Prognostic Significance of Clinical/Pathological Stage IA Non-Small-Cell Lung Cancer Showing Partially Solid or Solid Tumours on Radiological Exam

Hirofumi Uehara, MD, PhD,¹ Yosuke Matsuura, MD,¹ Masayuki Nakao, MD,¹ Mingyon Mun, MD, PhD,¹ Ken Nakagawa, MD,¹ Yuichi Ishikawa, MD, PhD,² and Sakae Okumura, MD¹

Purpose: Although curative resection is expected to be effective in patients with clinical (c-) stage IA/pathological (p-) stage IA non-small-cell lung cancers, recurrence is often observed. Hence, the aim of this study was to identify predictors of recurrence.

Methods: Between 2005 and 2009, 138 patients with c-stage IA/p-stage IA non-small-cell lung cancers underwent resection. Recurrence and recurrence-free survival (RFS) were compared with clinical, radiographic and pathological findings.

Results: The 5-year cancer-specific survival rate was 97% and the RFS rate was 89% at a median follow-up time of 91 months. Recurrence was observed in 10 patients (7.2%). Significant differences were observed in RFS according to tumour dimensions on the mediastinal window image (>1.5 cm), serum carcinoembryonic antigen levels (>5.0 ng/mL), maximum standardised uptake values (SUVmax >2.5) and angiolymphatic invasion. Patients were grouped according to the number of risk factors for poor RFS. Patients with 0–1 of the identified risk factors had an RFS of 97%, whereas those with 2–4 factors had an RFS of 68% (p <0.001).

Conclusion: Prognosis of patients exhibiting more than two of these risk factors is considerably poor. Thus, close observation and individualised adjuvant therapy may be beneficial to these patients.

Keywords: lung cancer surgery, pathologic stage IA, adjuvant therapy, limited surgery

Introduction

The detection of small-sized lung cancers has increased with the development of computed tomography (CT) screening. Although curative resection is expected to be effective for treatment of clinical (c-)/pathological (p-) stage IA non-small-cell lung cancer (NSCLC), recurrence is often observed.

Tumour size is widely accepted as a prognostic factor of NSCLC and, in 2009, the tumour-node-metastasis (TNM) classification for primary lung cancer was revised, in which T1 tumours are subcategorised as T1a (≤2.0 cm) and T1b (>2.0 cm and ≤3.0 cm) in the current seventh edition.¹³ However, this classification system considers only the maximum tumour diameter, which in most cases, is the lung window image size.

In pT1abN0M0 lung cancers, tumour size is not the only measure of malignancy, as tumour shadow disappearance rate (TDR),² visual estimation of the consolidation...
component, solid component size, maximum standardised uptake values (SUVmax) from 18F-fluorodeoxyglucose positron emission tomography (PET/CT), ratio of the size of solid attenuation to the maximum tumour dimensions (consolidation/tumour [C/T] ratio), lymphatic invasion, proportion of ground-glass opacity (GGO) and tumour necrosis have also been reported as prognostic factors.

Adjuvant chemotherapy should be considered in these patients, as the Lung Adjuvant Cisplatin Evaluation meta-analysis reported poorer survival among patients with stage IA disease treated with postoperative adjuvant chemotherapy and the guidelines of the Japan Lung Cancer Society recommend postoperative tegafur/uracil combination chemotherapy in patients with p-stage IA tumours classified as pT1bN0M0 (21–30 mm; grade B). However, recurrence may also be observed in patients with T1a cancer and those with pure GGO tumours have a good prognosis, which is the case even in patients with pT1bN0M0 cancer who did not undergo adjuvant therapy. Thus, to reduce recurrence, high-risk stage IA patients must be identified accurately.

The aim of this study was to identify predictors of recurrence in patients with c-stage IA/p-stage IA NSCLC who underwent complete resection and to reveal additional factors for chemotherapy.

Materials and Methods

Between 2005 and December 2009, 453 clinical stage IA NSCLC patients underwent surgical resection at the Cancer Institute Hospital, Japanese Foundation for Cancer Research (Tokyo, Japan). Among these patients, 315 were diagnosed with pathological stage IA lung cancer after resection. Of these patients, we excluded 105 tumours that were >10 mm on the lung window image or pure or nearly pure GGO lesions, and 72 cases that lacked lymph node sampling or underwent partial resection from this study. Finally, we enrolled 138 patients with c-/p-T1N0M0 stage IA NSCLC with partially solid or solid tumours on high-resolution CT (HRCT) and PET or PET/CT who were followed by complete R0 resection.

Because of the retrospective nature of this study, individual patients were not identifiable, thus the institutional review board waived the requirement to obtain patient consent.

All patients underwent preoperative assessment, including chest radiography, thoracic and upper abdominal CT scans, bone scans, brain magnetic resonance imaging or CT, basic blood tests and cardiopulmonary evaluations. Chest images were obtained using a 16-row multidetector CT independently of subsequent PET or PET/CT examinations. Pure GGO lesions were not detectable by PET or PET/CT and were considered as beyond the scope of this study.

High-resolution images of tumours were acquired under the following conditions: peak, 120-kV, 200 mA; section thickness, 2 mm; pitch, 1; section thickness, 1–2 mm; pixel resolution, 512 × 512; scanning duration, 0.5–1 s; and a spatial reconstruction algorithm with a 20-cm field of view and mediastinal (level, 40 HU [Hounsfield unit]; width, 400 HU) and lung (level, 600 HU; width, 1,600 HU) window settings. TDRs (%) were calculated using thin-section computed tomography (TSCT) images with the following equation: % TDR = major tumour dimensions on the mediastinal image/major tumour dimensions on the lung image × 100.

Histopathological studies were conducted according to the World Health Organisation criteria. Tumours were staged according to the seventh edition of TNM classification for malignant tumours.

All patients were followed-up after surgery with physical and chest radiography examinations performed every 3 months and chest and abdominal CT images every 6 months for the first 2 years. Thereafter, patients underwent physical examinations and chest radiography every 6 months, with annual chest CT imaging.

Tumour recurrence was defined as evidence of tumour involvement in the surgical margin, hilum or mediastinal lymph nodes (locoregional recurrence) or as evidence of tumours in other lobes or outside the hemithorax (distant recurrence). Time to recurrence was defined as that between surgery and the discovery of recurrence using either imaging or cytopathological examination. Patients with signs or symptoms that correlated with tumour recurrence or metastasis were evaluated using brain or bone CT scans, as needed.

Recurrence-free survival (RFS) was defined as the interval from the date of surgery until the first event (relapse or death from any cause) or the last follow-up visit. For cancer-specific survival, deaths that were attributed to cancer were treated as deaths, and survival durations were censored at the date of a patient becoming lost to follow-up, or the date of death from causes other than cancer. Survival duration was analysed using the Kaplan–Meier method and differences were assed using the log-rank test. Receiver-operating characteristic (ROC) curves of SUVmax, lung window image size and
mediastinal window image size to predict recurrence were generated to determine the cut-off value that yielded optimal sensitivity and specificity using the Youden index.16)

Survival rates from the date of surgery were calculated using the Kaplan–Meier life-table method and comparisons between groups were made using the log-rank test. Dichotomous variables are presented as percentages and were compared between groups using the chi-squared or Fisher’s exact test, where appropriate. Differences were considered significant when \( p \)-values were <0.05. Statistical analyses were performed using SPSS analytical software (ver. 19; SPSS, Inc., Chicago, Illinois, USA).

**Results**

The study cohort included 63 males and 75 females, with a median age of 64 years (range, 25–83 years). Among patients who received complete resections, 121 (87.7%) underwent lobectomies and 17 (12.3%) underwent segmentectomies. According to the World Health Organisation classification of histological types, 121 were adenocarcinomas, 11 were squamous cell carcinomas and 6 were other carcinomas. Patient clinical characteristics are summarised in Table 1.

Recurrence was reported in 10 patients, including regional recurrences (\( n = 1, 0.7\% \); 1 pleural dissemination) and distant recurrences (\( n = 9, 6.5\% \); 3 contralateral lung, 2 ipsilateral lung, 1 liver, 1 chest wall and 1 bone). One patient concomitantly developed bone and subrenal gland metastases. All patients underwent lobectomy and complete lymph node dissection.

Among all patients, 5-year cancer-specific survival (5YCSS) and 5-year RFS (5YRFS) rates were 97% and 89%, respectively (Fig. 1). The median follow-up time was 91 months.

For ROC curves to predict recurrence, the calculated optimal cut-off values of the lung window image size,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinicopathological characteristics of patients with c-stage IA/p-stage IA NSCLC (2005–2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>No. of patients</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (range) &lt;65/≥65 64 (25–83) 79/59</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/Female 63/75</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>Lung window Mean (range) 20 (11–30)</td>
</tr>
<tr>
<td>Mediastinal window</td>
<td>Mean (range) 11 (0–29)</td>
</tr>
<tr>
<td>Tumor disappearance rate</td>
<td>&gt;50%/≤50% 34/104</td>
</tr>
<tr>
<td>SUVmax</td>
<td>Mean (range) &gt;2.5/≤2.5 2.1 (0–12.2) 36/102</td>
</tr>
<tr>
<td>Operation</td>
<td>Segmental resection 17</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>121</td>
</tr>
<tr>
<td>CEA</td>
<td>≤5.0/&gt;5.0 127/11</td>
</tr>
<tr>
<td>Angiolympathic invasion</td>
<td>Yes/No 31/107</td>
</tr>
<tr>
<td>Pathological type</td>
<td>Adenocarcinoma 121</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Recurrence/No recurrence 10/128</td>
</tr>
<tr>
<td>Recurrence site</td>
<td>Local/distant 1/9</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
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</tbody>
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NSCLC = non–small-cell lung cancer; SUVmax = maximum standardized uptake values; CEA = serum carcinoembryonic antigen; c-stage IA/p-stage IA NSCLC = clinical stage IA/pathological stage IA non–small-cell -lung cancer
mediastinal window image size and SUVmax were 20 mm (area under the curve [AUC] = 0.738), 15 mm (AUC = 0.836) and 2.5 (AUC = 0.809), respectively (Fig. 2).

The associations between recurrence and clinicopathological variables of the cut-off values calculated by the ROC curve (Fig. 2) and the other factors. Close associations were demonstrated for mediastinal window images size of 15 mm (p = 0.003), SUVmax 2.5 (p = 0.003), carcinoembryonic antigen (CEA) >5 ng/mL (p = 0.004) and angiolymphatic invasion (p = 0.009), respectively.

Moreover, the recurrence rate was 19.4% (7/36) for patients with tumours >15 mm on the mediastinal window image and 2.9% (3/102) for patients with tumours ≤15 mm (p = 0.003). For SUVmax, the recurrence rate was 19.4% (7/36) for SUVmax of >2.5 and 2.9% (3/102 patients) for SUVmax of ≤2.5 (p = 0.003). Regarding CEA levels, the recurrence rate was 36.4% (4/11) for CEA levels of >5.0 mm and 4.7% (6/127) for CEA levels of ≤5.0 ng/mL (p = 0.004). Regarding angiolymphatic invasion, the recurrence rate was 19.4% (6/31) with positive invasion and 3.7% (4/107) with negative invasion (p = 0.009). No significant associations were found between recurrence and age, sex and lung window images size.

Subsequently, 5YRFS rates were compared according to tumour dimensions of the cut-off values calculated by the ROC curve (Fig. 3), mediastinal window images (Fig. 3A) and SUVmax (Fig. 3B). Regarding the lung window image, no significant differences were observed between 11–20- and 21–30-mm tumours with RFS rates of 93% and 85%, respectively (p = 0.094; figure not shown). Significant differences were observed in tumour dimensions on the mediastinal window image, with RFS rates of 94% and 76% for patients with tumours ≤15 mm and >15 mm, respectively. Tumours with diameters >15 mm on the mediastinal window image were significantly predictive of poor RFS (p < 0.001; Fig. 3A). Significant differences were observed in SUVmax, with RFS rates of 95% and 74% in patients with a SUVmax of 2.5 or ≥2.6, respectively. Tumours with SUVmax ≥2.5 were significantly predictive of poor RFS (p < 0.001; Fig. 3B). Significant differences were observed in RFS (p < 0.001) between tumours with serum CEA levels of >5.0 and ≤5.0 ng/mL (5YRFS ratio, 51% vs. 93%, respectively; Fig. 3C; p < 0.001) and between tumours with and without angiolymphatic invasion (5YRFS ratio, 78% vs. 93%, respectively; Fig. 3D; p = 0.007).

The other factors of age, sex and tumour disappearance rate were not significant.

Patients were grouped according to the number of risk factors for poor RFS, tumour dimensions on the mediastinal window image, serum CEA levels, SUVmax and angiolymphatic invasion. RFS rates were 97% for the 0-risk
factor group, 95% for the 1-risk factor group, 73% for the 2-risk factor group and 63% for the 3–4 risk factor group (Fig. 4A). Only one patient had four risk factors, so we grouped patients with three and four risk factors together for calculations. Since there were no significant differences between groups with 0 and one risk factor \((p = 0.667)\), or 2 and 3–4 risk factors \((p = 0.672)\), we grouped patients with 0–1 risk factors and those with 2–4 risk factors groups for calculations. The RFS rate was significantly greater for patients with 0–1 of the identified risk factors (low-risk group) than those with 2–4 factors (high-risk group) \((97\% \text{ vs. } 68\%, \text{ respectively, } p < 0.001; \text{Fig. 4B})\).

**Discussion**

Although the detection of small-sized lung cancer continues to increase, some problems, such as indications for reductive surgery, optimal adjuvant therapy and methods to evaluate the extent of malignancy, remain unsolved.
adenocarcinoma of the lung and the present analyses indicated that SUVmax >2.5 was associated with a significantly poorer 5YRFS rate (p < 0.001; Fig. 3B) for patients with c-stage IA/p-stage IA. This result indicates that PET is more effective not only for extraction of clinical N0/pathological N1–2 and clinical M0/pathological M1 patients, but also the prognosis for high SUVmax lung cancers is poor in patients with pathological stage IA lung cancer. About the optimal SUVmax cutoffs for recurrence, we regard SUVmax >2.5 as a high price for c-stage IA adenocarcinoma of the lung.

Recurrence occurred in 10 patients: regional in one (0.7%; pleural dissemination) and distant in nine (6.5%). However, the reason for the resulting pleural dissemination recurrence in one patient with p-stage IA lung cancer was unclear. In such cases, we usually determine the extent of pleural invasion (PL) by elastic staining. These analyses confirmed that this patient had no PL or angiolymphatic invasion. Thus, the mechanism of pleural dissemination recurrence remains unknown. Because no tumours were observed intraoperatively within the thoracic cavity, histological sections that were subjected to elastic staining were likely to be positive for PL. However, this procedure was not performed for all patients. Although the probability is very low, pleural dissemination can occur in patients with p-stage IA cancer.

Various prognostic factors for small-sized lung cancer have been reported to predict less invasive lung cancers.6–14 Accordingly, clinical trials of reductive surgery for various small lung cancers have been performed. Several studies have indicated that limited resection is an appropriate surgical procedure for non-solid nodules observed on HRCT and the majority of these nodules were pathologically shown to be adenocarcinoma in situ.13 Other studies have also demonstrated that lung adenocarcinoma manifests as partially solid nodules, with a greater proportion of GGO lesions and less invasive lung cancer types.6–14 Our adaptation of limited surgery included tumours of ≤20 mm under lung window conditions, those of <5 mm under TSCT mediastinum window conditions and for those with negative PET uptake and/or CEA levels of ≤5.0 ng/mL.19 In the present study, 17 of 138 (12.3%) patients underwent segmentectomy and lymph node dissection. Recurrence was not observed in any of these patients, indicating that the present adaptation of limited surgery had reasonable efficacy.

For adjuvant chemotherapy, the guidelines of the Japan Lung Cancer Society recommends that patients receiving postoperative tegafur/uracil combination therapy with p-stage IA tumours should be classified as pT1bN0M0 (21–30 mm; grade B).12–14 However, in the present study, we identified four factors of poor prognosis and observed poor convalescence of patients with two or more of these prognostic factors (Fig. 4B). Based on the above results, the appropriateness of adjuvant therapy should be considered in cases with more than two risk factors.

**Conclusion**

Prognosis of patients exhibiting more than two of these risk factors is considerably poor. Thus, close observation and individualised adjuvant therapy may be beneficial to these patients.

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**Disclosure Statement**

The authors report no conflicts of interest.

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