Surgical Treatment in Patient with Non–Small-Cell Lung Cancer with Fissure Involvement

Anatomical versus Nonanatomical Resection

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Objective: Despite the intense debate concerning the prognostic impact of fissure involvement (FI) in patients with non–small-cell lung cancer, no specific surgical strategies have been yet recommended when this condition occurs. In this setting, we report our monocentric 10-years experience to investigate this issue.

Methods: From January 2000 to January 2010, the clinical data of 40 non–small-cell lung cancer patients with FI undergoing curative resection were retrospectively reviewed. The sample was stratified according to the type of resection: group A (28 patients): anatomical resection (bilobectomy [21 patients], pneumonectomy [7 patients]); group B (12 patients): nonanatomical resection (lobectomy plus wedge resection [LWR]). The end-points were (1) impact of different surgical approach on the pulmonary function (measured before surgery and 1 month after discharge); (2) disease-specific survival; and (3) tumor recurrence.The *t* test, χ^2, and log-rank tests, Kaplan–Meier method, and Cox and logistic regression analyses were used for the statistical analysis.

Results: No differences between the two groups were found when comparing the clinical characteristics, histology, pN or pT status, p-stage, residual (R1) disease, tumor grading, or tumor size. Similarly, the baseline preoperative function (tested as forced expiratory volume in 1 second-%-predicted, FEV1%) was likewise comparable (92.5% ± 21.0% in group A versus 85.2% ± 20.0% in group B; p = not significant). The decline of FEV1% after surgery was slightly higher in group A (−24.9% ± 13.5%) when compared with that in group B (−19.5% ± 13.3%), but this difference was not statistically significant (p = ns). Nevertheless, the 5-year disease-specific survival was 56% for group A and 47% for group B (p = ns). The recurrence rate did not differ between the patients undergoing a LWR (3 of 12 patients) and those undergoing a bilobectomy or pneumonectomy (9 of 28 patients) (p = ns). The presence of FI extended for more than 3 cm was found to be the most significant prognostic factor when analyzing survival (p = 0.002) and recurrence rate ($p < 0.001$).

Conclusions: Our results suggest that nonanatomical resection (LWR) could be considered as a feasible surgical option (especially in "frail" patients with an extent of FI less than 3 cm) in the light of the similar oncological and functional outcome compared with anatomical resection. Further studies based on larger series are needed to confirm these preliminary data and also to investigate the impact on the postoperative quality of life.

Key Words: Fissure, Non–small-cell lung cancer, Visceral pleura, Forced expiratory volume in 1 second.

(*J Thorac Oncol.* 2014;9: 97–108)

Although visceral pleural invasion (VPI) is accepted as one of the most important prognostic factors in non–small-cell lung cancer (NSCLC) surgical series,[1,2] the prognostic impact of fissure involvement (FI) alone was only rarely analyzed and reported in the English literature.[3,4] The 6th tumor, node, metastasis (TNM) classification of the Union for International Cancer Control, as well, has not clearly defined the criteria to assign a specific T factor to a tumor that invades through the interlobar pleura into one of the adjacent lobes.[5] In the 7th TNM classification,[6] NSCLCs with FI are classified as T2a, unless other T factors induce a higher category, regardless of the type of FI (interlobar pleura only or transfissural into the parenchyma of the adjacent lobe). As the new TNM staging system does not consider the FI status, no specific surgical strategies have been yet recommended when this condition occurs. Moreover, available data refer mainly to survival and recurrence rates whereas reports focusing on the quality of life and postoperative pulmonary function are absent.

In this monocentric study, we have analyzed the long-term (5 year) survival outcomes and recurrence rates of NSCLCs that extend across the fissure into the adjacent lobe

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Disclosure: The authors declare no conflict of interest.Presented at the 21st European Conference on General Thoracic Surgery of the European Society of Thoracic Surgeons, Birmingham, May 26–29, 2013.

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ISSN: 1556-0864/14/0901-0097

and that required either an anatomical (bilobectomy or pneumonectomy) or a nonanatomical resection (lobectomy plus wedge resection [LWR]). Moreover, this study analyzes and reports about the impact of the type of resection on the early-term outcome in terms of pulmonary function.

PATIENTS AND METHODS

Patients Selection

After obtaining approval of this study by our Institutional Review Board, the clinical records of all patients (1080 cases) who underwent surgery for NSCLC in the Department of Thoracic Surgery at "Agostino Gemelli" General Hospital in the period between January 2000 and January 2010 were retrospectively reviewed. Patients with small-cell carcinoma, neoadjuvant treatment, macroscopic positive surgical margin, superior sulcus tumor, pathological N3 disease, or distant metastasis were excluded. Patients with pathological stages T2, T3 (tumor size higher than 7 cm or chest wall invasion), or T4 (satellite lesions in a separate lobe) were included in the study. We have identified 40 patients with direct adjacent lobe invasion, defined as contiguous extension of the primary tumor across the fissure into another lobe as confirmed by histopathologic examination. Lesions showing invasion as limited only into the visceral pleura of the adjacent lobe were also included. The preoperative workup included routine biochemical tests, electrocardiograph, chest radiograph, fiber-optic bronchoscopy, computed tomography scan, positron emission tomography scan (as of January 2005), and perfusion lung scan. Mediastinoscopy, endoscopic ultrasound–fine-needle aspiration, and endobronchial ultrasound-guided transbronchial needle aspiration were performed for diagnosing N2, N3, or M1 disease. The pulmonary function was measured using a volume-displacement body plethysmograph (Platinum Elite; Medical Graphics Corporation, St. Paul, MN). Lung volumes and single-breath diffusion capacity for carbon monoxide (DLCO) were measured according to the recent American Thoracic Society/European Respiratory Society guidelines. Functional tests were expressed as absolute values and as percent of the predicted; these were performed before surgery and 1 month after discharge. Pulmonary function tests were available for the half of the total sample. Resection types were stratified in two groups: bilobectomy or pneumonectomy (anatomical resection, group A) and LWR (nonanatomical resection, group B). Decision regarding the type of resection was based, in each patient, on the surgeon's preference according to the pulmonary reserve of the patient and the localization of the tumor if eligible for partial resection. Systematic mediastinal lymph node dissection was routinely performed in all patients. Pathological staging was carried out according to the 7th TNM classification.[6] Follow-up data regarding the clinical outcome were collected from the patients' charts and direct interviews of the patients, their next of kin, and their general practitioners. Oncological follow-up data were available for 90% of sample (36 patients).

Statistical Analysis

The sample characteristics were summarized by absolute and relative frequencies for categorical variables and by means ± SDs for continuous variables. Univariate analysis was performed to verify the comparability of group A and group B on major demographic, clinical, surgical, and oncological factors. The Student's t test was applied to continuous variable, with correction for unequal variances when required, and the Pearson's χ^2 test (or the Fisher's exact test for expected cell frequencies less than 5) for categorical variables. The groups of subjects who underwent one of the two different surgical procedures were compared with regard to all spirometric and blood gas parameters on the percentage change from baseline, this being calculated as Δ = [(postoperative − baseline/baseline) × 100] with a Student's t test.

The occurrence of postoperative complications and the need for hospital stay longer than 6 days were investigated by means of a logistic regression analysis. Potentially associated factors considered for these analyses were type of surgery, forced vital capacity (FVC) 85% or less, forced expiratory volume in 1 second (FEV1) 85% or less, DLCO 15 or less, pO_2 80 mmHg or less, comorbidities, and complications.

Mortality and recurrence were investigated with a survival analysis. Overall survival (OS) and disease-specific survival (DSS) were defined as the time from date of surgery until the event of interest (death from any cause [for OS] or disease-specific death [for DSS]) or alive at last follow-up (censored). Disease-free survival (DFS) was defined as the time from date of surgery until evidence of tumor recurrence (event) or no evidence of tumor recurrence at last follow-up (censored). Sociodemographic and clinically meaningful factors, potentially associated to these two outcomes, were age, sex, smoking habits, type of surgery, pR1 resection, extent of FI higher than 3 cm, pathological T and N status, tumor size, and histology. Kaplan–Meier analysis was performed and survival curves were compared with the log-rank test. Cox regression analysis was also implemented to explore the prognostic role of several variables on patients' DSS and DFS. Multivariable Cox proportional hazards regression models for DSS and DFS were selected in a forward-stepwise manner (forward selection): all factors listed above were fitted one at a time and the factor predictive of the highest statistically significant hazards of mortality was selected; subsequently, in a forward-stepwise manner, all remaining factors were fitted, one at a time, to the selected model and the new models evaluated for their statistical significance and reliability (acceptable hazard ratio [HR] estimates and 95% confidence intervals) in predicting mortality or recurrence hazards. The procedure continued, in loop, until no other factor could be entered with reliability and statistical significance into the models. Proportionality of hazards was tested for all factors with the Grambsch and Therneau's test.

A similar forward-stepwise procedure was applied to the logistic regression analysis. The limit for statistical significance was set at p value less than 0.05. All tests were two-sided. Given the small sample size, all analyses were intended as explorative. STATA/SE V12.0 software package was used for all statistical analyses.

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RESULTS

Clinical and Surgical Data

According to the histopathologic examination, we have identified 40 NSCLC patients with direct adjacent lobe invasion by the primary tumor. The demographic and clinicopathological characteristics of the total sample are summarized in Table 1. The primary tumor was in the right lung in 29 patients and in the left lung in 11 patients. The lesions were localized in the upper lobe in 21 cases, in the lower in 12 patients, and in the middle lobe in five patients; two patients had a cancer located centrally (hylum). Regarding the T factor, 28 lesions (70%) were pathologically classified as T2 (T2a in 22 cases and T2b in 6 cases), whereas T3 tumor was found in 11 patients (27.5%) (for tumor size higher than 7 cm and for chest wall invasion, respectively, in 10 and 1 case); only one patient was staged as T4 for the presence of a satellite lesion in a separate lobe. Among T2a lesions, a pure interlobar visceral pleura invasion was carried out in six patients only. Twenty-three patients (58%) had no nodal metastases (N0 disease), 11 (27%) had a N1 disease, and six (15%) had mediastinal nodal metastases (N2 disease). The histopathologic staging of the total sample was as follows: IB 32%, IIA 25%, IIB 15%, and IIIA 28%. Pathological examination identified squamous cell carcinoma in 13 patients (32%), adenocarcinoma (AC) in 15 (38%), and other histologies in 12 cases (30%). The average pathological tumor size was 4.69 ± 2.21 cm (range, 1.0–9.0 cm); the extent of FI higher than 3 cm was confirmed in 10 patients. A microscopic residual disease (R1) was detected in six patients (15%).

According to the extent of the pulmonary resection, we have stratified the sample in two groups: 28 patients with anatomical resection (group A) and 12 patients with nonanatomical resection (group B). Among those patients in the group A, we have performed 21 bilobectomies (75%) and seven pneumonectomies (25%). In all the patients of the group B, we have performed a LWR. No differences between the two groups were found when comparing the clinical characteristics, histology, pN or pT status, p-stage, residual (R1) disease, tumor grading, tumor size (Table 1). The presence of an FI higher than 3 cm was proven in 10 patients of the group A only ($p = 0.017$).

Pulmonary Function Data

Functional test values were performed before surgery (baseline) and 1 month after discharge (postoperative). Baseline lung volumes, DLCO, and blood gas analyses are summarized in Table 2. The baseline preoperative tests were likewise comparable between both groups: in particular, preoperative FEV1%-predicted of group A and group B were, respectively, 92.5% ± 21.0% and 85.2% ± 20.0% (p = ns).

To evaluate the impact of the two different surgical approaches on the early-term functional outcome, we have analyzed the decline of FEV1 % (ΔFEV1%) after surgery, measured before surgery and 1 month after discharge. The ΔFEV1% was slightly higher in patients undergoing bilobectomy or pneumonectomy (−24.9% ± 13.5%) if compared with those undergoing LWR (−19.5% ± 13.3%), but this difference was not statistically significant (p = ns). We reported similar results when comparing the decline of FVC %, DLCO, and pO_2 as well (Table 3).

Postoperative Data

Fifteen patients were admitted in the intensive care unit (ICU) with an average stay of 0.47 ± 0.68 days (range, 0–3 days). The mean hospital stay of the total sample was 11.72 ± 7.32 days (range, 5–33 days). Ten patients (25%) experienced a postoperative complication. Postoperative major and minor complications occurred, respectively, in six (15%) and in seven (17%) cases: in particular we evidenced pneumonia in one case, bleeding (not requiring reoperation) in four patients, respiratory failure (not requiring reintubation) in one case, atelectasis in one case, air leak in four patients, and atrial fibrillation in two cases. There was no 30-day postoperative mortality. After surgery, 22 patients (55%) received adjuvant therapy (chemotherapy in 18 and radiotherapy in 12 cases, 8 of which received both therapies).

No differences between group A and group B were found when comparing adjuvant treatment, postoperative complications, admission and length of stay in the ICU, and hospital stay (Table 1).

The type of resection, comorbidities, FVC% less than 85%, FEV1% less than 85%, DLCO less than 15, and po_2 less than 80 mmHg were evaluated as potential predictors of postoperative complications; however, logistic regression analysis found no statistically significant association with these factors (Table 4). Moreover, we did not find any correlation between hospital stay longer than 6 days and extent of surgery, postoperative complications, FVC% less than 85%, FEV1% less than 85%, DLCO less than 15, and po_2 less than 80 mmHg (Table 4).

Survival

The mean follow-up time was 41.64 ± 34.07 months (range, 6–154 months). The median OS time of the total sample (n = 36) was 49 months: in particular the median DSS time for group A and group B (n = 30) was, respectively, 64 and 60 months (p = ns). The 5-year OS rate was 42%. The 5-year OS based on resection type was 48% in group A and 33% in group B (p = ns; Fig. 1). In particular, the 5-year DSS was 56% for group A and 47% for group B (p = ns; Fig. 1): we have evidenced disease-specific deaths in group A and B, respectively, in eight and four patients.

The evaluated prognostic factors in statistical analyses were age, sex, smoking history, type of surgery, postoperative complications, histology, pT status, pN status, p-stage, tumor size, extent of FI, and pR1 resection. From the simple Cox regression analysis, it emerged that the hazards of mortality for extent of FI (FI >3 cm versus ≤3 cm: HR = 6.95 [2.02; 23.96]; $p = 0.002$) and pN (pN1 versus pN0: HR = 1.31 [0.33; 5.26]; $p = 0.70$; pN2 versus pN0: HR = 6.22 [1.27; 30.41]; $p = 0.024$) were statistically significant. In particular, the extent of FI was the strongest predictive factor (Fig. 1). When fitting this factor and, one at a time, all remaining variables into a multivariable Cox regression model, no other factor was found to be predictive of mortality hazards to a statistically significant level. Table 5 shows results for simple and multivariable Cox regression models.

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TABLE 1. Characteristics of the Total Sample and Comparison between Group A and Group B

	Total (n = 40)	Group A Bilobectomy/Pneumonectomy (n = 28)	Group B Lobectomy Plus Wedge Resection (n = 12)	*p*[a]
Age (yr)	66.32 ± 9.80	66.61 ± 10.42	65.67 ± 8.56	0.785
Age				
≤65 yr	13 (32%)	9 (32%)	4 (33%)	0.941
>65 yr	27 (68%)	19 (68%)	8 (67%)	
Sex				
Female	9 (22%)	6 (21%)	3 (25%)	0.804
Male	31 (78%)	22 (79%)	9 (75%)	
Smoker				
No	22 (69%)	16 (67%)	6 (75%)	0.660
Yes	10 (31%)	8 (33%)	2 (25%)	
Pack-years	39.16 ± 34.91	44.91 ± 34.99	24.79 ± 33.13	0.242
Pulmonary comorbidities				
No	13 (33%)	9 (33%)	4 (33%)	1.000
Yes	26 (67%)	18 (67%)	8 (67%)	
Cardiovascular comorbidities				
No	17 (44%)	11 (41%)	6 (50%)	0.590
Yes	22 (56%)	16 (59%)	6 (50%)	
Diabetes				
No	33 (85%)	22 (81%)	11 (92%)	0.416
Yes	6 (15%)	5 (19%)	1 (8%)	
Other comorbidities				
No	18 (46%)	12 (44%)	6 (50%)	0.748
Yes	21 (54%)	15 (56%)	6 (50%)	
Side				
Right	29 (72%)	21 (75%)	8 (67%)	0.589
Left	11 (28%)	7 (25%)	4 (33%)	
Localization				
Hilar	2 (5%)	2 (7%)	0 (0%)	0.205
Upper lobe	21 (52%)	17 (61%)	4 (33%)	
Middle lobe	5 (13%)	3 (11%)	2 (17%)	
Lower lobe	12 (30%)	6 (21%)	6 (50%)	
cT				
T1	8 (22%)	3 (12%)	5 (45%)	0.117
T2	20 (54%)	15 (58%)	5 (45%)	
T3	8 (22%)	7 (27%)	1 (9%)	
T4	1 (3%)	1 (4%)	0 (0%)	
cN				
N0	26 (68%)	19 (73%)	7 (58%)	0.609
N1	6 (16%)	3 (12%)	3 (25%)	
N2	5 (13%)	3 (12%)	2 (17%)	
N3	1 (3%)	1 (4%)	0 (0%)	
cStage				
IA	5 (14%)	2 (8%)	3 (27%)	0.581
IB	11 (30%)	9 (35%)	2 (18%)	
IIA	5 (14%)	4 (15%)	1 (9%)	
IIB	8 (22%)	5 (19%)	3 (27%)	
IIIA	7 (19%)	5 (19%)	2 (18%)	
IIIB	1 (3%)	1 (4%)	0 (0%)	
cTumor size (cm)	4.50 ± 2.19	4.80 ± 2.12	3.8 ± 2.28	0.206
PET				
No	27 (71%)	17 (65%)	10 (83%)	0.257
Yes	11 (29%)	9 (35%)	2 (17%)	

(*Continued*)

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TABLE 1. (*Continued*)

	Total (n = 40)	Group A Bilobectomy/Pneumonectomy (n = 28)	Group B Lobectomy Plus Wedge Resection (n = 12)	*p*[a]
Residual disease				
R0	34 (85%)	25 (89%)	9 (75%)	0.246
R1	6 (15%)	3 (11%)	3 (25%)	
Histology				
SCC	13 (32%)	9 (32%)	4 (33%)	0.420
AC	15 (38%)	9 (32%)	6 (50%)	
Other	12 (30%)	10 (36%)	2 (17%)	
pT				
T2	28 (70%)	18 (64%)	10 (83%)	0.450
T3	11 (27%)	9 (32%)	2 (17%)	
T4	1 (3%)	1 (4%)	0 (0%)	
pN				
N0	23 (58%)	15 (54%)	8 (67%)	
N1	11 (27%)	9 (32%)	2 (17%)	0.602
N2	6 (15%)	4 (14%)	2 (17%)	
p-Stage				
IB	13 (32%)	8 (29%)	5 (42%)	
IIA	10 (25%)	6 (21%)	4 (33%)	
IIB	6 (15%)	5 (18%)	1 (8%)	0.540
IIIA	11 (28%)	9 (32%)	2 (17%)	
pTumor size (cm)	4.69±2.21	4.94±2.12	4.12±2.41	0.289
Tumor size				
≤4 cm	19 (49%)	12 (44%)	7 (58%)	0.423
>4 cm	20 (51%)	15 (56%)	5 (42%)	
Fissure invasion				
≤3 cm	30 (75%)	18 (64%)	12 (100%)	0.017
>3 cm	10 (25%)	10 (36%)	0 (0%)	
Tumor grading				
G1	3 (8%)	2 (8%)	1 (10%)	0.973
G2	18 (50%)	13 (50%)	5 (50%)	
G3	15 (42%)	11 (42%)	4 (40%)	
ICU admission				
No	25 (62%)	17 (61%)	8 (67%)	0.722
Yes	15 (38%)	11 (39%)	4 (33%)	
ICU stay (days)	0.47±0.68	0.46±0.58	0.5±0.90	0.881
Hospital stay (days)	11.72±7.32	12.30±7.83	10.42±6.14	0.467
Major postoperative complications				
No	34 (85%)	24 (86%)	10 (83%)	0.847
Yes	6 (15%)	4 (14%)	2 (17%)	
Minor postoperative complications				
No	33 (83%)	22 (79%)	11 (92%)	0.318
Yes	7 (17%)	6 (21%)	1 (8%)	
Adjuvant therapy				
No	18 (45%)	14 (50%)	4 (33%)	0.332
Yes	22 (55%)	14 (50%)	8 (67%)	
Adjuvant chemotherapy				
No	22 (55%)	15 (54%)	7 (58%)	0.781
Yes	18 (45%)	13 (46%)	5 (42%)	
Adjuvant radiotherapy				
No	28 (70%)	22 (79%)	6 (50%)	0.071
Yes	12 (30%)	6 (21%)	6 (50%)	

[a]Statistical tests: Pearson's χ^2 test for categorical variables and Student's *t* test for continuous variables; statistical significance: $p < 0.05$.
PET, positron emission tomography; SCC, squamous cell carcinoma; AC, adenocarcinoma; ICU, intensive care unit.

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TABLE 2. Baseline Spirometric and Blood Gas Parameters of the Total Sample and Comparison between Group A and Group B

	Total (n = 40)	Group A (n = 28)	Group B (n = 12)	p^a
pH	7.42 ± 0.02	7.42 ± 0.02	7.43 ± 0.02	0.285
pCO_2 (mmHg)	38.93 ± 4.35	38.82 ± 4.52	39.42 ± 4.10	0.809
pO_2 (mmHg)	80.85 ± 8.85	81.21 ± 8.92	79.42 ± 9.74	0.729
FVC (liter)	3.08 ± 0.95	3.13 ± 1.04	2.89 ± 0.51	0.667
FVC (%)	100.19 ± 17.76	100.12 ± 19.07	100.5 ± 12.71	0.970
FEV1 (liter)	2.22 ± 0.68	2.27 ± 0.71	1.995 ± 0.57	0.480
FEV1 (%)	91.15 ± 20.52	92.53 ± 20.99	85.25 ± 19.99	0.537
TLC (liter)	5.20 ± 1.31	5.22 ± 1.36	5.14 ± 1.27	0.919
TLC (%)	92.74 ± 15.73	91.56 ± 14.61	97.75 ± 21.70	0.493
RV (liter)	1.97 ± 0.74	1.92 ± 0.63	2.21 ± 1.20	0.485
RV (%)	93.20 ± 28.65	91.07 ± 22.09	102.25 ± 52.29	0.701
DLCO	15.88 ± 5.75	14.84 ± 5.90	19.28 ± 4.11	0.185

[a]Statistical tests: Pearson's χ^2 test for categorical variables and Student's *t* test for continuous variables; statistical significance: $p < 0.05$.
FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; RV, residual volume.

TABLE 3. Spirometric and Blood Gas Analyses before Surgery (Baseline) and 1-Month after Discharge (Postoperative)

	Group A			Group B			Comparison between Type of Surgery on Δ^a
	Baseline	Postoperative	Δ^a	Baseline	Postoperative	Δ^a	*p*
FVC (%)	15	13	13	4	4	4	0.306
	99.60 ± 20.20	77.54 ± 16.59	−24.02 ± 14.31	100.50 ± 12.71	84.25 ± 12.37	−14.88 ± 17.89	
FEV1 (%)	15	13	13	4	4	4	0.494
	92.41 ± 22.43	70.92 ± 18.59	−24.9 ± 13.541	85.25 ± 19.99	66.75 ± 6.80	−19.49 ± 13.37	
TLC (%)	15	12	12	4	4	4	0.584
	92.03 ± 15.51	68.75 ± 10.65	−23.72 ± 10.16	97.75 ± 21.70	77.25 ± 17.00	−20.31 ± 11.71	
RV (%)	15	12	12	4	4	4	0.827
	93.21 ± 22.69	71.00 ± 22.71	−18.31 ± 27.18	102.25 ± 52.29	76.25 ± 31.36	−21.56 ± 16.91	
DLCO	12	9	8	4	3	3	0.386
	14.99 ± 6.14	10.64 ± 3.53	0.30 ± 55.12	19.28 ± 4.11	14.40 ± 2.00	−17.75 ± 3.01	
pH	15	11	11	4	4	4	0.569
	7.42 ± 0.03	7.41 ± 0.02	−0.02 ± 0.40	7.43 ± 0.02	7.42 ± 0.03	−0.16 ± 0.33	
pCO_2 (mmHg)	15	11	11	4	4	4	0.446
	38.93 ± 4.82	38.11 ± 2.76	2.68 ± 10.37	39.42 ± 4.10	38.60 ± 2.95	−1.73 ± 6.47	
pO_2 (mmHg)	14	11	11	4	4	4	0.508
	81.39 ± 9.44	90.29 ± 10.57	8.98 ± 17.46	79.42 ± 9.74	81.35 ± 10.68	2.64 ± 9.20	

Statistical tests: Student's *t* test for continuous variables; statistical significance: $p < 0.05$.
[a]Δ = (postoperative − baseline/baseline) × 100.
FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; RV, residual volume.

DFS Analysis

The overall DFS was 62 months (n = 34). Postoperative recurrence of total sample was observed in 12 patients: in particular the local recurrence and distant metastasis were found, respectively, in seven and six cases. The recurrence rate did not differ between the patients undergoing a LWR (3 of 12 patients) and those undergoing a bilobectomy or pneumonectomy (9 of 28 patients) (p = ns). The 5-year DFS was 56% for both groups (p = ns; Fig. 2).

The recurrence rate was compared according to age, sex, smoking history, type of surgery, histology, pT status, pN status, p-stage, tumor size, extent of FI, and pR1 resection. Similar to DSS, the simple Cox regression analysis evidenced that the hazards of recurrence for extent of FI (FI >3 cm versus ≤3 cm: HR = 12.42 [3.56; 43.24]; $p < 0.001$) and pR1 (pR1 versus pR0: HR = 4.70 [1.11; 19.89], $p = 0.035$) were statistically significant. The extent of FI was the strongest predictive factor for recurrence also (Fig. 2). When fitting the extent of FI and, one at a time, all remaining variables into a multivariable Cox regression model, no other factor was found to be predictive of recurrence hazards to a statistically significant level, with the exception of AC histology

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TABLE 4. Analysis on the Occurrence of Complications and on Hospital Stay

	Complications (n = 10 [25%])	No Complications (n = 30 [75%])	Unadjusted Odds Ratio	95% Confidence Interval	p^a
Surgery					
Group A	7 (70%)	21 (70%)	1.00		
Group B	3 (30%)	9 (30%)	1.00	0.21–4.77	1.000
Comorbidity					
No	1 (10%)	3 (10%)	1.00		
Yes	9 (90%)	26 (90%)	1.04	0.10–11.30	0.975
FVC (%)					
>85%	2 (50%)	13 (76%)	1.00		
≤85%	2 (50%)	4 (24%)	3.25	0.34–31.07	0.306
FEV1 (%)					
>85%	2 (50%)	10 (59%)	1.00		
≤85%	2 (50%)	7 (41%)	1.43	0.16–12.70	0.749
DLCO					
>15	2 (67%)	8 (57%)	1.00		
≤15	1 (33%)	6 (43%)	0.67	0.05–9.19	0.762
pO_2 (mmHg)					
≥80	2 (50%)	8 (47%)	1.00		
<80	2 (50%)	9 (53%)	0.89	0.10–7.86	0.916
	Hospital Stay ≤6 days (n = 7 [18%])	**Hospital Stay >6 days (n = 32 [82%])**	**Unadjusted Odds Ratio**	**95% Confidence Interval**	p^a
Surgery					
Group A	23 (72%)	4 (57%)	1.00		
Group B	9 (28%)	3 (43%)	0.52	0.10–2.81	0.449
Complications					
No	22 (69%)	7 (100%)	1.00		
Yes	10 (31%)	0 (0%)	Not computable		
FVC (%)					
>85%	11 (69%)	4 (80%)	1.00		
≤85%	5 (31%)	1 (20%)	1.82	0.16–20.71	0.630
FEV1 (%)					
>85%	8 (50%)	4 (80%)	1.00		
≤85%	8 (50%)	1 (20%)	4.00	0.36–44.11	0.258
DLCO					
>15%	8 (62%)	2 (50%)	1.00		
≤15%	5 (38%)	2 (50%)	0.63	0.07–5.97	0.683
pO_2 (mmHg)					
≥80%	8 (50%)	2 (40%)	1.00		
<80%	8 (50%)	3 (60%)	0.67	0.09–5.13	0.697

[a]Statistical tests: logistic regression analysis; statistical significance: $p < 0.05$.
FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; RV, residual volume.

($p = 0.034$). Table 6 shows results for simple and multivariable Cox regression models.

DISCUSSION

In the English literature, the frequency of NCSLC with FI is lower than that of tumors with VPI and ranges from 2.1% to 17.6%[7–12] of operated patients (3.7% in or series). The opportunity for a NSCLC to invade the fissure depends on its location and the specific lung anatomy: thus, there is more chance to observe a FI on the right (as in our series) than on the left. Moreover, in each patient the interlobar fissures vary in terms of completeness and the FI may be misinterpreted, in case of partially or totally incomplete fissure. On the contrary, although an interlobar FI was suspicious at the moment of operation when the operative field was explored, in most of the cases this was pathologically confirmed to be a simple interlobar fissure adhesion only.

The 6th TNM classification of the Union for International Cancer Control[5] has not clearly defined the prognostic impact of NSCLC with interlobar extension. On the basis of the

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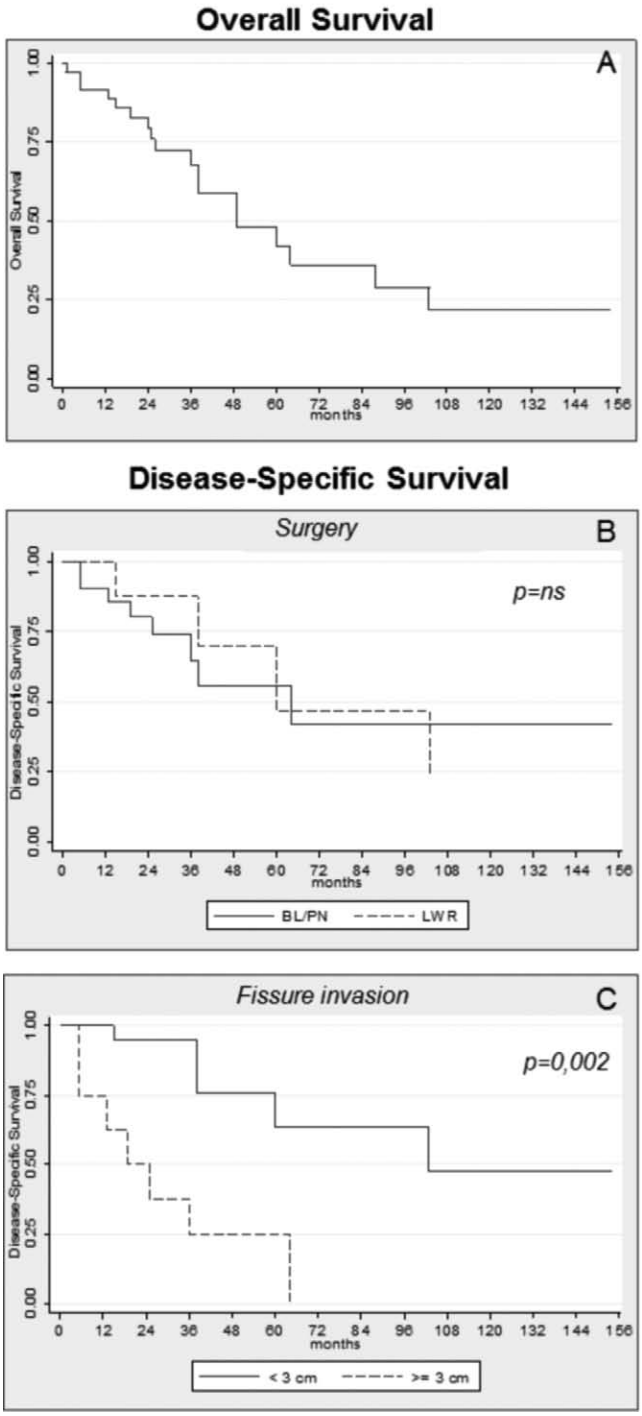

FIGURE 1. A, Overall survival curve of the total sample. B, Disease-specific survival curves according to type of surgery. C, Disease-specific survival curves according to extent of fissure invasion. BL, bilobectomy; PN, pneumonectomy; LWR, lobectomy plus wedge resection.

limited data available, the 7th TNM classification[6] recommended that tumors with direct invasion of an adjacent lobe across the fissure or by direct extension into a fissureless lung be categorized as T2a, unless other T factors result in a higher T category. Previous works on interlobar spread of NSCLC have resulted in highly variable conclusions. Miura et al.[3] concluded that interlobar pleural extension makes no difference to survival and should be classified as T2. On the contrary, Okada et al.[4] and Demir et al.[7] suggested that NCSLC with FI had similar survival to that of T3 tumors. According to the pathological stage, Joshi et al.[8] reported that the 5-year OS for tumors extending across the fissure is placed between those of stage I and stage II.

As well, previous data on survival rates are discordant. In a series of 50 patients, Nonaka et al.[9] reported a 5-year OS of 63%. Similar results were described by Haam et al.[10] (53%) and Joshi et al.[8] (50%). On the contrary, a lower survival was advocated by Okada et al.,[4] Demir et al.,[7] and Riquet et al.[11] which showed a similar 5-year OS (respectively 37%, 36%, and 38.9%).

The poor survival of patients with NSCLC with FI might be explained by the interrelationship between the interlobar visceral pleura and the invading tumor. Normally, VPI indicates biological tumor invasiveness and is associated with a poor outcome.[13] Moreover, lymphatic ducts and blood vessels are abundant in the subpleural space. By penetrating two different layers of the visceral pleura, tumors invading the fissure have a high probability to invade small lymphatic ducts and blood vessels. In fact, Ohtaki et al.[13] reported a statistically significant association between tumors with FI and vascular/lymphatic invasion, compared with NSCLCs invading an incomplete fissure. As reported in literature, this lymphatic invasion results in a high rate of lymph node involvement as well.[3,4,7,9] Although we evidenced a pN0 rate of 58%, other authors reported that pN0 is generally inferior to 50% of cases, whereas nodal involvement is present in more than two-third of patients as a result of drainage of invading tumor into the adjacent lobe lymphatic system. Even if not confirmed by multivariate analysis, our study reported that pN2 was associated to worse survival as well.

In our series, we reported a 5-year OS of 42%, in line with that reported by others.[4,7,11] Unlike analyzed in previous studies, we estimated the DSS oncologically more accurate than OS. In particular, the 5-year DSS was 52% for the total sample. According to DSS, the presence of FI higher than 3 cm (pathologically confirmed in 10 patients) was found to be an independent prognostic indicator. The worse survival associated with this pattern of invasiveness could be explained by two reasons:

1. In our series, these patients were associated with a greater pathological tumor size. The large size of NSCLC per se is a well-known factor of poorer prognosis: in fact, the 7th TNM classification reported that T3 tumors larger than 7 cm in their major axis have a significantly poorer prognosis than other categories of T3 (35% versus 41%).[14]
2. Seventy percent of patients with FI extended for more than 3 cm has a nodal involvement. This supports the above-mentioned theory of Ohtaki et al.,[13] confirming the significant association between tumors with FI and lymphatic invasion. However, further studies with larger number of patients are needed to confirm these data.

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TABLE 5. Analysis on Disease-Specific Mortality

	Disease-Specific Death (n = 12 [40%])	Alive (n = 18 [60%])	Unadjusted Hazard Ratio	95% Confidence Interval	*p*	Adjusted[a] Hazard Ratio	95% Confidence Interval	*p*	Follow-Up Period (Months)
Age (yr)									
≤65	6 (50%)	5 (28%)	1.63	0.52–5.13	0.403	0.88	0.25–3.08	0.839	103
>65	6 (50%)	13 (72%)	1			1			154
Sex									
Female	1 (8%)	6 (33%)	1			1			45
Male	11 (92%)	12 (67%)	1.86	0.23–15.29	0.564	1.24	0.14–10.64	0.846	154
Smoker									
No	6 (67%)	11 (73%)	1			1			71
Yes	3 (33%)	4 (27%)	0.82	0.2–3.41	0.787	0.28	0.05–1.59	0.153	56
Surgery									
Group A	8 (67%)	13 (72%)	1			1			154
Group B	4 (33%)	5 (28%)	0.89	0.26–2.98	0.848	4.90	0.55–44	0.156	103
Residual disease									
R0	9 (75%)	16 (89%)	1			1			154
R1	3 (25%)	2 (11%)	3.57	0.88–14.47	0.074	2.80	0.66–11.89	0.162	38
Fissure invasion									
≤3 cm	5 (42%)	17 (94%)	1						154
>3 cm	7 (58%)	1 (6%)	6.95	2.02–23.96	0.002[a]				64
pT									
T2	9 (75%)	13 (72%)	1			1			154
T3-T4	3 (25%)	5 (28%)	1.35	0.36–5.02	0.657	0.78	0.2–3.1	0.730	109
pN									
N0	6 (50%)	11 (61%)	1			1			154
N1	3 (25%)	5 (28%)	1.31	0.33–5.26	0.702	0.22	0.03–1.56	0.131	109
N2	3 (25%)	2 (11%)	6.22	1.27–30.41	0.024	1.42	0.22–9.07	0.711	36
p-Stage									
IB	4 (33%)	6 (33%)	1			1			154
IIA	2 (17%)	5 (28%)	0.67	0.12–3.7	0.645	0.25	0.03–1.89	0.178	103
IIB	2 (17%)	2 (11%)	5.56	0.82–37.44	0.078	3.27	0.39–27.54	0.275	33
IIIA	4 (33%)	5 (28%)	1.95	0.48–7.92	0.349	0.61	0.11–3.37	0.575	109
Tumor size									
≤4 cm	7 (58%)	8 (44%)	1			1			103
>4 cm	5 (42%)	10 (56%)	1.70	0.54–5.38	0.365	1.23	0.36–4.19	0.741	154
Histology									
SCC	5 (42%)	4 (22%)	1.88	0.45–7.97	0.389	2.57	0.55–12	0.230	103
AC	4 (33%)	5 (28%)	1.66	0.37–7.49	0.509	1.91	0.39–9.31	0.422	109
Other	3 (25%)	9 (50%)	1			1			154

[a]Adjusting covariate: Fissure Invasion. Statistical tests: Cox regression analysis; statistical significance: $p < 0.05$.
SCC, squamous cell carcinoma; AC, adenocarcinoma.

In the literature, controversies exist on the treatment of tumors with FI. Because radical resection of tumors with their lymphatic drainage is the accepted oncological procedure, curative resection can only be anticipated in lesions traversing the fissure if all of the involved tissue is anatomically removed (by at least bilobectomy or pneumonectomy). Yang et al.[15] reported that the patients who underwent pneumonectomy or bilobectomy had better survival than patients undergoing LWR. Okada et al.,[4] Nonaka et al.,[9] and Haam et al.[10] have reported that survival did not differ between the patients receiving a lobectomy with the partial resection and those receiving an anatomical resection. Furthermore, Demir et al.[7] suggested that LWR or bilobectomy on the right lung may be preferable over pneumonectomy in the case of adjacent lobe invasion, considering the high mortality and morbidity rate of the pneumonectomy. According to DSS, in our series we have evidenced a not statistically significant difference between patients undergoing anatomical resection (pneumonectomy or bilobectomy) and LWR (group A 56% versus group B 47%; p = ns). Moreover, we have analyzed the recurrence rate in

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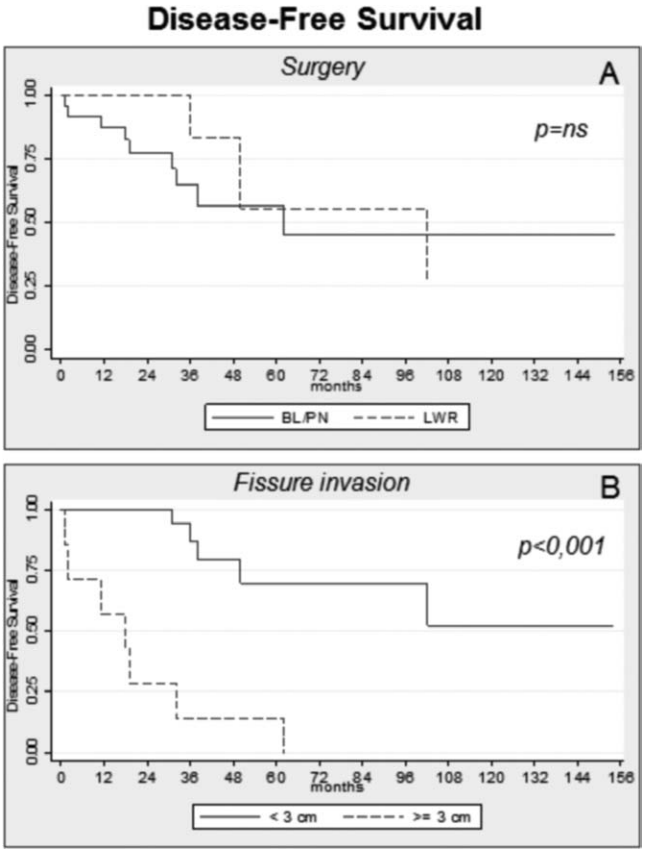

FIGURE 2. Disease-free survival curves according to type of surgery (A) and extent of fissure invasion (B).

both procedures, and as opposed to the evidence mentioned by other authors, three of 12 patients undergoing a LWR and nine of 28 patients undergoing a bilobectomy or pneumonectomy experienced a recurrence (p = ns). As already reported for the DSS analysis, the type of resection did not affect the recurrence rate and the presence of FI extended for more than 3 cm was found to be the most significant prognostic factor. On the other hand, we have reported that the postoperative course of both procedures did not differ in terms of complication rate, hospital stay, and admission in ICU.

It has been proven that the task of the preoperative functional assessment is to identify patients who are at increased risk of both perioperative complications and long-term disability from surgical resections of NSCLC. The ACCP guidelines[16] recommended the spirometric tests in all patients undergoing lung resection, in particular for analyzing FEV1 and DLCO. In fact, patients with FEV1 more than 80% predicted or more than 2 liters are suitable for resection including pneumonectomy without further physiologic evaluation. On the contrary, if either the FEV1 or DLCO is less than 80% predicted or $Paco_2$ is more than 45 mmHg (factors related to high postoperative complication rate), it is recommended that postoperative lung function be predicted through additional testing. According to these guidelines, we have analyzed the baseline and the postoperative (1 month after discharge) pulmonary function tests. The baseline preoperative tests were found to be comparable between both groups: in fact, preoperative FEV1%-predicted of group A and group B were, respectively, 92.5% ± 21.0% and 85.2% ± 20.0% (p = ns). Concerning the postoperative course of the total sample, we did not find any statistical correlation between FVC% less than 85%, FEV1% less than 85%, DLCO less than 15 or po_2 less than 80 mmHg, and complication rate or hospital stay. Indifferently from previous works, we have calculated the decline ΔFEV1% after surgery to compare both procedures in term of functional outcome. The ΔFEV1% was slightly higher in patients undergoing anatomical resection (−24.9% ± 13.5%) if compared with those undergoing LWR (−19.5% ± 13.3%), but this difference was not statistically significant (p = ns). Similar results were found when comparing the decline of FVC%, DLCO, and po_2 as well.

Considering the akin oncological results of both procedures, these data strongly support the evidence that anatomical or nonanatomical resection could lead to an acceptable and similar functional outcome in patients with NCSLC with FI. Thus, because radical resection of tumors with their lymphatic drainage is the accepted oncological procedure, bilobectomy or pneumonectomy should be performed in NSCLC patients with adjacent lobe invasion, whereas, in case of poor baseline function tests, LWR may be preferable over an anatomical resection when the extent of FI is less than 3 cm. In the light of the new evidence reported,[17] further studies are needed to evaluate the effect of a preoperative pulmonary rehabilitation in patients with FI and poor lung tests.

This study has several limitations. First, even if this work addresses the questions of how much the type of resections influences long-term survival outcome, recurrence, and early-term outcome of pulmonary function, the number of cases is limited. Studies with larger sample sizes would be more sensible in detecting statistically significant differences and could lead to different conclusions. Furthermore, due to the small number of patients, it has not been possible to perform a subgroup analysis to assess the prognostic impact of FI on the T-factor, by excluding patients with lymph node involvement: further studies with a large number of cases are needed to investigate this issue as well. Second, this study is retrospective, and the type of surgery was decided by the surgeon's preference without randomization. Moreover, as reported by others,[13] our pathological analysis lacks of data concerning the fissure completeness.

In conclusion, surgical strategy in NSCLC patients with FI is really a challenging issue. Our results suggest that nonanatomical resection (LWR) could be considered as a feasible surgical option (especially in "frail" patients with an extent of FI less than 3 cm) in the light of the similar oncological and functional outcome compared with anatomical resection (bilobectomy or pneumonectomy). However, prospective studies with a large number of patients are needed to confirm these preliminary data and also to investigate the impact of the two different surgical strategies on the postoperative quality of life.

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TABLE 6. Analysis on Tumor Recurrence

	Recurrence (n = 12 [35%])	No Recurrence (n = 22 [65%])	Unadjusted Hazard Ratio	95% Confidence Interval	*p*	Adjusted* Hazard Ratio	95% Confidence Interval	*p*	Follow-Up Period (Months)
Age (yr)									
≤65	6 (50%)	4 (18%)	2.13	0.68–6.67	0.192	0.55	0.12–2.49	0.439	103
>65	6 (50%)	18 (82%)	1			1			154
Sex									
Female	2 (17%)	6 (27%)	1			1			45
Male	10 (83%)	16 (73%)	0.74	0.14–3.75	0.713	0.55	0.1–3	0.491	154
Smoker									
No	6 (67%)	13 (72%)	1			1			71
Yes	3 (33%)	5 (28%)	0.92	0.23–3.71	0.905	0.39	0.07–2.15	0.278	88
Surgery									
Group A	9 (75%)	15 (68%)	1			1.00			154
Group B	3 (25%)	7 (32%)	0.6	0.16–2.23	0.443	2.09	0.35–12.57	0.423	103
Residual disease									
R0	9 (75%)	20 (91%)	1			1.00			154
R1	3 (25%)	2 (9%)	4.7	1.11–19.89	0.035	2.22	0.48–10.24	0.304	36
Fissure invasion									
≤3 cm	5 (42%)	22 (100%)	1						154
>3 cm	7 (58%)	0 (0%)	12.42	3.56–43.24	<0.001*				62
pT									
T2	9 (75%)	16 (73%)	1			1.00			154
T3-T4	3 (25%)	6 (27%)	1.37	0.37–5.14	0.639	1.63	0.39–6.78	0.503	109
pN									
N0	6 (50%)	14 (64%)	1			1.00			154
N1	4 (33%)	6 (27%)	2.42	0.67–8.76	0.177	0.37	0.06–2.27	0.281	109
N2	2 (17%)	2 (9%)	4.98	0.88–28.14	0.069	0.63	0.08–5.06	0.662	32
p-Stage									
IB	5 (42%)	7 (32%)	1			1			154
IIA	2 (17%)	7 (32%)	0.52	0.1–2.69	0.434	0.1	0.01–0.95	0.045	102
IIB	1 (8%)	3 (14%)	0.87	0.1–7.52	0.896	1.18	0.12–11.18	0.885	88
IIIA	4 (33%)	5 (23%)	2.14	0.56–8.19	0.268	0.58	0.12–2.84	0.502	109
Tumor size									
≤4 cm	7 (58%)	10 (45%)	1			1			103
>4 cm	5 (42%)	12 (55%)	1.83	0.58–5.8	0.303	1.82	0.51–6.54	0.358	154
Histology									
SCC	5 (42%)	6 (27%)	2.66	0.51–13.86	0.245	6.11	0.79–47.38	0.083	103
AC	5 (42%)	7 (32%)	2.37	0.46–12.29	0.304	10.96	1.2–99.75	0.034	109
Other	2 (17%)	9 (41%)	1			1			154

* Adjusting covariate: Fissure invasion. Statistical tests: Cox regression analysis; statistical significance: $p < 0.05$.
SCC, squamous cell carcinoma; AC, adenocarcinoma.

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