

## ORIGINAL ARTICLE

# Heterogeneous prognosis and adjuvant chemotherapy in pathological stage I non-small cell lung cancer patients

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## Keywords

Adjuvant chemotherapy; neoplasm grading; non-small cell lung carcinoma; prognosis; tumor staging.

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## Abstract

**Background:** Even after curative resection, the prognosis of pathological stage I non-small cell lung cancer (NSCLC) can be heterogeneous, and the use of adjuvant chemotherapy in these patients is controversial. We aimed to identify the prognostic factors and role of adjuvant chemotherapy in pathological stage I NSCLC.

**Methods:** We retrospectively analyzed the correlations between clinicopathological factors and survival in 179 patients with resected pathological stage I NSCLC.

**Results:** After a median follow-up of 93 months, overall and disease-free survival were not significantly different between pathological stage IA ( $n = 138$ ) and IB ( $n = 41$ ) patients. The prognosis of pathological stage I patients with poorly differentiated tumors was significantly worse than that of those with non-poorly differentiated tumors ( $P = 0.003$ ). Multivariate analysis revealed that poor tumor differentiation was an independent factor for poor survival (hazard ratio = 6.889). A marginally significant survival benefit was observed in poorly differentiated pathological stage I patients who received adjuvant chemotherapy ( $P = 0.053$ ). Pathological stage IA patients who received adjuvant chemotherapy had a worse prognosis than those who did not receive adjuvant chemotherapy ( $P < 0.001$ ), whereas pathological stage IA patients with poorly differentiated tumors who received adjuvant chemotherapy had better survival than who did not receive adjuvant chemotherapy ( $P < 0.001$ ).

**Conclusions** Poor differentiation is an independent prognostic factor in pathological stage I NSCLC after surgical resection. Adjuvant chemotherapy may be beneficial in poorly differentiated pathological stage IA NSCLC patients.

## Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Approximately 1.5 million new cases of lung cancer are diagnosed annually, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of these cases.<sup>1,2</sup> Most NSCLC patients are diagnosed with locally advanced or metastatic disease.<sup>3</sup>

Only approximately 25% of NSCLC patients are diagnosed with resectable tumors and are able to undergo surgery.<sup>4</sup> Five-year overall survival (OS) rates for resected pathological (p)-stage IA and IB disease range from 67–89% and 57–75%,

respectively, indicating some overlap in prognosis because of poor prognostic factors in some patients with the same stage of disease.<sup>5–7</sup>

Two large clinical studies have shown that adjuvant chemotherapy confers a survival benefit in patients with operable NSCLC.<sup>8,9</sup> However, the use of adjuvant chemotherapy in patients with p-stage I disease is unclear. Therefore, we conducted a retrospective study to identify the prognostic factors for poor survival and to explore the role of adjuvant chemotherapy in p-stage I NSCLC patients after complete surgical resection.

## Materials and methods

### Patients and study design

Between January 2005 and June 2010, 261 patients who were diagnosed with clinical stage I NSCLC underwent complete surgical resection at the Tri-Service General Hospital, Taiwan. We retrospectively reviewed 179 consecutive patients with p-stage I disease (138 p-stage IA patients and 41 p-stage IB). The pre-operative staging work-up included chest computed tomography (CT), whole body positron emission tomography-CT (PET-CT), abdominal ultrasonography, and whole body bone scanning. All patients underwent curative surgical intervention. Patients who received any pre-operative chemotherapy or radiation therapy and those with any prior history of lung cancer were excluded from the study. The Cancer Registry Group of the Tri-Service General Hospital approved this study and all patients provided informed consent. Patient confidentiality was maintained.

We examined the medical records of each patient to determine the following characteristics: gender; age; tumor size, location, histology, p-stage, differentiation grade, and recurrence; lymphovascular space invasion (LVSI); adjuvant chemotherapy; maximum standardized uptake value (SUVmax) of the tumor on PET; serum carcinoembryonic antigen (CEA) level; and survival status. All causes of death were cancer related with the exception of stroke in one patient and myocardial infarction in one patient. Histology was evaluated according to the World Health Organization (WHO) classification of lung tumors.<sup>10</sup> Tumors were staged using the tumor node metastasis system of the International Union Against Cancer.<sup>11</sup>

### Treatments and histopathological evaluation

The standard surgical treatment was anatomic resection with systemic mediastinal lymph node dissection. Adjuvant chemotherapy with a cisplatin-based regimen was considered for p-stage I patients who had undergone standard surgical treatment and with high-risk factors, such as poorly differentiated lung tumors (including neuroendocrine tumors), LVSI, and tumor size > 4 cm. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of  $\geq 2$  and those who refused further treatment were excluded as candidates for adjuvant chemotherapy.

Lymphovascular space invasion was defined as the presence of neoplastic cells within an arterial, venous or lymphatic lumen during routine histological evaluation with hematoxylin and eosin, Elastica van Gieson, and D2-40 stains. The differentiation grade of NSCLC was classified as non-poorly differentiated (well-differentiated and moderately differentiated) and poorly differentiated tumors. The WHO Classification of Tumors grading system was used to

define NSCLC.<sup>10</sup> The degree of differentiation was defined according to the extent of the squamous cell component, including keratinization, pearl formation, and/or intercellular bridges (Fig 1a-c). Grading of pulmonary adenocarcinomas was based on the extent of tumor components, including the extent to which the architectural pattern of the tumor resembled normal lung tissue and the extent of cytologic atypia (Fig 1d-f). Histopathological evaluation was performed by at least two experienced pathologists.

### Follow-up procedures

Postoperatively, patients underwent contrast-enhanced chest CT every three to six months, and their serum CEA levels were measured every three months. In addition, either a roentgenogram or chest CT scan was reviewed annually. PET-CT or magnetic resonance imaging was performed on an as-needed basis. Tumor recurrence was documented either radiographically or histologically in all cases.

### Statistical analyses

Statistically significant differences were determined using the Student's *t*-test for continuous variables and the  $\chi^2$  test for categorical variables. Survival rates were calculated using Kaplan–Meier survival analyses. Multiple logistic regression analysis was used to identify independent risk factors for patients with advanced disease. A *P* value of less than 0.05 was considered to be statistically significant. SPSS 14.0 software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

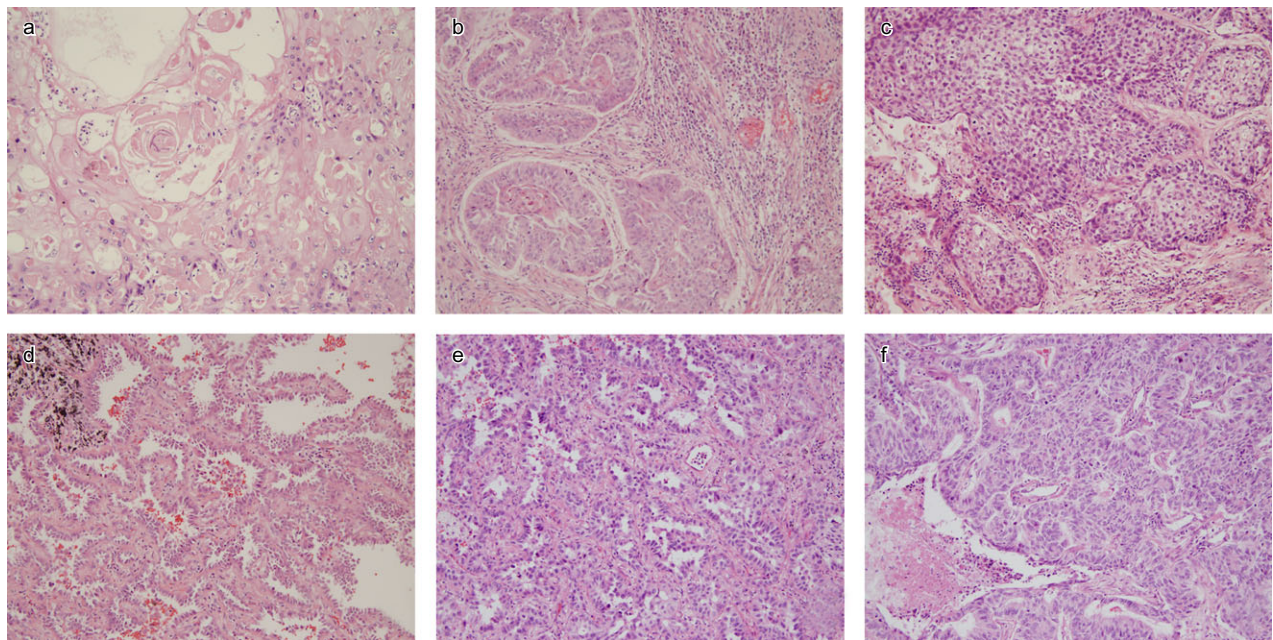
## Results

### Patient characteristics

A total of 179 patients had complete follow-up data (median, 93 months). The clinicopathological characteristics of these patients are listed in Table 1. Gender, histological type, LVSI, and the number of dissected lymph nodes were not significantly different between p-stage IA and p-stage IB patients. P-stage IA patients were younger ( $59.83 \pm 11.99$  years vs.  $64.05 \pm 11.92$  years) and had a lower SUVmax ( $2.98 \pm 2.68$  vs.  $6.89 \pm 3.76$ ), smaller tumor size ( $1.92 \pm 0.70$  cm vs.  $3.62 \pm 0.96$  cm), and lower CEA level ( $2.69 \pm 2.60$  ng/mL vs.  $8.71 \pm 22.53$  ng/mL) than p-stage IB patients. A higher proportion of p-stage IA patients had well-differentiated tumors (41.3% vs. 24.4%), peripheral tumor distribution (59.4% vs. 26.8%), and received adjuvant chemotherapy (84.8% vs. 58.5%) than p-stage IB patients.

### Overall survival (OS) and disease-free survival according to p-stage

The OS of p-stage IA and p-stage IB patients was  $88.11 \pm 4.64$  and  $87.07 \pm 6.04$  months, respectively ( $P = 0.592$ ; Fig 2a). The

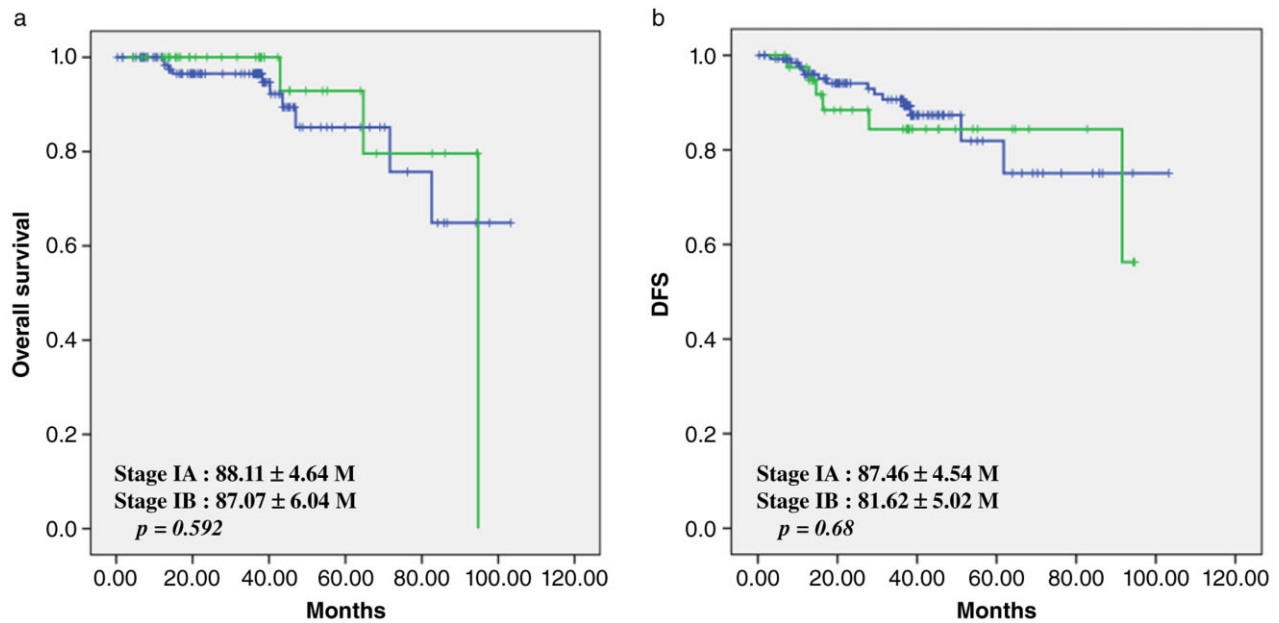


**Figure 1** Representative histopathological features of non-small cell lung cancers. (a) Well-differentiated squamous cell carcinoma. (b) Moderately differentiated squamous cell carcinoma. (c) Poorly differentiated squamous cell carcinoma. (d) Well-differentiated adenocarcinoma. (e) Moderately differentiated adenocarcinoma. (f) Poorly differentiated adenocarcinoma.

**Table 1** Characteristics of patients with stage I non-small cell lung cancer

Characteristic	Stage IA (n = 138)	Stage IB (n = 41)	P value
Gender			
Male, n (%)	55 (39.8%)	19 (46.3%)	0.475
Female, n (%)	83 (60.2%)	22 (53.7%)	
Age (years), mean (SD)	59.83 (11.99)	64.05 (11.92)	0.047
Tumor histology			
Adenocarcinoma, n (%)	126 (91.3%)	33 (80.5%)	0.063
Other, n (%)	12 (8.7%)	8 (19.5%)	
Tumor differentiation			
Well, n (%)	57 (41.3%)	10 (24.4%)	0.008*
Moderate, n (%)	51 (36.9%)	18 (43.9%)	
Poor, n (%)	20 (21.8%)	13 (31.7%)	
Tumor location			
Central, n (%)	56 (40.6%)	30 (73.2%)	<0.001*
Peripheral, n (%)	82 (59.4%)	11 (26.8%)	
LVSI			
Yes, n (%)	9 (6.5%)	3 (7.3%)	0.082
No, n (%)	129 (93.5%)	38 (92.7%)	
SUVmax of tumor, mean (SD)	2.98 (2.68)	6.89 (3.76)	<0.001*
Tumor size (cm), mean (SD)	1.92 (0.70)	3.62 (0.96)	<0.001*
CEA (ng/mL), mean (SD)	2.69 (2.60)	8.71 (22.53)	0.004*
Dissected LN, mean (SD)	12.19 (6.71)	10.88 (6.68)	0.276
Adjuvant chemotherapy			
Yes, n (%)	21 (15.2%)	17 (41.5%)	0.001*
No, n (%)	117 (84.8%)	24 (58.5%)	

\*Statistically significant ( $P < 0.05$ ). CEA, carcinoembryonic antigen; LN, lymph node; LVSI, lymphovascular invasion; SUVmax, maximum standardized uptake value; SD, standard deviation.



**Figure 2** (a) Overall survival and (b) disease-free survival in stage IA and stage IB patients. Stage:  $\square$ , 1A;  $\square$ , 1B;  $+$ , 1A-censored;  $+$ , 1B-censored.

disease-free survival of p-stage IA and p-stage IB patients was  $87.46 \pm 4.54$  and  $81.62 \pm 5.02$  months, respectively ( $P = 0.68$ ; Fig 2b).

### OS according to tumor size and tumor differentiation

The OS of p-stage I patients with tumor size  $>4$  cm and  $\leq 4$  cm was  $90.00 \pm 4.19$  and  $83.02 \pm 8.73$  months, respectively ( $P = 0.676$ ; Fig 3a). p-Stage I patients with poorly differentiated tumors had a worse prognosis than those with non-poorly differentiated tumors ( $P = 0.003$ ; Fig 3b).

### Multivariate analysis of predictors of OS

The results of multivariate analysis for the independent predictors of OS are summarized in Table 2. Poor differentiation was found to be the only independent prognostic factor of poor survival (hazard ratio [HR] = 6.889, 95% confidence interval [CI]: 1.720–27.593,  $P = 0.006$ ; Table 2).

### OS according to tumor differentiation and adjuvant chemotherapy group

A marginally significant survival benefit was observed in p-stage I patients with poorly differentiated tumors who received adjuvant chemotherapy compared with those who did not receive adjuvant chemotherapy ( $P = 0.053$ ; Fig 4a). However, the prognosis of p-stage I patients with non-poorly

differentiated tumors who received adjuvant chemotherapy was significantly worse than of those who did not receive adjuvant chemotherapy ( $P = 0.02$ ; Fig 4b).

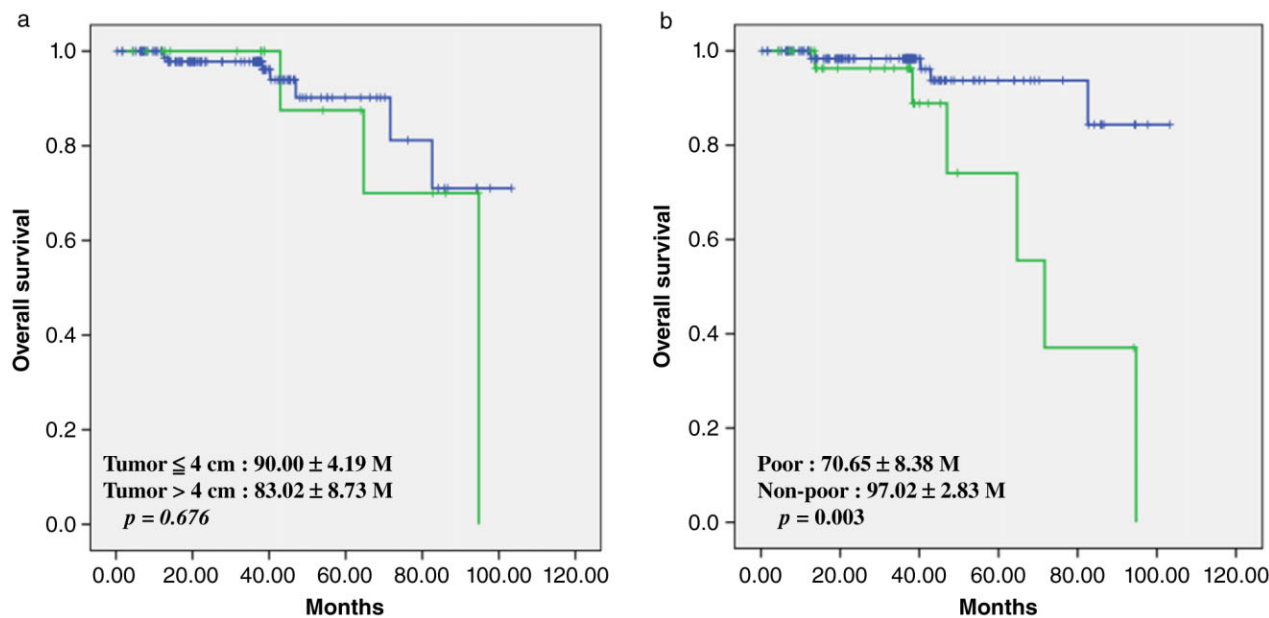
### OS in p-stage IA and IB patients according to adjuvant chemotherapy group

p-Stage IA patients in the adjuvant chemotherapy group had a worse prognosis than those in the no adjuvant chemotherapy group ( $P < 0.001$ ; Fig 5a). In contrast, OS was not significantly different between p-stage IB patients in the adjuvant chemotherapy and no adjuvant chemotherapy groups ( $P = 0.647$ ; Fig 5b).

### OS in p-stage IA and IB patients according to tumor differentiation and adjuvant chemotherapy

p-Stage IA patients with poorly differentiated tumors who received adjuvant chemotherapy had significantly better OS than those who did not receive adjuvant chemotherapy ( $P < 0.001$ ; Fig 6a). On the other hand, p-stage IA patients with non-poorly differentiated tumors who received adjuvant chemotherapy had a significantly worse prognosis than those who did not receive adjuvant chemotherapy ( $P < 0.01$ ; Fig 6b). The survival rate of p-stage IB patients with poorly differentiated tumors who received adjuvant chemotherapy was higher than that of those who did not receive adjuvant chemotherapy (88.9% vs. 75%). The survival rates of





**Figure 3** Overall survival in stage I patients according to (a) tumor size (>4 cm vs. ≤4 cm), and (b) tumor differentiation (poor vs. non-poor). (a) Tumor size: —□, ≤4 cm; —□, >4 cm; —+, 1-censored; —+, 2-censored. (b) Tumor differentiation: —□, No-poor; —□, poor; —+, 1-censored; —+, 2-censored.

p-stage IB patients with non-poorly differentiated tumors could not be calculated because of the small patient number.

### Discussion

The five-year survival rate of patients with p-stage I NSCLC after lobectomy is reported to be 45–65%, depending on whether the patients have associated prognostic factors.<sup>12</sup> These factors make the prognosis of NSCLC patients with the same stage of disease heterogeneous. In our study, poor tumor differentiation was the only independent predictor of OS in patients with p-stage I NSCLC after resection. Although we found that adjuvant chemotherapy tended to increase patient survival in p-stage I NSCLC patients with poorly differentiated tumors, this survival benefit was only marginally

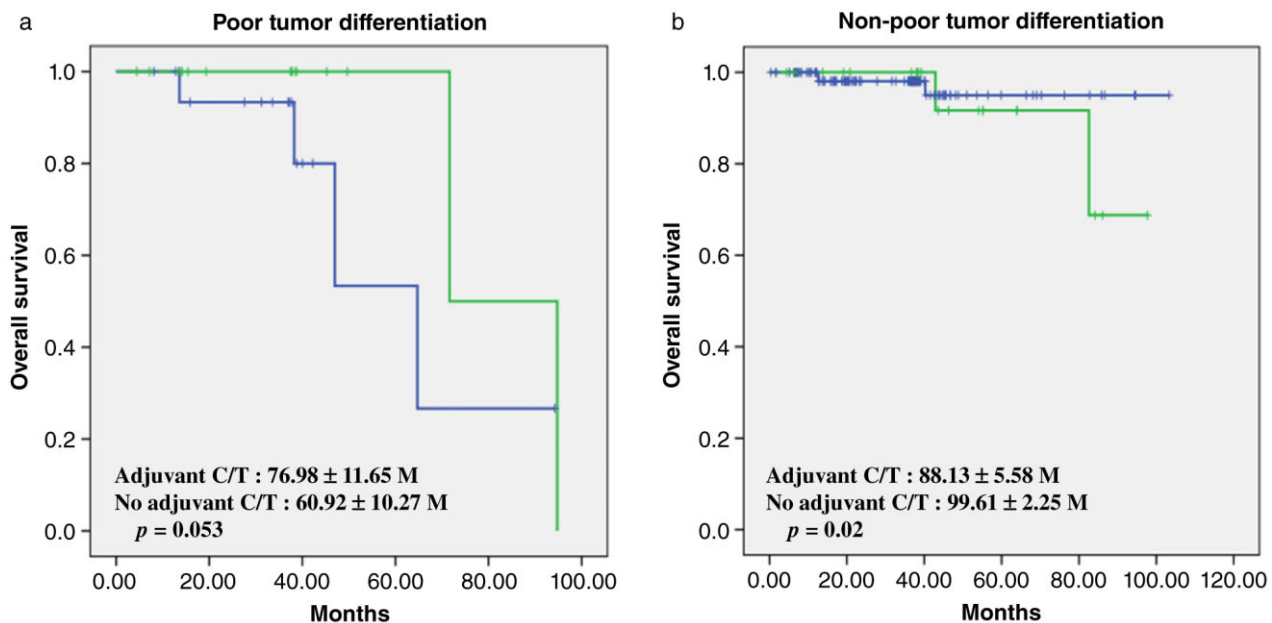
significant ( $P = 0.053$ ). However, subgroup analysis showed a highly significant survival benefit of adjuvant chemotherapy in p-stage IA NSCLC patients with poorly differentiated tumors ( $P < 0.001$ ).

Several previous reports have indicated that poor differentiation is not only an independent prognostic factor for poor survival but also a risk factor for recurrence in patients with stage I NSCLC.<sup>12–15</sup> Ou *et al.* reported that the risk of death was increased by 14% and 12% in stage IA and IB NSCLC patients with poorly differentiated tumors, respectively, compared with patients with well-differentiated tumors.<sup>12</sup> Similarly, Sun *et al.* found that stage I NSCLC patients with poorly/undifferentiated and moderately differentiated tumors had 2.1-fold (95% CI: 1.41–2.9) and 1.4-fold (95% CI: 1.0–1.9) increased risks of recurrence, respectively, compared with those with well-differentiated tumors. In the current study, we found that patients with poorly differentiated tumors had a 6.8-fold (95% CI: 1.720–27.593) increased risk of death compared with patients with non-poorly differentiated tumors. However, other studies have shown that histological grade is not an independent prognostic factor for lung cancer survival.<sup>16–19</sup> These inconsistencies on the prognostic role of histological grade in lung cancer may be a result of several factors, such as small sample sizes, different cell types, varied treatment modalities, and uneven grading criteria and grouping systems among pathologists.<sup>13</sup> In addition, poorly differentiated tumors may also be correlated with chemoresistance in NSCLC.<sup>20</sup> A recent study revealed that the expression of excision repair cross-complementing group 1

**Table 2** Multivariate predictors of overall survival in stage I non-small cell lung cancer patients after tumor resection

Predictor	HR (95% CI)	<i>p</i> value
SUVmax ≥ 3.3	2.612 (0.472–14.462)	0.272
CEA ≥ 3.5 ng/mL	1.498 (0.320–7.009)	0.608
LVSI	2.151 (0.204–22.730)	0.524
Pathological stage IB	1.096 (0.195–6.149)	0.917
Poor differentiation	6.889 (1.720–27.593)	0.006*
No chemotherapy	1.314 (0.289–5.969)	0.724

\*Statistically significant ( $P < 0.05$ ). CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; LVSI, lymphovascular invasion; SUVmax, maximum standardized uptake value.

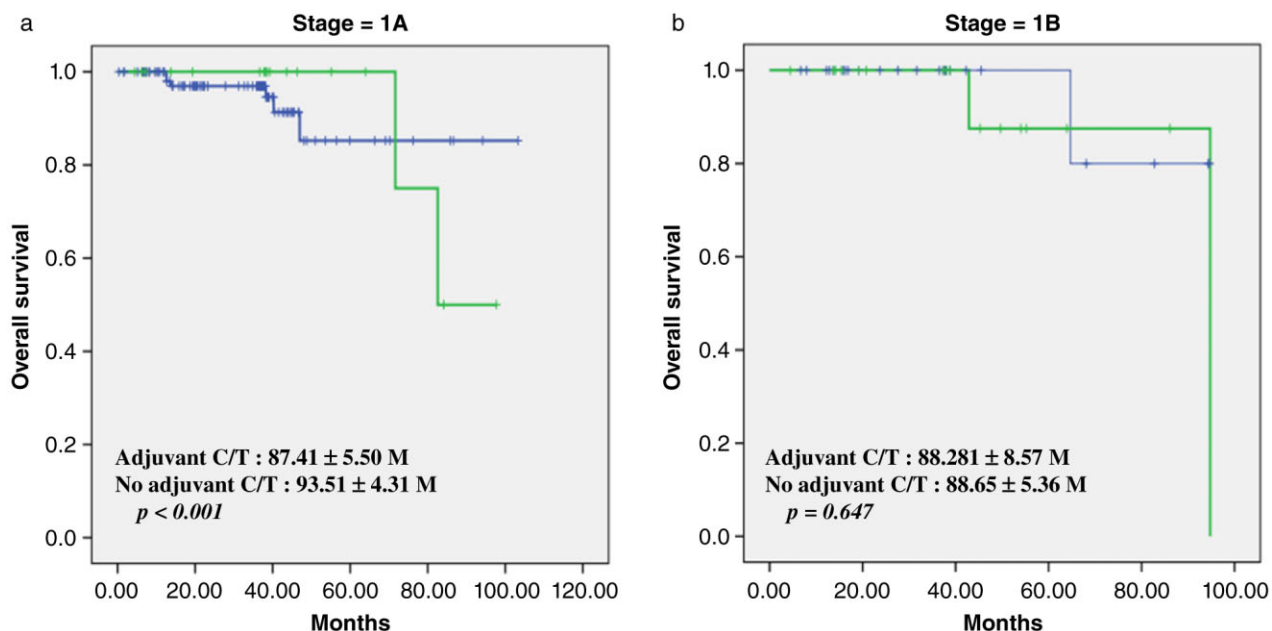


**Figure 4** Overall survival in (a) patients with poor tumor differentiation, and (b) patients with non-poor tumor differentiation according to adjuvant chemotherapy administration. Chemotherapy:  $\square$ , No;  $\square$ , Yes;  $+$ , 0-censored;  $+$ , 1-censored.

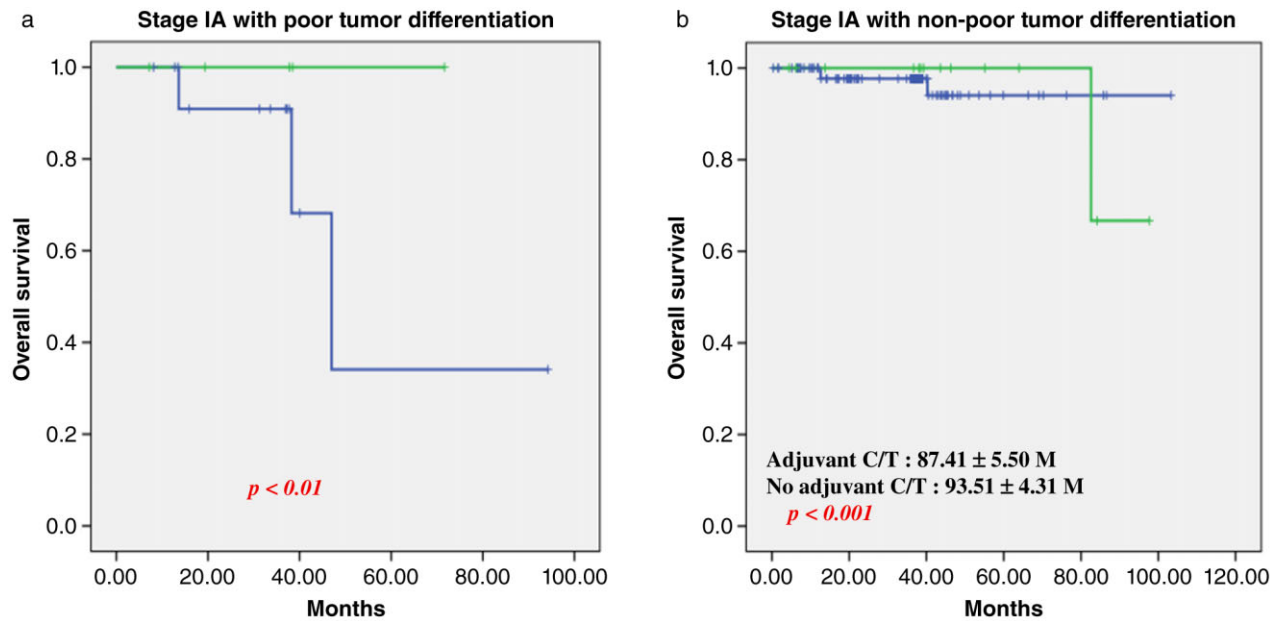
(ERCC1), which repairs platinum-induced DNA damage in patients with poorly differentiated adenocarcinoma, was significantly higher than that found in patients with well-moderately differentiated non-adenocarcinomas.<sup>21</sup> This finding suggests that high levels of ERCC1 expression in

poorly differentiated tumors may be predictive of a poor response to platinum-based chemotherapy in NSCLC.

In the most recent meta-analyses, cisplatin-based adjuvant chemotherapy was found to be associated with a five-year survival improvement of 4.0% (HR = 0.86, 95% CI: 0.81–



**Figure 5** Overall survival in (a) stage IA patients, and (b) stage IB patients, according to adjuvant chemotherapy administration. Chemotherapy:  $\square$ , No;  $\square$ , Yes;  $+$ , 0-censored;  $+$ , 1-censored.



**Figure 6** Overall survival in (a) stage IA patients with poor tumor differentiation, and (b) stage IA patients with non-poor tumor differentiation according to adjuvant chemotherapy administration. Chemotherapy:  $\square$ , No;  $\square$ , Yes;  $+$ , 0-censored;  $+$ , 1-censored.

0.91) to 5.4% (HR = 0.89, 95% CI: 0.82–0.96) in NSCLC patients, with the main survival benefit observed in patients with stage II and III disease.<sup>8,9</sup> Nevertheless, the management of resected stage I disease with adjuvant chemotherapy remains uncertain. The Lung Adjuvant Cisplatin Evaluation meta-analysis revealed a non-significant trend toward prolonged survival in stage IB disease patients treated with cisplatin-based adjuvant chemotherapy, whereas poorer survival was observed in patients with stage IA disease.<sup>8</sup> In contrast, another meta-analysis of six randomized trials showed that adjuvant chemotherapy with tegafur-uracil treatment improved OS in stage IA T1b NSCLC.<sup>22</sup> In the current study, p-stage IA patients in the adjuvant chemotherapy group had a poorer prognosis than the group who did not receive adjuvant chemotherapy. However, the use of adjuvant chemotherapy was associated with a survival benefit in p-stage IA patients with poorly differentiated tumors. This may be explained by our finding that poor tumor differentiation is an independent prognostic factor for poor survival in p-stage I NSCLC patients, and, thus, p-stage IA patients who have this risk factor derive a survival benefit from adjuvant chemotherapy. In previous studies, adjuvant chemotherapy after resection in NSCLC patients with p-stage IA disease may have been used indiscriminately rather than according to prognostic factors, such as poor tumor differentiation, as was followed in our study. Consequently, the toxic side effects of adjuvant chemotherapy may have surpassed the survival benefit. This factor may be responsible for the inconsistencies

in the outcomes of adjuvant chemotherapy in NSCLC patients with p-stage IA disease between our study and previous studies.

The Cancer and Leukemia Group B trial revealed a non-significant survival advantage of adjuvant paclitaxel/carboplatin in stage IB patients but a significant survival benefit in stage IB patients with tumors  $\geq 4$  cm.<sup>23</sup> In addition, a recent retrospective study showed that resected stage IB NSCLC patients who had larger tumors, moderate to poor differentiation, and a good performance status (ECOG 0) appeared to benefit from cisplatin-based chemotherapy.<sup>24</sup> In the current study, survival was not significantly different between p-stage IB patients in the adjuvant chemotherapy and non-adjuvant chemotherapy groups. However, in the subset analysis, p-stage IB patients with poorly differentiated tumors who received adjuvant chemotherapy had a higher survival rate than those who did not receive chemotherapy (88.9% vs. 75%). Because of the small number of patients in our study groups, further investigation is needed to clarify the benefit of adjuvant chemotherapy in p-stage IB patients with poorly differentiated tumors.

Our study had several limitations. First, because of its retrospective nature, our analysis was limited to the data obtained from medical records. Notably, these records did not include detailed information on chemotherapy regimens, such as the dose, number of cycles, and toxicity, which may have affected our results. Second, the relatively small number of p-stage IB patients with poorly differentiated tumors in

our study may have limited the statistical power to detect the true effect of adjuvant chemotherapy in these patients, although a trend of increasing survival was observed in the adjuvant chemotherapy group. Nevertheless, p-stage IA patients who had poorly differentiated tumors did derive a survival benefit from adjuvant chemotherapy in our study. Third, most patients in our study had adenocarcinomas; therefore, we cannot generalize our results to patients with other histological types of NSCLC.

## Conclusion

In conclusion, poor tumor differentiation was found to be a poor prognostic factor in patients with p-stage I NSCLC in this study. Furthermore, p-stage IA patients with poorly differentiated tumors may benefit from adjuvant chemotherapy. Prospective studies of p-stage I NSCLC patients stratified into low and high-risk categories according to tumor differentiation are needed to determine the true survival benefits of adjuvant chemotherapy.

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## Disclosure

No authors report any conflict of interest.

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