

Prognostic factors of tumor recurrence in completely resected non-small cell lung cancer

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Background: Patients with completely resected non-small cell lung cancer (NSCLC) have an excellent outcome; however tumor recurs in 30%–77% of patients. This study retrospectively analyzed the clinicopathologic features of patients with any operable stage of NSCLC to identify the prognostic factors that influence tumor recurrence, including intratumoral blood vessel invasion (IVI), tumor size, tumor necrosis, and intratumoral lymphatic invasion.

Methods: From January 2002 to December 2011, 227 consecutive patients were enrolled in this study. They were divided into two groups: the “no recurrence” group and the “recurrence” group. Recurrence-free survival was analyzed by multivariable Cox regression analysis, stratified by tumor staging, chemotherapy, and nodal involvement.

Results: IVI, tumor necrosis, tumor diameter more than 5 cm, and nodal involvement were identified as independent prognostic factors of tumor recurrence. The hazard ratio (HR) of patients with IVI was 2.1 times higher than that of patients without IVI (95% confident interval [CI]: 1.4–3.2) ($P = 0.001$). The HR of patients with tumor necrosis was 2.1 times higher than that of patients without tumor necrosis (95% CI: 1.3–3.4) ($P = 0.001$). Patients who had a maximum tumor diameter greater than 5 cm had significantly higher risk of recurrence than patients who had a maximum tumor diameter of less than 5 cm (HR 1.9, 95% CI: 1.0–3.5) ($P = 0.033$).

Conclusion: IVI, tumor diameter more than 5 cm, and tumor necrosis are prognostic factors of tumor recurrence in completely resected NSCLC. Therefore, NSCLC patients, with or without nodal involvement, who have one or more prognostic factors of tumor recurrence may benefit from adjuvant chemotherapy for prevention of tumor recurrence.

Keywords: intratumoral blood vessel invasion, recurrence, NSCLC

Introduction

Anatomical resection still remains the only method for curative treatment of non-small cell lung cancer (NSCLC) patients, not only in early stage (stage IA, IB and IIA, IIB), but also in a locally advanced stage (selected stage IIIA). Despite complete resection, recurrence occurs in the range of 30%–77%.^{1,2} The most important prognostic factor that may affect the tumor recurrence is nodal invasion; however previous studies have found other prognostic factors, such as intratumoral blood vessel invasion (IVI),³ intratumoral lymphatic invasion (ILI), visceral pleural invasion,⁴ or tumor size.⁵ Currently, there are no conclusions about prognostic factors for tumor recurrence in patients who have undergone a completely resected NSCLC. Also, the International Association for the Study of Lung Cancer (IASLC) does not include these factors in the TNM staging system.¹ Patients who have one or more prognostic factors may benefit from adjuvant chemotherapy even when nodal involvement is negative. This study attempted to clarify

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the prognostic factors associated with tumor recurrence in completely resected NSCLC patients.

Patients and methods

Between January 2002 and December 2011, 227 patients underwent anatomical resection (lobectomy, sleeve lobectomy, bilobectomy, and pneumonectomy) with systematic mediastinal lymph node dissection at Chiang Mai University Hospital, Chiang Mai, Thailand. We retrospectively reviewed these 227 cases from the medical recording system with regard to patient characteristics, signs and symptoms, tumor pathology report, and follow-up status to examine the prognostic factors of tumor recurrence in all of the completely resected NSCLC patients. In the preoperative evaluation, standard laboratory tests, such as complete blood count (CBC), liver and renal function test, electrolytes, posteroanterior and lateral chest film, computed tomographic (CT) scan of the thorax and the upper abdomen, pulmonary function test, and bronchoscopy, were obtained for all of the patients. Bone scan and CT of the brain were obtained only in patients who had evidence of bone or brain metastasis. No positron emission tomography (PET) was done in the routine workup because this was not easily available. Patients who received neoadjuvant or adjuvant chemotherapy were included in this study. Patients were excluded from this study if they: had a single brain metastasis and underwent a craniectomy to remove their tumor before pulmonary resection (five patients); had evidence of residual tumor at the resection margin (five patients); or died within first 30 day of the surgery (postoperative mortality) (three patients). Standard anatomical resection (lobectomy, bilobectomy, or pneumonectomy) with systematic mediastinal lymph node dissection were performed in all cases, and all nodal stations were labeled according to the staging manual in Thoracic Oncology.⁶

All excised specimens were formalin-fixed and sliced at 10 mm intervals. Histopathologic examination was performed by the same pathologist. Pathologic staging was determined according to the IASLC TNM staging classification of NSCLC.⁷ Histologic subtypes of lung cancer were determined according to World Health Organization classification⁸ and IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) International Multidisciplinary Classification of Lung Adenocarcinoma.¹ Visceral pleural invasion was defined as evidence of penetration of thick outer elastic lamina by tumor during elastic tissue staining. The presence of IVI was defined by the identification of conspicuous findings of intravascular

cancer clusters surrounded by an elastic layer at the maximum section of the primary lesion. The presence of ILI was defined by the identification of cancer cells within the lymphatic vessel lumen. Tumor necrosis was defined as coagulative necrosis identifiable in the tumor (macroscopic or microscopic finding). Tumor involvement of the epineurium was defined as perineural invasion.⁹

All patients were actively followed postoperatively at 2 weeks and at 3- to 6-month intervals for the first 2 years and yearly thereafter, with a CT scan of the chest and upper abdomen. Patients who had pathological nodal involvement (stages IIA, IIB, IIIA, and IIIB) received adjuvant chemotherapy. If patients developed signs or symptoms that correlated with tumor recurrence or metastasis, they would be worked up according to their signs or symptoms (ie, CT brain or bone scan). Tumor recurrence was defined as the evidence of tumor within the same lobe, the hilum, or the mediastinal lymph nodes (locoregional recurrence), or evidence of tumor in another lobe or elsewhere outside the hemithorax (distant recurrence). The interval to recurrence was defined as the interval between the time of the operation and the discovery of the recurrence by means of either imaging or cytopathologic examination.

Patients were divided into two groups: the “no recurrence” group and the “recurrence” group. Categorical variables were expressed as count and percent and were analyzed by univariable analysis, using the Fisher exact test. Continuous variables were expressed as mean and standard deviation (SD) and were analyzed by univariable analysis, using the Student *t*-test. The recurrence-free survival curves were estimated using the Kaplan–Meier method. Tumor recurrence was expressed by using “time zero” as the date of surgery and recurrence as the end point. Comparison of recurrence-free survival between both groups was investigated using a Cox multivariable regression model stratified by stage of disease, chemotherapy, and nodal involvement. We stratified the model by the stage of disease and chemotherapy because we already knew that these factors influence tumor recurrence and we wanted to make comparisons between stages, different uses of chemotherapy, and between different patterns of nodal involvement. Univariable prognostic factors significant at the 0.10 level were considered for the multivariable models, and stepwise regression was used. All tests were two-tailed and performed with commercial statistical software (STATA 11.0; StataCorp LP, College Station, TX, USA).

This study was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Results

Table 1 summarizes the patient population for the groups with and without tumor recurrence. Tumor recurrence was identified in 120 patients, whereas 107 did not have tumor recurrence. There was no statistically significant difference in any of the patient characteristic variables. Nearly 50% in both groups of patients presented with chronic cough and nonmassive hemoptysis.

The surgical procedures consisted of 197 lobectomies (86.8%), 26 bilobectomies (11.5%), and four pneumonectomies (1.8%). A total of 104 patients (45.8%) received adjuvant chemotherapy because of diagnosed pathological nodal involvement (stage IIA, IIB, IIIA, or IIIB). Six patients (2.6%) received neoadjuvant chemotherapy because of N2 disease preoperatively diagnosed by mediastinoscopy. The summary of chemotherapy use between both groups was shown in Table 2. No patients were treated with postoperative radiotherapy. The histopathologic results are summarized in Table 3. There were no intraoperative deaths. There were no statistically significant differences in the surgical procedure, chemotherapy, histologic types, tumor grading, pathological stage, tumor diameter, visceral pleural invasion, and neural invasion. Univariable analysis showed that the stage of disease, nodal involvement, and IVI were associated with tumor recurrence ($P = 0.041$,

Table 1 Patient characteristic between two groups

Characteristics	Nonrecurrence (n = 107)	Recurrence (n = 120)	P-value
Age, mean \pm SD	61.4 \pm 10.5	62.8 \pm 10.5	0.322
Male, n (%)	64 (59.8)	69 (57.5)	0.788
Smoking			0.820
Never smoked	30 (28.0)	30 (25.0)	
Stopped smoking	71 (66.4)	80 (66.7)	
Active smoker	5 (4.7)	7 (5.8)	
Passive smoker	1 (0.9)	3 (2.5)	
Packs per year, mean \pm SD	19.1 \pm 16.9	19.1 \pm 17.7	0.863
Family history of malignancy	7 (6.5)	5 (4.2)	0.555
Underlying disease			
Chronic lung disease	14 (13.1)	15 (12.5)	1.000
Diabetic mellitus	12 (11.2)	15 (12.5)	0.839
Essential hypertension	34 (31.8)	43 (35.8)	0.575
Dyslipidemia	18 (16.8)	15 (12.5)	0.451
Symptoms			
Hemoptysis	48 (44.9)	48 (40.0)	0.502
Chronic cough	48 (44.9)	52 (43.3)	0.894
Poor appetite	16 (15.0)	15 (12.5)	0.699
Significant weight loss	33 (30.8)	30 (25.0)	0.374
Chest pain	9 (8.4)	11 (9.2)	1.000
Dyspnea	17 (15.9)	25 (20.8)	0.393
Asymptomatic	38 (35.5)	43 (35.8)	1.000

Abbreviation: SD, standard deviation.

Table 2 Treatment modalities

Procedure and chemotherapy	Nonrecurrence (n = 107)	Recurrence (n = 120)	P-value
Surgical procedures			0.419
Lobectomy	89 (83.2)	108 (90.0)	
Bilobectomy (RUL and RML)	3 (2.8)	3 (2.5)	
Bilobectomy (RLL and RML)	12 (11.2)	8 (6.7)	
Pneumonectomy	3 (2.8)	1 (0.8)	
Chemotherapy			0.103
No chemotherapy	63 (58.9)	54 (45.0)	
Adjuvant chemotherapy	42 (39.3)	62 (51.7)	
Neoadjuvant chemotherapy	2 (1.9)	4 (3.3)	

Abbreviations: RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

$P = 0.003$, and $P < 0.001$, respectively). Median follow-up was 19 months (range, 0.7–144.9 months) in the nonrecurrent group and 24.5 months (range, 1.6–97.4 months) in the recurrent group. The overall mean interval to recurrence after the operation was 14.2 ± 13.9 months (range, 0.8–65.2 months). The sites of metastases are shown in Table 4. The lung was the most common metastatic site (49.1%), and the brain was the second most common (25.8%). The 2-year recurrence-free survival was 50.0% (95% confidence interval [CI]: 0.4%–0.6%), and the 5-year recurrence-free survival was 31.5% (95% CI: 0.2%–0.4%). The overall cumulative 2- and 5-year survival was 61.9% (95% CI: 0.5%–0.7%) and 31.5% (95% CI: 0.2%–0.4%), respectively. The mean survival was 32 months in the nonrecurrent group and was 24 months in the recurrent group.

Multivariable analysis demonstrated that tumor necrosis, IVI, and tumor diameter greater than 5 cm were the only independent prognostic factors for tumor recurrence, as shown in Table 5. The recurrence-free survival curves stratified according to tumor necrosis, IVI, and tumor diameter are shown in Figures 1 to 3 respectively.

Discussion

The seventh edition of IASLC staging of lung cancer¹ seems powerful in determining prognosis; however, many studies have tried to identify other prognostic factors of tumor recurrence in patients with completely resected NSCL patients. Histopathological examination may play an important role in this.¹⁰ There are several histopathological factors that affect tumor recurrence and survival, and which have been identified as prognostic factors, such as IVI,^{3,9,11,12} visceral pleural invasion,^{12–17} perineural invasion,^{10,18} mitotic index and nuclear atypia,¹⁹ and histologic grade.²⁰

Table 3 Histopathologic reports

Covariates	Nonrecurrence (n = 107)	Recurrence (n = 120)	P-value
Histologic types			0.848
Adenocarcinoma	61 (57.0)	72 (60.0)	
Squamous cell carcinoma	29 (27.1)	32 (26.7)	
Others*	17 (15.9)	16 (13.3)	
Tumor grading			0.644
Well differentiated	34 (31.8)	48 (40.0)	
Moderately differentiated	45 (42.1)	44 (36.7)	
Poorly differentiated	18 (16.8)	22 (18.3)	
Undifferentiated	4 (3.7)	3 (2.5)	
Mucinous type of adenocarcinoma in situ	3 (2.8)	2 (1.7)	
Nonmucinous type of adenocarcinoma in situ	3 (2.8)	1 (0.8)	
Pathological staging			0.041
IA	20 (18.7)	13 (10.8)	
IB	25 (23.4)	21 (17.5)	
IIA	17 (15.9)	21 (17.5)	
IIB	19 (17.8)	12 (10.0)	
IIIA	24 (23.4)	51 (42.5)	
IIIB	1 (0.9)	2 (1.7)	
Tumor diameter (cm)			0.325
≤5	75 (70.1)	76 (63.3)	
>5	32 (29.9)	44 (36.7)	
Nodal involvement			0.003
Nodal negative	72 (67.3)	57 (47.5)	
Nodal positive [#]	35 (32.7)	63 (52.5)	
Tumor necrosis	36 (33.6)	56 (46.7)	0.058
Visceral pleural invasion	19 (17.8)	29 (24.2)	0.258
Neural invasion	3 (2.8)	6 (5.0)	0.506
Intratumoral lymphatic invasion	84 (78.5)	104 (86.7)	0.115
Intratumoral blood vessel invasion	32 (29.9)	64 (53.3)	<0.001

Notes: *Other cell types include adenocarcinoma in situ,²⁴ large cell carcinoma, neuroendocrine tumor, adenoid cystic carcinoma, metastasis, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma, adenosquamous cell carcinoma; [#]nodal positive refers to the presence of malignant cells, in any node level (1–14).

The results of this study found that IVI, tumor necrosis, tumor size greater than 5 cm, and nodal involvement affected tumor recurrence in any stage of completely resected NSCLC and that IVI was the only prognostic factor of tumor recurrence in completely resected stage I NSCLC. There have been some previously published studies on the topic of IVI. Yilmaz et al⁹ reported that lymphovascular invasion can show a higher risk of mortality; however, they did not separate lymphatic invasion from vascular invasion, therefore, we did not learn how either lymphatic invasion or vascular invasion exactly affects tumor recurrence. Pechet et al³ concluded that the presence of arterial invasion in stage I

Table 4 Sites of metastases

Sites	Number of patients	%
Lung	59	49.1
Brain	31	25.8
Bone	17	14.2
Liver	6	5.0
Supraclavicular lymph node	5	4.2
Skin	5	4.2
Adrenal gland	4	3.3
Pleura	4	3.3
Mediastinal lymph node	3	2.5
Chest wall	2	1.7
Kidney	1	0.8
Cervical lymph node	1	0.8
Stomach	1	0.8

NSCLC patients was adversely associated with poor survival (hazard ratio [HR], 3.5) ($P < 0.001$). However, this study only studied and showed the survival rates of patients with stage I NSCLC. Miyoshi et al¹² and Shoji et al²¹ concluded that IVI was independent prognostic factor in pathological stage I NSCLC patients. In the contrast, other work has not shown relevant prognostic factors.¹⁰ Currently, there are no firm conclusions about the role of IVI and tumor recurrence. In our study, we included all completely resected NSCLC and used a multivariable Cox proportional hazard model, as previously described, to identify the prognostic factor for tumor recurrence. The results showed that IVI is a strongly prognostic factor for tumor recurrence (HR, 2.1; 95% CI: 1.4–3.2) ($P = 0.001$), in any stage of completely resected NSCLC.

Among the tumor factors, the maximum tumor diameter is an available prognostic factor based on gross specimen. The seventh edition of the IASLC classification of lung cancer adopted a diameter of 50 mm as the threshold of stratification between T2a and T2b, for improvement of the ability to provide a differential prognosis. However, some previous studies

Table 5 Multivariable Cox regression analysis stratified by tumor staging, chemotherapy treatment, and nodal involvement

Covariates	Hazard ratio	95% confidence interval	P-value
Age	1.0	0.9–1.0	0.556
Male	1.0	0.7–1.5	0.837
Tumor necrosis	2.1	1.3–3.4	0.001
Intratumoral blood vessel invasion	2.1	1.4–3.2	0.001
Intratumoral lymphatic invasion	1.0	0.5–1.7	0.825
Tumor diameter >5 cm	1.9	1.0–3.5	0.033

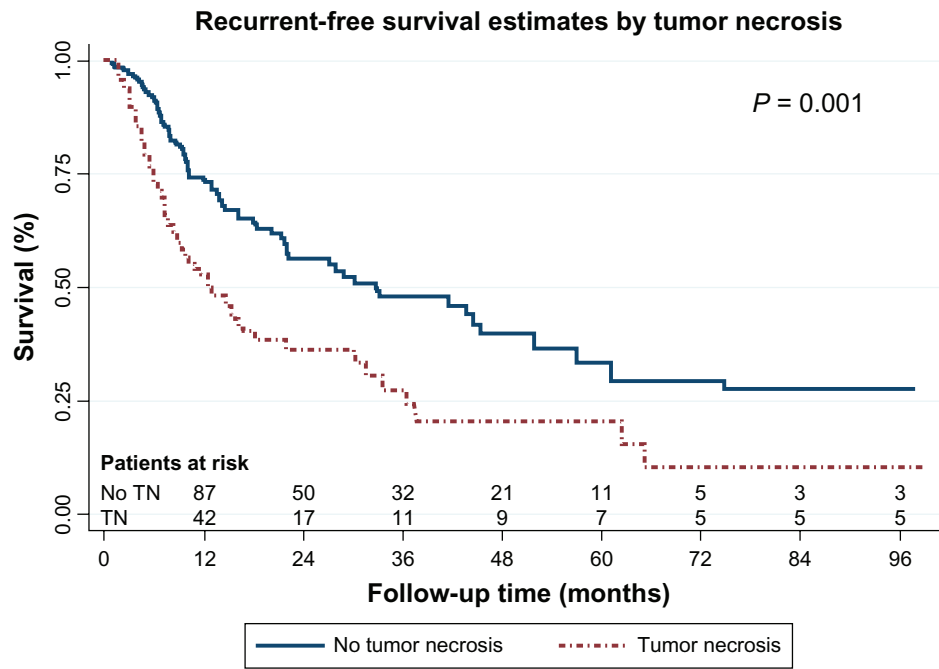


Figure 1 Recurrent-free survival curves by tumor necrosis.
Abbreviation: TN, tumor necrosis.

have shown no significance of tumor size for prognosis in resected (p-)stage I NSCLC, by multivariable analysis.^{5,22,23} One explanation is that even in a large adenocarcinoma in situ (a subtype of adenocarcinoma according to the IASLC/ATS/ERS Classification of Lung Adenocarcinoma),²⁴ growth

is slow and there is a lack of involved stroma and vessels; thus even despite a large size, this subtype has been known to have a good clinical outcome.²⁵ However, other work demonstrated that tumor size can predict survival in stage I and II NSCLC.²⁶ Our study showed that a maximal tumor diameter

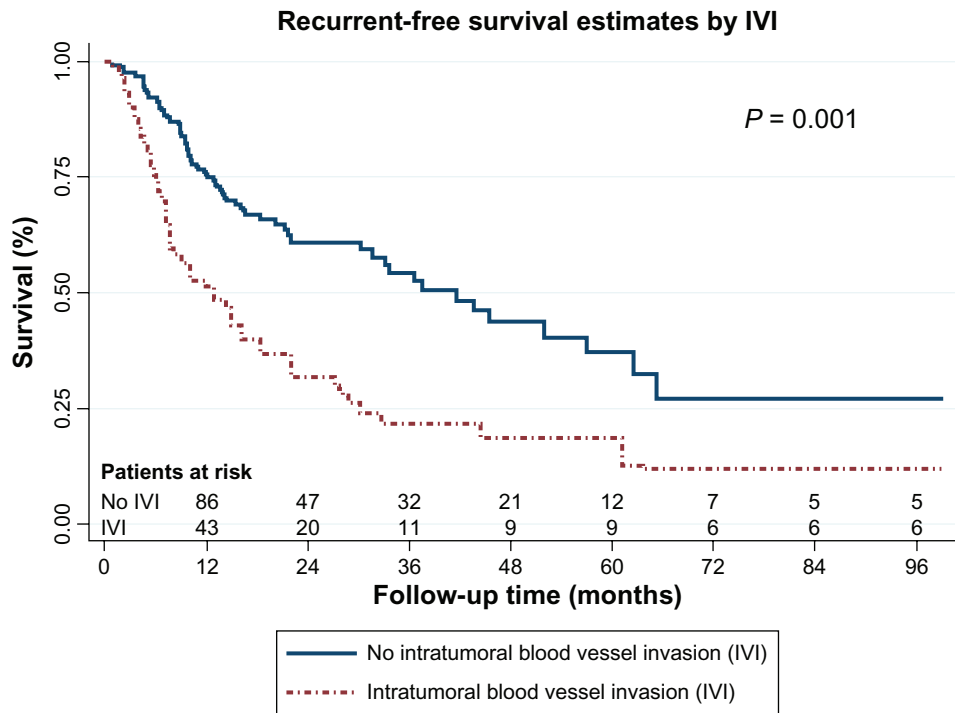


Figure 2 Recurrent-free survival curves by intratumoral blood vessel invasion (IVI).

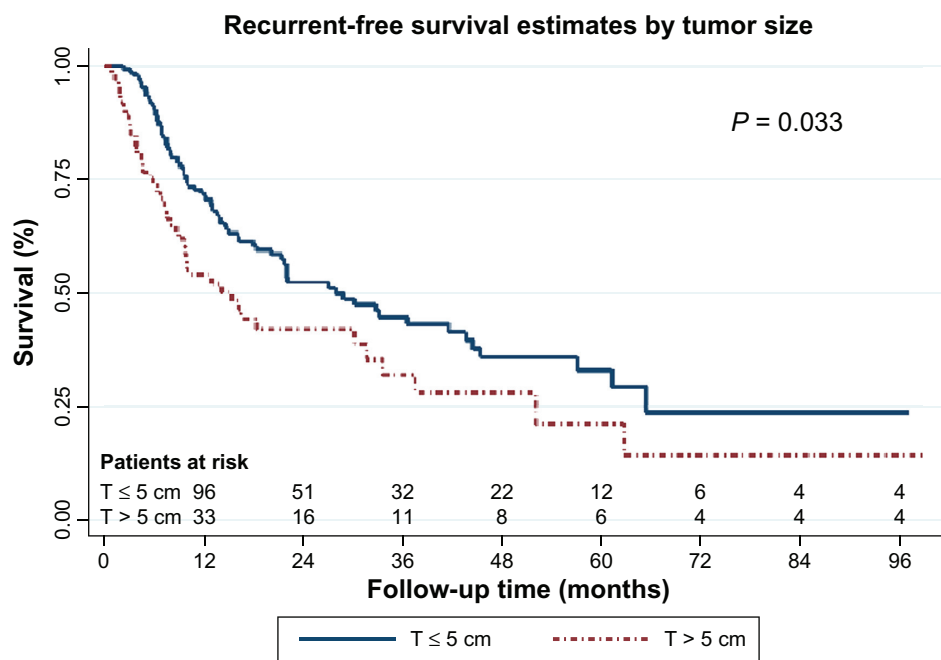


Figure 3 Recurrent-free survival curves by tumor size.
Abbreviation: T, maximal tumor diameter (cm)

of greater than 5 cm was associated with tumor recurrence (HR, 1.9; 95% CI: 1.0–3.5) ($P = 0.033$). This result was not contradicted by the characteristics of large adenocarcinoma in situ as described above, because we collected the data by separating adenocarcinoma in situ from adenocarcinoma. Our result supported the clinical relevance of tumor size as a prognostic factor for recurrence of completely resected NSCLC patients.

Tumor necrosis has not been mentioned as a prognostic factor of tumor recurrence before; however, in our study, this was shown to be a prognostic factor for tumor recurrence (HR, 2.1; 95% CI: 1.3–3.4) ($P = 0.001$). There was also a correlation between tumor size and tumor necrosis. Nearly 64% of the tumors with a size greater than 5 cm had the tumor necrosis, whereas 30% of the tumors with size less than 5 cm had tumor necrosis. The reason large tumors had more tumor necrosis was that there was a smaller vascular supply or blood vessels in the central part of the tumor; therefore, large tumors had a greater chances of presenting with tumor necrosis than did small ones.

Visceral pleural invasion has been recognized to be another strong prognostic factor associated with increased risk of recurrence and death;^{5,13,23,27–30} however, some researchers have found otherwise,⁴ and our study did not find any correlation with tumor recurrence.

ILI was previously reported to be a prognostic factor for tumor recurrence and survival, especially in completely resected stage I NSCLC patient;³¹ however our study did not

show a significant correlation (HR, 1.0; 95% CI: 0.5–1.7) ($P = 0.825$).

Although the survival benefit of adjuvant therapy for resected NSCLC has been expected in some trials^{32,33} it is, so far, controversial with regard to stage I disease. Shoji et al²¹ reported that distant recurrence was observed in patients with stage IA or IB NSCLC with IVI more frequently than in those without IVI, and they suggested that patient in these groups seemed to be candidates for adjuvant chemotherapy. Bodendorf et al³⁴ reported that the histologic evidence of IVI was more often followed by distant metastases than local recurrence and should be considered as an indication for adjuvant chemotherapy. The current series also supported the findings of their study.

Previously, five of the largest adjuvant trials³⁵ to date were included in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis.³⁶ Of the five, two trials – the National Cancer Institute of Canada (NCIC) JBR.10 and the Adjuvant Navelbine® International Trialist Association (ANITA) – exclusively examined cisplatin-vinorelbine combinations, while the other three – the Big Lung Trial (BLT),³⁹ the International Trialist Association Trial (IALT),³² and the Adjuvant Lung Project Italy (ALPI)⁴⁰ – allowed investigator choice of cisplatin-based regimens. The adjuvant trial demonstrating the most striking benefit, NCIC JBR.10,³⁷ included 482 patients with completely resected stage IB or II NSCLC, randomly assigned to observation or four cycles of weekly cisplatin 50 mg/m² on days 1 and 8 plus vinorelbine 25 mg/m²

on days 1, 8, 15, 22, of a 28-day regimen. The ANITA trial³⁸ evaluated adjuvant chemotherapy for 840 patients with completely resected stage IB–IIIA NSCLC, using cisplatin 100 mg/m² day 1 (4 doses) plus vinorelbine at 30 mg/m² on days 1, 8, 15, and 22 (16 doses), for four cycles, versus observation. Both the NCIC JBR.10 and the ANITA trials showed an overall survival benefit (HR 0.69 [$P = 0.004$] and HR 0.80 [$P = 0.017$], respectively); the survival benefit did not diminish over time and was 8.4% at the 7-year follow-up for ANITA trial.³⁸ Alternately, the BLT,³⁹ IALT,³² and ALPI³⁹ trials evaluated an investigator-chosen cisplatin-based regimen. These trials demonstrated an overall survival benefit at 5 years, but not at 7 years. Why a long-term overall survival benefit was not achieved remains an interesting question.

Targeting pathways has shown benefit for patients who express particular gene mutation, for example, epidermal growth factor receptor (EGFR) gene mutation. The BR.19 trial⁴⁰ randomized 503 patients with completely resected stage IB–IIIA NSCLC (only 21% of whom had EGFR mutations) to gefitinib versus placebo, but this trial was halted early because the interim analysis of the S0023 SWOG trial⁴² demonstrated that maintenance gefitinib was associated with a worse survival than placebo, after concurrent chemoradiation for stage III NSCLC. Recently, the Randomized Double-Blinded Trial in Adjuvant NSCLC with Tarceva® (RADIANT) trial was begun to evaluate the role of the EGFR-tyrosine kinase inhibitor (TKI) erlotinib in the adjuvant treatment of 945 patients with completely resected stage IB–IIIA NSCLC whose tumors have overexpression of EGFR detected by immunohistochemistry or fluorescence in situ hybridization (FISH). In this 2-year trial, patients have been randomized in a 2:1 ratio to erlotinib or placebo and may have up to four cycles of chemotherapy after surgery. Patients randomized to erlotinib began 6 months from the day of surgery for patients who get chemotherapy and 3 months from the day of surgery for those who do not get chemotherapy. The RADIANT trial is ongoing, but no longer recruiting participants.

Clinical trials of adjuvant therapy in well-selected populations with completely resected early stage NSCLC presenting with poor prognostic factors are needed. IVI should be considered as one of the prognostic factors for tumor recurrence in completely resected early stage NSCLC and should be considered in future trials of adjuvant therapy. Furthermore, tumor size greater than 5 cm and tumor necrosis were also found to be prognostic for tumor recurrence; therefore, patients who have a maximal diameter greater than 5 cm or presenting with tumor necrosis or intratumoral blood vessel invasion without nodal involvement may also benefit from adjuvant chemotherapy.

One limitation of this study is its retrospective nature. Although there was missing data, we think that missing data randomly occurred in both comparison groups. We also controlled the quality of data by doing a quality audit, and we found that the data quality was respectable.

Conclusion

Our analyses indicated intratumoral blood vessel invasion, tumor diameter more than 5 cm, and tumor necrosis are prognostic factors of tumor recurrence, in any stage of completely resected NSCLC. Therefore, NSCLC patients with or without nodal involvement who have one of the prognostic factors of tumor recurrence may benefit from adjuvant chemotherapy for prevention of tumor recurrence. Further clinical trials are needed to support this hypothesis.

Disclosure

The authors report no conflicts of interest in this work.

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