

1 **Tumor invasion of extralobar soft tissue beyond the hilar region does not affect**
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4 **the prognosis of surgically resected lung cancer patients.**
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7 Running title: Tumor invasion beyond the hilar region
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26 Key words: extralobar fat tissue, hilar region, pleural invasion, pleural elastic lamina.
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1 ***Abstract***
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4 ***Background:***
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7 Visceral pleural invasion (VPI), which is defined as tumor extension beyond the elastic lamina,
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10 is one of the most important prognostic factors in patients who have undergone curative resection
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13 for non-small cell lung cancer (NSCLC). However, in pathological slides, pleural elastic lamina
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16 could not be found in the hilar region where the pleura is reflected. Up to the present date, when
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19 cancer cells are seen in this region, a basic agreement dealing with T factor is controversial
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22 among pathologists. The purpose of this study is to evaluate the significance of tumor invasion
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25 of that region as a prognostic factor.
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29 ***Methods:***
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32 We reviewed 91 cases of surgically resected lung cancer in which invasion of the hilar region
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35 was visible macroscopically. By microscopic examination, we divided them into three groups: a
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38 group in which no cancer cells are seen in the soft tissue beyond the hilar region (Group A), a
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41 group in which cancer cells are seen in the soft tissue beyond the hilar region (Group B), and a
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44 group in which cancer cells could not be seen in the soft tissue beyond the hilar region but
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47 invade into the mediastinal visceral pleura at some other site (Group C). We then evaluated the
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50 clinicopathological characteristics of the patients and their outcome.
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55 ***Results:***
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58 There was no statistically significant difference in the 5-year overall survival rate or disease-free
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1 survival rate between Group A and Group B (overall: 55% vs. 48%; disease-free: 43% vs. 42%),
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4 but disease-free survival of Group C was significantly lower than that of Group A and Group B
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7 (A vs. C: $p = 0.022$; B vs. C: $p = 0.040$).
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10 ***Conclusion:***
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13 Tumor invasion of the soft tissue beyond hilar region would not be a prognostic factor in patients
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17 who have undergone curative resection for primary lung cancer, although investigation of larger
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20 number of cases will be needed to confirm the validity of our conclusion.
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4 ***Introduction***
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7 In the mid 1970s, visceral pleural invasion (VPI) was included as a specific entity in the TNM
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9 classification [1], and it is generally accepted that VPI is one of the most important prognostic
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11 factors in patients who have undergone curative resection for non-small cell lung cancer (NSCLC)
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13 [2, 3]. VPI has been adopted as a T2 descriptor in the TNM classification of the International
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15 Union Against Cancer (UICC) staging system for lung cancer [4]. VPI is defined as histological
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17 evidence of tumor extension beyond the elastic lamina of the visceral pleura, regardless of
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19 whether the tumor is exposed on the pleural surface in the new 7th edition of the TNM staging
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21 system [5].
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32 There are two regions where pleural elastic lamina could not be found in pathological slides.
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34 One is incomplete interlobar fissures, and the other is the hilar region where the pleura is
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36 reflected. Kamiyoshihara and colleagues demonstrated that incomplete interlobar fissures do not
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38 affect the prognosis after curative resection of stage I or II NSCLC [6]. According to the Japan
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40 Lung Cancer Society (JLCS), “invasion of the adjacent lobes where the interlobar borderline in
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42 case with incomplete lobe formation should be recorded as P0.” which is classified as T1[7]. In
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44 contrast, the new 7th edition of the TNM staging system [5] defined that, “tumor with direct
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46 invasion of an adjacent lobe, across the fissure or by direct extension at a point where the fissure
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48 is deficient, classified as T2a unless other criteria assign a higher T category”. Anatomic
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1 variation of the interlober fissure can potentially impact clinical and pathologic assessment of
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4 lung cancers for involvement of adjacent lobe [8].
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7 When a cancer arises in the hilar region, cancer cells sometimes invade the soft tissue beyond
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10 the hilar region. Anatomically, lung parenchyma and mediastinal tissues are covered by pleura.
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12 Lungs are covered by visceral pleura, and mediastinal tissues are covered by mediastinal pleura.
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14 The “pleural reflexion” is thought to be the boundary between lung and mediastinum. However,
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17 pleural reflexion is hard to be identified intraoperatively because visceral and mediastinal
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20 pleurae are continuous and there are no “mark” between them. Furthermore, during the surgical
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23 procedures, pleura around the boundary lesion are usually dissected. Therefore, there is no
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26 “pleural cover” on the soft tissue around the boundary lesion. We could not differentiate soft
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29 tissue tumor invasion beyond hilar structure from “intra lung” or “extra lung” invasion. The 7th
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32 edition of the TNM staging system defined that “tumor invasion into mediastinal fat is T4, if such
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35 invasion is clearly limited to fat within the hilum, classification as T2a or T2b is appropriate,
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38 depending upon size, unless other features dictate a higher T category” [5]. But there is no study
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41 to become grounds of this definition to date. The purpose of this study is to evaluate the
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44 significance of tumor invasion of this region as a prognostic factor.
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55 ***Patients and Methods***

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58 During the period from February 1992 to December 2005, 2684 consecutive primary lung
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1 cancer patients were surgically treated at our institution. For the purpose of this study, we first
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4 selected the cases according to the following criteria: 1) presence of macroscopically visible
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7 involvement of the hilar region, 2) having undergone curative resection, defined as lung resection
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10 more than lobectomy and complete removal of the ipsilateral hilar and mediastinal lymph nodes.
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13 Non-invasive carcinoma such as squamous cell carcinoma in situ in the bronchus was excluded,
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16 and the cases who had induction chemotherapy or radiotherapy, and the cases with evidence of
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19 residual tumor at the surgical margin were also excluded. We analyzed archival slides and medical
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22 records, and identified 91 cases (3.4%) that met these criteria.
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26 We divided these 91 cases into the following three groups based on the microscopic findings
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28 (Figure 1): a group in which no cancer cells are seen in either the soft tissue beyond the hilar
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30 region or the visceral pleura at other sites (Group A), a group in which the cancer cells are seen
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32 in the soft tissue (extralobar fat tissue) beyond the hilar region but do not invade beyond the
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34 elastic lamina of the visceral pleura at other sites (Group B) (Figure 2 A-D) and a group in which
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36 the tumor cells invade beyond the elastic lamina of the mediastinal pleura above and/or below
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38 the hilar region, but no cancer cells are seen in the soft tissue beyond the hilar region (Group C).
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41 Group C included the cases with PL1, 2 and 3 defined in the 7th edition of the TNM staging
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43 system. Furthermore cases with mediastinal invasion and cases with invasion of hilar region by
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45 lymph node metastatic tumor were excluded. There were 31 cases in Group A, 32 cases in Group
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48 B, and 28 cases in Group C.
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7 *Pathological evaluation:*
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10 The surgical specimen in each case had been fixed with 10% formalin or absolute methyl alcohol
11 and embedded in paraffin. The tumor had been cut into 5-10 mm slices, and serial 4- μ m sections
12 had been stained with hematoxylin and eosin (HE), or by the Victoria van-Gieson (VVG) method
13 to visualize the elastic lamina. The tumors were classified according to the criteria of the current
14 WHO histological classification [9]. VPI (p-factor) was evaluated by VVG-stained sections, and
15 classified by the 7th edition of the TNM staging system (PL0 to PL3) [5]. Presence of vascular
16 invasion (v factor) was evaluated by VVG-staining. Two observers (H.O and G.I) who had no
17 knowledge of the clinical data independently reviewed all slides. Whenever their evaluations
18 were discordant, they jointly reviewed the specimen through a multiheaded microscope, and
19 reached a consensus. Pathological staging was performed according to the classification of the
20 Union Internationale Contre le Cancer (UICC) 6th [4].
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48 *Statistical Analysis:*
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52 The Pearson χ^2 test or Fisher exact test was used to compare categorical and dichotomous
53 variables. Analysis of variance with life tables and Kaplan-Meier curves were used for the
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1 analyses of overall and disease-free survival. Differences between groups were analyzed by the
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4 log-rank test. Statistical significance was assumed to exist at two-tailed p values of < 0.05. All
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7 statistical analyses were performed using a statistical software package (Dr. SPSS II for Windows,
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16 **Results**

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

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20 The profiles of each group of patients in regard to gender, age, surgical procedure, histologic type,
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23 tumor size, and UICC- N and M stages are summarized in Table 1. There were 80 men and 11
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26 women. The median age was 61 years old (range; 36 to 79 years old). There were no statistically
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29 significant differences between the groups in gender, age distribution, and UICC- M stage.
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36 There were no significant differences in clinicopathological features between Group A and
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39 Group B, besides type of resection. In Group A, pneumonectomy was performed for all cases.
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42 Lobectomy was performed in a higher proportion of the cases in Group C than in Group A or
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45 Group B. The tumor size of Group C was significantly larger than that of Group A ($p = 0.032$). The
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48 proportion of adenocarcinoma cases in Group C was significantly and marginally higher than
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51 those in Group B and A, respectively ($p < 0.001$ and $p = 0.08$). N0 disease was more common in
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54 Group C than in Group A or Group B (Group A, 13%; Group B, 13%; Group C, 46%; A vs. C, $p =$
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57 0.005; B vs. C, $p = 0.035$). No statistical significant differences were found between the three
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1 groups in frequency of lymphatic infiltration. There was a significantly lower proportion of
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4 cases with vascular invasion in Group A than in Group B or Group C (Group A, 58%; Group B,
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7 88%; Group C, 86%; A vs. B, $p = 0.009$; A vs. C, $p = 0.019$).
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10 11 12 13 *Survival rates in each group*

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16 The overall 5-year survival rate was 55% in Group A, 48% in Group B, and 38% in Group C.
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20 There was no statistically significant difference in survival rate between Group A and Group B (p
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22 = 0.358) or between Group B and Group C ($p = 0.159$), but the overall survival rate in Group A
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26 was marginally higher than in Group C ($p = 0.082$).
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30 The disease free survival of each group were 43% in Group A, 42% in group B, and 27% in
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33 Group C. The difference in disease-free survival rate between Group A and Group B was not
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36 significant ($p = 0.758$), but the differences in disease-free survival rate between Group A and
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39 Group C, and between Group B and Group C were significant (A vs. C, $p = 0.022$; B vs. C, p
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41 =0.040).
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48 *Discussion*

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

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4 In the current study, VPI positive cases (Group C), showed worse survival rate than VPI negative
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7 cases (Group A and B). This result was consistent with many previously studies indicating the
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10 prognostic significance of VPI in NSCLC [2, 10-12], which would display the accuracy of the
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13 case selection process in the current study. In a study of 1074 cases of T1-2 NSCLC, Shimizu et al,
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16 identified visceral pleural invasion in 26.8% of the cases and found that it was significant
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19 prognostic factor [13]. They also reported significant prevalence of lymphatic and vascular
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22 invasion in the visceral pleural invasion (VPI) group, and their findings corroborated that tumors
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25 with VPI have high invasive and progressive potential. Mizuno et al, reviewed 413 surgically
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28 resected cases of stage I lung adenocarcinoma [14], and found that the 5-year survival rate of the
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31 stage IB patients without pleural invasion was 89.3%, as opposed to 62.5% in the stage IB patients
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34 with pleural invasion, and that it was significantly lower than in the stage IB cases without pleural
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37 invasion. A multivariate analysis revealed pleural invasion to be an independent prognostic factor.
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40 These observations suggest that tumor cell aggressiveness may depend somewhat on their ability
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43 to destroy the elastic lamina and invade subpleural tissue. In the present study, no statistically
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46 significant differences in frequency of lymphatic permeation were found between the three
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49 groups, but there was a significantly lower proportion of vascular-invasion-positive cases in
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52 Group A than in Group B or Group C (Group A, 58%; Group B, 88%; Group C, 86%; A vs. B, p
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55 = 0.009; A vs. C, p = 0.019). In view of the comparable rates in Group B and Group C, p factor
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1 may more strongly reflect the malignancy of a tumor than v factor does.
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4 It is well known that the presence of lymph node metastases is a negative prognostic factor for
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7 primary lung cancer [15, 16]. In the present study, however, Group C had a poorer outcome in
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10 terms of overall and disease-free survival than group A or Group B, in spite of the significantly
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13 higher proportion of N0 diseases relative to Group A and Group B (Group A, 13%; group B, 13%;
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16 group C, 46%; A vs. C, $p = 0.035$; B vs. C, $p = 0.005$). Edwin et al, reviewed 58 cases of
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19 pT1N1M0 disease[17], and found that the 5-year survival rate of patients with N 1 direct extension
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22 was higher than that of patients with N 1 metastases (68.6% vs. 31.2%; $p=0.0038$). In this study,
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25 cases with lymph node involvement by direct invasion in group A, B, and C was 20 cases (65%),
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28 17 cases (53%), and 10 cases (36%), respectively (data not shown). The frequency of direct N1
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31 cases was higher in Group A and Group B than in Group C. This difference may explain why
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36 Group A and Group B had a better outcome despite significantly higher lymph node involvement.
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39 In conclusion, tumor invasion to the soft tissue beyond the hilar region would not be a prognostic
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42 factor in patients who have undergone curative resection for primary lung cancer. Further
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45 investigation of larger number of cases will be needed to confirm the validity of our conclusion.
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1 Figure legends
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4 Figure 1: Scheme of cases with hilar region involvement
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7 Group A: No cancer cells are seen in either the soft tissue beyond the hilar region or visceral
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10 pleura at other sites.
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12 Group B: Cancer cells are seen in the soft tissue (extralobar fat tissue) beyond the hilar region,
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16 but do not invade beyond the elastic lamina of the visceral pleura at other sites.
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19 Group C: Cancer cells invade beyond the elastic lamina of mediastinal pleura above and/or
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23 below hilar region (included the cases with PL1,2 and 3 defined in the 7th edition of the TNM
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26 staging system), but no cancer cells are seen in the soft tissue beyond the hilar region.
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32 Figure 2: Macroscopic and microscopic findings in lung cancer with hilar region involvement
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36 A: Macroscopic appearance of lung cancer with hilar region involvement (Group B).
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39 B: Microscopic appearance of the boxed area in Figure 2A. Cancer cells (squamous cell
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42 carcinoma) are seen in the extralobar fat tissue (arrows and arrowheads) beyond the hilar region,
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45 but do not invade beyond the visceral pleura at other sites.
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48 C: High-power view of the area indicated by the arrowheads in Figure 2B.
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51 D: High-power view of the area indicated by the arrows in Figure 2B.
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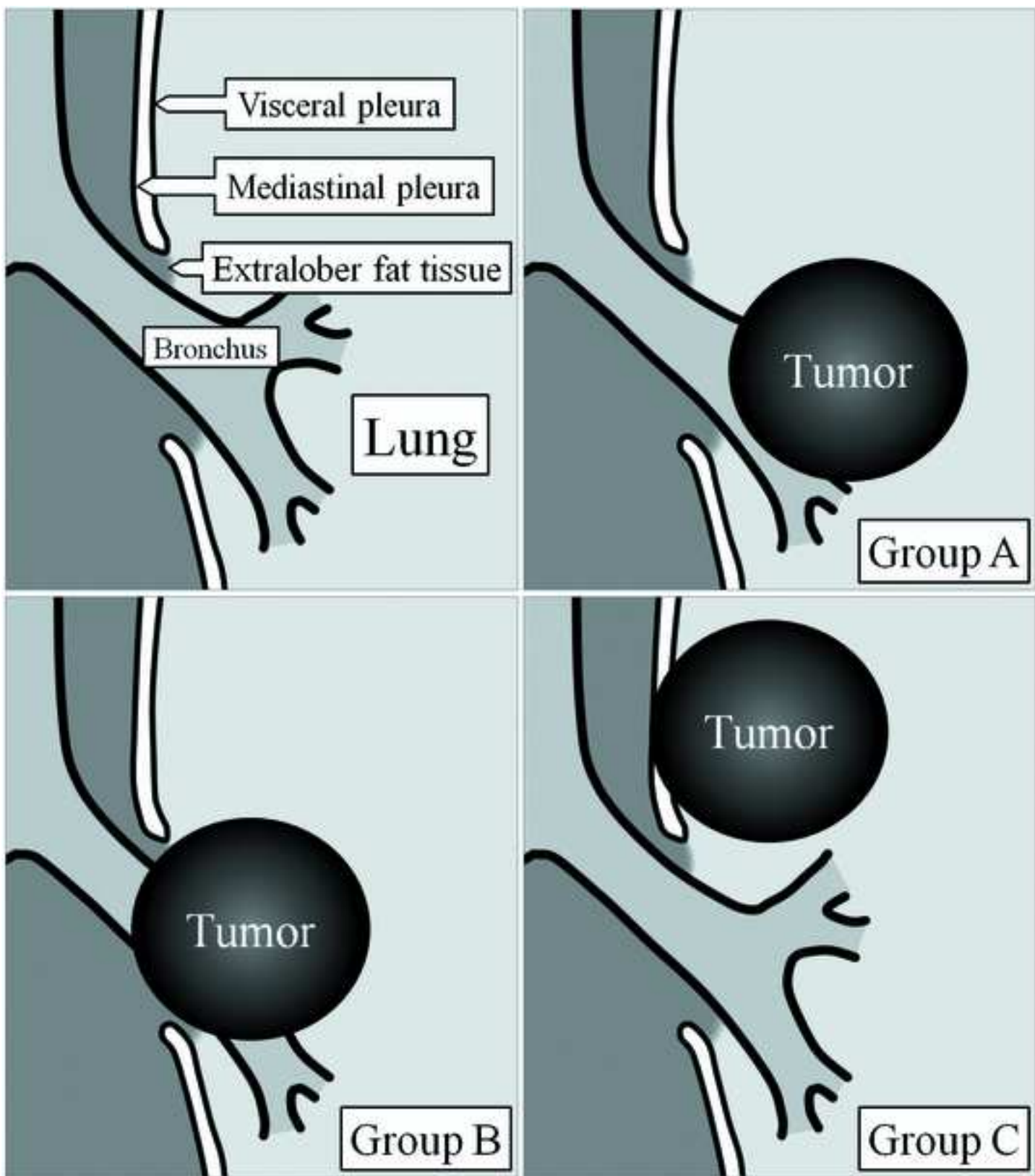
58 Figure 3: Survival curves of group A, B, and C
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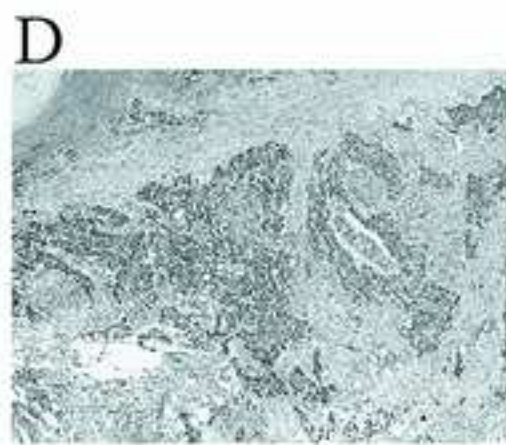
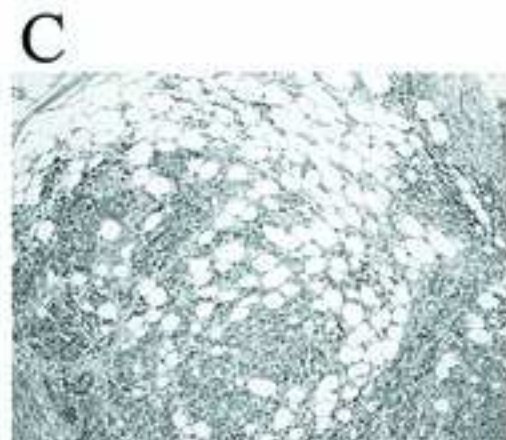
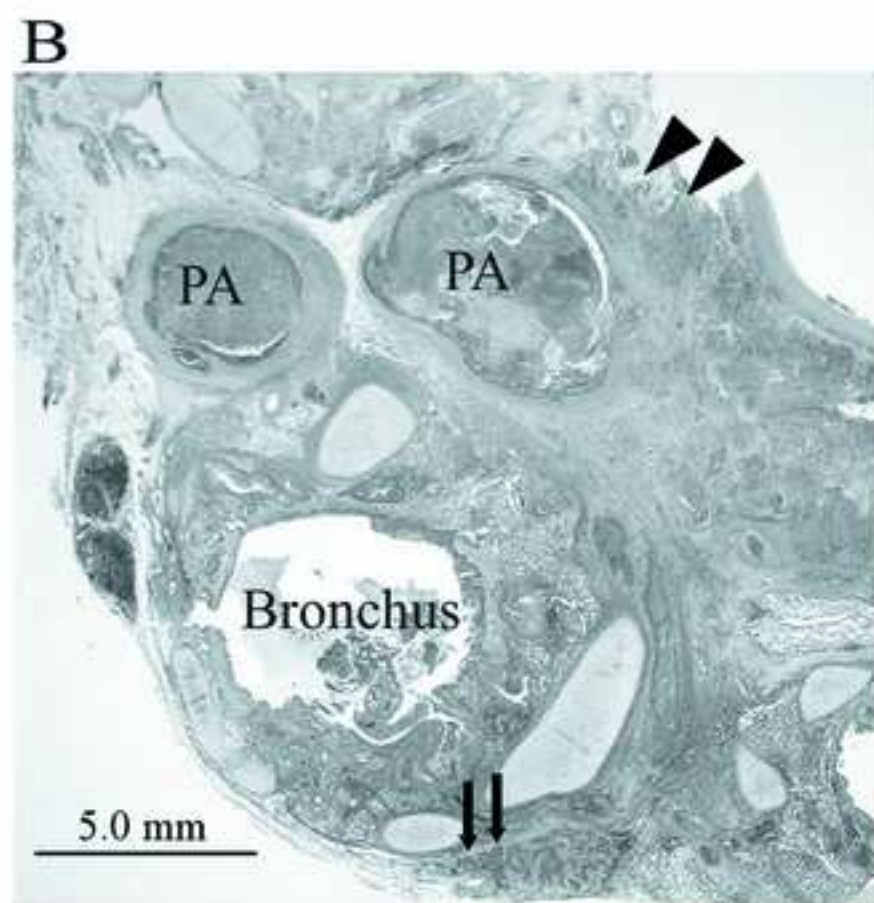
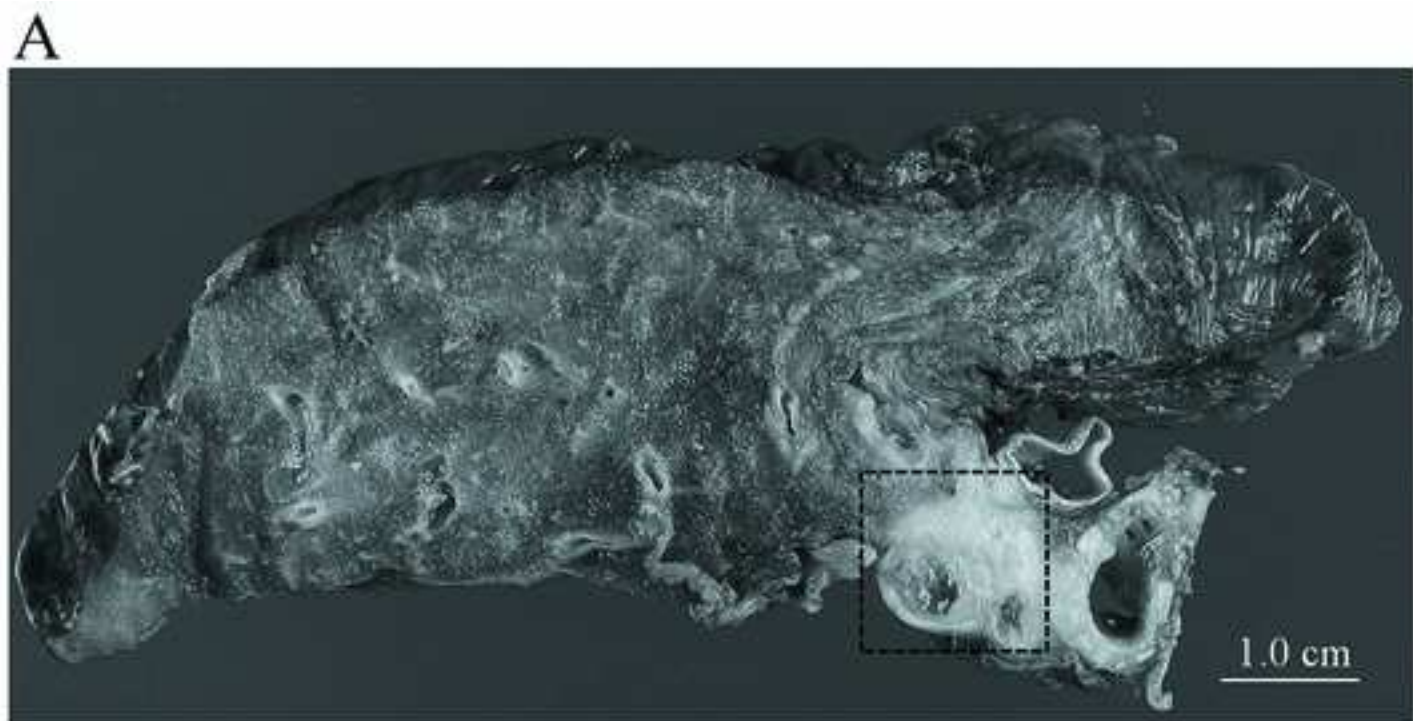
1 A: Overall survival curves: Group C had a marginally poor survival than that of Group A. (p =
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4 0.082). There was no significant difference in survival between Group A and Group B (p =
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7 0.358), or between Group B and Group C (p= 0.159).
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10 B: Disease-free survival curves
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13 The difference in survival between Group A and Group B was not significant (p = 0.758). The
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15 differences in disease-free survival between Group A and Group C, and Group B and Group C
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17 were significant (A vs. C, p = 0.022; B vs. C, p = 0.040).
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PA: plumonary artery

Figure

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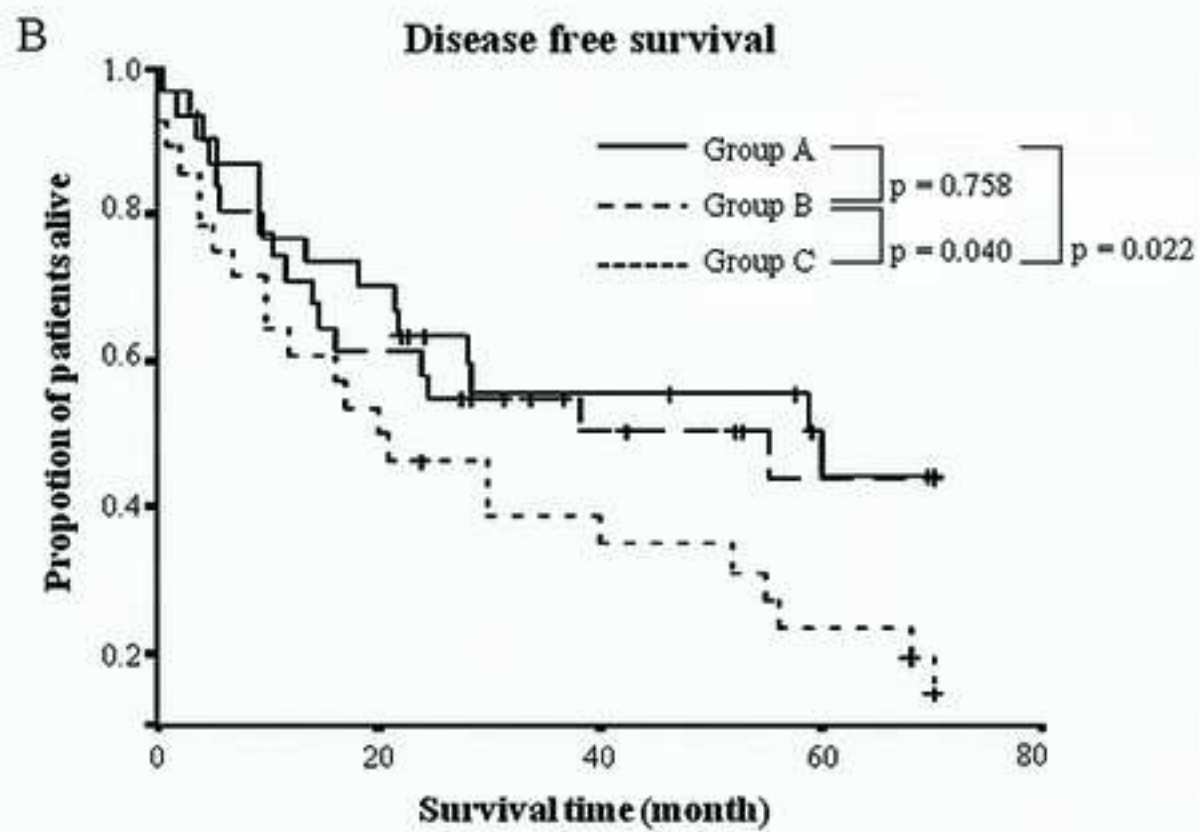
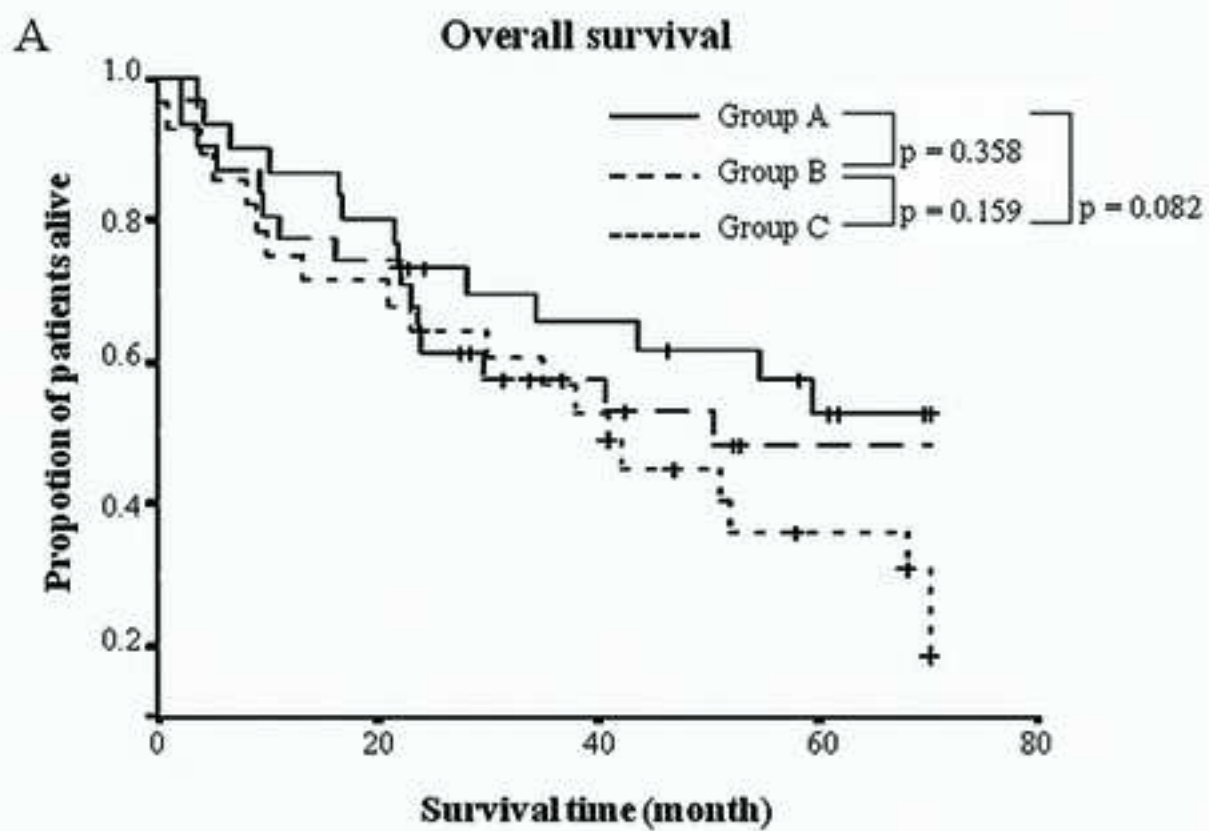


Table 1 Clinicopathologic features of group A, B, and C

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 \pm S.D.	4.8 \pm 1.7	4.3 \pm 2.3	5.2 \pm 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.