Lymph node metastasis and predictive factors in clinical stage IA squamous cell carcinoma of the lung based on radiological findings

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Abstract

Objectives

We aimed to clarify the incidence of lymph node (LN) metastasis and its predictive factors in clinical stage IA squamous cell carcinoma (SqCC) based on radiological classification to provide surgical indications for segmentectomy.

Methods

We retrospectively reviewed 192 patients with clinical stage IA SqCC who underwent complete resection with lobectomy and LN dissection at our institution between 2003 and 2019. To evaluate the incidence of LN metastasis from the perspective of indications for segmentectomy, we classified them into outer and inner groups based on the location of the tumor in the radiological findings.

Results

Regarding tumor location, 123 patients had tumors in the outer location and 69 patients had tumors in the inner location. The incidence of LN metastasis was 6% in clinical stage IA SqCC, which included 6% in the outer location and 7% in the inner location (p=0.669). In the outer location, all LN metastases were in N1 (6%), whereas in the inner location, the incidence of N1 and N2 metastasis were 6% and 1%, respectively. Only tumors sized >2.0cm were found to be significantly associated with LN metastasis in clinical stage IA SqCC.

Conclusions

We demonstrated that the incidence of LN metastasis in clinical stage IA SqCC was comparable to that of the previously

reported clinical stage IA NSCLC. The incidence of LN metastasis in the outer location was similar to that in the inner location. Tumor size was only a significant factor affecting LN metastasis in clinical stage IA SqCC.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Although lobectomy with lymph node (LN) dissection remains the standard initial therapy even in clinical stage IA non-small cell lung cancer (NSCLC), sublobar resection is indicated for some patients with clinical stage IA peripheral NSCLC, including small-sized lung cancer with ground-glass opacity (GGO). However, even in patients with clinical stage IA NSCLC, LN metastasis is sometimes observed on pathological examination. Among clinical stage IA NSCLC, the incidence of LN metastasis has been reported to be 12% –16% [1-3]. Therefore, the presence of LN metastasis is one of the most important factors in the adaptation of sublobar resection for clinical stage IA NSCLC. However, unlike adenocarcinoma, there are few factors that predict LN metastasis in squamous cell carcinoma (SqCC) of the lung [4]. Previous reports concerning LN metastasis have shown that the histological subtypes of these reports were mostly adenocarcinoma, whereas the proportion of SqCC included was very low at 3%–15% [2, 3, 5]. The Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG) conducted a randomized, phase III trial on lobectomy versus segmentectomy for small invasive peripheral lung cancer (JCOG0802/WJOG4607L). Although this trial included 1106 patients, only 73 (7%) patients had SqCC [6].

SqCC accounts for approximately 30% of all lung cancers and often arises in the central airways; it is often classified into two types based on anatomical location: peripheral and central. Recently, the tumor location based on radiological findings was found to be more useful than that based on anatomical classification in determining the indication for segmentectomy, but there have been few reports concerning LN metastasis based on radiological findings for SqCC only.

We aimed to clarify the incidence of LN metastasis and its predictive factors in clinical stage IA SqCC based on radiological classification to provide surgical indications for segmentectomy.

Materials and Methods

Patients

Between January 2003 and December 2019, 4463 consecutive patients underwent pulmonary resection for lung cancer at the National Cancer Center Hospital East (Kashiwa, Chiba, Japan). Of these, we reviewed 192 patients who were diagnosed with clinical stage IA SqCC according to the 8th edition of the Tumor-Node-Metastasis classification. In this study, patients underwent complete resection by lobectomy or greater and systemic lymphadenectomy including hilar and mediastinal node dissection. Complete resection was defined as the absence of residual cancer, both macroscopically and microscopically (R0). We excluded patients who met the following criteria: (1) preoperative therapy, (2) surgical history of lung cancer, (3) tumor located in bronchi as observed on CT findings, (4) synchronous multiple lung cancer, or (5) second primary lung cancer. To evaluate the difference in the incidence of LN metastasis and clinicopathologic characteristics based on the tumor location in clinical stage IA SqCC, we classified patients with clinical stage IA SqCC into the outer and inner locations based on radiological findings. We reviewed their medical records for the following clinicopathological factors: age, sex, smoking, carcinoembryonic antigen (CEA), serum cytokeratin-19 fragment

(CYFRA), maximum standardized uptake values (SUVmax), location, laterality, tumor size, clinical T factor (cT), pathological T factor (pT), N factor (pN), lymphatic infiltration, vascular invasion, and pleural invasion.

Radiological evaluation

Contrast-enhanced computed tomography (CT) scans at 5–10 mm collimation of the chest and upper abdomen were obtained to assess the clinical staging of all patients with lung cancer. Additionally, thin-sliced CT images at 1- to 2-mm collimation were reconstructed to evaluate the primary tumor size. The X-vigor CT system (Toshiba Medical Systems, Tokyo, Japan) was used to obtain the CT scans, and the CT images were evaluated on a monitor display with a window level of 600 HU and a window width of 1800 HU. Clinical LN staging was determined by contrast CT, positron emission tomography (PET), or both. A LN was diagnosed as a node-positive LN when the SUVmax was > 2.5 or the short axis was > 1.0 cm on thin-sliced CT. However, patients with abnormal and bilateral accumulation were considered false-positive and were not therefore excluded. PET or mediastinoscopy was not routinely performed preoperatively to confirm LN metastasis during the study period. In addition, most patients underwent systemic work-up, including contrast-enhanced brain magnetic resonance imaging or CT and bone scintigraphy. If patients underwent PET of the whole body, bone scintigraphy was often omitted. For this study, we restaged all cases according to the 8th edition of the Tumor-Node-Metastasis classification.

We classified SqCC located in outer and inner tumors based on a previous report by Nakamura et al. [7]. A tumor that was located in the outer one-third of the lung field on CT findings were considered “outer”, whereas those located in the

inner two-thirds of the lung were considered “inner”.

Pathological evaluation

The resected specimens were fixed with 10% formalin and embedded in paraffin. Serial 4-μm sections were stained with hematoxylin and eosin (HE). The Victoria blue-van Gieson (VVG) method was used to visualize the elastic fibers. Vascular invasion and lymphatic infiltration were histologically diagnosed by HE and VVG staining, and pleural invasion was evaluated by VVG staining. Pleural invasion was considered to be present when tumor cells were identified beyond the elastic layer of the visceral pleura, regardless of tumor exposure on the pleural surface. Histological analysis of LN metastasis was performed by HE stain. We also defined LN that was in direct contact with the tumor completely or partly connected as a direct pattern. On the other hand, we did not define LN with mediastinal or other N1 LN metastases as a direct pattern. Histologic type was reviewed according to the 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart [8].

Statistical Analysis

We used the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Univariate and multivariate regression analyses was conducted to identify the predictive factors for LN metastasis. A *p-value* of less than 0.05 was defined to indicate statistical significance. Data were analyzed using JMP for Macintosh version 16 (SAS Institute Inc., Cary, NC, USA).

Ethical consideration

All studies involving human participants were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. This study was approved by the Institutional Review Board of the National Cancer Center, Japan (IRB number: 2017-418), and the requirement for informed consent was waived. All extracted clinicopathological data were obtained from the database.

Results

Clinical characteristics of patients

The patients included 164 (85%) men and 28 (15%) women, with a median age of 71 years (range, 54–83 years). A total of 191 (99%) patients were current or past smokers, and only one patient was a never smoker. Tumor laterality was right in 109 (57%) patients and left in 83 (43%) patients. PET was performed in 95 (49%) patients. The median SUVmax was 7.30 (range, 1.40-21.13). Lobectomy was performed in all patients, only one of whom underwent bilobectomy. Systemic lymphadenectomy was performed as ND2a-1 in 104 (54%) patients and ND2a-2 in 88 (46%) patients. The median tumor size was 2.1 cm (range, 0.9–3.0 cm). In the clinical T classification, two patients (1%) had cT1a disease, 90 patients (47%) had cT1b disease, and 100 patients (52%) had cT1c disease. Regarding tumor location, 123 patients (62%) had tumors in the outer location and 69 patients (38%) had tumors in the inner location. Table 1 shows the correlation between tumor location and other clinical factors. There was no statistically significant difference between the two locations in terms of

clinical characteristics.

Incidence of lymph node metastasis

Lymph node metastasis was observed in 12 patients (6%) with clinical stage IA SqCC, of whom seven (6%) with the outer location had LN metastasis and five (7%) with the inner location had LN metastasis (p=0.669). There was no statistically significant difference regardless of the tumor location. Pathological factors are listed in Table 2. In the outer location, seven patients (6%) were diagnosed with pN1, and none were diagnosed with pN2, whereas in the inner location, four patients (6%) were diagnosed with pN1, and one patient (1%) were diagnosed with pN2. A significantly higher pleural invasion was detected in the outer location than in the inner location (p<0.001). Only one patient had direct LN metastasis in the outer location and two patients in the inner location. Patients with a tumor in the inner location and with N2 metastasis had not only mediastinal LN metastasis, but also intrapulmonary and hilar LN metastasis with no skip LN metastasis. The details of LN metastasis based on the tumor-dominant lobe are shown in Supplemental Table 1. In the inner location, mediastinal LN metastasis was found in one patient in the right lower lobe.

Associated clinical factors of lymph node metastasis

Table 3 shows the clinical factors associated with LN metastasis in patients with clinical stage IA SqCC. Univariate and multivariate analyses showed that tumor size was significantly associated with LN metastasis alone. When stratified by tumor size, the incidence of LN metastasis was 2% in tumors 2 cm or less in diameter and 10% in patients with tumors > 2 cm in diameter. Therefore, we compared the incidence of LN metastasis between the peripheral and central locations by

tumor size, but there was no significant difference between the two locations in either size (Supplemental Table 2). The analysis was limited to 95 patients who underwent PET at our institution, and we performed univariate analysis. However, the SUVmax of the tumor was not identified as a predictive factor ($p = 0.264$).

Discussion

In our study, we found the incidence of LN metastasis in clinical stage IA SqCC based on CT findings to be 6%. This study is one of the few reports showing the incidence of LN metastasis and its predictive factor in many clinical stage IA SqCC cases based on radiological findings. In adenocarcinoma, many predictive factors of LN metastasis such as the presence of GGO and SUVmax on PET have been reported [9-11], and it is reasonable to perform segmentectomy for these patients. On the other hand, there are few reports on early stage SqCC regarding the incidence and predictive factors of LN metastasis. As shown in Table 4, 6%–14% of patients with clinical stage IA SqCC reportedly had LN metastasis. These previous reports presented the classification based on radiological findings or anatomical findings. Peripheral SqCC defined anatomical classification in their report was based on bronchial bifurcation and implied a tumor in branches more peripheral than the subtertiary bronchus. Conversely, the classification in our study is based on the surgical procedure rather than oncological aspects. Although we cannot unequivocally compare the incidence of LN metastasis in outer SqCC based on radiological findings with that in anatomical findings, the incidence of LN metastasis in our study was similar to that reported in previous studies based on radiological findings. A study strength is our clarification of predictive factors

for lymph node metastasis and relationship with the tumor location on CT findings for squamous cell carcinoma only. These data may help inform surgical procedure selection for patients undergoing lung resection for squamous cell carcinoma.

In our study, tumor size was a predictive factor for LN metastasis. Some reports have indicated increased incidence of LN metastasis in stage I NSCLC with an increase in tumor size [2, 12]. Deng et al. reported that the pattern of LN metastasis in clinical stage IA peripheral NSCLC was significantly influenced by tumor size [2]. NSCLC ≤1 cm had no LN metastasis (0%), whereas NSCLC >2 cm, but ≤3 cm had a significantly higher incidence of LN metastasis (24%). Our study also found that the incidence of LN metastasis with tumor size >2 cm was higher than that with tumor size ≤2 cm (12% vs. 4%); therefore, tumor size is one of the most important predictive factors for LN metastasis regardless of the tumor location. In particular, segmentectomy will be appropriate only for SqCC in the peripheral location from the viewpoint of margin because SqCC is a solid tumor and is more likely to be centrally located than adenocarcinoma.

It is important to adequately resolve controversial issues concerning the choice of resection of peripheral small early NSCLC. Although there has been considerable discussion about limited resection for lung cancer with GGO component, sublobar resection for lung cancer with a solid appearance on CT is controversial. Koike et al. reported similar oncologic outcomes after lobectomy and segmentectomy among patients with radiologically pure solid NSCLC of ≤2 cm [13]. Conversely, it was reported that small size (≤ 2 cm) NSCLC has a poor prognosis in solid tumors [14]. A systematic review and meta-analysis showed that segmentectomy maybe a valuable alternative to lobectomy for NSCLC in tumors ≤ 2 cm in

size. However, it did not find significant differences in oncological outcomes for patients in stage IA included tumor sizes >2 cm [15].

The JCOG and the Cancer and Leukemia Group B (CALGB) trials, both of which included solid tumors ≤2 cm in size, should help thoracic surgeons decide the indication for sublobar resection of early NSCLC. In previous reports on the prognosis of segmentectomy for patients with early stage NSCLC, the most frequent histological type of patients included was adenocarcinoma[13]; therefore, it is not clear whether segmentectomy for patients with early SqCC is useful. The JCOG0802 had a very low proportion of SqCC at 7% [6], and even if this trial demonstrated non-inferiority of segmentectomy for patients with peripheral NSCLC with a tumor size ≤2 cm, segmentectomy may not be applicable to patients with SqCC. A prospective study involving only patients with SqCC may be needed to clarify the usefulness of segmentectomy for patients with peripheral stage IA SqCC.

We confirmed that patients with LN metastasis in clinical stage IA SqCC in the outer location had interpulmonary or hilar LN and no mediastinal LN metastasis in all cases. Some reports, which included a small number of peripheral SqCC (n=40 and 22), showed that the incidence of mediastinal LN metastasis in small (≤2 cm) peripheral SqCC was rare and indicated that mediastinal LN dissection could be omitted [16, 17]. Based on the abovementioned report and our study, it may be possible to perform segmentectomy in patients with clinical stage IA peripheral SqCC, confirming the absence of hilar LN metastasis intraoperatively. Moreover, occult N2 metastasis, which is defined as an intraoperative or postoperative pathologically positive mediastinal LN in clinical N0 or N1 patients by CT or PET, is an important indicator of the surgical

procedure. Several studies have confirmed that adenocarcinomas are associated with a high risk of occult N2 metastasis [18, 19]. In our study, the incidence of mediastinal LN metastasis was very low, especially in patients with small SqCC (<2 cm) in the outer location; therefore, mediastinal LN dissection may be omitted.

The present study has some limitations. First, the presented data were derived from a single institution, and there were not enough cases, especially the number of node-positive patients. In stage IA, the proportion of SqCC in NSCLC was very low, and many patients with SqCC are needed to statistically validate the incidence of LN metastasis. Therefore, multicenter data including patients with clinical stage IA SqCC are necessary to reach definitive conclusion. Second, as PET was not routinely performed for preoperative staging in all cases, preoperative assessment of LN metastasis and staging for indication of surgery may be inaccurate. In addition, the lymph node was not considered as metastatic on PET if the patient had abnormal and bilateral uptake of FDG. Finally, we drew our conclusions from the incidence of LN metastasis without survival analysis. The impact of our conclusions on long-term oncological outcomes remains unclear.

Conclusions

we demonstrated the incidence of LN metastasis in clinical stage IA SqCC, which was comparable to the previously reported clinical stage IA NSCLC. The incidence of LN metastasis in the outer location was similar to that in the inner location. Tumor size was only a significant factor affecting LN metastasis in clinical stage IA SqCC.

Conflict of interest statement

Conflict of interest: none declared.

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Table 1. Clinical characteristics of clinical stage IA squamous cell carcinoma

	Outer		Inner		
	n=123	(%)	n=69	(%)	p Value
Age (years)					
Median (range)	72	(58-83)	71	(54-82)	0.541[a]
Sex					
Male	104	(85)	60	(87)	0.651
Female	19	(15)	9	(13)	
Smoking					
Positive	122	(99)	69	(100)	0.453
Negative	1	(1)	0	(0)	
CEA (ng/mL)					
≤ 5.0	94	(76)	21	(70)	0.299
>5.0	29	(24)	48	(30)	
CYFRA (ng/mL)					
≤ 3.5	107	(87)	56	(81)	0.279
>3.5	16	(13)	13	(19)	
SUVmax [b]					
Median (range)	7.13	(1.4-21.13)	7.98	(2.6-19.7)	0.477[a]
Tumor laterality					
Right	67	(54)	42	(61)	0.391
Left	56	(46)	27	(39)	
Tumor size (cm)					
Median (range)	2.1	(0.9-3)	2	(1-3)	0.895[a]
cT classification					
T1a	1	(1)	1	(2)	0.792
T1b	56	(45)	34	(49)	
T1c	66	(54)	34	(49)	

CEA carcinoembryonic antigen, CYFRA serum cytokeratin-19 fragment, SUVmax maximum standardized uptake values

[a] Mann-Whitney U test

[b] SUVmax was examined in a total of 95 patients.

Table 2. Pathological characteristics of clinical stage IA squamous cell carcinoma

	Outer		Inner		
	n=123	(%)	n=69	(%)	p Value
Tumor size (cm)					
Median (range)	2.2	(1.1-3.6)	2	(0.7-3.5)	0.445[a]
pT classification					
T1a	0	(0)	2	(3)	0.284
T1b	51	(42)	35	(51)	
T1c	42	(34)	19	(27)	
T2a	26	(21)	11	(16)	
T3	3	(2)	2	(3)	
T4	1	(1)	0	(0)	
pN classification					
N0	116	(94)	64	(93)	0.408
N1	7	(6)	4	(6)	
N2	0	(0)	1	(1)	
Lymphatic infiltration					
Absent	112	(91)	66	(96)	0.240
Present	11	(9)	3	(4)	
Vascular invasion					
Absent	81	(66)	39	(57)	0.200
Present	42	(34)	30	(43)	
Pleural invasion					
Absent	95	(77)	66	(96)	<0.001
Present	28	(23)	3	(4)	

[a]Mann-Whitney U test

Table 3. Association of clinical factors with lymph node metastasis in clinical stage IA squamous cell carcinoma

	Total	LN Metastasis	Univariate Analysis			Multivariate Analysis		
	n=192	n(%)	OR	95% CI	P Value	OR	95% CI	P Value
Age (years)								
Age (continuous variable)			1.026	0.933 – 1.127	0.587			
Sex								
Male	164	9(5)	Reference			Reference		
Female	28	3(11)	2.066	0.523 – 8.159	0.300	1.848	0.457 – 7.475	0.389
CEA (ng/mL)								
≤ 5.0	142	8(6)	Reference					
>5.0	50	4(8)	1.456	0.418 – 5.063	0.554			
CYFRA (ng/mL) [a]								
≤ 3.5	163	9(6)	Reference					
>3.5	29	3(10)	1.974	0.501 – 7.778	0.331			
Location								
Outer	123	7(6)	Reference					
Inner	69	5(7)	1.294	0.394 – 4.245	0.670			
Tumor laterality								
Right	109	7(6)	Reference					
Left	83	5(6)	0.934	0.285 – 3.055	0.910			
Tumor size (cm)								
≤ 2.0	92	2(2)	Reference			Reference		
>2.0 and ≤ 3.0	100	10(10)	5.000	1.065 – 23.464	0.041	4.842	1.028 – 22.802	0.046

CEA carcinoembryonic antigen, CYFRA serum cytokeratin-19 fragment, LN lymph node

Table 4. Previous reports on lymph node metastasis of clinical stage IA squamous cell carcinoma

Author	n	procedure	LN evaluation	Tumor location		Size (cm)	Lymph node metastasis					
					classification		N0		N1		N2	
Asamura[16] (1996)	44	L, P	CT	peripheral	NM	≤3	38	(86)	1	(2)	5	(12)
						≤2	15	(94)	0	(0)	1	(6)
Watanabe[17] (2001)	20	L	CT	peripheral	NM	≤2	18	(90)	2	(10)	0	(0)
Tsutani[4] (2014)	100	S, L	CT, PET	NM	CT	≤3	88	(88)	10	(10)	2	(2)
Sakairi[1] (2019)	52	S, L	CT, PET	peripheral	CT	≤3	47	(88)	3	(6)	2	(6)

LN, lymph node; L: lobectomy; S, segmentectomy; P, pneumonectomy; CT, computed tomography; PET, positron emission tomography; NM, not mentioned

Supplemental Table 1. Distribution of lymph node metastasis based on the tumor location.

	Outer						Inner					
	N0	(%)	N1	(%)	N2	(%)	N0	(%)	N1	(%)	N2	(%)
Right upper lobe	27	(96)	1	(4)	0		18	(90)	2	(10)	0	
Right middle lobe	4	(100)	0		0		5	(100)	0		0	
Right lower lobe	34	(94)	2	(6)	0		16	(88)	1	(6)	1	(6)
Left upper lobe	22	(96)	1	(4)	0		15	(94)	1	(6)	0	
Left lower lobe	29	(91)	3	(9)	0		10	(100)	0		0	(0)

Supplemental Table 2. Lymph node metastasis based on the tumor location and tumor size

Tumor Size (cm) ≤ 2.0					
		Lymph node metastasis			
	Total	Positive		Negative	
	n	n	(%)	n	(%)	p-Value
Outer	57	1	(2)	56	(98)	0.724
Inner	35	1	(3)	34	(97)	
Tumor Size (cm) ＞ 2.0 and ≤ 3.0					
		Lymph node metastasis			
	Total	Positive		Negative	
	n	n	(%)	n	(%)	p-Value
Outer	66	6	(9)	60	(91)	0.673
Inner	34	4	(12)	30	(88)	