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Proximal bronchial extension with special reference to tumor localization in non-small cell lung cancer

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Abstract

Objective: Surgery is the optimal treatment in patients with non-small cell lung cancer (NSCLC) and tumor-negative bronchial resection margins should be maintained for a curative resection. The epidemiology of NSCLC, including the aspects of tumor localization, has been changing during the recent decades. The aim of this study was to evaluate microscopic proximal bronchial extension with special reference to the site of the tumor. **Methods**: Surgical specimens of 70 NSCLC cases were examined histologically for proximal bronchial extension of the tumor. The entire bronchial tree with the tumor was extracted from the specimen and serially cut at a thickness of 5 mm in the transverse plane of the bronchus. Microscopic proximal extension of the tumor was classified as either endobronchial or peribronchial. **Results**: Thirty-three (47.1%) tumors had central and 37 (52.9%) had peripheral localization. Among the central and peripheral tumors, 10 (30.3%) and seven (18.9%) had microscopic proximal extension, respectively. In total, the mean length of proximal extension was 10.94 ± 7.07 mm. The mean length of extension for peripheral tumors was 15.71 ± 8.38 mm, significantly greater than that of central tumors, which was 7.60 ± 3.47 mm ($P = 0.026$). Peripheral tumors showed a significant peribronchial extension ($P = 0.024$). **Conclusions**: A greater percentage of central tumors show microscopic proximal bronchial extension, whereas the length of microscopic proximal bronchial extension is significantly greater in peripheral tumors. Peripheral tumors preferentially have a peribronchial extension pattern. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Non-small cell lung cancer; Tumor localization; Bronchial extension

1. Introduction

Curative resection with negative margins still remains the optimal treatment for non-small cell lung carcinomas (NSCLC), which comprise 80–85% of lung carcinomas. Inadequate resection may result from residual tumor at the transection line, particularly the bronchial margin, and has unfavorable impacts on survival [1–3]. Overall opinion on the bronchial safety margin is that at least 1.9 cm (3/4 inches) of apparently normal bronchus should be severed to eliminate the risk of residual tumor in the bronchial stump to achieve a tumor-negative bronchial resection margin (BRM) [4]. However, no definitive criteria or international consensus has been achieved on the length of the bronchial safety margin. For this reason, completeness of resection depends on the surgeon's philosophy rather than on objective data. As a result, a thoracic surgeon can be confronted with a microscopical tumor at the BRM either intraoperatively or postoperatively. This situation creates a clinical problem for further management requiring revision surgery or adjuvant treatment.

Epidemiologic characteristics of NSCLC have been changing during the recent decades with the decrease in centrally located tumors and the increase of peripherally located tumors, particularly that of adenocarcinoma [5,6]. Although some authors previously studied the proximal spread of bronchogenic carcinoma [4,7–9], we are not aware of any study in which microscopic proximal extension of NSCLC with special emphasis on tumor localization has been evaluated. We investigated the proximal bronchial extension of the tumor with reference to the localization and clinicopathologic features in 70 surgically resected NSCLC specimens. It was anticipated that these results would provide additional resectional criteria for patients with non-small cell lung cancer (NSCLC).

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Table 1
Analysis of operative procedures ($n = 70$)

Operative procedure	No. (%) of patients		
	Right	Left	Total
Pneumonectomy	6 (9)	11 (16)	17 (24)
Upper lobectomy	8 (12)	13 (18)	
Lower lobectomy	15 (21)	11 (16)	
Total lobectomies	23 (33)	24 (34)	47 (67)
Bilobectomy	4 (6)	–	4 (6)
Segmentectomy	1 (1)	1 (1)	2 (3)
Total	34 (49)	36 (51)	70 (100)

2. Materials and methods

2.1. Patients and specimens

Surgical specimens were obtained from 70 consecutive cases with NSCLC who had undergone curative resection of the primary tumor with systematic lymph node dissection in İbn-i Sina Hospital of Ankara University School of Medicine between September 1994 and July 1996. All patients but one were male with a mean age of 56.2 ± 9.1 (range, 35–76 years).

The most frequently performed operative procedure were 15 (21.4%) lower lobectomies in the right and 13 (18.5%) upper lobectomies in the left hemithorax (Table 1). In total, there were 12 (17.1%) bronchial sleeve resection cases. Specimens of wedge bronchoplasties or post mortem materials were not included in this survey. Specimens, which had extracapsullary lymph node involvement at more proximal levels rather than BRM also were excluded to avoid false positive results.

Frozen section examination was performed in 22 (31.4%) cases and 13 (18.5%) showed tumor-positivity at the BRM. Among these cases, nine (12.8 %) further underwent reamputation of the bronchus, and four (5.7%) underwent extended resections such as sleeve lobectomy or pneumonectomy. The reamputated bronchus and the bronchial fragments were always evaluated together with the entire bronchial tree. Hence, we obtained tumor-negative margins in all but one (1.4%) specimen, which had microscopic tumor at the proximal resection margin at 6 mm cut serial. The tumors, which developed in a main or segmental bronchus, were classified as central type, and those arising from subsegmental or more distal bronchi were considered as peripheral type.

2.2. Technique

Fresh specimens were initially immersed into isotonic saline solution temporarily. After either blunt or sharp dissection of the entire bronchial tree (Fig. 1), the tumor-related bronchus was sectioned into serial blocks at a thickness of 5 mm in the transverse plane. The conjunction between the macroscopic tumor and apparently normal bronchus was called as '0' or the 'reference plane'. Beginning from the reference plane, consecutive ring-shaped cut serials involving the most proximally located BRM were obtained.

The most proximal edge of the tumor within the bronchus was considered as the reference plane if proximal tumor extension was macroscopically endobronchial and the most proximal part of the tumor extending out of the bronchial wall was taken as the reference plane if the most proximal part was peribronchial. If the tumor contained both of the extension patterns, the reference level was determined with reference to the most proximal extension pattern. Centrally located tumors, which were likely to be destroyed after a dissection, were extracted en bloc with BRM in six (8.5%) specimens.

Thereafter, cut serials were fixed in buffered formalin. Sections were stained with hematoxylin and eosin. We classified microscopic extension of the tumor as: (1) endobronchial extension, (2) submucosal lymphatic invasion, and (3) peribronchial extension outside the bronchial cartilage. Histochemical and immunohistochemical staining was

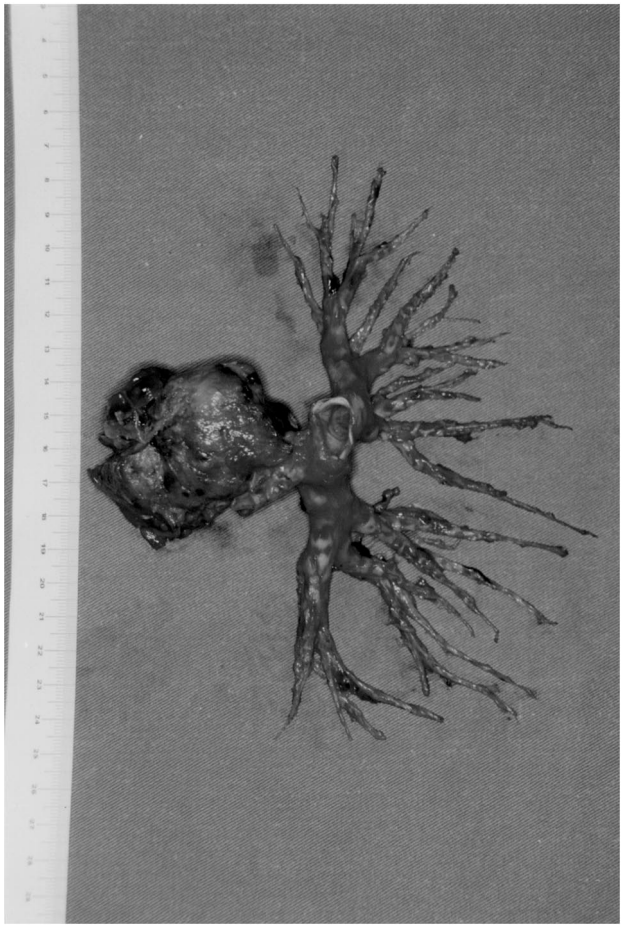


Fig. 1. The entire bronchial tree showing a centrally located tumor arising from the apical segment of the lower lobe in a left pneumonectomy specimen.

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performed for tumor typing if necessary. Tumors were classified according to the new 1999 WHO/IASLC classification of lung and pleural tumors [10].

2.3. Statistical analysis

Statistical comparisons of baseline data between groups were carried out by the chi-square and Fisher's exact tests as appropriate. Age, tumor size, operative procedure, histology, differentiation, and extension patterns were included in the assessment of statistical comparisons with tumor localization. Microscopic and macroscopic extension patterns were grouped as endobronchial and peribronchial, the former including the submucosal lymphatic invasion. Age was classified as a high- or low-group relative to the median value. Data were expressed as the mean ± standard deviation. The mean lengths of extension of different clinicopathological subgroups were analyzed by the Mann–Whitney *U*-test. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, version 8.0, Chicago, IL, USA).

3. Results

Thirty-three (47.1%) tumors had central and 37 (52.9%) had peripheral localization. The cut serials were tumor-positive and tumor-negative in 34 (48.5%) and 36 (51.5%) specimens, respectively. Among the 34 specimens, 17 (24.2%) had microscopic tumor only at the reference plane. In total, the remaining 17 (24.2%) showed microscopic tumoral extension at more proximal levels. Proximal bronchial extension was observed in 10 (30.3%) and seven (18.9%) central and peripheral tumors, respectively. With regard to the most proximal level, central tumors had a microscopic tumor at the reference plane in 10 (50%), 5 mm in five (25%), 6 mm in one (5%), 10 mm in three (15%), and 15 mm in one (5%) specimens. Peripherally located tumors showed a microscopic tumor at the reference plane in seven (51%), 5 mm in one (7%), 10 mm in two (14%), 15 mm in one (7%), 20 mm in two (14%), and 30 mm in one (7%) specimens (Table 2).

In total, the mean length of proximal extension was 10.94 ± 7.07 mm. The mean length of proximal extension for peripheral tumors was 15.71 ± 8.38 mm, significantly greater than that of central tumors which was 7.60 ± 3.47 mm ($P = 0.026$). No significant difference was found between the mean lengths of the subgroups of age, tumor size, operative procedure, histology, differentiation, and microscopic extension pattern (Table 3).

Macroscopic extension pattern correlated significantly with tumor localization ($P < 0.0001$). On gross examination, among the 33 central tumors, 30 (90.9%) showed endobronchial extension. Tumor localization did not have any effect on the presence of microscopic extension ($P = 0.268$). However, the microscopic extension pattern (endobronchial and peribronchial) showed a significant correlation with the tumor localization ($P = 0.024$). The microscopic extension pattern was endobronchial in seven (70.0%) of the central tumors and peribronchial in six (85.7%) of the peripheral tumors (Figs. 2 and 3). Tumors larger than 3 cm comprised 29 (78.3%) of the peripheral

Table 2
Analysis of cases which showed microscopic proximal bronchial extension ($n = 17$)

Case	Age (years)	Tumor localization	Operation[a]	Histology[b]	Extension pattern	Most proximal tumor (+) cut section (mm)
1	51	Central	RLSL	SCC	Endobronchial	5
2	56	Central	LUL + LR	SCC	Peribronchial	5
3	51	Central	LLL	SCC	Endobronchial[c]	5
4	49	Central	RTSP	SCC	Peribronchial	5
5	43	Central	LLSL	SCC	Endobronchial	5
6	48	Central	RUSL	ASC	Endobronchial	6
7	66	Central	LUL + LR	SCC	Peribronchial	10
8	59	Central	LP	SCC	Endobronchial	10
9	60	Central	RUSBL	SCC	Endobronchial	10
10	55	Central	RP	SCC	Endobronchial[c]	15
11	63	Peripheral	RUBL	AC	Peribronchial	5
12	56	Peripheral	LUL + LR	SCC	Peribronchial	10
13	37	Peripheral	LP	AC	Peribronchial	10
14	46	Peripheral	RUL	AC	Peribronchial	15
15	69	Peripheral	RLL	SCC	Endobronchial	20
16	54	Peripheral	RUBL	AC	Peribronchial	20
17	63	Peripheral	RLL	AC	Peribronchial	30

[a] RLSL, right lower sleeve lobectomy; LUL + LR, left upper lobectomy + lingular resection; LLL, left lower lobectomy; RTSP, right tracheal sleeve pneumonectomy; LLSL, left lower sleeve lobectomy; RUSL, right upper sleeve lobectomy; LP, left pneumonectomy; RUSBL, right upper sleeve bilobectomy; RP, right pneumonectomy; RUBL, right upper bilobectomy; RUL, right upper lobectomy; RLL, right lower lobectomy.
[b] SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma.
[c] Submucosal lymphatic invasion.

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Table 3
Comparison of length of microscopic proximal tumor extension (mm) in relation to clinicopathologic features

Variables	Mean ± SD	Maximum	Median	*P*-value[a]
Total	10.94 ± 7.07	30.00	10.00	
Localization				
Peripheral	15.71 ± 8.38	30.00	15.00	
Central	7.60 ± 3.47	20.00	5.50	0.026
Age (years)				
≤ 57	9.18 ± 5.32	20.00	6.00	
> 57	14.16 ± 9.17	30.00	10.00	0.211
Tumor size				
T ≤ 3 cm	8.71 ± 6.18	30.00	5.00	
T > 3 cm	12.50 ± 7.54	15.00	10.00	0.188
Operative procedure				
Lobectomy	11.23 ± 7.88	20.00	10.00	
Pneumonectomy	10.00 ± 4.08	30.00	10.00	0.907
Histology				
Squamous cell carcinoma	9.09 ± 4.90	15.00	10.00	
Adenocarcinoma	16.00 ± 9.61	30.00	10.00	0.124
Differentiation				
Well	10.00 ± 7.07	20.00	10.00	
Moderate/poor	11.06 ± 7.31	30.00	10.00	0.877
Microscopic extension pattern				
Endobronchial	9.50 ± 5.52	15.00	8.00	
Peribronchial	12.22 ± 8.33	30.00	10.00	0.583

[a] The mean lengths of extension between the subgroups of clinicopathologic features were compared by the Mann–Whitney *U*-test.

tumors, which was statistically significant ($P = 0.034$). Lobectomy was the choice of operative procedure in 34 (91.8%) of the peripheral tumors ($P < 0.0001$). Significant correlation existed between histology and tumor localization ($P = 0.003$). The most frequent cell type was squamous cell carcinoma (SCC) (75.7%) and adenocarcinoma (AC) (51.3%) in central and peripheral tumors, respectively. No significant association was found between age, differentiation, and tumor localization (Table 4).

4. Discussion

Curative resection is the main task in thoracic surgical oncology and it can be achieved with negative bronchial margins in addition to the removal of the gross tumor with regional and mediastinal lymphadenectomy in NSCLC. Since the initial reports of Griess and Cotton [4,7] concerning proximal bronchial extension in lung cancer, little attention has been paid to this issue [8,9,11]. To date, investigators have conducted studies on the prognostic impact of tumor-positivity at the BRM [1,2,3,8,12,13] rather than outlining the safe resection length related to clinicopathologic features. To our knowledge, this is the first detailed report highlighting the features of microscopic proximal bronchial extension with special reference to tumor localization.

In a previous study, we showed that microscopic proximal bronchial extension occurred in 24.2% of NSCLC cases [14]. A noteworthy finding of our previous study was that adenocarcinoma appeared to extend proximally more than SCC in length. In addition, SCC has a preferential central localization, whereas AC is frequently peripherally located [15]. Thus, we designed a study to examine proximal bronchial extension in NSCLC related to the tumor site to further outline the difference. In the presented data, we found that a greater percentage of central tumors showed proximal extension when compared with peripheral tumors. On the other hand, the length of microscopic proximal extension was greater in peripheral tumors with a significant peribronchial pattern. This finding may be attributed, at least in part, to the fact that AC constitutes a more aggressive histological subtype of NSCLC and comprises most of the peripheral tumors. In our series, adenocarcinomas accounted for 51.3% of the peripheral tumors in total and 71.4% of proximally extended peripheral tumors. Likewise, Griess et al., who were the first workers on bronchial extension of lung cancer, proposed that the bronchus should be severed at least 1.5 cm proximally from the gross tumor in SCC, but for AC more than 2 cm should be provided [7]. Moreover, the late onset of symptoms in peripheral tumors may result in a greater size and longer extension of tumors. Consistently, our data revealed that tumors larger than 3 cm significantly constituted 78% of peripheral tumors.

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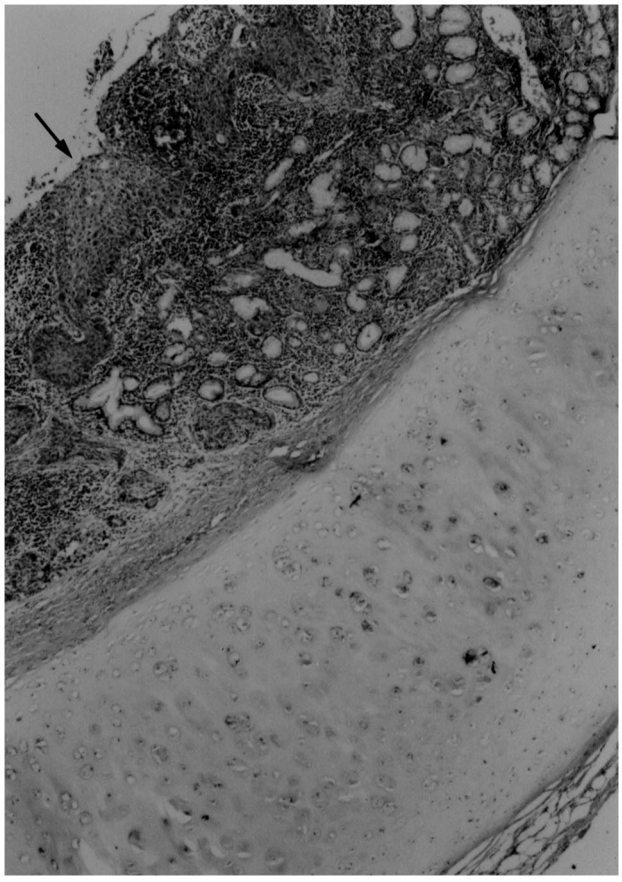


Fig. 2. Endobronchial tumor extension (arrow) at 10 mm cut serial in a left pneumonectomy specimen of a centrally located squamous cell carcinoma (HE × 20).

We previously reported that regardless of the tumor site, a bronchial resection of 1.5 cm from the edge of the macroscopic tumor would provide tumor-negative margins in 93% of NSCLC cases [14]. The results of the current study agree with those from previous studies [4,7,9,16] that indicated that 2 cm of a bronchial safety margin was adequate but when stratified by tumor localization, it is not valid for peripheral tumors as the mean length of extension in these tumors is significantly more than that in central tumors. We may reasonably suggest that a sufficient length of apparently normal bronchus should be provided, particularly for those compromised patients with peripheral NSCLC, who are candidates for limited operative procedures such as wedge resection or segmentectomy. Likewise, because it is unlikely to palpate the tumor in patients undergoing video-assisted thoracoscopic lobectomy, the surgeon should not solely rely on preoperative diagnostic procedures such as bronchoscopy. Microscopic extension of the tumor does not correspond to preoperatively determined findings at bronchoscopy. Bronchoscopy may give some clues about mucosal invasion of the tumor; however, it is inappropriate in detecting submucosal or peribronchial extension [9,11]. In addition, this study revealed that one fourth of NSCLC specimens (24.2%) showed microscopic tumors at the reference plane, which implies that microscopic findings are different from those observed macroscopically. Bronchoscopic and macroscopic findings are not always reliable for determining the resection line, as microscopic tumor extension might be different. Consequently, it is indispensable to verify tumor-negative margins with intraoperative frozen sections of the BRM.

In accordance with our data, other investigators have reported that peribronchial extension occurred more than both mucosal or submucosal extension in NSCLC tumors [2,4,7,13,17] and its prognostic impact on survival is more significant than other patterns of extension [8,18]. The intraoperative frozen section of BRM may reveal mucosal involvement more easily but peribronchial extension can be overlooked, particularly if the microscopic tumor is small in the BRM [2,17]. Considering that our results reveal that the mean length of peribronchial extension is more than that of endobronchial extension, careful examination of the peribronchial area should not be ignored in frozen sections [17].

In conclusion, a greater percentage of central tumors

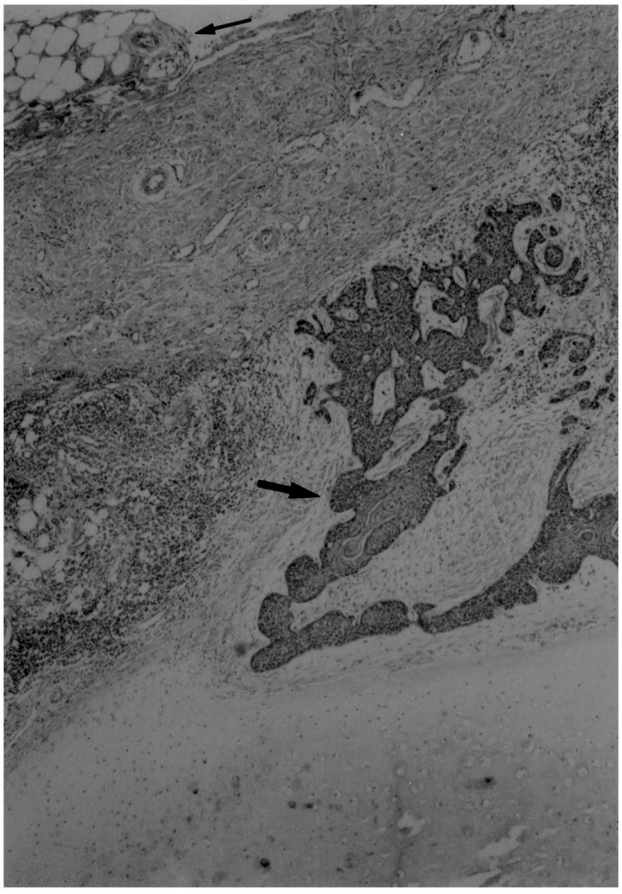


Fig. 3. Tumor islands (thick arrow) in the peribronchial area beneath the adipose tissue (thin arrow) and fibrous coat of the bronchus at 10 mm cut serial in a left upper lobectomy and lingular resection specimen of a centrally located squamous cell carcinoma (HE × 20).

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Table 4
Comparison of clinicopathologic features and tumor localization

Variables		Tumor localization (no. of patients (%))		
	n	Central	Peripheral	*P*-value
Total	70	33 (47)	37 (53)	
Macroscopic extension pattern				
Endobronchial	37	30 (91)	7 (19)	
Peribronchial	33	3 (9)	30 (81)	< 0.0001
Microscopic extension				
Present	17	10 (30)	7 (19)	
Absent	53	23 (70)	30 (81)	0.268
Microscopic extension pattern				
Endobronchial	8	7 (70)	1 (14)	
Peribronchial	9	3 (30)	6 (86)	0.024
Age (years)				
≤ 57	32	18 (55)	14 (38)	
> 57	38	15 (45)	23 (62)	0.161
Tumor size				
T $\leq$ 3 cm	23	15 (45)	8 (22)	
T $>$ 3 cm	47	18 (55)	29 (78)	0.034
Operative procedure				
Lobectomy	51	17 (52)	34 (92)	
Pneumonectomy	17	16 (48)	1 (3)	
Segmentectomy	2	–	2 (5)	< 0.0001
Histology				
Squamous cell carcinoma	38	25 (76)	13 (35)	
Adenocarcinoma	23	4 (12)	19 (51)	
Adenosquamous carcinoma	6	3 (9)	3 (8)	
Large cell carcinoma	3	1 (3)	2 (6)	0.003
Differentiation				
Well	7	5 (15)	2 (5)	
Moderate/poor	63	28 (85)	35 (95)	0.175

extend proximally along the bronchus than of peripheral tumors. On the other hand, the length of microscopic proximal bronchial extension of the tumor is significantly greater in peripheral tumors with a significant peribronchial pattern.

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