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# Tumor invasion of extralobar soft tissue beyond the hilar region does not affect the prognosis of surgically resected lung cancer patients.

Running title: Tumor invasion beyond the hilar region

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Key words: extralobar fat tissue, hilar region, pleural invasion, pleural elastic lamina.

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***Abstract***

***Background:***

Visceral pleural invasion (VPI), which is defined as tumor extension beyond the elastic lamina, is one of the most important prognostic factors in patients who have undergone curative resection for non-small cell lung cancer (NSCLC). However, in pathological slides, pleural elastic lamina could not be found in the hilar region where the pleura is reflected. Up to the present date, when cancer cells are seen in this region, a basical agreement dealing with T factor is controversial among pathologists. The purpose of this study is to evaluate the significance of tumor invasion of that region as a prognostic factor.

***Methods:***

We reviewed 91 cases of surgically resected lung cancer in which invasion of the hilar region was visible macroscopically. By microscopic examination, we divided them into three groups: a group in which no cancer cells are seen in the soft tissue beyond the hilar region (Group A), a group in which cancer cells are seen in the soft tissue beyond the hilar region (Group B), and a group in which cancer cells could not be seen in the soft tissue beyond the hilar region but invade into the mediastinal visceral pleura at some other site (Group C). We then evaluated the clinicopathological characteristics of the patients and their outcome.

***Results:***

There was no statistically significant difference in the 5-year overall survival rate or disease-free

survival rate between Group A and Group B (overall: 55% vs. 48%; disease-free: 43% vs. 42%), but disease-free survival of Group C was significantly lower than that of Group A and Group B (A vs. C: $p = 0.022$; B vs. C: $p = 0.040$).

***Conclusion:***

Tumor invasion of the soft tissue beyond hilar region would not be a prognostic factor in patients who have undergone curative resection for primary lung cancer, although investigation of larger number of cases will be needed to confirm the validity of our conclusion.

## *Introduction*

In the mid 1970s, visceral pleural invasion (VPI) was included as a specific entity in the TNM classification [1], and it is generally accepted that VPI is one of the most important prognostic factors in patients who have undergone curative resection for non-small cell lung cancer (NSCLC) [2, 3]. VPI has been adopted as a T2 descriptor in the TNM classification of the International Union Against Cancer (UICC) staging system for lung cancer [4]. VPI is defined as histological evidence of tumor extension beyond the elastic lamina of the visceral pleura, regardless of whether the tumor is exposed on the pleural surface in the new 7$^{th}$ edition of the TNM staging system [5].

There are two regions where pleural elastic lamina could not be found in pathological slides. One is incomplete interlobar fissures, and the other is the hilar region where the pleura is reflected. Kamiyoshihara and colleagues demonstrated that incomplete interlobar fissures do not affect the prognosis after curative resection of stage I or II NSCLC [6]. According to the Japan Lung Cancer Society (JLCS), “invasion of the adjacent lobes where the interlobar borderline in case with incomplete lobe formation should be recorded as P0.” which is classified as T1[7]. In contrast, the new 7$^{th}$ edition of the TNM staging system [5] defined that, ‘‘tumor with direct invasion of an adjacent lobe, across the fissure or by direct extension at a point where the fissure is deficient, classified as T2a unless other criteria assign a higher T category’’. Anatomic

variation of the interlober fissure can potentially impact clinical and pathologic assessment of lung cancers for involvement of adjacent lobe [8].

When a cancer arises in the hilar region, cancer cells sometimes invade the soft tissue beyond the hilar region. Anatomically, lung parenchyma and mediastinal tissues are covered by pleura. Lungs are covered by visceral pleura, and mediastinal tissues are covered by mediastinal pleura. The ‘‘pleural reflexion’’ is thought to be the boundary between lung and mediastinum. However, pleural reflexion is hard to be identified intraoperatively because visceral and mediastinal pleurae are continuous and there are no ‘‘mark’’ between them. Furthermore, during the surgical procedures, pleura around the boundary lesion are usually dissected. Therefore, there is no ‘‘pleural cover’’ on the soft tissue around the boundary lesion. We could not differentiate soft tissue tumor invasion beyond hilar structure from ‘‘intra lung’’ or ‘‘extra lung’’ invasion. The 7$^{th}$ edition of the TNM staging system defined that ‘‘tumor invasion into mediastinal fat is T4, if such invasion is clearly limited to fat within the hilum, classification as T2a or T2b is appropriate, depending upon size, unless other features dictate a higher T category’’ [5]. But there is no study to become grounds of this definition to date. The purpose of this study is to evaluate the significance of tumor invasion of this region as a prognostic factor.

## *Patients and Methods*

During the period from February 1992 to December 2005, 2684 consecutive primary lung

cancer patients were surgically treated at our institution. For the purpose of this study, we first selected the cases according to the following criteria: 1) presence of macroscopically visible involvement of the hilar region, 2) having undergone curative resection, defined as lung resection more than lobectomy and complete removal of the ipsilateral hilar and mediastinal lymph nodes. Non-invasive carcinoma such as squamous cell carcinoma in situ in the bronchus was excluded, and the cases who had induction chemotherapy or radiotherapy, and the cases with evidence of residual tumor at the surgical margin were also excluded. We analyzed archival slides and medical records, and identified 91 cases (3.4%) that met these criteria.

We divided these 91 cases into the following three groups based on the microscopic findings (Figure 1): a group in which no cancer cells are seen in either the soft tissue beyond the hilar region or the visceral pleura at other sites (Group A), a group in which the cancer cells are seen in the soft tissue (extralobar fat tissue) beyond the hilar region but do not invade beyond the elastic lamina of the visceral pleura at other sites (Group B) (Figure 2 A-D) and a group in which the tumor cells invade beyond the elastic lamina of the mediastinal pleura above and/or below the hilar region, but no cancer cells are seen in the soft tissue beyond the hilar region (Group C). Group C included the cases with PL1, 2 and 3 defined in the 7$^{th}$ edition of the TNM staging system. Furthermore cases with mediastinal invasion and cases with invasion of hilar region by lymph node metastatic tumor were excluded. There were 31 cases in Group A, 32 cases in Group B, and 28 cases in Group C.

*Pathological evaluation:*

The surgical specimen in each case had been fixed with 10% formalin or absolute methyl alcohol and embedded in paraffin. The tumor had been cut into 5-10 mm slices, and serial 4-μm sections had been stained with hematoxylin and eosin (HE), or by the Victoria van-Gieson (VVG) method to visualize the elastic lamina. The tumors were classified according to the criteria of the current WHO histological classification [9]. VPI (p-factor) was evaluated by VVG-stained sections, and classified by the 7$^{th}$ edition of the TNM staging system (PL0 to PL3) [5]. Presence of vascular invasion (v factor) was evaluated by VVG-staining. Two observers (H.O and G.I) who had no knowledge of the clinical data independently reviewed all slides. Whenever their evaluations were discordant, they jointly reviewed the specimen through a multiheaded microscope, and reached a consensus. Pathological staging was performed according to the classification of the Union Internationale Contre le Cancer (UICC) 6th [4].

*Statistical Analysis:*

The Pearson $\chi^2$ test or Fisher exact test was used to compare categorical and dichotomous variables. Analysis of variance with life tables and Kaplan-Meier curves were used for the

analyses of overall and disease-free survival. Differences between groups were analyzed by the log-rank test. Statistical significance was assumed to exist at two-tailed p values of $< 0.05$. All statistical analyses were performed using a statistical software package (Dr. SPSS II for Windows, version 11. 0. 1 J.).

## *Results*

### *Clinicopathological factors of Group A, Group B, and Group C*

The profiles of each group of patients in regard to gender, age, surgical procedure, histologic type, tumor size, and UICC- N and M stages are summarized in Table 1. There were 80 men and 11 women. The median age was 61 years old (range; 36 to 79 years old). There were no statistically significant differences between the groups in gender, age distribution, and UICC- M stage.

There were no significant differences in clinicopathological features between Group A and Group B, besides type of resection. In Group A, pneumonectomy was performed for all cases. Lobectomy was performed in a higher proportion of the cases in Group C than in Group A or Group B. The tumor size of Group C was significantly larger than that of Group A ($p = 0.032$). The proportion of adenocarcinoma cases in Group C was significantly and marginally higher than those in Group B and A, respectively ($p < 0.001$ and $p = 0.08$). N0 disease was more common in Group C than in Group A or Group B (Group A, 13%; Group B, 13%; Group C, 46%; A vs. C, $p = 0.005$; B vs. C, $p = 0.035$). No statistical significant differences were found between the three

groups in frequency of lymphatic infiltration. There was a significantly lower proportion of cases with vascular invasion in Group A than in Group B or Group C (Group A, 58%; Group B, 88%; Group C, 86%; A vs. B, p = 0.009; A vs. C, p = 0.019 ).

*Survival rates in each group*

The overall 5-year survivals rate was 55% in Group A, 48% in Group B, and 38% in Group C. There was no statistically significant difference in survival rate between Group A and Group B (p = 0.358) or between Group B and Group C (p = 0.159), but the overall survival rate in Group A was marginally higher than in Group C (p = 0.082).

The disease free survivals of each group were 43% in Group A, 42% in group B, and 27% in Group C. The difference in disease-free survival rate between Group A and Group B was not significant (p = 0.758), but the differences in disease-free survival rate between Group A and Group C, and between Group B and Group C were significant (A vs. C, p = 0.022; B vs. C, p =0.040).

## *Discussion*

In present study, we compared cases with soft tissue invasion beyond the hilar region (Group B) and cases without soft tissue invasion (Group A), and the results suggested that tumor invasion of the soft tissue beyond the hilar region where the elastic lamina is reflected does not affect the

survival.

In the current study, VPI positive cases (Group C), showed worse survival rate than VPI negative cases (Group A and B). This result was consistent with many previously studies indicating the prognostic significance of VPI in NSCLC [2, 10-12], which would display the accuracy of the case selection process in the current study. In a study of 1074 cases of T1-2 NSCLC, Shimizu et al, identified visceral pleural invasion in 26.8% of the cases and found that it was significant prognostic factor [13]. They also reported significant prevalence of lymphatic and vascular invasion in the visceral pleural invasion (VPI) group, and their findings corroborated that tumors with VPI have high invasive and progressive potential. Mizuno et al, reviewed 413 surgically resected cases of stage I lung adenocarcinoma [14], and found that the 5-year survival rate of the stage IB patients without pleural invasion was 89.3%, as opposed to 62.5% in the stage IB patients with pleural invasion, and that it was significantly lower than in the stage IB cases without pleural invasion. A multivariate analysis revealed pleural invasion to be an independent prognostic factor. These observations suggest that tumor cell aggressiveness may depend somewhat on their ability to destroy the elastic lamina and invade subpleural tissue. In the present study, no statistically significant differences in frequency of lymphatic permeation were found between the three groups, but there was a significantly lower proportion of vascular-invasion-positive cases in Group A than in Group B or Group C (Group A, 58%; Group B, 88%; Group C, 86%; A vs. B, $p = 0.009$; A vs. C, $p = 0.019$). In view of the comparable rates in Group B and Group C, p factor

may more strongly reflect the malignancy of a tumor than v factor does.

It is well known that the presence of lymph node metastases is a negative prognostic factor for primary lung cancer [15, 16]. In the present study, however, Group C had a poorer outcome in terms of overall and disease-free survival than group A or Group B, in spite of the significantly higher proportion of N0 diseases relative to Group A and Group B (Group A, 13%; group B, 13%; group C, 46%; A vs. C, p = 0.035; B vs. C, p = 0.005). Edwin et al, reviewed 58 cases of pT1N1M0 disease[17], and found that the 5-year survival rate of patients with N l direct extension was higher than that of patients with N l metastases (68.6% vs. 31.2%; p=0.0038). In this study, cases with lymph node involvement by direct invasion in group A, B, and C was 20 cases (65%), 17 cases (53%), and 10 cases ( 36% ) , respectively (data not shown). The frequency of direct N1 cases was higher in Group A and Group B than in Group C. This difference may explain why Group A and Group B had a better outcome despite significantly higher lymph node involvement.

In conclusion, tumor invasion to the soft tissue beyond the hilar region would not be a prognostic factor in patients who have undergone curative resection for primary lung cancer. Further investigation of larger number of cases will be needed to confirm the validity of our conclusion.

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Figure legends

Figure 1: Scheme of cases with hilar region involvement

Group A: No cancer cells are seen in either the soft tissue beyond the hilar region or visceral pleura at other sites.

Group B: Cancer cells are seen in the soft tissue (extralober fat tissue) beyond the hilar region, but do not invade beyond the elastic lamina of the visceral pleura at other sites.

Group C: Cancer cells invade beyond the elastic lamina of mediastinal pleura above and/or below hilar region (included the cases with PL1,2 and 3 defined in the 7$^{th}$ edition of the TNM staging system), but no cancer cells are seen in the soft tissue beyond the hilar region.

Figure 2: Macroscopic and microscopic findings in lung cancer with hilar region involvement

A: Macroscopic appearance of lung cancer with hilar region involvement (Group B).

B: Microscopic appearance of the boxed area in Figure 2A. Cancer cells (squamous cell carcinoma) are seen in the extralobar fat tissue (arrows and arrowheads) beyond the hilar region, but do not invade beyond the visceral pleura at other sites.

C: High-power view of the area indicated by the arrowheads in Figure 2B.

D: High-power view of the area indicated by the arrows in Figure 2B.

Figure 3: Survival curves of group A, B, and C

A: Overall survival curves: Group C had a marginally poor survival than that of Group A. (p = 0.082). There was no significant difference in survival between Group A and Group B (p = 0.358), or between Group B and Group C (p= 0.159).

B: Disease-free survival curves

The difference in survival between Group A and Group B was not significant (p = 0.758). The differences in disease-free survival between Group A and Group C, and Group B and Group C were significant (A vs. C, p = 0.022; B vs. C, p = 0.040).

Figure
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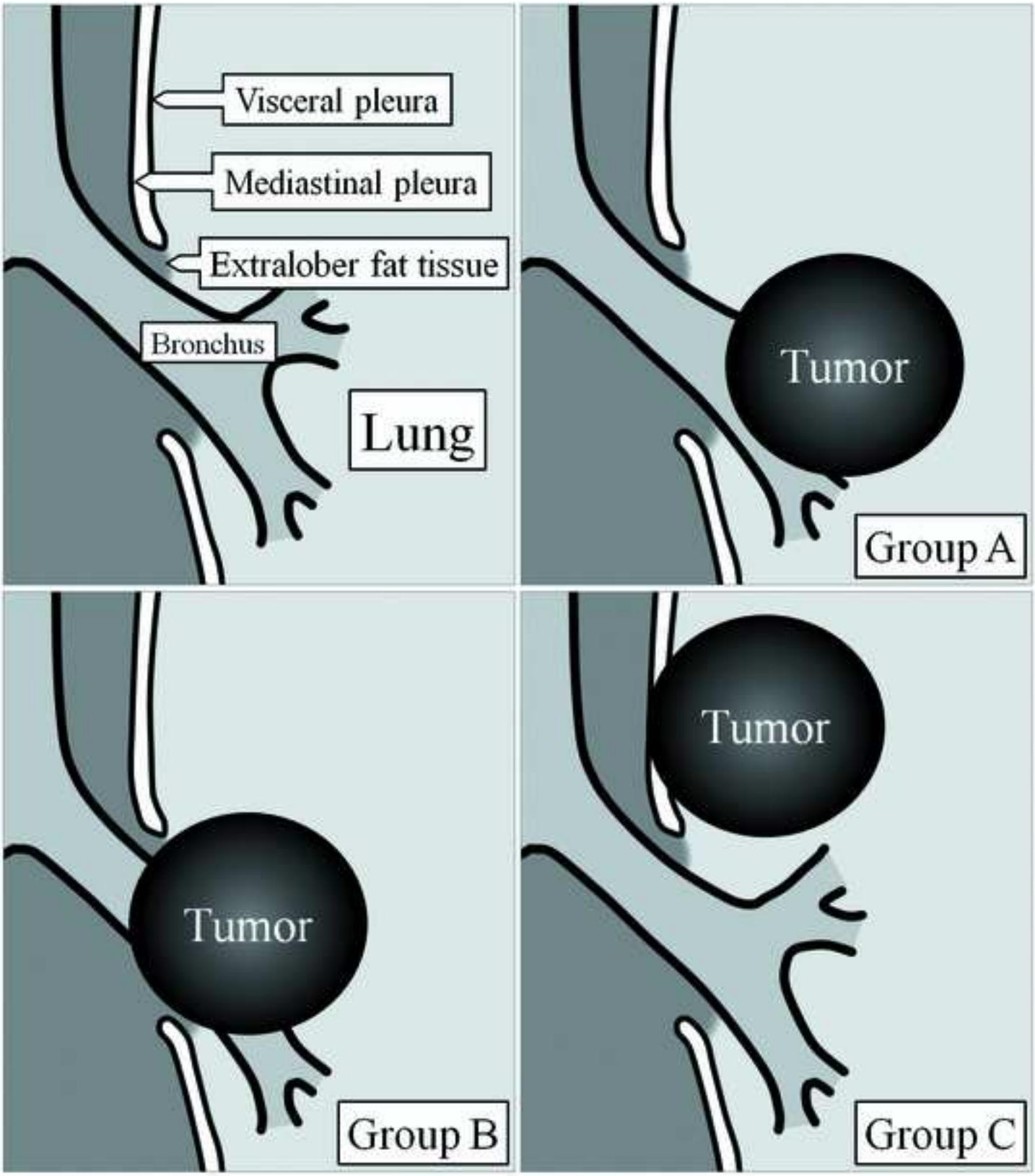

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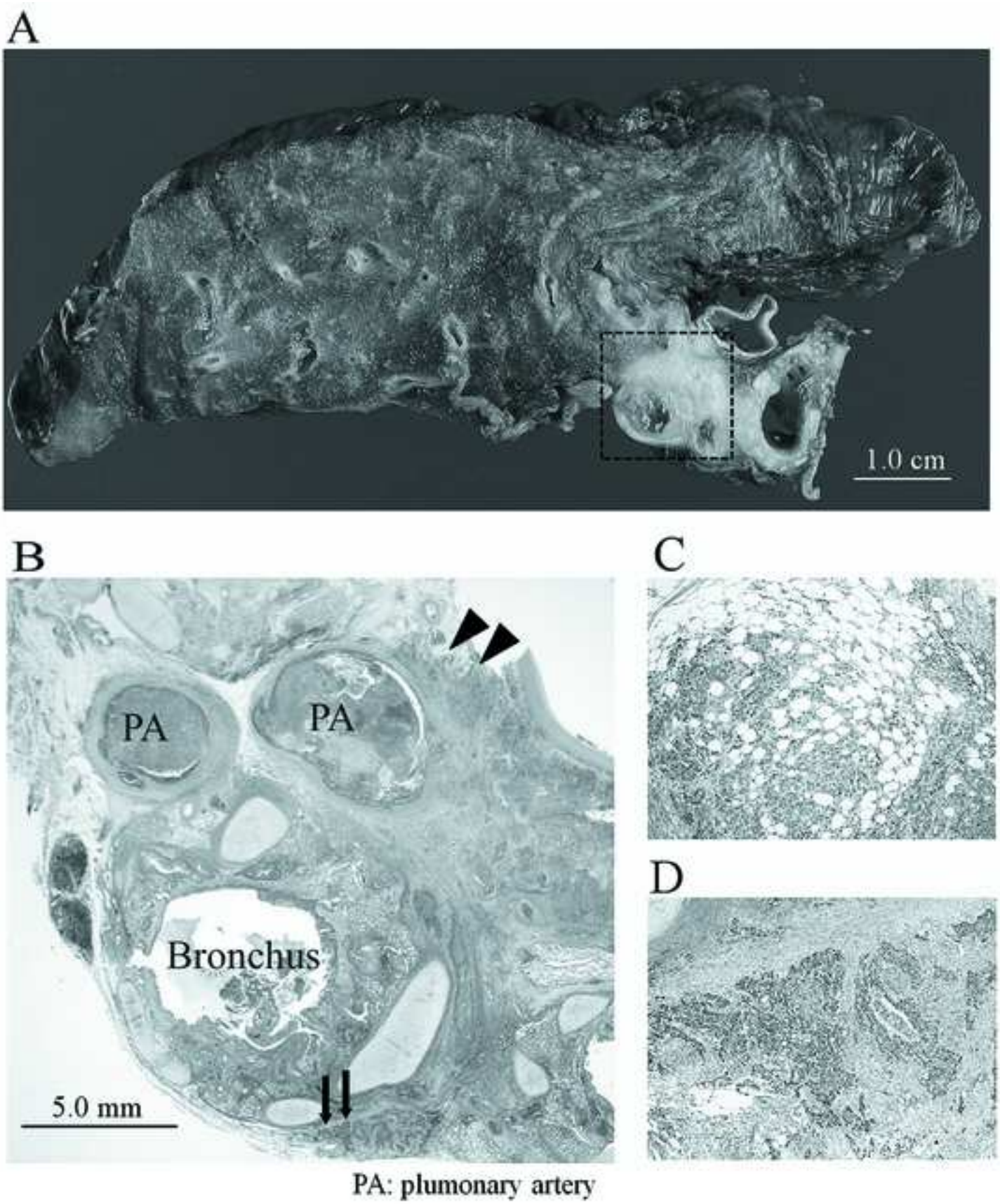


PA: plumonary artery

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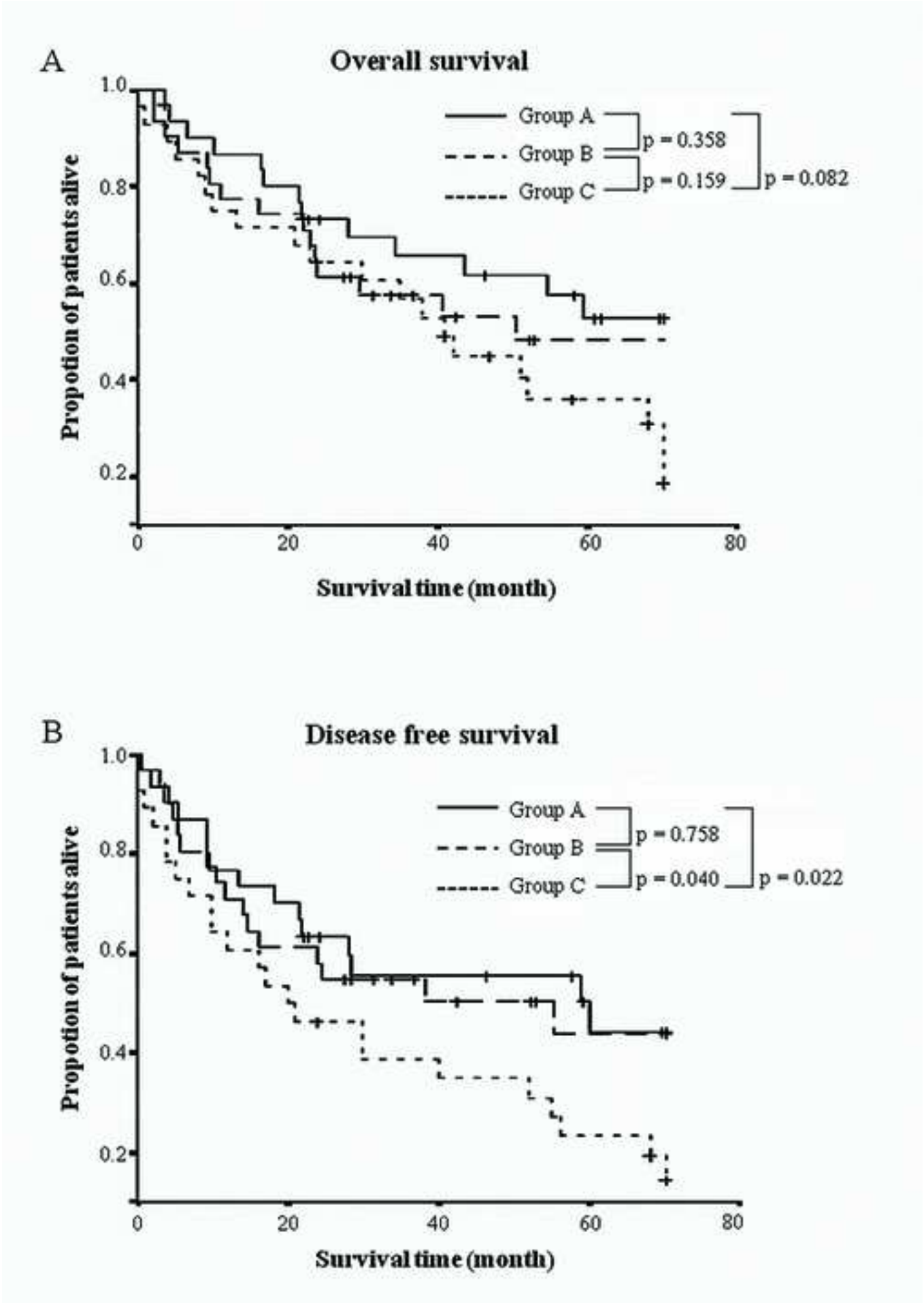

**Table**

Table 1　Clinicopathologic features of group A, B, and C

| Variables | Group A | Group B | Group C |
|---|---|---|---|
| **All cases** | 31 | 32 | 28 |
| **Age (years)** | | | |
| Median (range) | 59 (36 - 76) | 61 (45 - 75) | 63 (47 - 79) |
| **Sex** | | | |
| Male | 25 | 29 | 25 |
| Female | 6 | 3 | 3 |
| **Type of resection** | | | |
| Pneumonectomy | 31 | 26 | 12 |
| Lobectomy | 0 | 6 | 16 |
| **Histologic type** | | | |
| SqCC | 16 | 23 | 7 |
| Adeno | 11 | 5 | 16 |
| Adsq | 1 | 2 | 2 |
| LC | 1 | 1 | 2 |
| LCNEC | 0 | 1 | 0 |
| Small | 2 | 0 | 1 |
| **Tumor size （cm）** | | | |
| Mean ±S.D. | 4.8 ± 1.7 | 4.3 ± 2.3 | 5.2 ± 1.9 |
| **N stage** | | | |
| N0 | 4 | 4 | 13 |
| N1 | 20 | 17 | 10 |
| N2 | 7 | 11 | 5 |
| **M stage** | | | |
| M0 | 29 | 31 | 26 |
| M1 | 2 | 1 | 2 |

*SqCC: Squamous cell carcinoma, Adeno: Adenocarcinoma*

*AdSq: Adenosquamous carcinoma, LC: Large cell carcinoma*

*LCNEC: Large cell neuroendocrine carcinoma, Small: Small cell carcinoma.*