Visceral Pleural Invasion Classification in Non-small Cell Lung Cancer

Akikazu Kawase, MD,* Junji Yoshida, MD,* Genichiro Ishii, MD,† Tomoyuki Hishida, MD,* Mitsuyo Nishimura, MD,* and Kanji Nagai, MD*

Objective: We analyzed non-small cell lung cancer patient survival in our single institution database to evaluate the effect of visceral pleural invasion (VPI) on survival and to propose a method of incorporating VPI into T-status classification in future staging systems.

Methods: We reviewed 2725 consecutive surgically resected non-small cell lung cancer patients with T1a, T1b, T2a, T2b, or T3 tumors for their clinicopathologic characteristics and prognoses. Visceral pleural invasion was classified using the criteria of the 7th edition of the TNM Classification for Lung and Pleural Tumors.

Results: There were no significant differences in survival between PL1 and PL2 patients. Therefore, we decided to combine the PL1 and PL2 patient groups into a single VPI group, and compare survival with a PL0 (VPI–) group to analyze the effect of VPI on T classification. The best survival was observed in patients with a T1a/VPI– tumor, followed by those with a T1b/VPI– tumor. In comparison, survival was similarly worse among patients with a T1a/VPI+, T1b/VPI+, T2a/VPI–, or T2b/VPI– tumor. The worst survival was observed in patients with a T2a/VPI+, T2b/VPI+ or T3 tumor.

Conclusions: Otherwise T2 tumors with VPI, regardless of size, may be classified as T3 tumors in the next edition of the TNM Classification for Lung and Pleural Tumors.

Key Words: Visceral pleural invasion, Non-small cell lung cancer, TNM Classification, T-status.

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Visceral pleural invasion (VPI) by lung cancer is known as a poor prognostic factor.1–7 In 2004, Shimizu et al. found no statistically significant difference in survival between patients with tumor invasion beyond the elastic layer (PL1), and those with tumor invasion across the pleura with exposure on the pleural surface (PL2), regardless of tumor diameter. They concluded that PL1 and PL2 could be combined to define VPI,1 which was compatible with the findings by Osaki et al.6 In contrast, Sakakura et al.8 reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether they used elastic stains in diagnosing VPI status.1,6 In the 7th edition of the TNM Classification for Lung and Pleural Tumors, VPI is defined as comprising both PL1 and PL2.9–11

In the TNM Classification, using the VPI definition, tumors 3 cm or less (T1a and T1b) with VPI are upstaged as T2a,9,10 whereas tumors greater than 3 and 7 cm or less (T2a and T2b) with VPI remain T2.9,10 Shimizu et al.1 analyzed a cohort of more than 1600 patients using the same VPI definition and proposed that a tumor of 3 cm or less with VPI should remain classified as a T2 tumor, as described in the 6th edition of the TNM Classification for Lung and Pleural Tumors, whereas tumors greater than 3 cm with VPI should be upgraded to T3. In 2009, Yoshida et al.7 analyzed survival in a large cohort of more than 9700 patients based on a nation-wide multiinstitutional database and proposed that the T status of tumors 7 cm or less with VPI should be upgraded to the next T level. However, their database did not include details of elastic staining, or how accurately VPI evaluation was done in each participating institution.

It is still unclear whether PL1 and PL2 are equivalent and whether they can be combined to define VPI, or how tumors with VPI should be classified, especially T2 tumors. We retrospectively analyzed the survival of more than 2700 pulmonary non-small cell lung cancer patients whose VPI status was evaluated by elastic staining, to evaluate any PL1 and PL2 equivalence or possible effect of VPI on T-status classification and survival.

PATIENTS AND METHODS

From January 1979 to December 2006, 2725 consecutive non-small cell lung cancer patients with T classifications of either T1a, T1b, T2a, T2b, or T3, as defined in the 7th edition of the TNM Classification for Lung and Pleural Tumors, underwent complete resection. We defined complete resection as segmentectomy or greater with systematic ipsilateral hilar and mediastinal lymph node dissection and no evidence of residual cancer either macroscopically or histologically. Patients who had induction chemotherapy or radiotherapy, patients with evidence of residual tumor at the surgical margin, or patients with malignant effusion or distant peritoneal carcinomatosis were excluded.

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metastasis verified intraoperatively or by means of postoperative pathologic examination were excluded from this study. In the 7th edition of the TNM Classification for Lung and Pleural Tumors, a tumor with direct invasion of an adjacent lobe, either across the fissure or by direct invasion in an area of fissure defect, is classified as T2a unless other criteria indicate a higher T category. During the study period, however, because there were only 70 tumors with direct invasion to adjacent lobes, we excluded these patients from the study. As most pT4 tumors invaded adjacent organs and were classified as PL3 by definition, it was inappropriate to include them in comparing the impact of VPI, and they were excluded from this study.

Cases were pathologically staged based on the 7th edition of the TNM Classification for Lung and Pleural Tumors. Histopathologic studies were done according to the World Health Organization criteria, and VPI was reviewed in detail. Tumor sections were stained with hematoxylin and eosin and Victoria blue-van Gieson stains. VPI was classified according to the Japan Lung Cancer Society classification of VPI, which is identical to the 7th edition of the TNM Classification for Lung and Pleural Tumors: PL0 (p0 as defined by the Japan Lung Cancer Society) is defined as a tumor within the subpleural lung parenchyma or which invades superficially into the pleural connective tissue beneath the elastic layer; PL1 (p1) is defined as a tumor that invades beyond the elastic layer; PL2 (p2) is defined as a tumor that invades the pleural surface; and PL3 (p3) is defined as a tumor that invades any component of the parietal pleura.

Overall survival was estimated using the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. Zero time was the date of pulmonary resection, and the end point was defined as the date of death from any cause. The last follow-up observation was censored when the patient was alive or lost to follow-up. All p values were two-sided and p values less than 0.05 were considered statistically significant. We planned to compare survival between PL1 and PL2 patients and, if there were no significant differences in survival between them, to combine the PL1 and PL2 groups into one VPI group. If VPI was confirmed by multivariate analyses using the Cox proportional hazards model, to be independently prognostic among other factors including gender (man versus woman), histologic type (adenocarcinoma versus nonadenocarcinoma), pathologic T classification (T1 versus T2), and pathologic N classification (N0 versus N1 + 2), we planned to analyze the relative effect of VPI status on T classification.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient in this retrospective study was waived by the institutional review board in January 2010.

RESULTS

Patient Characteristics and VPI

Table 1 shows the patient characteristics. There were 1762 men and 963 women aged 22 to 90 years (median, 66 years). More than 90% of all patients underwent lobectomy including bilobectomy. Adenocarcinoma was the major histologic type (64%), and more than 70% had no node involvement.

Survival Difference

The overall survival curves of PL0, PL1, PL2, and T3 patients are shown in Figure 1. The differences in survival were statistically significant (p < 0.001) between PL0 and PL1, PL0 and PL2, PL0 and T3, and PL1 and T3. In contrast, the differences in survival were not statistically significant between PL1 and PL2 (p = 0.114) or PL2 and T3 (p = 0.085). We decided to combine the PL1 and PL2 patient groups into VPI+ group and compare survival with a PL0 (VPI−) group in the following analyses.

The results of multivariate analyses of VPI, gender, histologic type, pathologic T classification, and pathologic N classification, as prognostic factors are shown in Table 2. VPI status proved to be independently prognostic (HR 1.531, p < 0.001), and we analyzed the relative effect of VPI status on T classification.

According to the tumor diameter (≤2 cm; T1a, 2.1–3 cm; T1b, 3.1–5 cm; T2a, or 5.1–7 cm; T2b), VPI status (− or +), and T3 factor, we divided all patients into nine groups. The overall 5-year survival rates for nine groups and their survival curves are shown in Figure 2. The differences in survival between T1a/VPI− and T1b/VPI−, T1b/VPI− and T1a/VPI+, T1b/VPI− and T1b/VPI+, T1b/VPI− and T2a/VPI−, T1b/VPI− and T2b/VPI−, T1b/VPI− and T2b/VPI+, T1b/VPI− and T2a/VPI+, T1b/VPI− and T2b/VPI+, T1b/VPI− and T3, T2a/VPI+ and T2b/VPI−, T2b/VPI− and T3, and T2b/VPI− and T3 were statistically significant. However, the differences in survival were not statistically significant between T1a/VPI− and T1b/VPI+, T1a/VPI+ and T2a/VPI−, T1a/VPI− and T2b/VPI−, T1b/VPI− and T2b/VPI+, T2a/VPI− and T2a/VPI+, and T2b/VPI− and T3. Therefore, we were able to stratify the nine groups into four categories: (1) T1a/VPI−, (2) T1b/VPI−, (3) T1a/VPI+, T1b/VPI−, T2a/VPI+, and T2b/VPI−, and (4) T2a/VPI+, T2b/VPI+, and T3, in decreasing order of survival.

DISCUSSION

In the 7th edition of the TNM Classification for Lung and Pleural Tumors, the extent of VPI is classified into four groups (PL0, PL1, PL2, and PL3). PL1 and PL2 are combined to define VPI, in the presence of which T1 tumors are upstaged to T2a.

On the basis of a cohort of more than 1600 patients, Shimizu et al. found no statistically significant differences in survival between PL1 and PL2 patients, regardless of tumor diameter. They concluded that PL1 and PL2 can be combined to define VPI, which was compatible with the findings of Osaki et al. In contrast, Sakakura et al. reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether they used elastic stains in diagnosing VPI status. In our series, there were no statistically significant differences in survival between PL1 and PL2 patients. We combined PL1 and PL2 patients into a VPI+ group, and confirmed VPI+ to be an independent unfavorable prognostic factor by multivariate analyses. This supports the conclusion by Shimizu et al. and Osaki et al. and...
is in accordance with the VPI definition in the 7th edition of the TNM Classification for Lung and Pleural Tumors. Shimizu et al. proposed otherwise T1 and T2 tumors with VPI should be classified as T2 and T3, respectively, in the 6th edition of TNM Classification for Lung and Pleural Tumors.7 Similarly, using the 7th edition, Yoshida et al. proposed the T status of tumors 7 cm or less with VPI should be upgraded to the next T level, which was compatible with the conclusion of Shim et al.4

When we analyzed VPI effect on T-status classification in our series, the best survival was observed in patients with a VPI tumor 2 cm or less (T1a), followed by those with a VPI tumor of 2.1 to 3 cm (T1b). In comparison, survival was similarly worse in patients with a VPI tumor 3.1 to 5 cm (T1c), 5.1 to 7 cm (T1d), and 7.1 cm or more (T1e). However, survival was significantly better in patients with a VPI tumor 2 cm or less (T1a) compared to those with a VPI tumor 2.1 to 3 cm (T1b) (p < 0.001). Similarly, survival was significantly better in patients with a VPI tumor 2 cm or less (T1a) compared to those with a VPI tumor 3.1 to 5 cm (T1c) (p = 0.001). Survival was also significantly better in patients with a VPI tumor 2 cm or less (T1a) compared to those with a VPI tumor 5.1 to 7 cm (T1d) (p = 0.001). Survival was significantly better in patients with a VPI tumor 2 cm or less (T1a) compared to those with a VPI tumor 7.1 cm or more (T1e) (p = 0.001).
T1a/VPI tumor, T1b/VPI tumor, VPI− tumor of 3.1 to 5 cm (T2a), or VPI− tumor of 5.1 to 7 cm (T2b). These results suggest that otherwise T1a and T1b tumors with VPI should be upstaged to T2. However, there was no significant difference in survival between patients with a T2a/VPI− tumor and those with a T2b/VPI− tumor. It was unclear whether T1a and T1b tumors with VPI should be further classified as either T2a or T2b.

FIGURE 2. A, All survival curves stratified by tumor size and VPI status. B, Survival curves of T1a/VPI− and T1b/VPI−. C, Survival curves of T1b/VPI−, T1a/VPI+ and T2a/VPI−. D, Survival curves of T1a/VPI+, T1b/VPI+, T2a/VPI−, and T2b/VPI−. E, Survival curves of T1b/VPI+, T2b/VPI−, T2a/VPI+, and T3. VPI, visceral pleural invasion.
TABLE 3. T Classification Comparison

<table>
<thead>
<tr>
<th>Group</th>
<th>Tumor Diameter (cm)</th>
<th>VPI Status</th>
<th>7th Edition T Classification</th>
<th>Our Proposal</th>
</tr>
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<tr>
<td>1</td>
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<td>–</td>
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<tr>
<td>4</td>
<td>2.1–3</td>
<td>+</td>
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<td>T2(a)</td>
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<tr>
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<td></td>
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<td>T2a</td>
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<tr>
<td>6</td>
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<td>T3</td>
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<tr>
<td>7</td>
<td>5.1–7</td>
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<td>T2b</td>
<td>T2b</td>
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<tr>
<td>8</td>
<td>5.1–7</td>
<td>+</td>
<td>T2b</td>
<td>T3</td>
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</table>

VPI− = PL0, VPI+ = PL1 or PL2.
T classifications in bold in our proposal differ from those in the 7th edition T classification.

The worst survival was observed among patients with a T2a/VPI+ tumor, T2b/VPI+ tumor, or a T3 tumor. These results suggest that otherwise T2 tumors with VPI, regardless of size, should be upstaged to T3. These suggestions are summarized as our proposal in Table 3.

It is not clear why VPI is associated with a worse outcome. In our cohort, nodal metastases were significantly more frequent in patients with VPI than in those without VPI in each tumor size group (p < 0.001, χ² test). This supports the suggestion by Shimizu et al.¹ that there is a possible VPI tumor cell pathway through the subpleural lymphatics, hilar lymph nodes, and the mediastinal lymph nodes. We also analyzed only pN0 patients to exclude confounding effects with lymph node involvement, but survival curves did not estrange each other as clearly as in the entire cohort. This may be because of the small number of patients in each subgroup.

Although this study is retrospective, it included a large number of patients, and evaluated VPI status in all patients with elastic stains. However, proposals on how to incorporate VPI status into the T classification vary. Therefore, we need to collect more VPI data internationally and accurately using elastic stains, based on the 7th edition of the TNM Classification for Lung and Pleural Tumors, in cooperation with the International Association for the Study of Lung Cancer.

In conclusion, this study indicates that PL1 and PL2 status are mostly equivalent and can be combined within the category of VPI. Otherwise T2 tumors with VPI, regardless of size, may be classified as T3 in the next edition of the TNM Classification for Lung and Pleural Tumors.

REFERENCES

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