.0%)	<0.001
Prolonged air leak (>7 d)	71 (16.1%)	18 (18.0%)	0.64
Pneumonia	35 (7.9%)	22 (22.0%)	0.001
Atrial fibrillation	22 (5.0%)	5 (5.0%)	1
Respiratory failure	14 (3.2%)	6 (6.0%)	0.18
Re-operation	12 (2.7%)	9 (9.0%)	0.003
Anastomosis insufficiency	1 (0.2%)	19 (19.0%)	<0.0001
Bleeding	11 (2.5%)	4 (4.0%)	0.41
Recurrent laryngeal nerve injury	4 (0.9%)	1 (1.0%)	0.93
Pleural empyema	4 (0.9%)	0	0.34
Other	37 (8.4%)	12 (12.0%)	0.26
Postoperative mortality	3 (0.7%)	6 (6.0%)	<0.001

CRP, C-reactive protein; FEV1, forced expiratory volume in 1 second.

(18.5%) the anastomosis was classified as critical (grade ≥3). Patients with critical anastomotic healing spent more time in hospital (16.7 *vs.* 12.0 days, P<0.0001) and had a longer drainage treatment time (8.2 *vs.* 6.8 days, P<0.05) compared to patients with a satisfactory anastomotic healing. Furthermore, patients with critical anastomoses suffered more complications (61.0% *vs.* 40.1%, P<0.001) and had a higher postoperative mortality (6.0% *vs.* 0.7%, P<0.001) than patients with satisfactory anastomosis. The most frequent complications were prolonged air leak (18.0% *vs.* 16.1%, P=0.64 and pneumonia (22.0% *vs.* 7.9%, P=0.001).

A total of 20 patients (3.7%) developed anastomotic insufficiency. In four patients, insufficiency (grade 5) was discovered during routine bronchoscopy on the seventh postoperative day, 16 patients developed an insufficiency in the further clinical course. 19 patients with anastomotic insufficiency were in the group with critical anastomotic healing and one in the group with satisfactory anastomotic healing (P<0.0001).

In patients who received neoadjuvant radiation insufficiency rate was 6.8% (7 from 103 patients) and in patients without neoadjuvant radiation 3.0% (13 from 438 patients, P=0.06).

Table 3 shows characteristics, initial surgery and clinical course of the patients with anastomotic insufficiency. Nine patients (45%) with anastomotic insufficiency underwent revision surgery, including four with revision of the anastomosis, four with completion pneumonectomy and one with middle lobe resection and reimplantation of the upper lobe to the main bronchus. One patient initially underwent revision of the anastomosis and later underwent pneumonectomy. In 12 patients (60%), anastomotic insufficiency was treated conservatively with antibiotics. Five patients (25%) with anastomotic insufficiency died during hospitalization. Mortality was 22% (2 of 9) in reoperated patients and 25% (3 of 12) in patients initially treated conservatively.

Table 3 Characteristics, initial surgery and clinical course of patients with anastomotic insufficiency

No.	Sex	Age	Preop. CRP	Preop. FEV1	Preop. RT	Initial surgery	AG POD 7	Postoperative course
1	M	54	9	66	No	Lower bilobectomy	4	Detection of insufficiency on POD 14. Conservative treatment. Discharged on POD 34
2	M	64	17	64	Yes	Upper bilobectomy, thymic flap	4	Massive hemoptysis on POD 17. Intraoperative detection of anastomosis insufficiency with broncho-pulmonary artery fistula. Completion pneumonectomy. Patient died shortly after surgery
3	M	81	29	55	No	Right upper lobe	4	Detection of insufficiency on POD 10. No surgery due to critical condition. Patient died of pneumogenic sepsis on POD 11
4	M	55	290	52	No	Left lower lobe	4	Detection of insufficiency on POD 28. Infarction of the remnant lung in CT-scan. Completion pneumonectomy. Discharged on POD 39
5	M	72	180	56	No	Left upper lobe, PA-angioplasty	4	Detection of insufficiency on POD 13. Conservative treatment. Discharged on POD 25
6	M	75	65	80	Yes	Right upper lobe, thymic flap	5	Detection of insufficiency on POD 7. Initially conservative treatment. Reoperation with Revision of the anastomosis on POD 30 due to persistent healing disorders. Reoperation due to empyema on POD 70. Died of pneumogenic sepsis on POD 110
7	F	72	14	59	No	Upper bilobectomy	4	Detection of insufficiency on POD 10. Conservative treatment. Discharged on POD 30
8	M	66	10	56	No	Right lower lobe	4	Detection of insufficiency on POD 16. Conservative treatment. Discharged on POD 23
9	M	51	116	62	Yes	Right upper lobe, thymic flap	5	Detection of insufficiency on POD 7. Conservative treatment. Died due to massive hemoptysis on POD 8
10	M	66	90	55	No	Right lower lobe	4	Detection of insufficiency on POD 10. Conservative treatment. Discharged on POD 19
11	M	64	81	70	No	Right lower lobe	5	Detection of insufficiency on POD 7. Conservative treatment. Discharged on POD 12
12	M	70	79	70	No	Right upper lobe, PA-angioplasty	5	Detection of insufficiency on POD 7. Reoperation with revision of the anastomosis and covering with thymic flap. Completion pneumonectomy on POD 10 due to necrosis of the remnant lung. Died of pneumogenic sepsis on POD 12
13	M	69	69	79	Yes	Right upper lobe and thymectomy, pectoralis mayor flap	3	Detection of insufficiency on POD 12. Reoperation with revision of the anastomosis. Discharged on POD 22
14	F	65	45	53	Yes	Right upper lobe, PA-angioplasty, thymic flap	3	Detection of insufficiency on POD 20. Completion pneumonectomy. Discharged POD 62
15	M	62	18	53	Yes	Left lower lobe	4	Detection of insufficiency on POD 10. Conservative treatment. Discharged on POD 20
16	M	64	7	78	Yes	Right lower lobe, thymic flap	3	Detection of insufficiency on POD 21. Conservative treatment. Discharged on POD 23

Table 3 (*continued*)

Table 3 (*continued*)

No.	Sex	Age	Preop. CRP	Preop. FEV1	Preop. RT	Initial surgery	AG POD 7	Postoperative course
17	M	67	49	61	No	Right lower lobe	4	Detection of insufficiency on POD 12. Reoperation with middle lobe resection and reimplantation of the upper lobe to the main bronchus. Discharged on POD 30
18	M	59	75	59	No	Left lower lobe, PA-angioplasty, aorta en bloc resection and reconstruction. Latissimus dorsi flap	3	Detection of insufficiency on POD 10. Reoperation with revision of the anastomosis. Discharge on POD 16
19	M	68	0	61	No	Right upper lobe	1	Detection of insufficiency on POD 12. Reoperation with revision of the anastomosis. Discharged on POD 19
20	M	61	40	89	No	Lower bilobectomy, thymic flap	3	Detection of insufficiency on POD 10. Conservative treatment. Discharged on POD 24

M, male; F, female; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 second; RT, radiotherapy; PA, pulmonary artery; AG, anastomosis grading; POD, postoperative day.

In the univariate analysis (*Table 2*) male sex, squamous tumor differentiation, sleeve bilobectomy, preoperative elevated CRP, longer operation time, reduced FEV1 and neoadjuvant radiotherapy showed positive correlation with critical anastomotic healing. These variables were included in a logistic regression analysis. The results are summarized in *Table 4*. Bilobectomy, preoperative serum CRP level >40 mg/L, FEV1 <80% and neoadjuvant radiation were independent predictors of critical anastomotic healing.

Long-term survival

Median overall survival was 49 months in the satisfactory anastomosis group and 31 months in the critical anastomosis group (P=0.06). The 5- and 10-year overall survival was 35% and 12% in the critical and 44% and 15% in the satisfactory anastomosis group (*Figure 2*). Median cancer specific survival was 58 months in the satisfactory and 34 months in the critical anastomosis group (P=0.09). The 5- and 10-year cancer specific survival was 43% and 24% in the critical and 49% and 33% in satisfactory anastomosis group (*Figure 3*).

Discussion

Anastomotic insufficiency is a feared complication after bronchial sleeve resection and correlates with high mortality and morbidity. Standardization of surgical techniques and improvement of postoperative care led to a reduction in insufficiency rates. Nevertheless, anastomotic complication rates of up to 8% are described in the literature (9,11-14). In our study the insufficiency rate was 3.7%. Insufficiency was thus a rather rare event compared to other complications, but in case of occurrence it had serious consequences. Forty-five percent of the patients with anastomotic insufficiency had to undergo reoperation, resulting in completion pneumonectomy in near half of the cases. One quarter of the patients with anastomosis insufficiency died during the postoperative course.

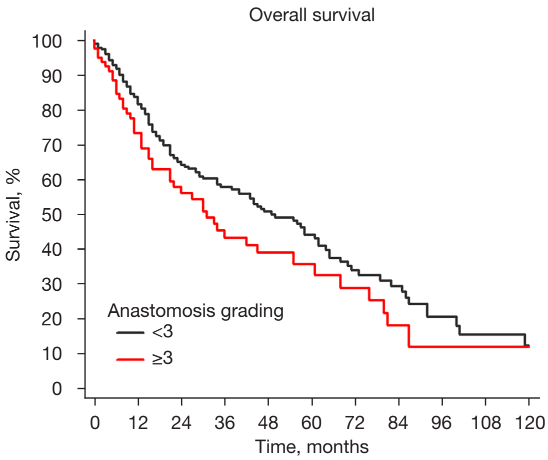
These figures underline the importance of early detecting impaired bronchial healing. In this regard, an important finding of our study is that the classification of anastomotic healing developed in our institution is a reliable tool for detecting anastomoses at risk (1). Based on bronchoscopic evaluation on the seventh postoperative day, the anastomosis is considered critical when signs of ischemia and/or necrosis in the distal mucosa are present (grade 3 or higher). In our study 100 of 541 patients (18.4%) showed critical healing of the anastomosis. All but one insufficiency (19 of 20) occurred in the critical group which underscores the accuracy of the classification for identifying at-risk patients. In addition, we know that we can safely discharge patients with grade 1 and 2 anastomoses. A higher mortality and morbidity rate in patients with critical anastomosis compared to those with a satisfactory anastomosis emphasize the importance of intensified medical care when impaired bronchial healing is eminent.

The choice of the seventh postoperative day for

Table 4 Risk factors for impaired anastomotic healing (multivariate analysis)

Variables	P value	OR	95% CI
Neoadjuvant radiation/chemoradiation	0.0043	2.181	1.277–3.724
Bilobectomy	0.0001	3.508	1.851–6.648
CRP >40 mg/L	0.0024	2.139	1.309–3.495
FEV1 <80%	0.0007	2.847	1.557–5.206

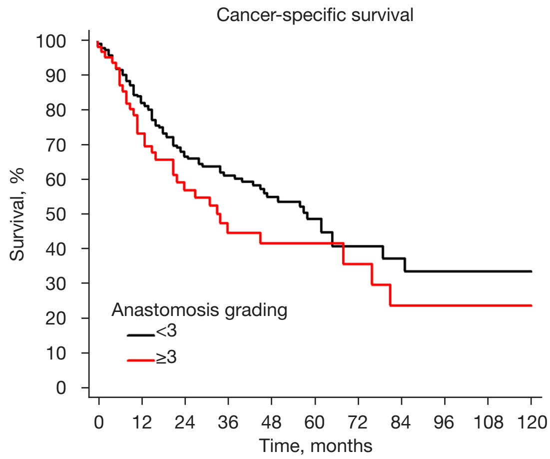
OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 second.



Number at risk

	0	12	24	36	48	60	72	84	96	108	120
Grading <3	294	210	128	92	63	40	24	18	9	6	4
Grading ≥3	77	50	33	21	15	11	8	3	1	1	1

Figure 2 Overall survival depending on anastomosis grading (P=0.06).



Number at risk

	0	12	24	36	48	60	72	84	96	108	120
Grading <3	246	172	102	70	45	25	14	10	5	4	3
Grading ≥3	64	40	26	16	11	8	6	2	1	1	1

Figure 3 Cancer specific survival depending on anastomosis grading (P=0.09).

bronchoscopy was defined based on pathophysiological considerations, according to which revascularization of the distal bronchus occurs after 7 days (1,15). However, systematic validation by means of a study has not been performed. We do not know whether an earlier bronchoscopy, for example on day 5, would have yielded the same results. In this regard, further studies could determine the correct timing for bronchoscopy.

In our analysis, we found that neoadjuvant radiation, bilobectomies, reduced preoperative FEV1 and elevated preoperative CRP levels were negative predictors for anastomotic healing. Circumferential transection, as well as denudation of the bronchus during lymphadenectomy, inevitably leads to ischemia of the distal bronchial mucosa. Healing of the anastomosis ultimately occurs via revascularization, which is mainly induced by surrounding vital tissue (10). A lack of coverage of the anastomosis or deterioration of the natural covering tissue due to external influences may lead to impaired revascularization and thus healing of the anastomosis. An adverse effect of preoperative radiotherapy on bronchial healing could be demonstrated previously. Yamamoto *et al.* analyzed the effects of radiotherapy, chemotherapy and lymphadenectomy on bronchial mucosal blood flow after lung resection. Patients who received preoperative radiotherapy showed a 70% reduction in mucosal blood flow compared with untreated patients or those who received chemotherapy alone. Patients who received preoperative radiotherapy showed ischemic changes to the bronchial stump more frequently than patients without radiotherapy. In contrast, after lymphadenectomy no significant changes in bronchial mucosal blood flow and satisfactory bronchial healing could be shown. The authors concluded that the reduction in bronchial blood flow due to bronchial artery dissection can be compensated by arteriolar communication from the pulmonary circulation. However, irradiation leads to hyalinization and fibrosis of the arterioles, resulting in deterioration of the bronchial microcirculation (10). We were recently able to demonstrate the effect of neoadjuvant radiation on anastomotic healing after bronchial sleeve resection. In a retrospective analysis on 501 patients, preoperative radiation was associated with a worse anastomotic healing and a higher rate of insufficiencies compared with patients without pretreatment or chemotherapy alone (8).

The influence of sleeve bilobectomy on anastomotic complications has not been analyzed yet. However, previous studies demonstrated that lower bilobectomies were associated with an increased rate of bronchial fistula and pleural space complications, whereas upper bilobectomies had the same risks as lobectomies (16,17). The discrepancy between the remnant lung and the volume of the pleural cavity was discussed as a possible cause (16). In our study the rate of sleeve bilobectomies was 9.4%. We could demonstrate that this procedure is associated with a worse anastomotic healing and a higher risk of developing insufficiency. However, because of the small number of lower bilobectomies in our study, it was not possible to make a serious statement about the difference with upper bilobectomies. Technical challenges of sleeve bilobectomies include discrepancies in bronchial diameter, proximity to the pulmonary artery, poor exposure of the mediastinal side of the anastomosis and the short length of the upper lobe bronchus, resulting in higher tension on the anastomosis (9,18,19).

In our study, the preoperative CRP level was an independent predictor of postoperative anastomotic healing. Patients with elevated preoperative CRP exhibited healing disorders more frequently. Significant impairment was found with an increase above 40 mg/L, whereas patients with CRP between 3 mg/L (detection limit) and 40 mg/L showed no differences regarding anastomotic healing compared with patients with values below 3 mg/L. CRP is a highly sensitive but non-specific marker of acute phase response. An increase is often observed in lung cancer patients as a sign of inflammation and increased tumor burden (20). A relationship between preoperatively elevated inflammatory markers and postoperative complications has been demonstrated in previous studies. Amar *et al.* showed an association between postoperative complications after thoracic surgery and preoperatively elevated CRP and IL-6 levels (21). Preoperatively elevated CRP above 40mg/L was an independent risk factor for increased postoperative morbidity and mortality after thoracic surgery for lung cancer (22).

Infectious complications, especially pneumonia, are among the most common complications after pulmonary resection. The prevalence of pneumonia varies from 2% to 40%, depending on type of resection, patient population and diagnostic criteria. After lung surgery pneumonia is associated with a significant increase of morbidity and mortality (23,24). Postoperative pneumonia was the second most frequent complication in our study, affecting 10.9% of all patients. Pneumonia was more frequent (22%) in the group of patients with critical anastomoses compared to those with satisfactory bronchial healing (7.9%). We assume that infectious complications may have been a predisposing factor for the development of anastomotic healing disorders in our study.

We demonstrated an association between decreased FEV1 and impaired anastomotic healing. Several studies have previously demonstrated an association between decreased FEV1 and/or the presence of COPD and elevated CRP levels. This is generally attributed to the fact that chronic obstructive pulmonary disease is associated with systemic inflammation (25-27). Thus, many lung cancer patients have a systemic inflammatory state due to their underlying disease and comorbidities. These patients seem to be predisposed to postoperative complications, as surgery must be considered as an additional trigger for the inflammatory response (22).

Analysis of the clinical courses of anastomotic insufficiencies (*Table 3*) in our study highlights the severity of this complication and the complexity of its management. Many of the patients have a significantly prolonged hospital stay with infectious complications, reoperations, and high mortality. Regarding conservative treatment of insufficiency, it was successful in 9 cases, secondary surgery was performed in 1 case, and the course was ultimately fatal in 3 cases. Revision of the anastomosis was performed in 5 cases (one case after initially convervative therapy), of which 3 could be discharged and 2 died in the further postoperative course. A general recommendation when an insufficiency should be treated conservatively and when surgically cannot be derived from our data. Neither for the decision whether a revision of the anastomosis or a secondary pneumonectomy should be performed. The decision on how to treat anastomotic insufficiency is always individual and depends on various factors such as the extent of necrosis, the condition of the remaining lung and the clinical condition of the patient.

In patients at increased risk for developing bronchial healing disorders, wrapping the anastomosis with a pedicled flap has been suggested (9,12,13,28). This recommendation is based on pathophysiological studies that demonstrated the ingrowth of capillaries from the flap into the submucosal bronchial plexus (29,30). However, clinical studies showing an effect on anastomotic healing do not exist. Therefore, some centers do not protect the anastomosis even after neoadjuvant radiation, arguing that with careful airway management and preservation of peribronchial tissue, additional anastomotic protection is not required (14).

At our institution, covering the anastomosis is performed as a standard procedure after neoadjuvant radiotherapy. Nevertheless, the insufficiency rate in this group was 6.8%. Therefore, it is reasonable to question whether the benefit of wrapping is not as great as previously thought. Storelli *et al.* reported a series of 103 sleeve resection over 11 years. No anastomotic complications were reported even after neoadjuvant radiation (14). However, comparability may be limited because only 5 patients underwent preoperative irradiation in this study. Campisi *et al.* compared patients that underwent bronchial wrapping (n=60) and patients that did not (n=30) after sleeve resection for lung cancer. None of the patients underwent neoadjuvant radiotherapy. Although there was no significant difference regarding overall anastomotic complication rate, anastomotic dehiscence was 3% in the wrapped group and 10% in the non-wrapped group (31). Overall, the question of coverage or non-coverage cannot be answered at present. Only prospective studies could help to clarify this question. Although the benefit of this procedure is controversial, preparing a flap of pericardial fat or intercostal muscle is a simple and fast to perform technique that may prevent serious anastomotic complications or allow conservative treatment in case of initially impaired anastomotic healing (7,14,32).

In our study, patients with critical anastomoses tended to have lower overall and cancer-specific survival than patients with satisfactory anastomoses. There were no significant differences between the two groups with respect to postoperative tumor stage, radicality and histology. However, the higher rate of pretreated patients and bilobectomies in the group with critical anastomoses suggests that larger and more advanced tumors were present prior to therapy. Moreover, risk factors leading to impaired anastomotic healing may also have an impact on survival.

We acknowledge that this study was limited by its single-institutional retrospective design. In addition, our compilation of risk factors for impaired anastomotic healing is incomplete. Our data lack information on preexisting conditions such as diabetes, use of steroids, or the patient‘s performance status. Since it can be assumed that the surgeon‘s experience has an influence on the occurrence of anastomotic complications, it can be considered a limitation that this variable was not included in this study.

Conclusions

In conclusion, sleeve resection can be performed with acceptable morbidity and mortality. Anastomotic insufficiency is a rare but serious complication with a mortality rate of 25%. Therefore, patients must be closely monitored throughout the postoperative course. In this context, bronchoscopic assessment of anastomotic healing has proven to be an effective tool to detect anastomoses at risk. Neoadjuvant radiation, bilobectomies, and acute or chronic inflammation were independent risk factors for impaired bronchial healing and should be considered at the planning stage of surgery.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1627/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1627/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1627/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1627/coif). ES is a past president of the German Society of Thoracic surgery (2017-2019). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics committee of the University of

Witten Herdecke (Nr. 51/2017). All participants gave informed consent before taking part in the study. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Lopez-Pastorini A, Eckermann C, Koryllos A, Galetin T, Ludwig C, Hammer-Hellmig M, Stoelben E. Clinical and bronchoscopic aspects of bronchial healing after sleeve resection for lung cancer: a multivariate analysis on 541 cases. J Thorac Dis 2022;14(4):927-938. doi: 10.21037/jtd-21-1627

