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Original Article

Lymphovascular space invasion and tumor differentiation are predictors for postoperative recurrence in patients with pathological stage I nonsmall cell lung cancer

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Abstract

Background: We investigated factors predicting postoperative recurrence in patients with pathological Stage I nonsmall cell lung cancer (NSCLC).
Methods: All patients with clinical Stage I NSCLC who underwent surgical resection at Tri-Service General Hospital in Taiwan between January 2002 and June 2006 were reviewed retrospectively. All study patients underwent standard staging workups. We reviewed the records of 261 patients with an average follow-up of 93 months; we then included 179 patients with pathological Stage I.
Results: Two hundred sixty-one patients with clinical Stage I NSCLC were eligible. There were no significant differences in sex, tumor histopathology, location, and age between the two groups (recurrence and nonrecurrence), except for tumor differentiation ($p = 0.002$), survival rate ($p < 0.001$), lymphovascular space invasion (LVSI; $p = 0.007$), advanced pathology stage ($p = 0.022$), maximum standard uptake value (SUVmax; $p = 0.027$), tumor size ($p < 0.011$), and carcinoembryonic antigen (CEA) levels ($p = 0.013$). Overall survival was significantly related to postoperative recurrence ($p < 0.001$) in patients with pathological Stage I, in whom recurrences developed in 11.17%. Only 179 patients with pathological Stage I NSCLC, including 20 patients with postoperative recurrences, were selected. Tumor differentiation (odds ratio 3.581, $p = 0.058$) and LVSI (odds ratio 5.374, $p = 0.020$) were independent factors predicting recurrence.
Conclusion: Tumor differentiation and LVSI were predictors of postoperative relapse for patients with pathological stage I NSCLC. Risk factors of postoperative recurrence in patients with pathological Stage I NSCLC may enable us to optimize the patient selection for postoperative adjuvant therapies to prevent possibly occult micrometastases.

Keywords: nonsmall cell lung cancer; postoperative recurrence; prognostic factors; survival rate

1. Introduction

Nonsmall cell lung cancer (NSCLC) remains the leading cause of cancer-related death and has a dismal prognosis. Despite advances in radiation therapy, chemotherapy, and newly developed molecular targeting therapies, long-term survival after resection for patients with NSCLC remains less than 50%. Most mortality following surgical resection is associated with tumor recurrence. Studies have investigated

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the clinical, pathological, and genetic factors that are associated with decreased survival after resection for NSCLC.[1,2] Accurate preoperative staging is important in determining the appropriate treatment. It is well known that the clinical stage does not fully predict the pathology stage. Nodal metastasis or occult micrometastasis might be a key or link to postoperative recurrence in patients with Stage I NSCLC.[3] Our study investigated factors predicting postoperative recurrences in patients with pathological Stage I NSCLC. These clinicopathologic variables may enable us to optimize the patient selection for adjuvant therapy in order to reduce recurrences and improve the survival rate.

2. Methods

All patients who underwent complete resection for clinical Stage I NSCLC at Tri-Service General Hospital, Taipei, Taiwan, between January 2002 and June 2006, were reviewed retrospectively. The preoperative staging workups included chest and upper abdomen computed tomography (CT), bronchoscopy, positron emission tomography (PET) scan, and whole-body bone scans. Brain magnetic resonance imaging (MRI) was routinely undertaken prior to surgery, especially when the patients had neurogenic symptoms, such as headache, dizziness, or unstable gait. Mediastinoscopy was not a routine preoperative staging procedure, and was performed only when enlarged mediastinal lymph nodes (diameter > 1.0 cm) were shown by the CT scan to prove nodal status of staging. No patients received neoadjuvant chemotherapy. Determinations of cancer stage were based on the tumor-node-metastasis (TNM) classification (7th edition) of the American Joint Committee on Cancer.[4] Histopathology refers to the microscopic examination with staining methods of surgical specimen by a pathologist, after the specimen has been processed and histological sections have been placed onto glass slides. The lymphovascular space invasion (LVSI) was a histopathological examination, and the interpretation was made by the pathologist. The findings of tumor cell within the vascular lumen by specific stain or tumor cell infiltrated within the surrounding lymph node tissue was called LVSI. Serum carcinoembryonic antigen (CEA) level was measured as part of the routine preoperative evaluation and postoperative follow-up. Serum CEA level was calculated by means of the two-site immunoenzymometric assay (CEA test; CIS Bio International, Gif-sur-Yvette, France; reference range <5.0 ng/mL) following the manufacturer's instructions. The upper limit of normal in our hospital defined as 3.5 ng/mL based on the 95% specificity level for benign lung disease.

After evaluation of the resectability and operability of the tumors, a total of 261 patients with clinical Stage I NSCLC (tumor size < 5 cm, no enlarged lymph node, no direct invasion to peripheral organs, and no pleural effusions) were enrolled and underwent surgical resection with dissection of the mediastinal lymph nodes. The indication of adjuvant chemotherapy in our study was based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (2009) and used in the high-risk patients, who were defined by poorly differentiated tumor, LVSI, wedge resection, and minimal margins. All of our patients received complete resection with adequate surgical margins proven by pathology. Postoperatively, patients were initially seen at 2–3 weeks after resection by the thoracic surgeon and then again every 3–6 months at the outpatient department, where they underwent contrast-enhanced chest CT at these appointments during the follow-up period. The serum CEA level was routinely measured after surgery every 3 months. Subsequent to these visits, either a roentgenogram or CT scan of the chest was reviewed annually. PET-CT or MRI was used as clinically warranted. All visits were completed in concert with the referring oncologist. Recurrence was documented either radiographically or histologically in all cases. Secondary primary lung cancer was differentiated from recurrent NSCLC according to the criteria proposed by Martini.[5] The recurrences included local recurrence and distant metastasis. Clinicopathologic variables were investigated for their influence on time to postoperative recurrence. We reviewed 261 patients with an average follow-up of 93 months. Patient consent was obtained after explaining the purpose of study and surgical procedure.

2.1. Statistical analysis

Descriptive data are expressed as the mean ± standard deviation. Student t test was used to investigate continuous variables and the χ^2 test was used to compare categorical variables between groups. Survival from the date of surgery was calculated using Kaplan–Meier survival analysis. Multiple logistic regression analyses were used to identify independent risk factors for patients with recurrences. SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for all analyses and statistical significance was defined as $p < 0.05$.

3. Results

Two hundred and sixty-one patients with clinical Stage I NSCLC after complete resection and dissection of mediastinal lymph nodes were reviewed. Of these, 37 patients (14.2%) developed postoperative recurrences. Twenty (7.66%) of the total of 261 patients had distant metastases. The most common sites of distant metastasis were brain (9/20, 45%) and bone (8/20, 40%). Two of 20 patients had liver metastases and only one patient had adrenal gland metastasis. Among these 20 patients, five (25%) had LVSI.

The demographic characteristics in patients with clinical Stage I NSCLC are shown in Table 1. There were no statistically significant differences in sex, tumor histopathology, tumor location, or age (Table 1). Comparisons between two groups showed statistical significance in tumor differentiation ($p = 0.002$), survival rate ($p < 0.001$), LVSI ($p = 0.007$), pathological staging ($p = 0.022$), SUVmax of tumor (6.60 ± 3.98 vs. 4.39 ± 4.01, $p = 0.027$), tumor size (3.35 ± 1.36 vs. 2.66 ± 1.52 cm, $p < 0.011$), and CEA level (10.31 ± 23.34 vs. 4.45 ± 9.47 ng/mL, $p = 0.013$). Among those with clinical Stage I tumors, 16 patients (16/37, 43.24%)

Table 1
Characteristics of patients with or without tumor recurrence after resection for clinical Stage I nonsmall cell lung cancer.

	No recurrence (n = 224)	Recurrence (n = 37)	p[a]
Sex			
Male	101 (45.09)	16 (43.24)	0.834
Female	123 (54.91)	21 (56.76)	
Histopathology			
Adenocarcinoma	193 (86.16)	33 (89.19)	0.616
Other	31 (13.84)	4 (10.81)	
Differentiation			
Well	94 (41.96)	8 (21.62)	**0.002**
Moderate	89 (39.73)	13 (35.14)	
Poor	41 (18.3)	16 (43.24)	
Location			
Central	113 (50.45)	23 (62.16)	0.186
Peripheral	111 (49.55)	14 (37.84)	
Survival			
Yes	209 (93.3)	17 (45.95)	**<0.001**
No	15 (6.7)	20 (54.05)	
LVSI			
Absent	207 (92.41)	29 (78.38)	**0.007**
Present	17 (7.59)	8 (21.62)	
p-stage			
I	159 (70.98)	20 (54.05)	**0.022**
II	37 (16.52)	10 (27.03)	
III	28 (12.5)	6 (16.22)	
IV	0 (0)	1 (2.7)	
Age (y)	61.21 ± 12.50	62.62 ± 10.1	0.513
SUVmax	4.39 ± 4.01	6.06 ± 3.98	**0.027**
Tumor size (cm)	2.66 ± 1.52	3.35 ± 1.36	**< 0.011**
CEA (ng/mL)	4.45 ± 9.47	10.31 ± 23.34	**0.013**

Data are presented as n (%) or mean ± SD.
CEA = carcinoembryonic carcinogen; LVSI = lymphovascular space invasion; p-stage = pathology stage; SCC = squamous cell carcinoma; SUVmax = maximum standard uptake value.
[a] Significance was assessed using χ^2 tests. Statistically significant p values are depicted in bold.

with recurrence and 41 (41/224, 18.30%) without recurrence had poor tumor differentiation. The aggressiveness of tumors was associated with postoperative recurrence ($p < 0.001$). In the group without recurrence, eight patients (7.6%) had been identified with LVSI versus 17 patients (46%) in the recurrence group. Sixty-five patients (65/224, 29.02%) in the group without recurrence had postoperative upstaging versus 17 patients (17/37, 45.95%) with recurrence.

According to the pathological stage, we selected 179 patients with pathological Stage I NSCLC to investigate predictors of postoperative recurrences. Fig. 1 reveals the relationship between postoperative recurrence and overall survival in patients with pathological Stage I NSCLC. The median survival rate was 94.87 months for patients without recurrence versus 71.46 months for patients with recurrence ($p < 0.001$). Therefore, surgical outcome of these patients is associated with postoperative recurrences. In the multiple logistic regression analysis for the risk factors of postoperative recurrence in patients with pathological Stage I NSCLC (Table 2), tumor differentiation [odds ratio (OR): 3.581, $p = 0.058$] and LVSI (OR: 5.374, $p = 0.020$) were independent factors associated with postoperative recurrence. Figs. 2 and 3 show the overall survival curves with LVSI and tumor differentiation. Preoperative SUVmax ≥ 3.3 (OR: 0.497, $p = 0.481$), CEA ≥ 3.5 ng/mL (OR: 1.995, $p = 0.158$), and tumor size > 2 cm (OR: 2.141, $p = 0.143$) did not predict postoperative recurrences. The overall recurrent rate in patients with clinical Stage I NSCLC was 14.17% (11.17% for pathology Stage I and 20.73% for other stages).

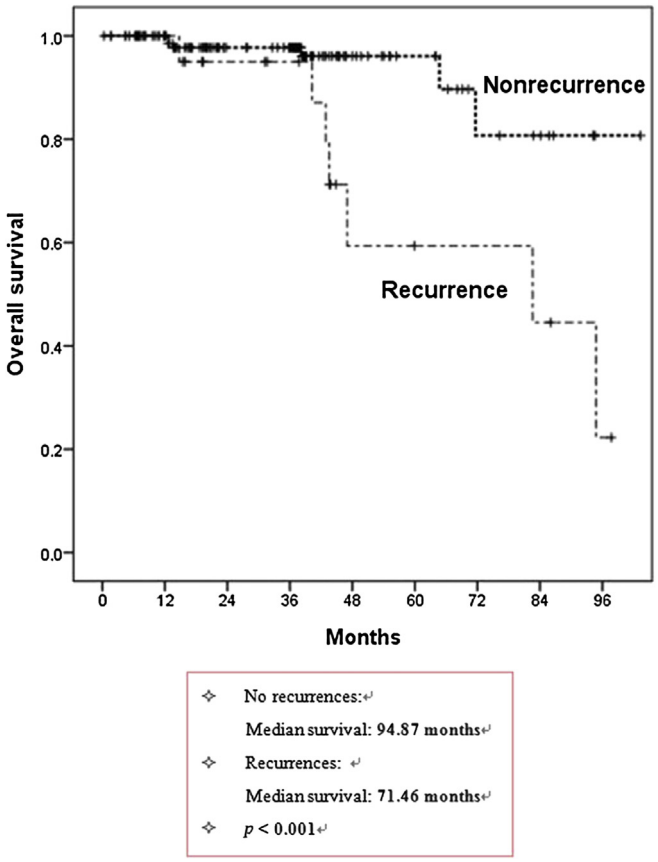

Fig. 1. The relationship of overall survival rate with and without recurrence in pathological Stage I nonsmall cell lung cancer.

4. Discussion

Lung cancer has the highest incidence and mortality rates of any major cancer worldwide. The 5-year survival rate has

Table 2
Multiple logistic regression analysis for the risk factors of postoperative recurrence in the patients with pathological Stage I nonsmall cell lung cancer.

Factors	OR (95% CI)	p[a]
SUVmax ≥ 3.3	0.497 (0.495–1.485)	0.481
CEA ≥ 3.5 ng/mL	1.995 (0.149–0.450)	0.158
Tumor size > 2 cm	2.141 (0.130–0.418)	0.143
Tumor differentiation	3.581 (0.124–0.359)	**0.058**
LVSI	5.374 (1.285–5.061)	**0.020**

CEA = carcinoembryonic carcinogen; CI = confidence interval; LVSI = lymphovascular space invasion; OR = odds ratio; SUVmax = maximum standard uptake value.
[a] Statistically significant p values are depicted in bold.

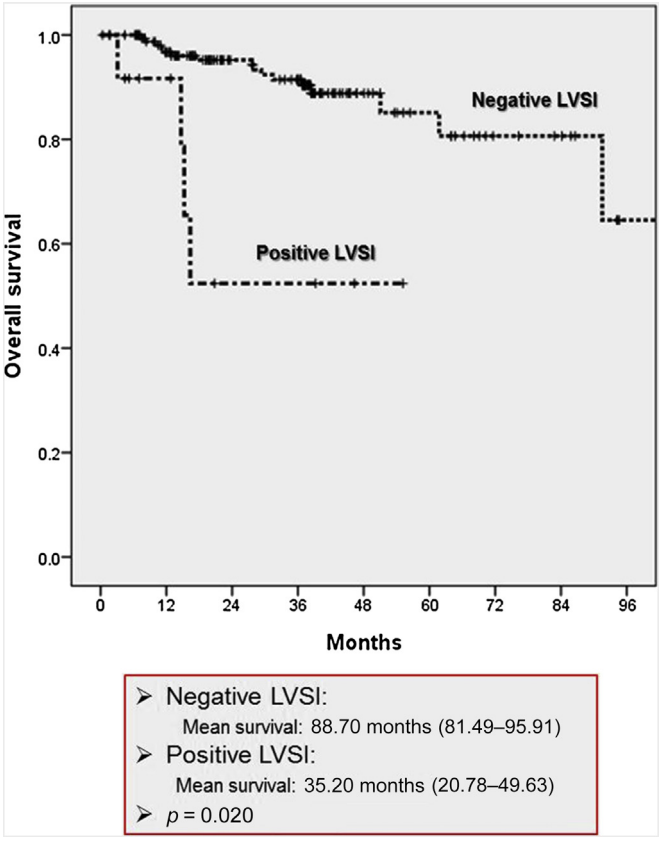

Fig. 2. The relationship of overall survival rate with and without lymphovascular space invasion in patients with pathological Stage I nonsmall cell lung cancer.

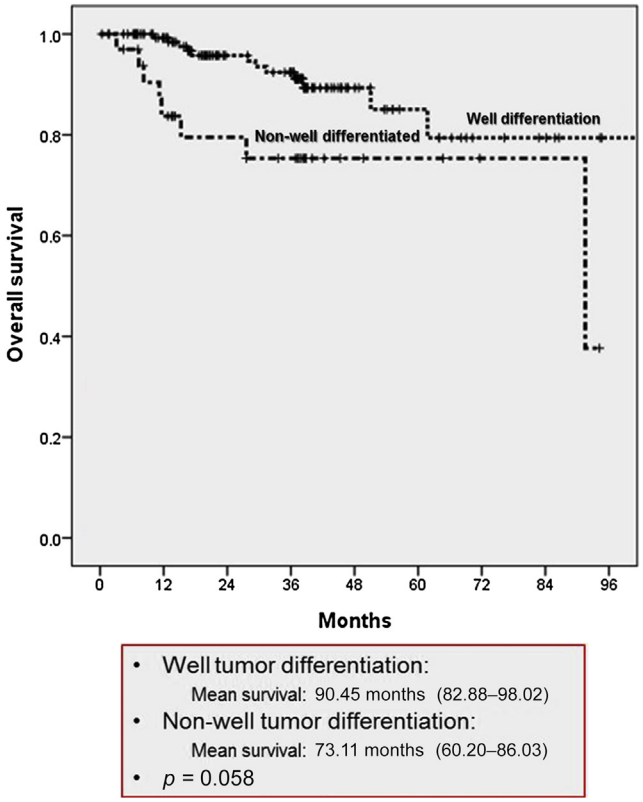

Fig. 3. The relationship of overall survival rate with and without poorly differentiated tumor in patients with pathological Stage I nonsmall cell lung cancer.

been reported to be 73% for patients with pathology Stage IA and 58% for patients with pathological Stage IB.[6] In our study, we used the same population to probe surgical outcome on the occurrence of postoperative recurrence. Fig. 1 shows significant differences between overall survival and postoperative recurrences in patients with pathological Stage I NSCLC. The survival rate is strongly associated with postoperative recurrence, which mechanism was not well established to date. Godfrey et al[3] stated that one possible reason for this may be that those patients with a poor outcome actually have more extensive disease, with occult locoregional and/or distant metastasis than originally identified by routine pathologic staging techniques. One of the most convincing etiology of postoperative recurrence was occult tumor cell spread to lymph nodes or bone marrow in patients with NSCLC.[3] Biswas et al[7] thought the detection of bone marrow micrometastasis changes the staging and management of lung cancer, especially in NSCLC, where treatment with curative intent is planned, which can be suitably done by morphological study of bone marrow aspirate and biopsy. However, the cost effect of bone marrow aspiration is high and the invasiveness of the procedure may produce more complications. Therefore, we searched clinicopathologic factors, which were cost-effective and available after surgery, to predict postoperative recurrences in patients with pathological Stage I NSCLC. Then, we could optimize the patient selection for postoperatively adjuvant treatment to reduce recurrent rate and improve survival rate. In our data of postoperative recurrence, the poor prognostic factors were poor tumor differentiation, LVSI, advanced pathology stage, SUVmax of tumor, tumor size, and CEA level in patients with clinical Stage I NSCLC (Table 1). Furthermore, only tumor differentiation and LVSI were identified as independent predictors in patients with pathological Stage I NSCLC for postoperative recurrence.

Preoperative clinical staging is a key factor influencing the decision regarding initial therapy for patients with lung cancer. In this regard, PET–CT with fluorodeoxyglucose (^{18}F) uptake (FDG) plays an established role in the treatment of patients with NSCLC. FDG uptake, which reflects the tumor's glucose metabolic rate, varies widely and depends on the histopathology type and aggressiveness of the tumor.[8,9] Consideration of this parameter enhances the accuracy of clinical staging, improving patient selection for surgical treatment. Several studies have reported that the preoperative SUVmax has prognostic value in patients with early stages of NSCLC.[10,11] Koo et al[12] investigated factors associated with recurrence in 310 patients with Stages I or II disease. There were 106 recurrences in the study population and SUVmax $\geq$ 4.5 was found to be an independent predictor of recurrence after resection, with an OR of 5.45. In addition, Shiono et al[13] demonstrated that SUVmax $\geq$ 4.7 was found to be an independent predictor of recurrence in patients with Stage I NSCLC. These two studies did not stratify patients based on

the location of recurrence to determine whether SUVmax was more predictive for locoregional than for distant recurrences. In another study, subgroup analysis found that SUVmax > 5 was associated with distant recurrences, whereas the predictive nature of SUVmax > 5 did not reach statistical significance among patients with locoregional recurrences.[14] It is important for the clinician to understand that SUVmax is a semi-quantitative index and can vary from one center to another. Although the metabolic activity of tumors has been shown to contribute significant information in terms of prognosis,[15,16] the cutoff values for SUV measurements vary widely, making their clinical application difficult. In our study, the cutoff point of SUVmax of 3.3 was used according to our previous study.[17] However, the SUVmax of our results did not show statistical significance in prediction of postoperative recurrences.

There was concordance between the pathological stage and the preoperative clinical stage in 68.6% of patients in the current study. Eighty-two patients (31.4%) had advanced disease after surgery. This rate was higher than the rates of upstaging tumors of 14.3–17% reported in the literature.[18,19] Kelsey et al[20] reported that the overall risk of recurrence was 36% after surgical resection for patients with Stages I or II NSCLC. Varlotto et al[21] investigated factors associated with recurrence in 373 patients with Stages I–IIIA NSCLC who underwent resection. An advanced pathology stage was associated with an increased risk of distant recurrence. Although these two studies established the importance of the pathological stage for the risk of recurrence, they used the 6th edition and not the most recent 7th edition of the TNM staging system. Pepek et al[22] compared the ability of the 7th edition TNM staging systems to detect locoregional recurrence in comparison to the 6th edition. Converting from the system used in the 6th edition to that in the 7th edition resulted in a 21% migration in stage classification (13% up-staged and 8% downstaged). This might explain the high rate of postoperative upstaging in our study, because we used the 7th edition of the TNM staging system for all patients. In our study, the recurrent rate was 14.17% (11.17% for pathological Stage I and 20.73% for non-Stage I patients). The 47 patients with pathologic Stage II and 34 patients with pathologic Stage III were upstaged because of positive nodal status proved by pathologists. The only patient with pathologic Stage IV had so minimal pleural effusion that it was hard to detect in imaging studies. The malignant pleural effusion was found during operation and confirmed after complete surgery.

Sublobar resection has been found to be an independent predictor of locoregional recurrence.[14] The tumor size in that report was not associated with an increased risk of recurrence in the sublobar resection group (2.3 cm in the group with recurrence, 2.2 cm in the group without recurrence; $p < 0.3$). By contrast, Bando et al[23] reported that a higher recurrence rate is associated with sublobar resection in patients with tumors larger than 2 cm. In their study, patients with tumors smaller than 2 cm had locoregional recurrence rates of 1.9% compared with 33% in patients with tumors larger than 2 cm. The different conclusions in these studies might be associated with the larger sample size in the former study and the fact that only 50% of the patients underwent wedge resection. By contrast, in the latter study, all patients underwent segmentectomy. In our study, only 16 patients had wedge resection and others underwent lobectomy. For patients with tumor diameter smaller than 2 cm, the postoperative recurrence rate was 6.1% versus 19.4% for patients with tumors larger than 2 cm. After adjustment for the other factors, tumor size with a cutoff of 2 cm was not found to be an independent predictor in the multiple logistic regression analysis in patients with pathological Stage I NSCLC.

Histopathology markers were found to be prognostic predictors in patients with NSCLC.[24] CEA is a well-known tumor marker for substantial malignant tumors, including NSCLC. Evaluating serum CEA level is useful for monitoring response to chemotherapy and predicting relapse of advanced NSCLC.[25] Sawabata et al[26] assessed 297 consecutive patients with clinical Stage I NSCLC for evaluation of CEA level and the upper limit of normal defined as 7.0 ng/mL. They saw CEA level as a useful predictor of survival for patients with clinical Stage I NSCLC, and a persistently high CEA level after surgery as an especially strong indicator of a very poor prognosis. In another study, Buccheri and Ferrigno[27] reported that the frequency of abnormal serum concentrations of CEA is low (17%), but it is important to identify such a small group of high-risk patients as many of them (55% and 70% of those with a CEA value in excess of, respectively, 5 ng/mL and 10 ng/mL, normal reference values < 5 ng/mL) will develop an early postoperative recurrence. Although there was a significant difference in the serum CEA level between the two groups in our study, higher serum CEA level ($\geq$ 3.5 ng/mL) was not an independent predictor for postoperative recurrence in multiple logistic regression analysis.

LVSI is an established negative prognostic factor and an indication for postoperative radiation therapy in several epithelial malignancies, including cervix, endometrial, vulvar, and head and neck cancers. Kristin et al[28] proposed a study to evaluate LVSI in patients with early-stage NSCLC undergoing surgical resection. They found LVSI was associated with an increased risk of harboring regional lymph node involvement and also an adverse prognostic factor for the development of distant metastases and long-term survival. National comprehensive cancer network clinical practice guidelines in NSCLC (version 1.2014, page NSCL-3) showed that high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors), vascular invasion, wedge resection, tumor larger than 4 cm, visceral pleural involvement, and incomplete lymph node sampling. These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy. Therefore, adjuvant chemotherapy is still equivocal for high-risk patients with pathological Stage I NSCLC. In our study, tumor differentiation and LVSI were independent predictors of postoperative relapse for pathological Stage I NSCLC. Risk factors of postoperative recurrence in patients with pathological Stage I NSCLC may enable us to optimize the patient selection for postoperative adjuvant therapies to reduce recurrent rate, and

further studies are needed to investigate the outcomes of adjuvant treatment in high-risk patients.

As a retrospective, single-institute study, patient selection bias and time-trend bias were inevitable. In addition, we did not address the risk factors for different recurrence patterns (locoregional and distant). It was difficult to obtain performance status from the charts. Although performance status is clearly an important factor in Stage IV NSCLC, its importance in Stage I disease has not yet been established. Lack of data about performance status might have little significance in the analysis of death and recurrence in our study. The 261 patients were operated on by different surgeons; it is generally recognized that different surgeons have different levels of dexterity, leading to different rates of recurrence. Furthermore, the fact that the predictors demonstrated in our study were not all consistent with other reports highlights the possibility of false positive findings. Further studies of clinical information combined with histopathological markers might provide valuable indicators for recurrences. Prospective multi-institutional studies are mandatory to further validate the predictors of recurrence in pathological Stage I NSCLC.

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