T-stage of non-small cell lung cancer directly invading an adjacent lobe†

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Abstract

OBJECTIVES: Non-small cell lung cancer (NSCLC) invading the visceral pleura is classified as T2 stage, and NSCLC invading the chest wall, diaphragm, phrenic nerve, mediastinal pleura or parietal pleura is classified as T3. But, there is no definition as to whether tumours directly invading an adjacent lobe beyond the fissure should be classified as T2 or T3. We assessed whether these tumours should be classified as T2 or T3.

METHODS: We evaluated patients with NSCLC who, between 1992 and 2009, underwent complete resection and were pathologically diagnosed as T2 or T3 according to the 7th edition of the TNM classification. To evaluate the effect of the T-stage only, the patients with nodal- and distant metastasis were excluded.

RESULTS: Among 837 patients, 499 (59.6%) were pathologically staged as T2a, 91 (10.9%) as T2b and 201 as T3 (24.0%). Forty-six (5.5%) patients had NSCLC with a direct invasion of the adjacent lobe. The mean age (P = 0.102) and sex distribution (P = 0.084) were not statistically significant, but there were more adenocarcinomas in the T2 group than that in the T3 group. The overall survival of the patients with adjacent lobe invasion was statistically worse than that of T2 patients (P = 0.042), but was not statistically different from that of T3 (P = 0.368) patients. There was no difference between the disease-free survival of patients with adjacent lobe invasion and T3 patients (P = 0.306), but disease-free survival of the patients with adjacent lobe invasion was worse than that of T2 (P = 0.003) patients.

CONCLUSIONS: Considering that the overall survival and disease-free survival of patients with direct adjacent lobe invasion are similar to those of T3, NSCLC with direct invasion to the adjacent lobe should be classified as T3 rather than T2.

Keywords: Non-small cell lung cancer • Adjacent lobe invasion • TNM staging

INTRODUCTION

The TNM staging system is helpful for selecting proper treatment options and for predicting the prognosis of patients with non-small cell lung cancer (NSCLC) [1]. In 2009, the International Association for the Study of Lung Cancer (IASLC) proposed the 7th revision of the TNM staging system for NSCLC with unprecedentedly extensive evidences [2–5]. However, several definitions of tumour extension remain ambiguous, and the prognosis of patients with these tumours is also controversial [5, 6]. From such uncertainties, there has been a controversy about whether tumours invading an adjacent lobe are T2 or T3. The aim of this study was to determine the T-stage of NSCLC directly invading an adjacent lobe by comparing the prognosis of these tumours and that of pathological T2 or T3 NSCLC.

MATERIALS AND METHODS

We retrospectively evaluated 2687 NSCLC patients who, from 1992 to 2009, were pathologically diagnosed in Severance Hospital and Gangnam Severance Hospital and underwent the complete surgical resection of lung cancer. We applied the 7th revision of the IASLC for staging [2–5] and the World Health Organization classification for the pathological type [7].

We excluded patients with incomplete medical records, deaths within 1 month after surgery and patients who underwent neoadjuvant therapy. Patients with pathological nodal- (N1, N2 and N3) and distant metastasis (M1a and M1b) were also excluded from this study in order to evaluate the effect of the
T-stage only. The subjects who satisfied the above-mentioned criteria were divided into three groups: T2 patients (T2 group), T3 patients (T3 group) and patients with an adjacent lobe invasion (invasion group). Accordingly, the invasion group was defined as patients with tumours of <7 cm size and with a direct invasion to the adjacent lobe, but without the invasion of the chest wall, diaphragm, phrenic nerve, mediastinal pleura and parietal pericardium.

Before surgery, the patients underwent chest computed tomography (CT), brain magnetic resonance imaging, abdominal sonography and a whole-body bone scan. After the introduction of positron emission tomography (PET) to our institutions in 2004, abdominal sonography and whole-body bone scan (WBBS) were selectively performed according to the physician’s discretion. Mediatiniscopy was performed in the patients with mediastinal nodes of >1 cm on the chest CT or an increased maximum standard uptake value of mediastinal nodes on PET.

Types of surgery included the wedge resection, segmentectomy, lobectomy, bilobectomy, pneumonectomy and lobectomy with the partial resection of the invasion lobe. Radical mediastinal lymph node dissection was our principle method, but systemic node sampling was performed in some patients. After surgery, the patients with an advanced pathological stage received adjuvant chemotherapy, radiotherapy or concurrent chemoradiotherapy.

During the follow-up, the recurrence and metastasis were diagnosed by radiological evaluation. In some patients, pathological evaluation was performed. The patients with recurrence or distant metastasis also underwent additional treatments.

Numerical values including age and tumour size were expressed as mean ± standard deviation. To compare the mean of numerical values, the Kruskall–Wallis test was used. Pearson’s chi-square test was used for analysis of distributions of gender, cell types and chemotherapy among the groups. Overall survival was defined as the interval between the time of surgery and the date of death or censoring. Disease-free survival was defined as the length of time after surgery during which recurrence or metastasis was found. SPSS 18.0 software was used for statistical analysis. Patients’ overall survival and disease-free survival were calculated by the Kaplan–Meier method and the differences among the groups were evaluated by the log-rank test.

**RESULTS**

Among 2687 NSCLC patients, 837 patients who met the criteria were retrospectively reviewed. Five hundred and ninety patients (70.5%) were pathologically staged as T2, including 499 patients (59.6%) as T2a and 91 patients (10.9%) as T2b. A total of 201 patients (24.0%) were staged as T3. Forty-six (5.5%) patients had a direct invasion of tumours to the adjacent lobe.

Table 1 shows the patients’ characteristics. The mean age (P = 0.102) and sex distribution (P = 0.084) were not statistically significant, but there were more adenocarcinomas in the T2 group than in the T3 group and the invasion group (P = 0.031). As T-stage is determined mainly by the tumour size, the mean tumour size in the T3 group was the largest (P < 0.0001). The objective of surgery was anatomical resection such as lobectomy, bilobectomy or pneumonectomy, but some patients with poor cardiopulmonary function underwent the wedge resection or segmentectomy. Posterolateral thoracotomy was routinely used, but video-assisted thoracic surgery has mainly been performed in the NO patients since 2005. Mediastinal lymph node dissection was performed in 815 patients (97.4%), and 22 patients underwent mediastinal node sampling. More patients received adjuvant chemotherapy in the T3 group and the invasion group (P = 0.001).

The mean follow-up time was 50.1 ± 1.6 months (range: 5–203 months). In the T2 group, survival rates at 3 and 5 years were 74% and 68%, respectively. In the T3 group, survival rates at 3 and 5 years were 54% and 49%, respectively. In the invasion group, survival rates at 3 and 5 years were 68% and 53%, respectively. The median survival times in the T2, T3 and invasion groups were 175, 68 and 146 months, respectively.

Comparing the overall survival rates between the T2 and T3 groups, the survival rate of the T2 group was significantly better than that of the T3 group (P < 0.0001). The overall survival rate of

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics</th>
<th>T2 group (n = 590)</th>
<th>T3 group (n = 201)</th>
<th>Invasion group (n = 46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>62.0 ± 10.3</td>
<td>61.2 ± 9.9</td>
<td>60.9 ± 10.8</td>
<td>0.102</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>416 (70.5%)</td>
<td>165 (82.1%)</td>
<td>37 (80.4%)</td>
<td>0.084</td>
</tr>
<tr>
<td>Female</td>
<td>174 (29.5%)</td>
<td>36 (17.9%)</td>
<td>9 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>Cell types</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adenocarcinoma</td>
<td>262 (44.4%)</td>
<td>66 (32.8%)</td>
<td>14 (30.4%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>241 (40.8%)</td>
<td>101 (50.2%)</td>
<td>24 (52.2%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>87 (14.7%)</td>
<td>34 (16.9%)</td>
<td>8 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Tumour size (cm, mean ± SD)</td>
<td>3.9 ± 1.3</td>
<td>6.4 ± 2.8</td>
<td>4.7 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Types of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge resection</td>
<td>2 (0.3%)</td>
<td>2 (1.0%)</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>444 (75.3%)</td>
<td>124 (61.7%)</td>
<td>4 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>75 (12.7%)</td>
<td>16 (8.0%)</td>
<td>11 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>68 (11.5%)</td>
<td>59 (29.4%)</td>
<td>27 (58.7%)</td>
<td></td>
</tr>
<tr>
<td>Lobectomy with partial resection of invasion lobe</td>
<td>0</td>
<td>0</td>
<td>3 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>287 (48.6%)</td>
<td>128 (63.7%)</td>
<td>26 (56.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>303 (51.4%)</td>
<td>73 (36.3%)</td>
<td>20 (43.5%)</td>
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</tr>
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</table>
invasion as T3 [2]. Invasion into an adjacent lobe is defined as T2 [8]. Nevertheless, it remains controversial as to whether these tumours should be defined as T2 or T3. Miura et al. [9] and Nonaka et al. [10] suggested that NSCLC with invasion beyond the interlobar pleura should be categorized as T2, whereas Okada et al. [11], Demir et al. [12] and Yang et al. [6] suggested that these tumours should be regarded as T3.

However, the above-mentioned studies have several limitations. The first is the limited number of cases, because NSCLC with an adjacent lobe invasion is rare. In this study, among 837 patients, only 46 patients (5.5%) had an adjacent lobe invasion. Even in other studies where N1 or N2 patients were included, only 18–50 patients had an adjacent lobe invasion [6, 9–12]. Although an interlobar fissure invasion was suspicious in the operation field, it was pathologically confirmed to be a simple interlobar fissure adhesion in most of the cases.

The second limitation is the various definitions of adjacent lobe invasion. In the 7th revision of the IASLC staging system, there was no clear definition of adjacent lobe invasion. Yang et al. [6] defined adjacent lobe invasion as tumours whose centres were beyond the debouchment of the segmental bronchus and excluded central tumours whose centres were at the proximal side of the debouchment of the segmental bronchus in their study. Demir et al. [12] defined adjacent lobe invasion as direct invasion of the adjacent lobar parenchyma by the tumour, only a centimetre in depth or width. However, such definitions are very ambiguous. Furthermore, other authors [9–11] did not clearly define what adjacent lobe invasion was. In this study, we defined adjacent lobe invasion as direct invasion of the ipsilateral adjacent lobar parenchyma regardless of invasion site, unless tumours were obviously confirmed to be T3. Therefore, this study contained a broader extent of lobar invasion when compared with the studies by Yang and Demir. Because there was no clear definition of adjacent lobe invasion in the 7th revision of the TNM staging system, it is irrational to restrict adjacent lobe invasion to a minimal or peripheral direct lobar invasion.

The third limitation is the heterogeneous nodal status. Nodal stage is the major prognostic factor in NSCLC [3], but N0, N1 and N2 patients were included in the previously reported studies [9–12] without corrections of the N stage effect except in a study by Yang et al. [6]. We excluded the N1, N2 and N3 NSCLC to evaluate the effect of T-stage only.

In our study, the overall survival rate of the invasion group was statistically worse than that of the T2 group (P = 0.042), but it was not statistically different from that of the T3 group (P = 0.368) (Fig. 1).

As to the disease-free survival rate, there was a significant difference between the T2 and the T3 groups (P = 0.009). The disease-free survival rate of the invasion group was worse than that of the T2 group (P = 0.003), but there was no difference between the disease-free survival rate of the invasion group and that of the T3 group (P = 0.306) (Fig. 2).

**Discussion**

According to the 7th revision of the IASLC staging system, the visceral pleura invasion is classified as T2 and the parietal pleura invasion as T3. Invasion into an adjacent lobe is defined as T2 [8]. Nevertheless, it remains controversial as to whether these tumours should be defined as T2 or T3. Miura et al. [9] and Nonaka et al. [10] suggested that NSCLC with invasion beyond the interlobar pleura should be categorized as T2, whereas Okada et al. [11], Demir et al. [12] and Yang et al. [6] suggested that these tumours should be regarded as T3.

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In our study, the overall survival rate of the invasion group was statistically worse than that of the T2 group (P = 0.042), but it was not statistically different from that of the T3 group (P = 0.368). Therefore, we suggest that NSCLC with an adjacent lobe invasion should be classified as T3 rather than T2. Additionally, in an aspect of the disease-free survival rate, the invasion group was similar to the T3 (P = 0.306) rather than the T2 group (P = 0.003).

It is controversial as to which type of lung resection is proper for NSCLC with an adjacent lobe invasion. Yang et al. [6] reported that the patients who underwent pneumonectomy had better survival prognoses than those receiving lesser resections such as lobectomy with the wedge resection. On the basis of this result, they suggested that pneumonectomy or at least bilobectomy is more reasonable than lobectomy plus wedge for NSCLC with an adjacent lobe invasion, because these tumours should be treated as two primary tumours. Okada et al. [11] and Nonaka et al. [10] have reported that survival did not differ between the patients receiving a lobectomy with the partial lobectomy and the patients receiving a pneumonectomy.
resection and those receiving a pneumonectomy or bilobectomy. Furthermore, Demir et al. [12] have reported that the survival rates of the patients who underwent pneumonectomy were worse. Therefore, they suggested that lobectomy with wedge resection or bilobectomy on the right lung may be preferable over pneumonectomy in the case of adjacent lobe invasion, considering the high mortality and morbidity of the pneumonectomy. Because anatomical resection has been a principle method in our institutions until recently, bilobectomies and pneumonectomies were performed more than lobectomies with partial resection of the invasion lobe in the adjacent lobe invasion patients. In this study, we could not determine which type of surgery is the most appropriate for these patients due to a limited number of lobectomies with the partial resection of invasion lobe.

This study has several limitations. First, the number of cases is small. However, this study has relatively more cases than the previous studies, even though the patients with a positive nodal status are excluded. Secondly, because this study is retrospective, the type of surgery was decided by the surgeon’s preference without randomization. Pneumonectomy is a well-known risk factor for worse survival in lung cancer [13–15], but the pneumonectomies were performed in the invasion group much more than the T2 and T3 groups. So, we analysed the survival rate of 154 patients who underwent pneumonectomy in the respective groups. In this analysis, the survival rate of the T3 group was significantly worse than that of the T2 group (P = 0.019). However, there was no statistical difference between the invasion group and the T2 (P = 0.351) or the T3 groups (P = 0.250).

In conclusion, our results suggest that NSCLC with the direct invasion to the adjacent lobe should be classified as T3 rather than T2, considering the overall survival and disease-free survival of patients with direct adjacent lobe invasion are similar to those of T3. However, a large number of patients were needed to determine the optimal resection type in NSCLC with direct invasion to the adjacent lobe.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Dusmet (London, UK): This is a very important issue, and I know that it does interest the IASLC staging group. The reason it was not included in the 7th version is simply because they did not have adequate data to address this issue and it is work in progress, which hopefully will be addressed in the 8th staging system. Of course, at least conceptually, there is the problem of how we define the problem of adjacent tumour invasion. I quite liked your definition because it is clear, it is concise, and it is widely encompassing. But, at least theoretically, there is a difference between tumours that are crossing a virtual or a non-existing fissure (such as is often the case with the middle lobe and the upper lobe) and a tumour which is breaches the visceral pleura twice to invade, which would, at least to common sense, indicate perhaps a more aggressive tumour biology.

The methodology of this paper is extremely sound. The fact that all positive nodal disease has been excluded really focuses the issue on T2, T3, or crossing the fissure. There is a large number of patients, and it is good to see that the 7th version of the staging system was used, so at least we all know what we’re talking about. This is, however, a retrospective review and the majority of patients did undergo a pneumonectomy, and we do know that pneumonectomy is an adverse prognostic indicator, perhaps of the same order of magnitude as the difference you have shown. So my first question must be, do you think that the difference in survival, the less good survival, is due to the fact that crossing the fissure truly upstages the tumour, or do you think that it is mostly due to the fact that the patient had a pneumonectomy in the vast majority of cases? Secondly, do you have any data about the difference between tumours crossing a virtual fissure as opposed to tumours crossing the visceral pleura twice?

Dr Haam: We know that pneumonectomy has a high morbidity and mortality, but at the beginning of the study our principle was anatomic resection instead of partial resection. In the study there are a lot of cases of pneumonectomy, but now we intend to perform partial resection instead of anatomic resection, such as bilobectomy and pneumonectomy. Your second question?

Dr Dusmet: Is there any difference between a tumour which crosses an intact visceral pleura twice, as opposed to a tumour that crosses a non-existing fissure where there is no visceral pleura twice for invasion of an adjacent lobe? Do you have any data indicating differences in survival?

Dr Haam: Sorry?
Revisions to the 7th edition of TNM for lung cancer: data are good but prospective data are better!

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Keywords: Lung cancer • Staging • Prognostic factors • Pathological classification

The 7th edition of the TNM Classification for Lung Cancer was enacted on 1 January 2010 [1]. The changes in this edition were the product of the International Staging Project of the International Association for the Study of Lung Cancer (IASLC) [2]. The database developed for this project contained over 100 000 cases of lung cancer, 20 times the size of that which had informed earlier revisions, and for the first time it included cases from around the globe, treated by all modalities of care. However, even this data source could not validate all of the descriptors which had been accumulated within the TNM classification over the previous 30 years. Indeed, many of the finer points of classification which were carried over into the 7th edition had little or no statistical basis but were established by consensus to ensure uniform use and to facilitate data analysis in the future. Invasion of the visceral pleura (VPI) has been a T2 descriptor since the 4th edition, published in 1987, and in the 3rd edition of the TNM Supplement: In A Commentary on Uniform Use [3], published in 2003, we are provided with the additional advice that a ‘tumour with local invasion of another ipsilateral lobe without tumour on the visceral pleural surface should be classified as T2 also’. In the 7th edition the T2 category was split into T2a and T2b by the introduction of a new size cut-point of 5 centimetres. Hence, in the IASLC Staging Manual in Thoracic Oncology [4], published to accompany the 7th edition, the situation is clarified by the statement that a ‘tumour with direct invasion of an adjacent lobe, across the fissure or by direct extension at a point where the fissure is deficient, should be classified as T2a unless other criteria assign a higher T category’.

The data provided in this edition of the journal by Haam et al. [5] is therefore to be welcomed. They retrospectively assessed the prognostic impact of direct invasion to an adjacent lobe in resectable non-small-cell lung cancer by comparing the survival of 46 cases with this feature with that of 499 T2a and 91 T2b cases, combined in the analysis into 590 T2 cases, and 201 T3 cases resected over the same 18-year period in a single centre in Korea. They conclude that direct invasion of an adjacent lobe should be reclassified as a T3 descriptor.

Is this sufficient evidence to make this change in the 8th edition? Unfortunately, no! In any retrospective database it is impossible to untangle the relative impact of multiple prognostic factors. We could not quantify the competing prognostic impact of VPI and the increasing size in our database of over 100 000 cases and it is unrealistic to expect Haam et al. to produce an unequivocal answer to another question of classification with 837 cases, of which only 46 had the feature under study. Whilst their series is larger than previous papers on this topic and more homogeneous by the exclusion of node-positive cases, the study groups remain heterogeneous, conflating size with VPI, and other T2 and T3 descriptors such as the proximity of bronchial involvement, invasion of other structures and the extent of atelectasis/obstructive pneumonitis. In addition, an internationally accepted definition of VPI was established only in the 7th edition [6] and one doubts if this feature was retrospectively reviewed by their pathologists. Significantly, there were far more pneumonectomies in the group with direct invasion and we know that this operation has an adverse impact on survival independent of stage. Indeed, the authors looked at this aspect in their study and in 154 pneumonectomies found no difference in the survival between the three study groups.

To properly assess the independent prognostic impact of each descriptor and to study their inter-relationships, we need a