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ORIGINAL ARTICLE – THORACIC ONCOLOGY

The Differences in Clinicopathologic and Prognostic Characteristics Between Surgically Resected Peripheral and Central Lung Squamous Cell Carcinoma

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ABSTRACT

Background. Pulmonary peripheral-type squamous cell carcinoma (p-SqCC) has been increasing in incidence. However, little is known about the clinicopathologic features of p-SqCC. This study aimed to investigate the clinicopathologic characteristics and clinical outcomes of p-SqCC compared with central-type SqCC (c-SqCC) in a large cohort of surgically resected lung SqCC patients with long-term follow-up results.

Methods. The study included 268 patients with SqCC who underwent surgical resection at the authors' institute from January 1990 to September 2013. The mean follow-up period was 67.1 months. The clinicopathologic and genetic characteristics were investigated in relation to their association with progression-free survival (PFS) and overall survival (OS) based on tumor location.

Results. The study cohort included 120 patients with p-SqCC and 148 patients with c-SqCC. Compared with c-SqCC, p-SqCC was correlated with older age ($p = 0.002$), female sex ($p = 0.033$), better performance status ($p < 0.001$), smaller tumor ($p = 0.004$), less lymph node metastasis ($p < 0.001$), and an earlier pathologic stage ($p < 0.001$). Despite the clinicopathologic differences, tumor location was not significantly correlated with clinical outcomes. For the p-SqCC patients, the multivariate analysis showed a significant correlation of lymphovascular invasion (PFS, $p < 0.001$; OS, $p < 0.001$) and lymph node metastasis ($p = 0.007$; OS, $p = 0.022$) with poor PFS and OS, but a significant correlation of incomplete tumor resection (PFS, $p = 0.009$) only with poor PFS.

Conclusions. The clinicopathologic features differed between the p-SqCC and c-SqCC patients. Lymphovascular invasion and lymph node metastasis were independent prognostic factors of p-SqCC. These prognostic factors may be potentially used as indicators for adjuvant therapies to be used with patients who have p-SqCC.

Yih-Leong Chang and Chen-Tu Wu contributed equally as corresponding authors to this work.

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Lung cancer is the leading cause of cancer deaths worldwide.[1] In recent decades, adenocarcinoma has replaced squamous cell carcinoma (SqCC) as the most common histologic type of lung cancer. However, SqCC still accounts for 20–30% of patients with non-small cell lung cancer (NSCLC).[2] Lung SqCC can be classified into a peripheral type (p-SqCC) and a central type (c-SqCC) based on the tumor location.[3–10] Although most lung

SqCCs are reported to develop in the central region of the lung, the incidence of p-SqCC has been increasing recently.[3–10]

In 2003, Funai et al.[3] first reported that c-SqCC and p-SqCC have different clinicopathologic characteristics and should be classified in different categories. However, only a few reports on the clinicopathologic characteristics and prognostic factors of p-SqCC have been published,[3–10] whereas the characteristics of c-SqCC have been well studied.

This study aimed to investigate the clinicopathologic features and clinical outcomes of p-SqCC compared with c-SqCC in a large cohort of surgically resected lung SqCC patients with long-term follow-up results.

METHODS

Study Design

The study included a cohort of 268 patients with pulmonary SqCC who underwent surgical resection by our team at the National Taiwan University Hospital from January 1990 to September 2013. The hospital's Research Ethics Committee approved the study (project approval no. 201412139RINC). Due to the retrospective nature of the study, informed consent was waived.

Surgical Procedures

The preoperative staging workups and surgical risk evaluations included chest radiography; computed tomography (CT) of the chest, abdomen, and brain; bone scanning or positron emission tomography (PET) scans; and pulmonary function tests. All the patients had undergone lung tumor resection including sublobar resection, lobectomy, sleeve lobectomy, bilobectomy, and pneumonectomy. The approach methods included thoracotomy and video-assisted thoracoscopic surgery (VATS). All the patients had undergone systematic lymph node dissection including hilar, interlobar, lobar, intralobar, and ipsilateral mediastinal lymph nodes.

Clinicopathologic parameters were collected from chart reviews and by telephone interviews. The tumor location was retrospectively determined according to the finding from preoperative bronchoscopy, imaging studies, or both. A central tumor location was defined as a tumor located in or more central to the third branching bronchus according to the previous reports.[3,8,9] In contrast, a peripheral tumor location was defined as a tumor located in or more peripheral to the fourth branching bronchus.

Pathology Studies

Formalin-fixed, paraffin-embedded tissue tumor specimens were sectioned for microscopic examination. Histopathologic evaluations were performed according to the 2015 World Health Organization classification.[11] Histologic diagnosis and pathologic features were retrospectively collected from the pathologic analysis documents at the National Taiwan University Hospital, including degree of differentiation, lymphovascular invasion (LVI), and pleural invasion.

Complete resection was defined as no tumor invasion at the resection margin by microscopic examination. The study defined LVI by clear-cut tumor cells identified within a lymphatic lumen, which may contain few lymphocytes and lymph fluid, or by invasion of apparent cancer cells through smooth muscle-containing blood vessel walls, which often were associated with fibrin thrombi or covered by endothelium.

Information regarding the pathologic features lacking in the previous documents was provided via re-examination by two pathologists (C-T.W. and Y-L.C.). Pathologic staging was reevaluated according to the American Joint Committee on Cancer (AJCC) TNM Classification for Lung and Pleural Tumors (8th ed).[12] After the two pathologists carefully reviewed the pathology of the surgical specimens for all the patients, we confirmed that this cohort had no adenosquamous carcinoma.

Follow-Up Evaluation

After surgery, the patients were monitored in the outpatient clinic with a physical examination, chest radiography, serum carcinoembryonic antigen (CEA) measurement two to four times per year, and chest CT two to four times per year for the first 2 years. Thereafter, the patients were regularly monitored in the outpatient clinic, where they received a physical examination, chest radiography, serum CEA measurement, and chest CT every 6 months or annually. Brain CT, magnetic resonance imaging (MRI), bone scanning, PET scanning, and other necessary tests were performed whenever any symptoms or signs of tumor recurrence were noted. After the image exam showed suspect recurrence lesions, the diagnosis of recurrence was further confirmed by needle biopsy or surgery when clinically feasible or by thoracocentesis of malignant pleural effusion when clinically feasible.

Outcome Measures

Progression-free survival (PFS) was defined as the time from surgery to any disease progression, death due to any reason, or the last follow-up visit. Overall survival (OS)

TABLE 1 The association between tumor location and clinicopathologic characteristics

Variables	*n* (%)	Peripheral	Central	*p* value
Patients	268	120	148	
Mean age: years (range)	67.7 ± 8.7 (40–84)	69.4 ± 8.3 (42–84)	66.3 ± 8.8 (40–83)	0.002
Male	234 (87.3)	99 (82.5)	135 (91.2)	0.033
Smoker	196 (73.1)	83 (69.2)	113 (76.4)	0.187
ECOG				< 0.001
0	66 (24.6)	44 (36.7)	22 (14.9)	
≥ 1	202 (75.4)	76 (63.3)	126 (85.1)	
Tumor size (cm)				0.004
≤ 3	82 (30.6)	41 (34.2)	41 (27.7)	
3–5	107 (39.9)	56 (46.7)	51 (34.5)	
5–7	49 (18.3)	17 (14.2)	32 (21.6)	
> 7	30 (11.2)	6 (5.0)	24 (16.2)	
Tumor location				0.006
LUL	66 (24.6)	28 (23.3)	38 (25.7)	
LLL	53 (19.8)	25 (20.8)	28 (18.9)	
Left main bronchus	7 (2.6)	0 (0.0)	7 (4.7)	
RUL	73 (27.2)	42 (35.0)	31 (20.9)	
RML	14 (5.2)	4 (3.3)	10 (6.8)	
RLL	48 (17.9)	21 (17.5)	27 (18.2)	
Right intermediate bronchus	7 (2.6)	0 (0.0)	7 (4.7)	
Differentiation				0.582
Well/moderate	243 (90.7)	107 (89.2)	136 (91.9)	
Poor	25 (9.3)	13 (10.8)	12 (8.1)	
Tumor invasion				0.176
Visceral pleural invasion	14 (5.2)	10 (8.3)	4 (2.7)	
Parietal pleural invasion	25 (9.3)	10 (8.3)	15 (10.1)	
Great vessel invasion	4 (1.5)	1 (0.8)	3 (2.0)	
Lymphovascular invasion	29 (10.8)	8 (6.7)	21 (14.2)	0.143
Lymph node metastasis				< 0.001
N0	170 (63.4)	93 (77.5)	77 (52.0)	
N1	67 (25.0)	14 (11.7)	53 (35.8)	
N2	31 (11.6)	13 (10.8)	18 (12.2)	
Pathologic stage				< 0.001
1A1	1 (0.4)	0 (0.0)	1 (0.7)	
1A2	21(7.8)	10 (8.3)	11 (7.4)	
1A3	36 (13.4)	24 (20.0)	12 (8.1)	
1B	32 (11.9)	24 (20.0)	8 (5.4)	
2A	28 (10.4)	15 (12.5)	13 (8.8)	
2B	74 (27.6)	23 (19.2)	51 (34.5)	
3A	65 (24.3)	21 (17.5)	44 (29.7)	
3B	11 (4.1)	3 (2.5)	8 (5.4)	
Surgical procedure				< 0.001
Sublobar resection	5 (1.9)	5 (4.1)	0 (0.0)	
Lobectomy	172 (64.2)	109 (90.8)	63 (42.6)	
Sleeve lobectomy	28 (10.4)	4 (3.3)	24 (16.2)	
Bilobectomy	41 (15.3)	2 (1.7)	39 (26.4)	
Pneumonectomy	22 (8.2)	0 (0.0)	22 (14.9)	

TABLE 1 continued

Variables	*n* (%)	Peripheral	Central	*p* value
Approach method				< 0.001
Thoracotomy	205 (76.5)	71 (59.2)	134 (90.5)	
VATS	63 (23.5)	49 (40.8)	14 (9.5)	
Mean no. of dissected lymph nodes (range)	15.4 ± 9.0 (0–53)	15.2 ± 8.9 (1–42)	15.6 ± 9.2 (0–53)	0.669
Mean no. of dissected lymph node stations (range)	4.2 ± 1.4 (0–7)	4.4 ± 1.4 (1–7)	4.1 ± 1.4 (0–7)	0.142
Complete resection	253 (94.4)	116 (96.7)	137 (92.6)	0.147
Recurrence	155	60	95	0.199
Local recurrence	18 (11.6)	6 (10.0)	12 (12.6)	
Regional recurrence	79 (51.0)	36 (60.0)	43 (45.3)	
Distant metastasis	58 (37.4)	18 (30.0)	40 (42.1)	

ECOG Eastern Cooperative Oncology Group, *LUL* left upper lobe, *LLL* left lower lobe, *RUL* right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *VATS* video-assisted thoracoscopic surgery

was defined as the time from surgery to death or the last follow-up visit.

Local recurrence was defined as recurrence at the resection margin. Regional recurrence was defined as malignant pleural effusion or pleural nodules, new ipsilateral lung nodules, or ipsilateral lymph node recurrence. Lymph node recurrence was defined as a lymph node 1 cm or larger in the short axis on chest CT or a hypermetabolic node diagnosed by PET. Distant metastasis was defined as a metastatic lesion in the contralateral lung or any other organ.

Statistical Analysis

Clinical characteristics, histologic findings, surgical procedures, approach methods, and patient outcomes were compared between groups using Fisher's exact tests for categorical variables (frequency and percentages). We assessed whether the peripheral or central tumor location was correlated with the clinicopathologic parameters. Both PFS and OS were evaluated using Kaplan–Meier survival plots and log-rank tests. Prognostic factors for PFS and OS were analyzed by univariate analysis, and comparisons were made using log-rank tests. The variables achieving statistical significance in the univariate analysis were included in the multivariate analysis using a Cox proportional hazards regression model. All tests were two-sided, and p values lower than 0.05 were considered significant. The Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Patient Demographic, Clinicopathologic, and Genetic Characteristics

Of the 268 patients included in the study cohort, 120 (44.8%) had p-SqCC and 148 (55.2%) had c-SqCC (Table 1). The mean follow-up period was 67.1 months (overall range 1–313 months). The mean age was 67.7 years (range 40–84 years), and 73.1% (196/268) of the patients were smokers. Males accounted for 87.3% (234/268) of the study population.

The findings showed that the patients with p-SqCC were more likely to be older ($p = 0.002$), higher percentage of female ($p = 0.033$), and to have a better performance status ($p < 0.001$), a smaller tumor ($p = 0.004$), less lymph node metastasis ($p < 0.001$), and an earlier pathologic stage ($p < 0.001$). More c-SqCC patients underwent extensive surgical resection (sleeve lobectomy, bilobectomy, and pneumonectomy; $p < 0.001$) using the thoracotomy approach method ($p < 0.001$) due to the central tumor location.

Tumor recurrence was noted in 155 patients. Local progression was observed in 18 patients (11.6%), regional progression in 79 patients (51.0%), and distant metastases in 58 patients (37.4%). The recurrence pattern did not significantly differ between the patients with p-SqCC and the patients with c-SqCC.

Overall, 204 patients had information available on epidermal growth factor receptor (*EGFR*), *KRAS*, and *BRAF* genetic mutations for further analysis. We found that tumor location was not significantly correlated with these three genetic mutations (Table S1).

TABLE 2 Correlation between tumor location, clinicopathologic features, and survival in surgically resected lung squamous cell carcinoma

Variables	Patients (*n*).	No. of recurrences (%)/ % of 5-year PFS	*p* value	No. of deaths (%)/ % of 5-year OS	*p* value
(A) Univariate analysis					
Total patients	268	155 (57.8)/46.9		149 (55.6)/52.4	
Age (years)			0.477		0.229
> 65	177	105 (59.3)/46.0		102 (57.6)/50.7	
≤ 65	91	50 (54.9)/48.5		47 (51.6)/55.4	
Sex			0.131		0.094
Female	34	16 (47.1)/65.8		15 (44.1)/68.4	
Male	234	139 (59.4)/44.3		134 (57.3)/50.1	
ECOG			0.220		0.156
0	66	41 (62.1)/40.5		40 (60.6)/46.6	
≥ 1	202	114 (56.4)/49.1		109 (54.0)/54.2	
Smoking status			0.818		0.852
Smoker	72	42 (58.3)/46.8		39 (54.2)/53.6	
Nonsmoker	196	113 (57.7)/47.0		110 (56.1)/51.9	
Surgical method			0.013		0.004
Sublobar resection, lobectomy	177	93 (52.5)/53.0		87 (49.2)/58.4	
Extensive surgical resection	91	62 (68.1)/35.4		62 (68.1)/41.2	
Approach method			0.373		0.337
Thoracotomy	205	124 (60.5)/44.2		121 (59.0)/50.0	
VATS	63	31 (49.2)/56.3		28 (44.4)/60.8	
Tumor location			0.017		0.015
Peripheral	120	60 (50.0)/56.8		56 (46.7)/63.4	
Central	148	95 (64.2)/38.9		93 (62.8)/43.5	
Tumor size (cm)			0.291		0.245
≤ 3	82	48 (58.5)/50.0		44 (53.7)/56.1	
3–5	107	57 (53.3)/49.9		56 (52.3)/56.0	
5–7	49	32 (65.3)/37.9		32 (65.3)/39.3	
> 7	30	18 (60.0)/43.1		17 (55.6)/49.8	
Differentiation			0.517		0.722
Well/moderate	243	142 (58.4)/46.0		136 (56.0)/52.1	
Poor	25	13 (52.0)/55.4		13 (52.0)/55.1	
Tumor invasion			0.002		0.001
Negative	225	126 (56.0)/49.6		121 (53.8)/55.7	
Positive	43	29 (67.4)/33.4		28 (65.1)/34.5	
Visceral pleural invasion	14	10 (71.4)/35.7		9 (64.3)/41.7	
Parietal pleural invasion	25	15 (60.0)/38.6		15 (60.0)/37.3	
Great vessel invasion	4	4 (100)/0.0		4 (100)/0.0	
Lymphovascular invasion			0.020		0.009
Negative	239	135 (56.5)/48.9		129 (54.0)/55.0	
Positive	29	20 (69.0)/30.6		20 (69.0)/30.0	
Complete resection			0.001		0.002
Yes	253	141 (55.7)/49.6		136 (53.8)/54.6	
No	15	14 (93.3)/6.7		13 (86.7)/15.0	

TABLE 2 continued

Variables	Patients (n).	No. of recurrences (%)/ % of 5-year PFS	p value	No. of deaths (%)/ % of 5-year OS	p value
N stage			< 0.001		< 0.001
0	170	87 (51.2)/57.6		83 (48.8)/63.6	
1	67	42 (62.7)/35.3		41 (61.2)/38.7	
2	31	26 (83.9)/10.7		25 (80.6)/17.4	
Pathologic stage			< 0.001		0.001
1	90	47 (52.2)/57.1		43 (47.8)/65.2	
2	102	56 (54.9)/50.3		55 (53.9)/54.6	
3	76	52 (68.4)/30.2		51 (67.1)/33.9	

Variables	PFS			OS		
	HR	95% CI	p value	HR	95% CI	p value
(B) Multivariate analysis						
Surgical method						
Extensive surgical resection	1.000			1.000		
Sublobar resection, lobectomy	0.910	0.600–1.379	0.656	1.029	0.676–1.567	0.892
Tumor location						
Peripheral	1.000			1.000		
Central	1.278	0.862–1.894	0.221	1.227	0.820–1.836	0.320
Tumor invasion						
Negative	1.000			1.000		
Positive	1.909	1.266–2.878	0.002	2.065	1.359–3.139	0.001
Lymphovascular invasion						
Negative	1.000			1.000		
Positive	1.276	0.778–2.094	0.334	1.415	0.859–2.332	0.173
Complete resection						
Yes	1.000			1.000		
No	2.183	1.222–3.899	0.008	2.076	1.141–3.777	0.017
N stage						
0	1.000			1.000		
1–2	1.949	1.367–2.778	< 0.001	1.811	1.262–2.599	0.001

PFS progression-free survival, *OS* overall survival, *ECOG* Eastern Cooperative Oncology Group, *VATS* video-assisted thoracoscopic surgery, *HR* hazard ratio, *CI* confidence interval

Survival Correlations for Clinicopathologic Characteristics in Surgically Resected Lung SqCC (n = 268)

The 5-year PFS of the 268 patients in this study was 46.9%. In the multivariate analysis, the presence of tumor invasion ($p = 0.002$), incomplete tumor resection ($p = 0.008$), and the presence of lymph node metastasis ($p < 0.001$) remained statistically significant (Table 2). Notably, tumor location was not significantly correlated with tumor recurrence ($p = 0.221$).

The 5-year OS of the 268 patients included was 52.4%. In the multivariate analysis, the presence of tumor invasion ($p = 0.001$), incomplete tumor resection ($p = 0.017$), and the presence of lymph node metastasis ($p = 0.001$) remained statistically significant (Table 2). Notably, tumor location was not significantly correlated with OS ($p = 0.320$).

Survival Correlations for Clinicopathologic Characteristics in Surgically Resected Lung p-SqCC (n = 120)

The 5-year OS of the 120 p-SqCC patients was 63.4%. The univariate analysis identified four significant risk factors for poor OS: age olderthan 65 years, the presence of LVI, incomplete tumor resection, and the presence of lymph node metastasis. In the multivariate analysis, the

TABLE 3 Correlation between clinicopathologic features and survival in peripheral-type squamous cell carcinoma

Variables	Patients (%)	No. of recurrences (%)/ % of 5-year PFS	*p* value	No. of deaths (%)/ % of 5-year OS	*p* value
(A) Univariate analysis					
Total patients	120	60 (50.0)/56.8		56 (46.7)/63.4	
Age (years)			0.097		0.030
> 65/	91	49 (53.8)/52.1		47 (51.6)/58.5	
≤ 65	29	11 (37.9)/71.4		9 (31.0)/79.0	
Sex			0.293		0.217
Female	21	9 (42.9)/79.8		8 (38.1)/85.2	
Male	99	51 (51.5)/52.2		48 (48.5)/59.1	
ECOG			0.431		0.241
0	44	23 (52.3)/53.1		22 (50.0)/55.6	
≥ 1	76	37 (48.7)/59.0		42 (44.7)/67.9	
Smoking status			0.290		0.095
Smoker	83	44 (53.0)/53.6		43 (51.8)/59.7	
Nonsmoker	37	16 (43.2)/63.7		13 (35.1)/71.7	
Surgical method			0.928		0.907
Sublobar resection, lobectomy	114	57 (50.0)/56.2		53 (46.5)/63.2	
Extensive surgical resection	6	3 (50.0)/66.7		3 (50.0)/66.7	
Approach method			0.654		0.819
Thoracotomy	71	36 (50.7)/54.7		35 (49.3)/62.6	
VATS	49	24 (49.0)/60.1		21 (42.9)/64.5	
Tumor size (cm)			0.982		0.821
≤ 3	41	20 (48.8)/58.2		17 (41.5)/66.4	
3–5	56	29 (51.8)/56.9		28 (50.0)/65.1	
5–7	17	8 (47.1)/55.3		8 (47.1)/55.0	
> 7	6	3 (50.0)/50.0		3 (50.0)/50.0	
Differentiation			0.509		0.695
Well/moderate	107	55 (51.4)/55.3		51 (47.7)/62.7	
Poor	13	5 (38.5)/69.2		5 (38.5)/69.2	
Tumor invasion			0.262		0.230
Negative	99	49 (45.5)/58.1		46 (46.5)/64.9	
Positive	21	11 (52.4)/51.1		10 (47.6)/56.2	
Visceral pleural invasion	10	7 (49.5)/40.0		6 (46.5)/48.0	
Parietal pleural invasion	10	3 (70.0)/74.1		3 (30.0)/74.1	
Great vessel invasion	1	1 (100)/0.0		1 (100)/0.0	
Lymphovascular invasion			< 0.001		< 0.001
Negative	112	53 (47.3)/60.0		49 (43.7)/67.1	
Positive	8	7 (87.5)/12.5		7 (87.5)/12.5	
Complete resection			0.002		0.040
Yes	116	56 (48.3)/58.9		53 (45.7)/64.0	
No	4	4 (100.0)/0.0		3 (75.0)/50.0	
N stage			0.003		0.004
0	93	43 (46.2)/62.7		40 (43.0)/69.9	
1	14	7 (50.0)/52.6		6 (42.9)/55.0	
2	13	10 (76.9)/17.6		10 (76.9)/25.4	

TABLE 3 continued

Variables	Patients (%)	No. of recurrences (%)/ % of 5-year PFS	p value	No. of deaths (%)/ % of 5-year OS	p value
Pathologic stage			0.184		0.109
1	58	27 (46.6)/61.8		24 (41.4)/71.3	
2	38	19 (50.0)/61.1		18 (47.4)/64.8	
3	24	14 (58.3)/36.7		14 (58.3)/41.0	

Variables	PFS			OS		
	HR	95% CI	p value	HR	95% CI	p value
(B) Multivariate analysis						
Age (years)						
> 65/	1.000			1.000		
≤ 65	0.665	0.343–1.290	0.228	0.519	0.251–1.074	0.077
Lymphovascular invasion						
Negative	1.000			1.000		
Positive	5.108	2.190–11.912	< 0.001	5.177	2.193–12.225	< 0.001
Complete resection						
Yes	1.000			1.000		
No	4.045	1.412–11.590	0.009	2.904	0.884–9.544	0.079
N stage						
0	1.000			1.000		
1–2	1.621	1.143–2.297	0.007	1.526	1.062–2.191	0.022

PFS progression-free survival, *OS* overall survival, *ECOG* Eastern Cooperative Oncology Group, *VATS* video-assisted thoracoscopic surgery, *HR* hazard ratio, *CI* confidence interval

presence of LVI and the presence of lymph node metastastasis remained significant (Table 3).

The 5-year OS of the 120 p-SqCC patients was 63.4%. The univariate analysis identified four significant risk factors for poor OS: age older than 65 years, the presence of LVI, incomplete tumor resection, and the presence of lymph node metastasis. In the multivariate analysis, the presence of LVI and the presence of lymph node metastasis remained significant (Table 3).

Survival Correlations for Clinicopathologic Characteristics in Surgically Resected Lung c-SqCC (n = 148)

The 5-year PFS of the 148 c-SqCC patients was 38.9%. The univariate analysis identified three significant risk factors for recurrence: Eastern Cooperative Oncology Group (ECOG) performance status of 0, the presence of tumor invasion, and the presence of lymph node metastasis. In the multivariate analysis, the presence of tumor invasion and the presence of lymph node metastasis remained significant, independent risk factors for recurrence (Table 4).

The 5-year OS of the 148 c-SqCC patients was 43.5%. The univariate analysis identified three significant risk factors for poor OS: the presence of tumor invasion, incomplete tumor resection, and the presence of lymph node metastasis. In the multivariate analysis, the presence of tumor invasion and the presence of lymph node metastasis remained significant (Table 4).

LVI as an Up-Staging Factor in Surgically Resected Lung p-SqCC

The p-SqCC group comprised eight patients with LVI. Among these eight patients, three had N0, two had N1 and three had N2 disease. We proposed that LVI may be regarded as a new upstaging factor in p-SqCC patients and tried to regard it as stage 3 disease due to the same poor prognosis as for stage 3 patients. The difference in PFS and OS was more significant between stage 1 or 2 and stage 3 after upstaging of the LVI (Fig. S1).

DISCUSSION

Although lung SqCC typically arises in the central airways, the prevalence of p-SqCC has been increasing in recent years.[3–10] In this study, the patients with p-SqCC accounted for 44.8% (120/268) of the total cohort. Based

TABLE 4 Correlation between clinicopathologic features and survival in central-type squamous cell carcinoma

Variables	Patients (n)	No. of recurrence (%)/ % of 5-year PFS	p value	No. of deaths (%)/ % of 5-year OS	p value
(A) Univariate analysis					
Total patients	148	95 (64.2)/38.9		93 (62.8)/43.5	
Age (years)			0.918		0.720
> 65	86	56 (65.1)/39.2		55 (64.0)/42.4	
≤ 65	62	39 (62.9)/37.7		38 (61.3)/44.6	
Sex			0.513		0.481
Female	13	7 (53.8)/46.2		7 (53.8)/43.3	
Male	135	88 (65.2)/38.3		86 (63.7)/43.5	
ECOG			0.045		0.068
0	22	18 (81.8)/13.6		18 (81.8)/28.1	
≥ 1	126	77 (61.1)/43.1		75 (59.5)/46.0	
Smoking status			0.077		0.074
Smoker	69	(61.1)/42.0		35 (74.3)/34.6	
Nonsmoker	35	26 (74.3)/29.1		113 (59.3)/46.3	
Surgical method			0.153		0.076
Sublobar resection, lobectomy	63	36 (57.1)/47.2		34 (54.0)/49.6	
Extensive surgical resection	85	59 (69.4)/33.0		59 (69.4)/39.1	
Approach method			0.470		0.634
Thoracotomy	134	88 (65.7)/38.6		86 (64.2)/43.0	
VATS	14	7 (50.0)/40.4		7 (50.0)/47.6	
Tumor size (cm)			0.505		0.572
≤ 3	41	28 (68.3)/42.2		27 (65.9)/46.9	
3–5	51	28 (54.9)/41.7		28 (54.9)/45.0	
5–7	32	24 (75.0)/29.3		24 (75.0)/32.0	
> 7	24	15 (62.5)/41.3		14 (58.3)/49.7	
Differentiation			0.859		0.956
Well/moderate	136	87 (64.0)/38.6		85 (62.5)/43.7	
Poor	12	8 (66.7)/41.7		8 (56.7)/41.7	
Tumor invasion			< 0.001		< 0.001
Negative	126	77 (61.1)/42.6		75 (59.5)/48.1	
Positive	22	18 (81.8)/18.2		18 (81.8)/18.2	
Visceral pleural invasion	4	3 (75.0)/25.0		3 (75.0)/25.0	
Parietal pleural invasion	15	12 (80.0)/20.0		12 (80.0)/20.0	
Great vessel invasion	3	3 (100)/0.0		3 (100)/0.0	
Lymphovascular invasion			0.857		0.680
Negative	127	82 (64.6)/39.2		80 (63.0)/44.6	
Positive	21	13 (61.9)/37.6		13 (61.9)/36.7	
Complete resection			0.084		0.030
Yes	137	85 (62.0)/41.6		83 (60.6)/46.6	
No	11	10 (90.9)/9.1		10 (90.9)/9.1	
N stage			< 0.001		< 0.001
0	77	44 (57.1)/51.4		43 (55.8)/56.4	
1	53	35 (66.0)/30.9		35 (66.0)/34.3	
2	18	16 (88.9)/6.0		15 (83.3)/11.8	

TABLE 4 continued

Variables	Patients (*n*)	No. of recurrence (%)/ % of 5-year PFS	*p* value	No. of deaths (%)/ % of 5-year OS	*p* value
Pathologic stage			0.009		0.029
1	32	20 (62.5)/47.6		19 (59.4)/53.8	
2	64	37 (57.8)/43.8		37 (57.8)/48.5	
3	52	38 (73.1)/27.2		37 (71.2)/30.7	

Variables	PFS			OS		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
(B) Multivariate analysis						
ECOG						
0	1.000			1.000		
≥ 1	0.608	0.357–1.036	0.067	0.610	0.359–1.038	0.069
Tumor invasion						
Negative	1.000			1.000		
Positive	2.242	1.324–3.796	0.003	2.356	1.389–3.999	0.001
Complete resection						
Yes	1.000			1.000		
No	1.863	0.946–3.672	0.072	2.135	1.076–4.236	0.030
N stage						
0	1.000			1.000		
1–2	1.812	1.193–2.751	0.005	1.808	1.186–2.757	0.006

PFS progression-free survival, *OS* overall survival, *ECOG* Eastern Cooperative Oncology Group, *VATS* video-assisted thoracoscopic surgery, *HR* hazard ratio, *CI* confidence interval

on the findings from previous studies, the incidence of p-SqCC has ranged from 37 to 72%.[3–7,9] As time passes, SqCC is more likely to grow in the periphery than in the center.[3,5,7,9]

The large range in the incidence may be related to the different definitions for the peripheral location. In this study, p-SqCC was defined as a tumor located in or more peripheral to the fourth branching bronchus according to the previous studies.[3,8,9] Our study showed that patients with p-SqCC were more likely to be older and of the female sex, and that they were more likely to have a better performance status, a smaller tumor, less lymph node metastasis, and an earlier pathologic stage at initial presentation.

Four previous studies have investigated the clinicopathologic differences based on different tumor locations (Table 5).[3–6] In 2003, Funai et al.[3] investigated 204 patients with stages 1–4 disease. Their study was the first to report the difference in clinicopathologic characteristics between p-SqCC and c-SqCC patients. The patients with p-SqCC were characterized by older age, less frequent lymph node metastasis, an earlier pathologic stage, good differentiation, less LVI, and less pleural invasion. These findings are similar to those from our study.

Differences in driver mutations and cytokeratin expression patterns between p-SqCC and c-SqCC patients also have been reported.[4–6] More *EGFR* mutations and cytokeratin 7 expression and less cytokeratin 19 expression have been reported as significant differences between p-SqCC and c-SqCC patients. Zhang et al.[4] further analyzed the so-called "adenocarcinoma markers" and found that more frequent thyroid transcription factor-1 (TTF-1) and surfactant protein A (SPA) expression occurred in p-SqCC patients. The relatively higher proportion of *EGFR*, *KRAS,* and *HER2* mutations in p-SqCC patients also indicated adenocarcinoma features.[4] However, we examined the correlation between tumor location and the presence of *EGFR*, *KRAS*, and *BRAF* mutations and found no significant difference between p-SqCC and c-SqCC patients.

The findings from both our study and those previously published show distinct clinicopathologic features for p-SqCC patients compared with c-SqCC patients.[3–7,9] The findings from these previous studies are summarized in Table 5. Despite the difference in the clinicopathologic and genetic features between the p-SqCC and c-SqCC patients, our study showed no significant difference in the clinical outcome based on the two different tumor locations. Our

TABLE 5 Summary of existing studies on peripheral-type squamous cell carcinoma patients

	Study period	No. of patients (p-SqCC/c-SqCC)	Stage	Clinicopathologic features of p-SqCC patients	Driver mutations and IHC features of p-SqCC patients	Significant prognostic factors for p-SqCC patients	Tumor location and clinical outcome
Current study	1990–2013	268 (120/148)	1–3B	Older age, less LN metastasis, earlier stage, better performance status, smaller tumor size, female	No significant correlation	Lymphovascular invasion, LN metastasis	No correlation
Zhang et al.[4]	2007–2014	705 (261/444)	1–3	Older age, earlier stage, female, never-smoker	More EGFR mutations, more TTF-1, CK7, SPA expression, less TP63 expression	N/A	No correlation
Kinoshita et al.[9]	1995–2011	280 (202/78)	1–3	N/A	N/A	Vascular and pleural invasion, higher serum SCC level	N/A
Hayashi et al.[5]	2005–2010	50 (35/15)	N/A	Emphysema, interstitial pneumonia	More CK7 expression	N/A	No correlation
Nagashima et al.[10]	1989–2010	71 (All p-SqCC)	T1	(≤ 3 cm)	N/A	N/A	LN metastasis, older age, higher serum CEA level
N/A							
Saijo et al.[6]	1992–2004	41 (20/21)	T1	(≤ 3 cm)	Older age, less vascular invasion, less pleural invasion, less squamous metaplasia of bronchus	More CK7 expression, less CK19 expression	N/A
N/A							
Sakurai et al.[8]	1995–2001	70 (All p-SqCC)	T1	(≤ 3 cm)	N/A	N/A	N/A
N/A							
Funai et al.[3]	1992–1998	204 (109/95)	1–4	Older age, less LN metastasis, earlier stage, well differentiated; less vascular invasion, less pleural invasion	N/A	Older age, LN metastasis	No correlation
Mizushima et al.[7]	1985–1997	235 (129/106)	1–3B	N/A	N/A	N/A	No correlation

p-SqCC peripheral-type squamous cell carcinoma, *c-SqCC* central-type squamous cell carcinoma, *LN* lymph node, *EGFR* epidermal growth factor receptor, *TTF-1* thyroid transcription factor-1, *CK* cytokeratin, *SPA* surfactant protein A, *TP63* tumor protein 63, *N/A* not available, *SCC* squamous cell carcinoma antigen, *CEA* carcinoembryonic antigen findings were consistent with those from previous studies.[3–5,7] Although the p-SqCC patients were more likely to have an earlier pathologic stage, less lymph node metastases, and fewer invasive pathologic characteristics, tumor location was not an independent prognostic factor for the SqCC patients[3–5,7]

Only two previous studies have reported on the clinicopathologic factors influencing the prognosis for resected p-SqCC.[5,7] These prognostic factors included the presence of vascular and pleural invasion, high preoperative serum CEA and squamous cell carcinoma antigen (SCC) levels, lymph node metastasis, and old age.[5,7] We retrospectively analyzed the clinicopathologic characteristics among the p-SqCC patients to seek reliable prognostic factors. We found similar results. Our findings showed that LVI and lymph node metastasis were two independent factors of a poor prognosis for p-SqCC patients.

In addition, LVI has been identified as an independent risk factor for recurrence in NSCLCs.[13,14] In 2007, Tsuchiya et al.[15,16] first proposed that upstaging of NSCLC patients (those with 39.4% of SqCC) with LVI allows for differentiation of patients with poor prognosis and improves the prediction of prognosis in cases of lung cancer. Several other studies also have shown that patients with LVI should be upstaged in the tumor-node-metastasis (TNM) classification of NSCLC.[17,18] However, to date, LVI has not been included as an indicator for recurrence in the current eighth TNM staging system.[12]

Evidence also was lacking among SqCC patients. We showed that LVI may play a key role in the tumor invasion and metastasis of p-SqCC, and may lead to a poor prognosis. In our study, the 5-year OS was 12.5% for the patients with LVI and 67.1% for those without LVI. Our results showed that the difference of PFS and OS was more significant between stage 1 or 2 and stage 3 after upstaging based on LVI (Fig. S1). More studies related to SqCC are necessary to validate our study results.

This study had some potential limitations and biases. As a retrospective, single-institution study, time-trend bias and patient-selection bias were inevitable. Patients might have had different preoperative evaluations, postoperative care, adjuvant chemotherapy regimens, and follow-up evaluation during the course of the 23-year study period (1990–2013).

Despite these limitations, the study cohort included an adequate number of patients with long follow-up periods. We demonstrated the clinicopathologic differences between p-SqCC and c-SqCC patients. Despite these differences, the clinical outcomes did not differ significantly between the p-SqCC and c-SqCC patients. Incomplete tumor resection, LVI, and lymph node metastasis were independent risk factors for tumor relapse, whereas lymph node metastasis and LVI were two independent factors for a poor p-SqCC prognosis.

Based on our results and the current evidence, LVI could potentially be used for further refinement of the next TNM staging system. Patients with these factors should be considered for adjuvant therapies to improve their prognosis.

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