Received: 1 July 2022 | Accepted: 3 August 2022

DOI: 10.1111/1759-7714.14616

ORIGINAL ARTICLE

WILEY

Invasive area to tumor ratio is a significant prognostic factor for non-small cell lung cancer

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Abstract

Background: Although T factor is defined as the size of invasive area rather than total tumor size in the eighth edition of the TNM classification, whether the pathological invasive area to tumor ratio (ITR) is a prognostic factor has not yet been evaluated.

Methods: In total, 432 lung adenocarcinoma patients were analyzed, among which 266 patients with pathological stage IA were used to perform a subanalysis.

Results: Smoking status (odds ratio [OR]: 0.43, $p = 0.01$), neutrophil-to-lymphocyte ratio (NLR) (OR: 1.97, $p = 0.03$), maximum standardized uptake value (SUV_{max}) (OR: 3.62, $p < 0.01$), and ITR (OR: 6.76, $p < 0.01$) were significantly different in univariate analysis. Smoking status (OR: 0.34, $p < 0.01$), SUV_{max} (OR: 3.05, $p < 0.01$), and ITR (OR: 5.44, $p < 0.01$) were risk factors for recurrence in multivariate analysis. In patients with pathological stage IA disease, smoking status (OR: 0.34, $p = 0.03$), NLR (OR: 2.30, $p = 0.04$), SUV_{max} (OR: 3.63, $p < 0.01$), pathological invasive area (OR: 4.00, $p < 0.01$), and ITR (OR: 6.03, $p < 0.01$) were significantly different in univariate analysis. Smoking status (OR: 0.27, $p = 0.02$), SUV_{max} (OR: 3.93, $p < 0.01$), and ITR (OR: 4.38, $p < 0.01$) were significant risk factors for recurrence in multivariate analysis.

Conclusions: SUV_{max} and ITR are risk factors for recurrence. These results suggest that SUV_{max} is important for deciding the indication for limited resection or adjuvant chemotherapy, and ITR is an adaptation criterion for adjuvant chemotherapy for early-stage lung adenocarcinoma patients.

KEYWORDS
early stage, invasive area to tumor ratio, non-small cell lung cancer, standardized uptake value

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for more than 80% of all cases.[1] Several prognostic factors in patients with early-stage NSCLC have been reported.[2–9] Although the prognosis of stage IA NSCLC is considered good compared with that of advanced stages, age, gender, carcinoembryonic antigen (CEA), tumor size, operative procedure, surgical margin, pleural invasion, lymphatic invasion, histological type, and presence of combined pulmonary fibrosis and emphysema (CPFE) have been reported to be prognostic factors in patients with early-stage NSCLC. Furthermore, the risk factors are varied and not consistent among reports.

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee collected a new database of 94 708 cases donated from 35 sources in 16 countries around the globe that were developed for the T, N, and M categories of the eighth edition of the TNM Classification for lung cancer in 2016.[10] Some new stage groupings are defined for this new classification, such as the division of the category T1 into T1mi, T1a, T1b, and T1c on the basis of invasive area of, which are categorized as 0.5, 1, and 2 cm. Because these groupings reflect statistically

significant differences in prognosis, a tumor's invasive size is defined as a prognostic factor.

Consolidation to tumor ratio (CTR) in computed tomography (CT) has been reported to be another prognostic factor for early-stage NSCLC.[11–14] Furthermore, the ratio of cancer cells to stroma within the invasive area in lung adenocarcinoma has been reported to be a histological prognostic parameter.[15] Although the size of the tumor's invasive area rather than total tumor size is defined as T factor in the eighth edition of the TNM classification, whether pathological invasive area to tumor ratio (ITR) is a prognostic factor in NSCLC has not been assessed.

In this study, we retrospectively evaluated the prognostic value of ITR in lung adenocarcinoma patients who underwent pulmonary resection.

METHODS

Patients

Among 675 NSCLC patients who underwent pulmonary resection at Kanazawa Medical University between 2017 and 2021, 432 lung adenocarcinoma patients were enrolled in this retrospective study. Furthermore, 266 lung adenocarcinoma patients with pathological stage IA disease were selected for subanalysis (Figure 1). This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review committee of Kanazawa Medical University approved the protocol (approval number: I392), and all patients gave written informed consent.

Data including clinical factors such as gender, age, comorbidities, smoking history, carcinoembryonic antigen (CEA), neutrophil-to-lymphocyte ratio (NLR), maximum standardized uptake value (SUV_{max}) on 18F-fluoro-2-deoxy-glucose positron emission tomography, and lung cancer lobe involvement were collected. Although NLR is defined as the ratio of neutrophil-to-lymphocyte counts and is a parameter of systemic inflammation and stress in critically ill surgical and medical patients,[16] NLR has been reported to be a prognostic factor for NSCLC patients who have undergone pulmonary resection.[17–19] Comorbidities were evaluated using the Charlson comorbidity index (CCI).[20]

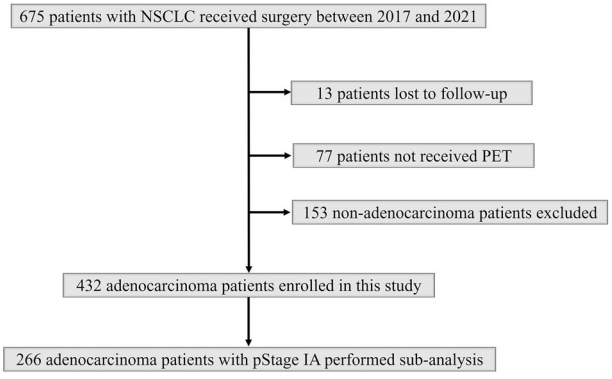

FIGURE 1 Patient flow diagram

Operative factors and postoperative complications

Operative approaches were divided into three categories: video-assisted thoracic surgery (VATS), robot-assisted thoracic surgery (RATS), and open thoracotomy. Operative procedures were stratified into seven categories: wedge resection, segmentectomy, lobectomy, lobectomy combined chest wall resection, lobectomy combined segmentectomy, sleeve lobectomy, and bilobectomy.

Pathological factors

Lymphatic invasion, vascular invasion, maximum pathological tumor diameter, and pathological invasive area of tumors were collected. Tumor specimens were sectioned into 5 to 10 mm slices and the maximum diameter of tumor was macroscopically or microscopically measured. In some cases, 3D construction was performed and measured. Furthermore, ITR which is defined as the invasive area to tumor diameter ratio on pathological findings, was calculated.

Statistical analysis

We used Pearson's chi-square test of independence to compare frequencies of the variables. Cumulative survival was calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. The cutoff values of factors associated with recurrence were calculated using receiver operating characteristic (ROC) curve analysis, and prognostic analyses were performed on the basis of these cutoff values. Risk factors associated with recurrence were analyzed using logistic regression analysis. All statistical analyses were two-sided, with the statistical significance set at $p < 0.05$. Statistical analyses were performed using JMP software version 13.2 (SAS Institute Inc.).

RESULTS

Patient characteristics

Clinicopathological characteristics of the 432 lung adenocarcinoma patients are listed in Table 1. Among them, 222 were men and the median age was 71.7 years. The median Brinkman index was 125. Altogether, 299 patients had comorbidities, with CCI categorized as 0 in 232 patients, one in 87, two in 81, three in 29, and four in three. The median CEA level was 3.3 ng/ml, median NLR was 2.27, and median SUV_{max} was 2.21. The resected pulmonary lobes

TABLE 1 Patient characteristics

Variables	Values
Gender (male/female)	222/210
Age, medial, range (y)	71.7 (22–92)
Comorbidity	299 (69.2%)
Charlson comorbidity index (0/1/2/3/4)	232/87/81/29/3
Brinkman index, median (range)	125 (0–2550)
CEA, median, range (ng/ml)	3.3 (0.5–165.6)
NLR, median (range)	2.27 (0.48–24.51)
SUV_{max} of tumor	2.21 (0–46.8)
Lobe of tumor (RU/RM/RL/LU/LL)	130/21/103/105/73
Operative approach (Open/VATS/RATS)	25/357/50
Operative procedure (Wedge/Seg/Lob/Lob+CW/Lob+Seg/SLob/Bilob)	79/84/260/1/5/2/1
Pathological stage (0/IA1/IA2/IA3/IB/IIA/IIB/IIIA/IIIB/IVA/yIA1)	50/115/115/47/45/6/23/25/2/1/3
Lymphatic invasion (absent/present)	322/110
Vascular invasion (absent/present)	294/138
Maximum pathological tumor diameter (mm)	19 (2–130)
Pathological invasive area of tumor (mm)	15 (0–111)
ITR	0.94 (0–1)

Abbreviations: Bilob, bilobectomy; CEA, carcinoembryonic antigen; CW, chest wall resection; ITR, invasive area to tumor diameter ratio on pathological finding; LL, left lower; Lob, lobectomy; LU, left upper; NLR, neutrophil-to-lymphocyte ratio; Open, open thoracotomy; RATS, robotic-assisted thoracic surgery; RL, right lower; RM, right middle; RU, right upper; Seg, segmentectomy; SLob, sleeve lobectomy; SUVmax, maximum of standardized uptake value; VATS, video-assisted thoracic surgery; Wedge, wedge resection; y, yield to treatment.

included the right upper lobe in 130 patients, right middle lobe in 21, right lower lobe in 103, left upper lobe in 105, and left lower lobe in 73.

Operative factors and postoperative complications

VATS was performed in 357 patients, RATS in 50, and open thoracotomy in 25. Wedge resection was performed in 79 patients, segmentectomy in 84, lobectomy in 260, lobectomy combined chest wall resection in one, lobectomy combined segmentectomy in five, sleeve lobectomy in two, and bilobectomy in one. Postoperative complications were observed in 100 patients (23.1%).

Pathological factors

Pathological stage was categorized as stage 0 in 50 patients, IA1 in 115, IA2 in 115, IA3 in 47, IB in 45, IIA in six, IIB in 23, IIIA in 25, IIIB in two, IV in one, and yield to treatment (y)IA in three. Lymphatic invasion was present in 110 patients, and vascular invasion was present in 138. The median maximum tumor diameter was 19 mm, the median tumor invasive area was 15 mm, and the median ITR was 0.94.

Univariate and multivariate analysis

First, relationships between clinicopathological characteristics or operative factors of the patients and recurrence were analyzed (Table 2). The cutoff values of factors associated with recurrence were calculated using ROC curve analysis. The following cutoff values were determined: NLR, 2.26; SUV_{max}, 3.05; and ITR, 0.85. Smoking status ($p = 0.01$), NLR ($p = 0.03$), SUV_{max} ($p < 0.01$), and ITR ($p < 0.01$) were significantly different in the univariate analysis among patients stratified by recurrence.

TABLE 2 Univariate and multivariate analysis of risk factor for recurrence

Univariate analysis					Multivariate analysis		
Variables		**Odds ratio**	**95% CI**	***p*-value**	**Odds ratio**	**95% CI**	***p*-value**
Gender	Male	0.81	0.450–1.484	0.50			
Age	≥75	1.27	0.684–2.364	0.44			
Charlson comorbidity index	≥3	1.12	0.377–3.360	0.83			
Smoking status	BI ≥600	0.43	0.213–0.868	0.01	0.34	0.162–0.714	<0.01
CEA	>5	1.00	0.520–1.942	0.98			
NLR	>2.26	1.97	1.059–3.672	0.03	1.51	0.778–2.937	0.22
SUV_{max}	>3.05	3.62	1.923–6.813	<0.01	3.05	1.547–6.024	<0.01
Operative approach	TS	0.63	0.343–1.177	0.15			
Operative procedure	Lobectomy or more	1.59	0.828–3.058	0.16			
Lymphatic invasion	present	0.72	0.349–1.507	0.39			
Vascular invasion	present	1.70	0.930–3.126	0.08			
Pathological invasive area	≤30 mm	0.54	0.248–1.207	0.13			
ITR	≥0.85	6.76	2.814–16.270	<0.01	5.44	2.219–13.355	<0.01

Abbreviations: BI, Brinkman index; CEA, carcinoembryonic antigen; CI, confidence interval; ITR, invasive area to tumor diameter ratio; NLR, neutrophil-to-lymphocyte ratio; SUV, standardized uptake value; TS, thoracoscopic surgery.

Furthermore, smoking status (odds ratio [OR]: 0.34, 95% confidence interval [CI]: 0.16–0.71, $p < 0.01$), SUV_{max} (OR: 3.05, 95% CI: 1.54–6.02, $p < 0.01$), and ITR (OR: 5.44, 95% CI: 2.21–13.35, $p < 0.01$) were risk factors for recurrence in the multivariate analysis.

TABLE 3 Patient characteristics with pathological stage IA

Variables	Values
Gender (male/female)	136/130
Age, medial, range (y)	71.7 (22–92)
Comorbidity	194 (72.9%)
Charlson comorbidity index (0/1/2/3/4)	142/50/54/18/2
Brinkman index, median (range)	0 (0–2550)
CEA, median, range (ng/ml)	2.9 (0.6–54.9)
NLR, median (range)	2.15 (0.53–6.99)
SUV_{max} of tumor	1.8 (0.49–23.35)
Lobe of tumor (RU/RM/RL/LU/LL)	75/14/61/73/43
Operative approach (Open/VATS/RATS)	9/222/35
Operative procedure (Wed/Seg/Lob/Lob+CW/Lob+Seg/SLob)	52/57/154/1/1/1
Pathological stage (IA1/IA2/IA3)	102/111/53
Lymphatic invasion (absent/present)	218/48
Vascular invasion (absent/present)	208/58
Maximum pathological tumor diameter (mm)	17.5 (4–130)
Pathological invasive area of tumor (mm)	13 (0–30)
ITR	0.9 (0–1)

Abbreviations: CEA, carcinoembryonic antigen; CW, chest wall resection; ITR, invasive area to tumor diameter ratio on pathological finding; LL, left lower; Lob, lobectomy; LU, left upper; NLR, neutrophil-to-lymphocyte ratio; Open, open thoracotomy; RATS, robotic-assisted thoracic surgery; RL, right lower; RM, right middle; RU, right upper; Seg, segmentectomy; Slob, sleeve lobectomy; SUVmax, maximum of standardized uptake value; VATS, video-assisted thoracic surgery; Wed, wedge resection.

Subanalysis

We next evaluated prognostic factors for lung adenocarcinoma patients with pathological stage IA disease in a subanalysis. Clinicopathological characteristics of the 266 lung adenocarcinoma patients with pathological stage IA disease are listed in Table 3. The median NLR was 2.15, and the median SUV_{max} was 1.80. Pathological stage was categorized as stage IA1 in 102 patients, IA2 in 111, and IA3 in 53. The median maximum tumor diameter was 17.5 mm, the median tumor invasive area was 13 mm, and the median ITR was 0.9. Relationships between clinicopathological

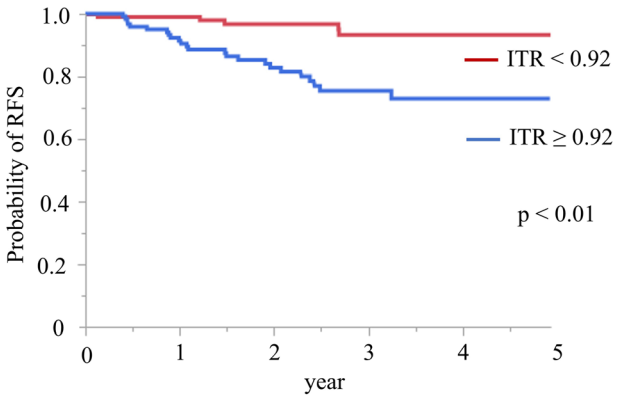

FIGURE 2 Relapse free survival for non-small cell lung cancer patients with pathological stage IA. The prognoses significantly differed between in the group of invasive area to tumor ratio (ITR) divided by 0.92

TABLE 4 Univariate and multivariate analysis of risk factor for recurrence in patients with pathological stage IA

Univariate analysis					Multivariate analysis		
Variables		**Odds ratio**	**95% CI**	***p* value**	**Odds ratio**	**95% CI**	***p*-value**
Gender	male	0.87	0.406–1.903	0.74			
Age	≥ 75	1.89	0.868–4.155	0.10			
Charlson comorbidity index	≥ 3	1.49	0.409–5.440	0.54			
Smoking status	BI ≥600	0.34	0.125–0.923	0.03	0.27	0.094–0.827	0.02
CEA	> 5	1.10	0.447–2.727	0.82			
NLR	> 2.26	2.30	1.029–5.175	0.04	1.87	0.778–4.492	0.16
SUV_{max}	> 3.35	3.63	1.649–7.992	<0.01	3.93	1.636–9.482	<0.01
Operative approach	TS	0.87	0.366–2.068	0.75			
Operative procedure	Lobectomy or more	1.62	0.708–3.711	0.25			
Lymphatic invasion	present	0.49	0.142–1.698	0.26			
Vascular invasion	present	1.42	0.595–3.407	0.42			
Pathological invasive area	> 20 mm	4.00	1.785–8.5967	<0.01	1.99	0.802–4.936	0.13
ITR	≥ 0.92	6.03	2.226–16.354	<0.01	4.38	1.517–12.690	<0.01

Abbreviations: BI, Brinkman index; CEA, carcinoembryonic antigen; CI, confidence interval; ITR, invasive area to tumor diameter ratio on pathological finding; NLR, neutrophil-to-lymphocyte ratio; SUV, standardized uptake value; TS, thoracoscopic surgery.

characteristics or operative factors of the patient and recurrence were then analyzed (Table 4). Cutoff values of factors associated with recurrence were calculated using ROC curve analysis. The following cutoff values were determined: NLR, 2.26; SUV_{max}, 3.35; and ITR, 0.92. Smoking status ($p = 0.03$), NLR ($p = 0.04$), SUV_{max} ($p< 0.01$), pathological invasive area ($p < 0.01$), and ITR ($p < 0.01$) were significantly different in univariate analysis. Smoking status (OR: 0.27, 95% CI: 0.09–0.82, $p = 0.02$), SUV_{max} (OR: 3.93, 95% CI: 1.63–9.48, $p < 0.01$), and ITR (OR: 4.38, 95% CI: 1.51–12.69, $p < 0.01$) were risk factors for recurrence in multivariate analysis. Figure 2 details relapse-free survival outcomes and prognoses, which were significantly different in the groups divided at ITR = 0.92 ($p < 0.01$).

DISCUSSION

In this study, we analyzed prognostic factors for patients with lung adenocarcinoma who underwent pulmonary resection. Our findings demonstrated that SUV_{max} and ITR were significant prognostic factors for recurrence in lung adenocarcinoma patients. SUV_{max} has been reported to be a predictor of recurrence in patients with surgically resected NSCLC.[21–23] Because it has been reported that the SUV_{max} of squamous cell carcinoma is higher than that of adenocarcinoma,[23–25] we analyzed the validity of using SUV_{max} as a prognostic factor only for lung adenocarcinoma in this study. We also found that SUV_{max} was a risk factor of recurrence in lung adenocarcinoma patients with pathological stage IA; therefore, SUV_{max} can be important for deciding the indication for limited resection or adjuvant chemotherapy.

Although the size of a tumor's invasive area instead of total tumor size has been defined as T factor in the eighth edition of the TNM classification,[26] the utility of ITR as a prognostic factor has not been investigated. Because CTR in CT has been reported to be a prognostic factor for early-stage NSCLC,[11–14] we made the hypothesis that ITR is a risk factor of recurrence for early-stage NSCLC. In this study, ITR was revealed to be a significant risk factor of recurrence not only in lung adenocarcinoma patients who received pulmonary resection but also in pathological stage IA lung adenocarcinoma patients. Furthermore, ITR was found to be a strong prognostic factor of recurrence in lung adenocarcinoma patients with pathological stage IA instead of pathological invasive size. After a meta-analysis in Japan showed that adjuvant chemotherapy with oral tegafur/uracil (UFT) was beneficial in patients with tumors >2 cm without node metastasis,[27,28] UFT has been recommended for NSCLC patients with pathological stage IA3 to IB disease. Therefore, ITR can be an adaptation criterion for adjuvant chemotherapy, such as UFT, for early-stage lung adenocarcinoma patients.

This study had several limitations. First, this study was retrospective in nature and potentially involved unobserved cofounding and selection biases. Second, the study was performed at a single institution, and the study population was relatively small.

In conclusion, our findings describe the prognostic factors for lung adenocarcinoma patients who underwent pulmonary resection. This study revealed that SUV_{max} and ITR are risk factors for recurrence. These results suggest that for early-stage lung adenocarcinoma patients, SUV_{max} is important for deciding the indication for limited resection or adjuvant chemotherapy and ITR is an adaptation criterion for adjuvant chemotherapy.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How to cite this article: Motono N, Mizoguchi T, Ishikawa M, Iwai S, Iijima Y, Uramoto H. Invasive area to tumor ratio is a significant prognostic factor for non-small cell lung cancer. Thorac Cancer. 2022;13(21):2935–40. https://doi.org/10.1111/1759-7714.14616