Clinicopathological features of small-sized peripheral squamous cell lung cancer

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Abstract. Recent advances in imaging technology have enhanced the detection rate of small-sized peripheral lung cancers. The present study aimed to identify the clinicopathological differences between patients with small-sized peripheral squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Patients with lung cancer who underwent radical surgical resection at Gunma University Hospital between July 2007 and October 2012 were retrospectively analyzed. Patients who exhibited small-sized peripheral tumors (pathological size, ≤2 cm) located within the outer-third of the lung field on preoperative computed tomography were enrolled in the present study. A total of 26 patients were diagnosed with SCC and 214 with ADC. The results revealed that patients with SCC exhibited higher rates of pleural invasion, vascular invasion and lymphatic invasion compared with ADC patients. Additionally, the rate of postoperative recurrence was higher in patients with SCC compared with ADC patients. Patients with ADC were subsequently into two groups: Solid ADCs (sADC) and non-solid ADCs (nsADC), which included pure ground glass nodules and part-solid ADCs. The results revealed that the incidence of pleural invasion, vascular invasion and lymphatic invasion, and the rate of postoperative recurrence in patients with sADCs were similar to those with SCC, but were also significantly higher when compared with nsADC patients. The present study concluded that patients with SCC and sADC may not be suitable candidates for sublobar resection, despite exhibiting small tumors that are located in the peripheral lung.

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Introduction

Recent advances in imaging technology have enhanced the detection rate of small-sized peripheral lung cancers. Prior studies that analyzed the relationship between tumor size and prognosis revealed a favorable prognosis for small-sized tumors, especially those ≤2 cm in diameter (1,2). Both randomized and non-randomized studies have revealed good outcomes for patients who underwent sublobar resection of these small-sized tumors (3,4).

Squamous cell carcinoma (SCC) used to be a representative histological type of centrally-located lung cancer, but recent studies have reported an increase in peripherally-located SCCs. The incidence of peripherally-located SCCs, which was 15-30% around 25 years ago (5,6), increased to nearly 50% of diagnosed or resected SCC cases (7). Previous reports have revealed a difference in clinicopathological features between central-type and peripheral-type SCCs (8,9). A retrospective study showed that peripheral-type SCC had lower pathological stage, less lymphatic and vessel involvement, and less lymph node metastasis, but no significant difference in overall survival compared with central-type SCC (8). However, the frequency of lymph node metastasis in peripheral-type SCC differs between reports (10-12), and current information is insufficient to define the malignant potential or prognosis of such small-sized peripheral SCCs.

Most previous studies defined peripheral tumors as tumors located in or more peripheral to the fourth branching bronchus (12,13). However, this definition is difficult to use in clinical practice, and several studies of sublobar resection have thus defined peripheral tumors as tumors located within the outer third of the lung field on preoperative computed tomography (3,4), which is an easier clinical definition. However, no study has reported on the use of this definition to compare the clinicopathological and prognostic features of peripheral SCC and peripheral adenocarcinoma (ADC).

We therefore investigated the malignant potential of small-sized peripheral SCC by retrospectively comparing its clinicopathological features with those of ADC in surgically resected cases, based on the definition of 'peripheral' as the outer third of the lung field on preoperative computed tomography.

Patients and methods

Patients. We retrospectively analyzed lung cancer patients who underwent radical surgical resection at Gunma University Hospital (Maebashi, China) between July 2007 and October 2012. We included all patients with tumors located within the outer third of the lung field on preoperative computed tomography, which were ≤2 cm in pathological size. Because our study mainly focuses on pathological characteristics, we used more accurate pathological size in this study rather than clinical size like other reports (12,14). Because the aim of this study is to investigate the malignant potential of tumor itself, and not the prognostic value, we included all surgical procedures; i.e., lobectomy, segmentectomy, and wedge resection. Standard procedure was lobectomy but segmentectomy was mainly applied for tumor with predominant ground glass nodule (GGN) component and wedge resection was applied for the patients with poor performance status or pulmonary function.

Medical records for each patient were reviewed for the following clinical data: Age, sex, smoking history, disease history, procedure of operation, pathological tumor size, pleural invasion, vascular invasion, lymphatic invasion, recurrence. Because our study included cases of wedge resection with no lymph node dissection, we did not include the information of pathological lymph node metastasis. We focused our analysis on the malignant potential of the primary tumor.

The present study was approved by the Institutional Review Board of Gunma University Hospital (approval no. 2017-027). Written informed consent was obtained from all patients prior to enrolment.

Statistical analysis. Associations between histological type and clinicopathological features were analyzed using χ^2, Fisher's, or *t*-tests. A two-sided value of P<0.05 was considered statistically significant. All analyses were performed using SPSS 25 (IBM Co., Chicago, IL, USA).

Results

Clinical characteristics. Twenty-six patients were diagnosed with SCC and 214 with ADC. The clinical characteristics of the patients are shown in Table I. Patients with SCC were significantly older than those with ADC (74 years vs. 65 years; P<0.01), and 80% of SCC patients were male and almost all were smokers, compared with only half of ADC patients being male and smokers, respectively. There was no significant difference in the prevalence of coexisting or previously treated other cancers (46% vs. 34%; P=0.19) or lung comorbidities (27% vs. 14%; P=0.07) between the two groups. Wedge resection was performed more frequently in SCC compared with ADC patients (31% vs. 13%, respectively), while segmentectomy was performed more frequently in ADC compared with SCC patients (25% vs. 12%, respectively).

Pathological characteristics. The pathological characteristics of the patients are shown in Table II. SCC tumors tended to be larger than ADC tumors, but the difference was not significant (1.59±0.36 vs. 1.43±0.39 P=0.05). The incidences of pleural invasion (33% vs. 13%; P<0.01), vascular invasion (50% vs. 15%; P<0.01), and lymphatic invasion (50% vs. 19%; P<0.01) were significantly higher in the SCC compared with the ADC group.

Postoperative recurrence. The median follow-up periods were 38.5 months for SCC patients and 58.0 months for ADC patients (Table III). The rate of postoperative recurrence was higher in SCC compared with ADC patients (23% vs. 10%; P=0.04). SCC tended to be associated with distant metastases whereas ADC was associated with locoregional metastases, though there was no significant difference in the pattern of recurrence (P=0.08).

Comparison between SCC and two types of ADC. Because ADCs with GGN component are well known to be tumors with good prognosis, we divided ADCs into two groups; solid ADC (sADC) and non-solid ADC (nsADC) including pure GGN and part-solid GGN. There was no SCC with GGN feature. The incidences of pleural invasion, vascular invasion, and lymphatic invasion of SCC were similar with sADC but significantly higher compared with the nsADC group (Table IV). The rate of postoperative recurrence was similar with sADC but significantly higher compared with the nsADC group (Table V).

Discussion

In this study, we retrospectively examined the clinicopathological features of small-sized peripheral SCC in relation to its malignant potential. The incidences of pleural invasion, vascular invasion, and lymphatic invasion were all significantly higher in SCC compared with ADC, and SCC patients had a significantly higher postoperative recurrence rate when compared with ADC patients. However, there was no difference when we compared between SCC and sADC.

Previous studies have shown various results regarding the malignancy of peripheral SCC. The studies which compared peripheral and central SCC revealed that growth pattern, morphology, and immunophenotype differ between peripheral and central SCC, although there was no difference in prognosis (8,9). The studies which compared SCC and ADC showed that small-sized peripheral SCC had a poorer prognosis than ADC (15,16). In this study, we analyzed the malignant potential limited to peripheral small-sized tumor according to CT definition. We analyzed only post-operative recurrence and our results showed that SCC patients had a higher postoperative recurrence rate compared with ADC patients. Because various previous studies including ours of small-sized peripheral SCC contained small sample size, further large-scale analysis is required for further conclusion.

The present study found significantly higher incidences of pleural invasion, vascular invasion, and lymphatic invasion in patients with SCC compared with ADC. Visceral pleural invasion has been reported as a factor associated with poor prognosis, and the presence of pleural invasion increased the T stage from T1 to T2 in a recent TNM classification (17-19). Several reports suggested a possible cancer cell pathway from a tumor with pleural invasion through the pleural cavity and subpleural lymphatics and from hilar lymph nodes into the mediastinal lymph nodes (17,20). Vascular invasion was

Table I. Clinical characteristics of patients with SCC and ADC.

Variables	SCC (n=26)	ADC (n=214)	P-value
Median age, years (range)	74 (59-82)	65 (33-87)	<0.01
Sex			
Male	21 (81%)	108 (50%)	<0.01
Female	5 (19%)	106 (50%)	
Smoking history			
Never	1 (4%)	99 (46%)	<0.01
Current or former	25 (96%)	114 (54%)	
Lung comorbidity			
Absent	19 (73%)	185 (86%)	0.07
Present	7 (27%)	29 (14%)	
COPD	3	25	
IP	3	3	
CPFE	1	1	
Coexisting or previously treated other cancer			
Absent	14 (54%)	142 (66%)	0.19
Present	12 (46%)	72 (34%)	
Surgical procedure			
Lobectomy	15 (58%)	133 (62%)	0.05
Segmentectomy	3 (12%)	53 (25%)	
Wedge resection	8 (31%)	28 (13%)	

SCC, squamous cell carcinoma; ADC, adenocarcinoma; COPD, chronic obstructive pulmonary disease; IP, interstitial; CPFE, combined pulmonary fibrosis and emphysema.

Table II. Pathological characteristics of patients with SCC and all ADC.

Variables	SCC (n=26)	ADC (n=214)	P-value
Mean tumor size ± SD (mm)	1.59±0.36	1.43±0.39	0.05
Pleural invasion			
Negative	16 (67%)	185 (87%)	<0.01
Positive	8 (33%)	27 (13%)	
Vascular invasion			
Negative	12 (50%)	179 (85%)	<0.01
Positive	12 (50%)	32 (15%)	
Lymphatic invasion			
Negative	12 (50%)	171 (81%)	<0.01
Positive	12 (50%)	40 (19%)	

SCC, squamous cell carcinoma; ADC, adenocarcinoma; SD, standard deviation.

Table III. Postoperative recurrence and survival rates of patients with SCC and all ADC.

Variables	SCC (n=26)	ADC (n=214)	P-value
Median follow-up period (months)	38.5	58.0	
Recurrence			
Absent	20 (77%)	193 (90%)	0.04
Present	6 (23%)	21 (10%)	
Pattern of recurrence			
Locoregional	2	15	0.08
Distant	3	3	
Both simultaneously	1	3	

SCC, squamous cell carcinoma; ADC, adenocarcinoma.

identified as a poor-prognosis factor, even in stage IA non-small cell lung cancer, because of a higher rate of distant metastasis (21-23). Lymphatic invasion was also related to a poor prognosis in stage IA non-small cell lung cancer (24,25), and several studies found that lymphatic invasion was correlated with a higher rate of lymph node metastasis (26). The association between small-sized peripheral SCC and these malignant factors may contribute to its higher postoperative recurrence rate.

Several reports have shown a favorable prognosis for ADC with GGN component compared with solid ADC (27,28). Similarly, our results showed worse malignant potential of solid ADC compared with ADC with GGN component. The

Table IV. Pathological characteristics of patients with SCC and two groups of patients with ADC.

Variables	SCC (n=26) (%)	sADC (n=61) (%)	nsADC (n=153) (%)	P-value†	P-value‡
Pleural invasion					
Negative	16 (67)	42 (69)	143 (95)	<0.01	<0.01
Positive	8 (33)	19 (31)	8 (5)		
Vascular invasion					
Negative	12 (50)	35 (58)	144 (95)	<0.01	<0.01
Positive	12 (50)	25 (42)	7 (5)		
Lymphatic invasion					
Negative	12 (50)	34 (57)	137 (91)	<0.01	<0.01
Positive	12 (50)	26 (43)	14 (9)		

†P-value comparing the SCC group with the nsADC group; ‡P-value comparing the sADC group with the nsADC group. SCC, squamous cell carcinoma; sADC, solid adenocarcinoma; nsADC, non-solid adenocarcinoma.

Table V. Postoperative recurrence and survival rates of patients with SCC and two groups of patients with ADC.

Variables	SCC (n=26)	sADC (n=61)	nsADC (n=153)	P-value†	P-value‡
Median follow-up period (months)	38.5	56.2	59.6		
Surgical procedure					
Lobectomy	15 (58%)	46 (75%)	87 (57%)	0.06	0.06
Segmentectomy	3 (12%)	9 (15%)	44 (29%)		
Wedge resection	8 (31%)	6 (10%)	22 (14%)		
Recurrence					
Absent	20 (77%)	47 (77%)	146 (95%)	<0.01	<0.01
Present	6 (23%)	14 (23%)	7 (5%)		
Pattern of recurrence					
Locoregional	2	10	5	0.47	1.00
Distant	3	2	1		
Both simultaneously	1	2	1		

†P-value comparing the SCC group with the nsADC group; ‡P-value comparing the sADC group with the nsADC group. SCC, squamous cell carcinoma; sADC, solid adenocarcinoma; nsADC, non-solid adenocarcinoma.

incidences of pleural invasion, vascular invasion, lymphatic invasion, and postoperative recurrence of the SCC were similar with solid ADC. Therefore, small peripheral tumors can be divided into two groups; solid tumor and non-solid tumor, in terms of malignant potential. Although wedge resection was lower in sADC group compared to SCC, the recurrence rate was almost same. This data may reflect the higher malignant potential of sADC, i.e., ADC with micropapillary pattern which is a well-known malignant factor (29,30).

Previous studies demonstrated that sublobar resection was a potentially valid surgical option for small-sized tumors (3,4), while the results of large-scale multi-institutional prospective randomized trials are awaited to confirm this (e.g., JCOG0802 and CALGB140503). Furthermore, ADCs with a high proportion of ground glass opacity are classified as minimally invasive or non-invasive ADC (ADC *in situ*) (31), and complete resection of such minimally invasive or non-invasive ADCs leads to an extremely favorable prognosis (32,33). ADC has thus been regarded as a good candidate for sublobar resection, and large-scale multi-institutional prospective randomized trials are currently exploring this issue (e.g., JCOG0804). In contrast, the present study showed that even small-sized SCCs and sADC in the peripheral lung had malignant potential such as higher incidence of pleural, vascular, and lymphatic invasion, suggesting that solid tumors may not be a good candidate for sublobar resection. Further prospective randomized trials are awaited.

The present study had several limitations. First, this study was conducted retrospectively in a single institute and the sample size was too small to obtain a definitive conclusion. Second, we included patients who underwent wedge resection. Although the proportion of wedge resection was higher in the SCC cohort, there was no difference in the rate of local recurrence. Third, we did not perform analysis regarding lymph node metastasis, because our study included cases of wedge resection and segmentectomy with no mediastinal lymph node dissection. Fourth, since our aim in this study was focused on

SCC, we just divided ADC into the current two categories. There might be further clinicopathological difference between part-solid GGN and pure GGN (28).

In summary, pleural invasion, vascular invasion, and lymphatic invasion are more common in patients with SCC compared with ADC, while SCC is also associated with a higher postoperative recurrence rate. In addition, incidence of these factors in SCC are similar with sADC. SCC and sADC may not be candidates for sublobar resection even if they are small-sized and located in the peripheral lung.

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Availability of data and materials

All data and materials in the present study were anonymized. All data generated or analyzed during this study are included in this published article.

Authors' contributions

TK and KiS conceived and designed the study. SN, MI, YO, YA, KO, TN, AM, HK, KeS and TY obtained the data. TK, KiS and SN analyzed and interpreted the data. TK, KiS, SN and YO drafted the manuscript. MI, YA, KO, TN, TY, AM, HK and KeS critically revised the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Gunma University Hospital (Maebashi, China) (approval no. 2017-027). Written informed consent was obtained from all patients prior to enrolment.

Patient consent for publication

All patients consented for their data and/or images to be published at the time of their surgeries.

Competing interests

The authors declare that they have no competing interests.

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