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Surgically resected sarcomatoid carcinoma of the lung: a nationwide retrospective study in 2010

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Abstract

Background Sarcomatoid carcinoma of the lung is a rare histological type of non-small cell lung cancer with a poor prognosis. We aimed to investigate the clinicopathological characteristics and prognostic factors of surgically resected sarcomatoid carcinoma of the lung.

Methods We retrospectively reviewed 14999 patients who underwent surgical resection for non-small cell lung cancer accumulated by the Japanese Joint Committee of Lung Cancer Registry in 2010. Clinicopathological characteristics and survival were compared between the sarcomatoid carcinoma and other non-small cell cancer groups. The prognostic factors in the sarcomatoid carcinoma group were identified using a multivariate Cox proportional hazard model.

Results Patients with sarcomatoid carcinoma comprised 1.4% of all patients. The sarcomatoid carcinoma group demonstrated a more aggressive pathology with presentation at more advanced stages, requiring more frequent extensive surgical resections. The sarcomatoid carcinoma group had remarkably poorer overall and recurrence-free survival than the other non-small cell lung cancer group. Adjuvant chemotherapy was associated with improved survival for pathological stage II–III sarcomatoid carcinoma cases rather than for pathological stage I disease. In the multivariate analysis, larger tumor size, lymphatic permeation, and no adjuvant chemotherapy were associated with the sarcomatoid carcinoma group's overall and recurrence-free survival.

Conclusions Surgically resected sarcomatoid carcinoma of the lung has a higher aggressive and metastatic potential and a worse prognosis than other non-small cell lung cancers. Adjuvant chemotherapy, which was associated with enhanced survival in patients with pathological stage II–III of the disease, could be considered for treating patients with pathological stage II–III sarcomatoid carcinoma of the lung.

Keywords Lung cancer, Adjuvant chemotherapy, Aggressive pathology, Prognosis, Survival

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Background

Lung cancer is the main cause of cancer death in the world [1]. Sarcomatoid carcinoma of the lung is a rare histological type of non-small cell lung cancer (NSCLC) with poor differentiation and features of differentiation, such as sarcoma or sarcoma-like. The incidence rate of sarcomatoid carcinoma of the lung is < 1% among all pulmonary malignant carcinoma types [2–4]. Sarcomatoid carcinoma of the lung was classified into the following five subtypes in the 2004 World Health Organization (WHO) classification of lung tumors: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. Among these, the most common subtype is pleomorphic carcinoma. The classification of sarcomatoid carcinoma of the lung in the WHO classification of 2021 is similar to that of 2004 [5, 6].

Compared with the NSCLC histologies, such as adenocarcinoma, sarcomatoid carcinoma of the lung is associated with a poor prognosis. A study using the Surveillance, Epidemiology, and End Results database revealed that patients diagnosed with sarcomatoid carcinoma of the lung were significantly associated with worse overall and disease-specific survival compared to patients with other NSCLCs [3]. Another study using the National Cancer Database revealed that the median survival of patients with sarcomatoid carcinoma of the lung was approximately half of that of patients with other NSCLCs; moreover, this poor survival was significantly present in all the stages [2]. In a review article, the 5-year overall survival (OS) of sarcomatoid carcinoma of the lung was reportedly 14.4–54.3% in several studies [7]. Although several studies have shown similar prognoses between patients with sarcomatoid carcinoma of the lung and those with NSCLC [8, 9] the overall data currently demonstrate that sarcomatoid carcinoma of the lung is a much more aggressive pathology that presents at more advanced stages [10], has a greater predisposition for vascular invasion [11], metastasizes at higher rates [9], and is associated with a worse prognosis than other NSCLCs [3, 6, 12, 13]. These results highlight the pressing need for improving the standard of treatment of sarcomatoid carcinoma of the lung, comprising resection and perioperative treatment. One of the major unresolved issues in the treatment of sarcomatoid carcinoma of the lung is the efficacy of adjuvant chemotherapy. To date, there is no consensus on a recommended regimen. Thus, determining the importance of adjuvant chemotherapy for managing resected sarcomatoid carcinoma of the lung using real-world data is considered crucial.

Therefore, this study aimed to investigate the clinicopathological characteristics and prognostic factors of surgically resected sarcomatoid carcinoma of the lung.

Methods

Patients

The 7th Japanese Joint Committee of Lung Cancer Registry (JJCLCR) conducted a nationwide retrospective registry study of patients who underwent surgical resection for lung cancer [14]. The committee requested that 629 teaching hospitals accredited by the Japanese Board of General Thoracic Surgery participate in the study. Registration was conducted in accordance with the ethical guidelines for epidemiological studies, approved by the review committee of Osaka University Hospital, where the registry office was located (approval No. 15321, approved on November 12, 2015), and the requirement for informed consent was waived owing to the retrospective study design. Ultimately, the committee registered 18973 patients from 297 hospitals. The study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (identification No. 000020215). Based on the 7th JJCLCR database, we investigated the clinicopathological characteristics and prognostic factors of surgically resected sarcomatoid carcinoma of the lung.

This study's inclusion criteria were pathological diagnosis of NSCLC; pathological stages I, II, or III (according to the 7th Edition of the tumor-node-metastasis (TNM) classification system); residual tumor status R0, R1, or R2; and patients who underwent lung resection. The exclusion criteria were preinvasive lesion; small-cell lung cancer; carcinoid tumor; salivary gland-type tumor; unclassified carcinoma; unknown histology; unassessable or unknown residual tumor status; pathological stages IV or unknown; and surgery without lung resection. Finally, 14,999 patients (sarcomatoid carcinoma group, $n = 217$; other NSCLC group, $n = 14{,}782$) were included in this study.

Patients were diagnosed with sarcomatoid carcinoma of the lung according to the 2015 WHO classification of tumors of the lung, pleura, thymus, and heart as follows [15]: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.

Additionally, the registered data included the background characteristics of the patients, surgical information, pathological type, tumor diameter and other pathological T, N, and M descriptors in the 7th Edition, mutation status for the epidermal growth factor receptor (EGFR) if available, recurrence, and prognosis.

Patients were assigned to one of two groups based on their histological type as follows: sarcomatoid carcinoma and other NSCLC groups. The sarcomatoid carcinoma group was further categorized into the following subgroups according to their histological subtype: pleomorphic carcinoma and other sarcomatoid carcinoma groups

(spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma). Furthermore, clinicopathological characteristics and survival were compared among the groups. Of these patients, data from the sarcomatoid carcinoma group where R0 resection was achieved were extracted, and prognostic factors were identified using a multivariate Cox proportional hazard model.

Survival

Postoperative recurrence was recorded based on diagnoses by the doctor in charge at the medical institution [14]. OS and recurrence-free survival (RFS) were defined as the time intervals from surgical resection to all-cause mortality and the time of first recurrence or death, respectively. Data on RFS were censored at last visit for those patients who were still living.

Statistical analysis

The data were analyzed and compared using the Kaplan–Meier method and the log-rank test, respectively. Patients whose recurrence time was unavailable were excluded from the RFS analyses. Clinicopathological data were evaluated through univariate analysis. Means and standard deviations for continuous variables and percentages for categorical variables, which were compared using Mann–Whitney U and Fisher's exact tests, were included in the descriptive statistics. Multivariate analyses for prognostic factors were conducted using Cox proportional hazards regression models to estimate the hazard ratios (HR) and 95% confidence intervals (CIs). Statistical significance was considered at $p < 0.05$. All statistical analyses were performed independently by a biostatistician (E.M.).

Results

Patients' characteristics

Clinicopathological characteristics according to the histological type are shown in Table 1. Overall, patients with sarcomatoid carcinoma comprised 1.4% (217 of 14,999) of all patients. In the sarcomatoid carcinoma group, 172 (79.3%), 13 (6.0%), 9 (4.1%), 8 (3.7%), 4 (1.8%), and 11 (5.1%) patients had pleomorphic carcinoma, which was the most common pathological subtype, followed by spindle cell carcinoma, carcinosarcoma, giant cell carcinoma, pulmonary blastoma, and unknown pathological subtype, respectively.

The sarcomatoid carcinoma group comprised mainly males (79.3%) with a mean age of 66.1 years and had more smokers ($p < 0.001$), emphysema ($p = 0.004$), location in the upper and middle lobe ($p = 0.017$), larger tumor size ($p < 0.001$), pleural invasion ($p < 0.001$), lymphatic permeation ($p < 0.001$), vascular invasion ($p < 0.001$), lymph node metastasis ($p < 0.001$), and more advanced pathological stage ($p < 0.001$) than the other NSCLC group. Regarding operative outcomes, the sarcomatoid carcinoma group had more patients with lobectomy or larger surgery ($p < 0.001$), combined resection of the adjacent organ ($p < 0.001$), bronchoplasty or angioplasty ($p = 0.001$), and incomplete resection ($p < 0.001$) than the other NSCLC group.

Among the 5785 patients tested for EGFR mutation status, the sarcomatoid carcinoma group had fewer EGFR mutation-positive cases ($p < 0.001$) than the other NSCLC group. Only 8 patients (3.7%) were EGFR mutation-positive in the sarcomatoid carcinoma group.

Based on imaging findings, most patients with sarcomatoid carcinoma of the lung had pure solid tumors (86.6%: 188 of 217 patients). The consolidation tumor ratio, calculated as the ratio of the tumor consolidation diameter to the tumor maximum diameter on computed tomography of patients with sarcomatoid carcinoma of the lung, was > 0.5 in all cases.

Thereafter, we compared the clinicopathological features between the two groups as follows: pleomorphic carcinoma and other sarcomatoid carcinoma groups. As shown in Supplementary Table 1 (see Additional file 1), the pleomorphic carcinoma group had more pleural invasion ($p = 0.023$), vascular invasion ($p = 0.032$), and more advanced pathological stage ($p = 0.001$) than the other sarcomatoid carcinoma group.

Recurrence sites and subtypes

We compared the recurrence rate and the pattern of initial recurrence between the sarcomatoid carcinoma and other NSCLC groups (Table 2). In the sarcomatoid carcinoma group, 48.4% of patients experienced recurrence. Additionally, the sarcomatoid carcinoma group had more recurrence ($p < 0.001$) and distant metastases ($p = 0.030$) than the other NSCLC group.

Adjuvant chemotherapy

We compared the clinicopathological characteristics of completely resected sarcomatoid carcinoma according to whether or not adjuvant chemotherapy was administered (see Additional file 1, Supplementary Table 2). The patient group comprising individuals with older age ($p < 0.001$) and in more advanced pathological stage was selected as the adjuvant chemotherapy group ($p = 0.015$). However, no significant difference was observed in the other clinicopathological characteristics between the two groups. We compared the adjuvant chemotherapy agents in patients with completely resected sarcomatoid carcinoma of the lung according to their pathological stage (see Additional file 1, Supplementary Table 3). The pathological stage I group was administered more

Table 1 Clinicopathological characteristics of sarcomatoid carcinoma and other NSCLCs

Characteristics	Total (*n* = 14,999)	No. Patients (%)		*p* value
		Sarcomatoid carcinoma (*n* = 217)	Other NSCLC (*n* = 14,782)	
Age at operation (years), mean ± SD		66.1 ± 10.8	68.2 ± 9.3	0.005
Sex				
Female	5684	45 (20.7)	5639 (38.1)	< 0.001
Male	9315	172 (79.3)	9143 (61.9)	
Performance Status				
0–1	14,329	204 (94.0)	14,125 (95.6)	0.280
≥ 2	319	10 (4.6)	309 (2.1)	
Unknown	351	3 (1.4)	348 (2.3)	
Smoking status				
Non-smoker	5281	36 (16.6)	5245 (35.5)	< 0.001
Current or former smoker	9252	177 (81.6)	9075 (61.4)	
Unknown	466	4 (1.8)	462 (3.1)	
Preoperative serum CEA, ng/mL				
≤ 5	10,203	155 (71.4)	10,048 (68.0)	0.362
> 5	4299	56 (25.8)	4243 (28.7)	
Unknown	497	6 (2.8)	491 (3.3)	
FEV1%, %				
< 70	4414	74 (34.1)	4340 (29.4)	0.064
≥ 70	10,071	129 (59.4)	9942 (67.3)	
Unknown	514	14 (6.5)	500 (3.3)	
Interstitial pneumonia				
Absent	14,346	206 (94.9)	14,140 (95.7)	0.613
Present	653	11 (5.1)	642 (4.3)	
Emphysema				
Absent	12,934	172 (79.3)	12,762 (86.3)	0.004
Present	2065	45 (20.7)	2020 (13.7)	
Tumor location				
Upper and middle lobe	9386	148 (68.2)	9238 (62.5)	0.017
Lower lobe	5582	67 (30.9)	5515 (37.3)	
Others	31	2 (0.9)	29 (0.2)	
Neo-adjuvant therapy				
Absent	14,581	207 (95.4)	14,374 (97.2)	0.139
Present	418	10 (4.6)	408 (2.8)	
Chemotherapy	184	5	179	
Radiotherapy	33	1	32	
Chemoradiotherapy	201	4	197	
Extent of pulmonary resection				
Sublobar resection	1757	5 (2.3)	1752 (11.9)	< 0.001
Wedge resection	247	2	245	
Segmentectomy	1510	3	1507	
Lobectomy or larger	13,242	212 (97.7)	13,030 (88.1)	
Lobectomy	12,570	186	12,384	
Bilobectomy	375	13	363	
Pneumonectomy	294	13	283	
Lymph node dissection				
≤ ND1b	2907	34 (15.7)	2873 (19.4)	0.170
≥ ND2a	11,883	182 (83.9)	11,701 (79.2)	

Table 1 (continued)

Characteristics	Total ($n=14,999$)	No. Patients (%)		*p* value
		Sarcomatoid carcinoma ($n=217$)	Other NSCLC ($n=14,782$)	
Unknown	209	1 (0.4)	208 (1.4)	
Combined resection of adjacent organ				
Absent	13,749	145 (66.8)	13,604 (92.0)	< 0.001
Present	1250	72 (33.2)	1178 (8.0)	
Bronchoplasty or angioplasty				
Absent	14,589	203 (93.5)	14,386 (97.3)	0.001
Present	410	14 (6.5)	396 (2.7)	
Histological type				
Adenocarcinoma	10,768	-	10,768 (72.9)	
Squamous cell carcinoma	3225	-	3225 (21.8)	
Large cell carcinoma	478	-	478 (3.2)	
Adenosquamous carcinoma	311	-	311 (2.1)	
Pleomorphic carcinoma	172	172 (79.3)	-	
Spindle cell carcinoma	13	13 (6.0)	-	
Carcinosarcoma	9	9 (4.1)	-	
Giant cell carcinoma	8	8 (3.7)	-	
Pulmonary blastoma	4	4 (1.8)	-	
Others	11	11 (5.1)	-	
Maximum tumor size (cm), mean ± SD		4.7 ± 2.3	2.8 ± 1.7	< 0.001
Pleural invasion				
Absent	10,691	80 (36.9)	10,611 (71.8)	< 0.001
Present	4202	136 (62.7)	4066 (27.5)	
Unknown	106	1 (0.4)	105 (0.7)	
Lymphatic permeation				
Absent	8316	95 (43.8)	8221 (55.6)	< 0.001
Present	4342	88 (40.6)	4254 (28.8)	
Unknown	2341	34 (15.6)	2307 (15.6)	
Vascular invasion				
Absent	8379	58 (26.7)	8321 (56.3)	< 0.001
Present	4570	135 (62.2)	4435 (30.0)	
Unknown	2050	24 (11.1)	2026 (13.7)	
Pulmonary metastasis				
Absent	14,503	210 (96.8)	14,293 (96.7)	1.0
Present	496	7 (3.2)	489 (3.3)	
Lymph node metastasis				
N0	11,895	142 (65.4)	11,753 (79.5)	< 0.001
N1-2	3104	75 (34.6)	3029 (20.5)	
Pathological stage				
Stage I	10,423	73 (33.6)	10,350 (70.0)	< 0.001
Stage II–III	4576	144 (66.4)	4432 (30.0)	
Residual tumor				
R0	14,417	196 (90.3)	14,221 (96.2)	< 0.001
R1-2	582	21 (9.7)	561 (3.8)	
EGFR mutation (in examined cases)				
Negative	3586	84 (38.7)	3502 (23.7)	< 0.001
Positive	2099	8 (3.7)	2091 (14.1)	

Table 1 (continued)

Characteristics	Total ($n=14,999$)	No. Patients (%)		*p* value
		Sarcomatoid carcinoma ($n=217$)	Other NSCLC ($n=14,782$)	
Adjuvant chemotherapy				
Absent	10,066	115 (53.0)	9951 (67.3)	< 0.001
Present	4715	94 (43.3)	4621 (31.3)	
Platinum-based	2391	64	2327	
Not platinum-based	94	6	88	
Oral	2165	24	2141	
Unknown	65	0	65	
Unknown	218	8 (3.7)	210 (1.4)	

NSCLC Non-small cell lung cancer, *SD* Standard deviation, *CEA* Carcinoembryonic antigen, *FEV1%* Forced expiratory volume in 1 s, *EGFR* Epidermal growth factor receptor

Table 2 Comparison of the recurrence rate and the pattern of initial recurrence between sarcomatoid carcinoma and other NSCLCs

Characteristics	Total ($n=14,999$)	No. Patients (%)		*p* value
		Sarcomatoid carcinoma ($n=217$)	Other NSCLC ($n=14,782$)	
Recurrence				
Absent	11,082	109 (50.2)	10,973 (74.2)	< 0.001
Present	3842	105 (48.4)	3737 (25.3)	
Unknown	75	3 (1.4)	72 (0.5)	
Initial recurrence sites				
Loco-regional	1564	32 (14.8)	1532 (10.4)	0.030
Distant	2278	73 (33.6)	2205 (14.9)	

NSCLC Non-small cell lung cancer

oral agents (82.6%), while the pathological stage II–III group was administered more intravenous agents (90.5%) ($p < 0.001$).

Survival analysis

Survival curves and 5-year survival for OS and RFS

Figure 1A and B show the survival curves for OS and RFS, respectively, according to the histological type in all the cases. In the sarcomatoid carcinoma group, the 5-year OS and RFS rates were 50.1% and 42.8%, respectively. Patients with sarcomatoid carcinoma had the worst prognosis in all the cases.

Supplementary Fig. 1A and B (see Additional file 2) show the survival curves for OS and RFS, respectively, according to the histological type in pathological stage I cases. In pathological stage I cases, the 5-year OS and RFS rates in the sarcomatoid carcinoma group were 64.7% and 55.8%, respectively, which were lower than those in the other NSCLC group. Supplementary Fig. 2A and B (see Additional file 2) illustrate the survival curves for the OS and RFS, respectively, according to the histological type in pathological stage II–III cases. In pathological stage II–III cases in the sarcomatoid carcinoma group, the 5-year OS and RFS rates were 41.6% and 35.1%, respectively; both rates were lower than those in the other NSCLC group.

The survival curves for OS and RFS according to the histological subtype in the sarcomatoid carcinoma group are shown in Supplementary Fig. 3A and B (see Additional file 2), respectively. No significant differences were observed in the OS and RFS between the pleomorphic carcinoma and other sarcomatoid carcinoma groups.

Figure 2A and B show the survival curves for OS and RFS, respectively, according to the adjuvant chemotherapy in the pathological stage I sarcomatoid carcinoma cases. No significant differences were observed in the OS and RFS according to the adjuvant chemotherapy.

Figures 2C and D illustrate the survival curves for OS and RFS, respectively, according to adjuvant chemotherapy in the pathological stage II–III sarcomatoid carcinoma cases. In the cases with adjuvant chemotherapy, the 5-year OS and RFS rates were 54.2% and 42.3%, respectively. The prognosis of the pathological stage II–III sarcomatoid carcinoma cases with adjuvant chemotherapy was significantly better than that of those without adjuvant chemotherapy.

Univariate and multivariate survival analyses of factors associated with the OS and RFS of the sarcomatoid carcinoma group

The univariate and multivariate survival analysis results of the factors associated with the sarcomatoid carcinoma group's OS are shown in Table 3. The univariate analysis revealed that older age, no adjuvant chemotherapy, larger tumor size, lymphatic permeation, vascular invasion, and

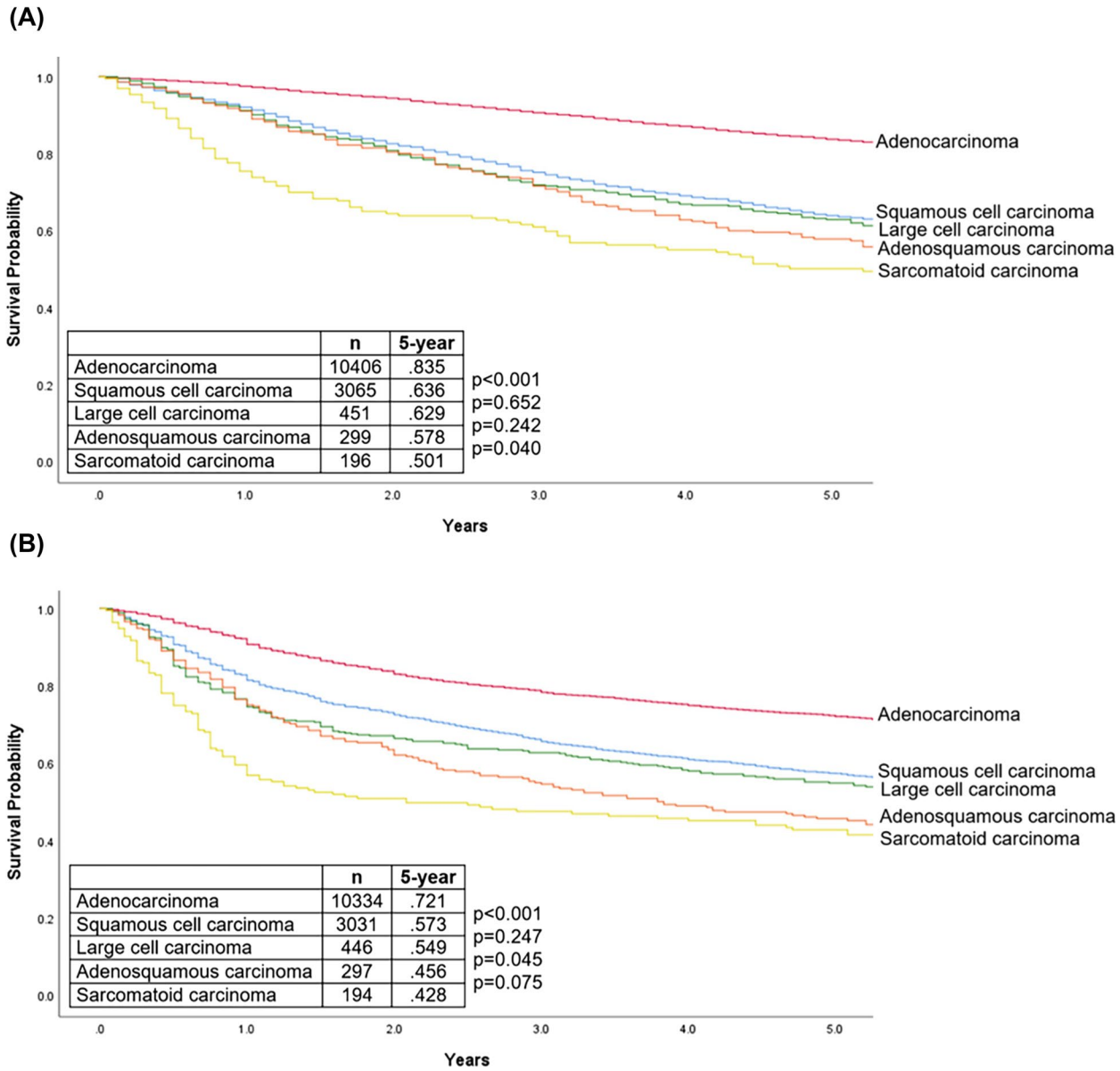

Fig. 1 Survival curves for overall survival (**A**) and recurrence-free survival (**B**), according to the histological type in all cases

advanced pathological stage were the factors associated with unfavorable OS, whereas no adjuvant chemotherapy, larger tumor size, and lymphatic permeation were the factors in the multivariate analysis.

Table 4 presents the results of the univariate and multivariate survival analyses of factors associated with the sarcomatoid carcinoma group's RFS. The univariate analysis revealed that no adjuvant chemotherapy, larger tumor size, lymphatic permeation, vascular invasion, and advanced pathological stage were the factors associated with unfavorable RFS. In the multivariate analysis, unfavorable RFS were associated with no adjuvant chemotherapy, larger tumor size, and lymphatic permeation. Furthermore, similar prognostic factors as in OS were also identified as being associated with RFS.

Discussion

Here, we investigated the clinicopathological characteristics and prognostic factors of surgically resected sarcomatoid carcinoma of the lung using the largest nationwide cohorts in Japan with patients with NSCLC who underwent surgical resection.

Sarcomatoid carcinoma of the lung is a rare type of NSCLC with a poor prognosis. Most previous

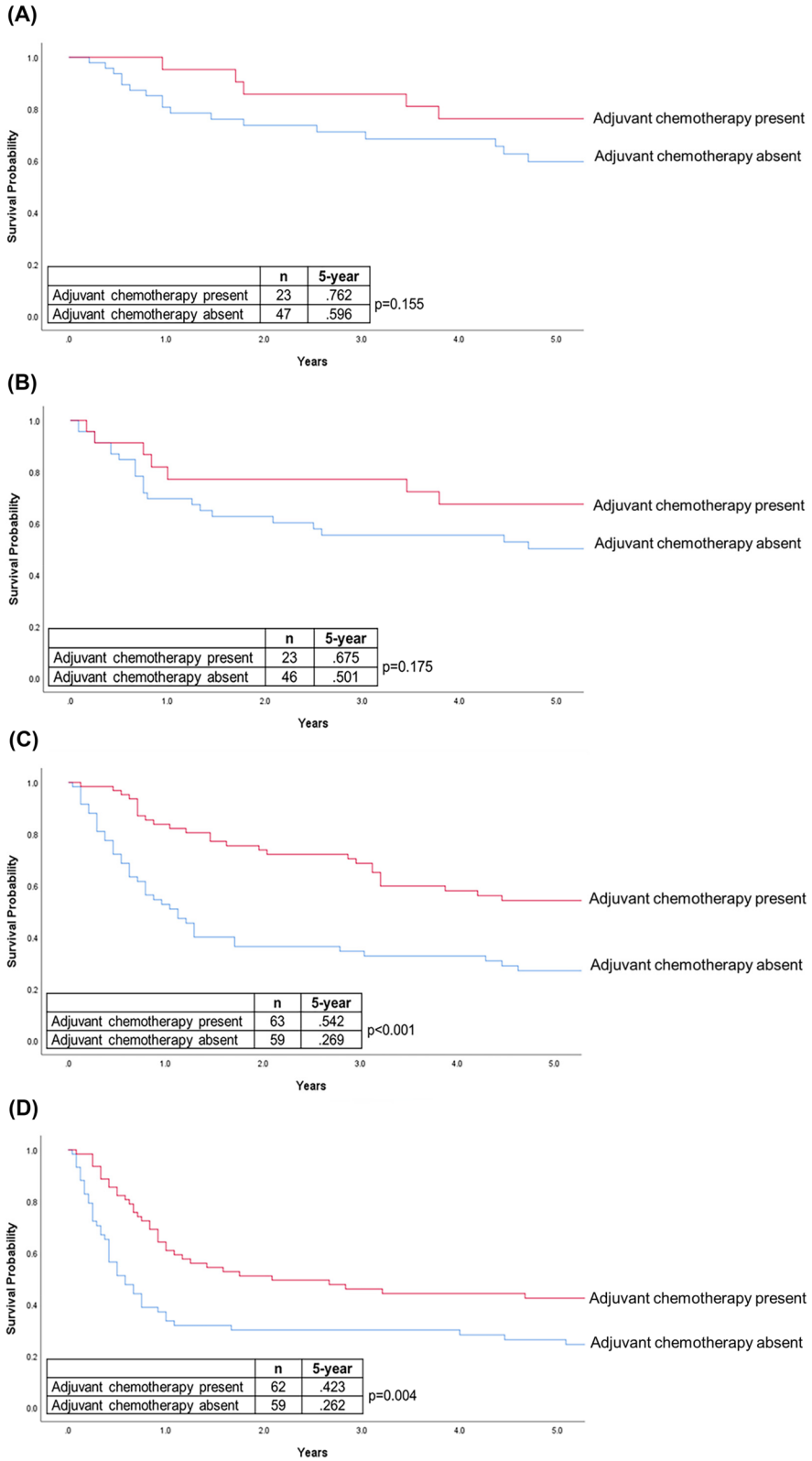

Fig. 2 Survival curves for overall survival (**A**) and recurrence-free survival (**B**), according to the adjuvant chemotherapy in the sarcomatoid carcinoma group in pathological stage I cases. Survival curves for overall survival (**C**) and recurrence-free survival (**D**), according to adjuvant chemotherapy in the sarcomatoid carcinoma group in pathological stage II–III cases

Table 3 Clinicopathological predictors of overall survival according to uni- and multivariate analyses

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at operation, years				
1 year older	1.026 (1.006–1.047)	0.010	1.023 (0.998–1.048)	0.072
Sex				
Male	1			
Female	0.674 (0.398–1.140)	0.141		
Smoking status				
Nonsmoker	1			
Current or former smoker	1.460 (0.812–2.624)	0.206		
Preoperative serum CEA, ng/mL				
≤ 5	1			
> 5	1.060 (0.669–1.678)	0.804		
Neo-adjuvant therapy				
Absent	1			
Present	1.144 (0.464–2.818)	0.770		
Adjuvant chemotherapy				
Absent	1		1	
Present	0.526 (0.343–0.807)	0.003	0.413 (0.236–0.724)	0.002
Histological subtype				
Pleomorphic carcinoma	1			
Others	0.709 (0.413–1.214)	0.210		
Tumor size, cm				
1 cm larger	1.127 (1.048–1.211)	0.001	1.135 (1.033–1.247)	0.008
Pleural invasion				
Absent	1			
Present	1.253 (0.816–1.925)	0.302		
Lymphatic permeation				
Absent	1		1	
Present	1.712 (1.099–2.667)	0.018	1.920 (1.151–3.202)	0.012
Vascular invasion				
Absent	1		1	
Present	1.931 (1.130–3.300)	0.016	1.038 (0.566–1.904)	0.904
Pathological stage				
Stage I	1		1	
Stage II–III	2.072 (1.302–3.298)	0.002	1.666 (0.898–3.090)	0.106

HR Hazard ratio, *CI* Confidence interval, *CEA* Carcinoembryonic antigen

studies on sarcomatoid carcinoma of the lung were case reports with small scale or database analyses [16, 17]. Male patients and particularly heavy smokers can be easily prone to sarcomatoid carcinoma of the lung, as reported in our study. The primary subtype of sarcomatoid carcinoma of the lung is pleomorphic carcinoma [3, 16]. Notably, it was also the most common pathological subtype in this study. Our results demonstrated that the pleomorphic carcinoma cases had more pleural invasion, vascular invasion, and more advanced pathological stages than the other sarcomatoid carcinoma cases. However, no significant differences in OS and RFS were observed between the pleomorphic carcinoma and the other sarcomatoid carcinoma cases.

Metastatic locations of sarcomatoid carcinoma of the lung resemble those of the other NSCLCs, including pleura, lung, brain, adrenal glands, and bone [12, 18–20]. Here, the sarcomatoid carcinoma group had more distant metastases than the other NSCLC group, which reflects the high aggressive and metastatic potential of sarcomatoid carcinoma of the lung.

Table 4 Clinicopathological predictors of recurrence-free survival according to uni- and multivariate analyses

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at operation, years				
1 year older	1.013 (0.996–1.031)	0.136		
Sex				
Male	1			
Female	0.854 (0.535–1.363)	0.508		
Smoking status				
Nonsmoker	1			
Current or former smoker	1.165 (0.694–1.956)	0.563		
Preoperative serum CEA, ng/mL				
≤ 5	1			
> 5	1.109 (0.731–1.681)	0.627		
Neo-adjuvant therapy				
Absent	1			
Present	0.976 (0.398–2.395)	0.957		
Adjuvant chemotherapy				
Absent	1		1	
Present	0.654 (0.445–0.962)	0.031	0.428 (0.275–0.665)	< 0.001
Histological subtype				
Pleomorphic carcinoma	1			
Others	0.837 (0.524–1.336)	0.456		
Tumor size, cm				
1 cm larger	1.101 (1.027–1.180)	0.007	1.098 (1.003–1.203)	0.042
Pleural invasion				
Absent	1			
Present	1.174 (0.795–1.733)	0.420		
Lymphatic permeation				
Absent	1		1	
Present	1.696 (1.134–2.536)	0.010	1.772 (1.115–2.817)	0.016
Vascular invasion				
Absent	1		1	
Present	1.912 (1.180–3.100)	0.009	1.205 (0.693–2.096)	0.508
Pathological stage				
Stage I	1		1	
Stage II–III	1.906 (1.257–2.889)	0.002	1.549 (0.905–2.652)	0.111

HR Hazard ratio, *CI* Confidence interval, *CEA* Carcinoembryonic antigen

Surgical resection is considered the main therapeutic approach for managing sarcomatoid carcinoma of the lung, particularly in cases of early-stage disease [16, 21, 22] This study revealed that sarcomatoid carcinoma of the lung is frequently diagnosed at a locally advanced stage, which is prone to invasion of the neighboring structure and vascular tissue, requiring more frequent extensive surgical resections than other NSCLCs.

Of note, our study demonstrated that patients with sarcomatoid carcinoma of the lung had a poorer prognosis than those with other NSCLCs, which is consistent with the findings of previous studies [2, 7, 12, 13]. When performing Cox proportional hazards regression for patients with sarcomatoid carcinoma of the lung, there are more positive cases for RFS when reviewing the survival curves of OS and RFS, and the statistical power for RFS should be stronger. However, the final analysis revealed that the pathological stage is an independent influencing factor for OS but not for RFS.

Previous studies have demonstrated the TNM stage to be the major prognostic factor; moreover, pleural invasion and spread of the tumor through air spaces also

influence the prognosis of sarcomatoid carcinoma of the lung [23, 24]. In this study, larger tumor size, lymphatic permeation, and no adjuvant chemotherapy were significant prognostic factors for OS and RFS.

The frequently described prognostic factors, such as tumor size, as well as lymph node invasion, are strongly associated with locally advanced disease. Tumor size, which reflects the T factor in the TNM classification, is an important prognostic factor in patients with sarcomatoid carcinoma of the lung [25]. In the present study, the sarcomatoid carcinoma group had larger tumor size. Owing to its aggressive behavior, extended resection, such as pneumonectomy, bilobectomy, combined resection of adjacent organ, and bronchoplasty or angioplasty, are frequently required.

Several studies have reported the prognostic impact of lymphatic permeation on resected NSCLC [26–28]. However, lymphatic permeation remains an unconfirmed upstaging factor for NSCLCs. Our results may be useful for predicting postoperative survival and detecting suitable patients who require adjuvant chemotherapy among those with sarcomatoid carcinoma of the lung. Anti-D2-40 immunohistochemical staining was useful in identifying lymphatic vessels; better visualization with this staining enables pathologists to more precisely evaluate the presence of lymphatic permeation [29, 30]. However, performing anti-D2-40 staining in all cases is not considered feasible owing to its high cost.

One of the main unsolved problems in the treatment of sarcomatoid carcinoma of the lung lies in the advantage of adjuvant chemotherapy, for which no consensus exists. Therefore, thoracic surgeons and thoracic oncologists are unable to provide sufficient evidence concerning the prognosis and advantage of adjuvant chemotherapy to patients with sarcomatoid carcinoma of the lung. Although numerous previous studies have reported the insufficient effect of adjuvant chemotherapy in patients with sarcomatoid carcinoma of the lung [10, 20, 31], few reports have revealed benefits of survival with adjuvant chemotherapy, resulting in uncertain agreement on the effect of chemotherapy in patients with sarcomatoid carcinoma of the lung, which makes the formulation of evidence-based guidelines challenging. In some studies, pathological stage II–III patients who received adjuvant chemotherapy demonstrated a superior outcome concerning the OS, whereas those in pathological stage I did not show improvement [22, 32, 33]. Moreover, patients with sarcomatoid carcinoma of the lung can easily experience traditional chemotherapy resistance [20]. Here, adjuvant chemotherapy correlated with better survival for pathological stage II–III sarcomatoid carcinoma cases rather than pathological stage I cases. This trend differs from that of other NSCLC subtypes with poor prognoses, including large-cell neuroendocrine carcinoma, for which adjuvant chemotherapy is effective in the early stages [34].

In the present study, the pathological stage I group was administered more oral agents; however, early-stage cases may need more effective intravenous platinum-based agents to improve the prognosis. This analysis clearly shows that adjuvant chemotherapy is associated with enhanced OS in patients with pathological stage II–III and should be properly examined to determine the therapeutic strategy for these patients.

In addition, although the advantage of adjuvant chemotherapy without definite regimens in this nationwide database might be concluded from this study, the type of regimens most effective against sarcomatoid carcinoma of the lung remains significantly controversial. Some studies have reported that sarcomatoid carcinoma of the lung is resistant to platinum agents, whereas regimens with gemcitabine and docetaxel are considered viable based on evidence with soft tissue sarcomas [35]. Despite the efficacy of adjuvant chemotherapy confirmed in this study, the prospect of systemic therapy for sarcomatoid carcinoma of the lung might be substituted with targeted therapy and immunotherapy together with or in place of traditional chemotherapy.

Owing to the limited studies concerning the effectiveness of chemotherapy in sarcomatoid carcinoma of the lung and the superior efficacy of targeted therapy and immunotherapy reported in other NSCLCs, many studies on the effectiveness of targeted therapy and immunotherapy in sarcomatoid carcinoma of the lung have been recently conducted. In patients with sarcomatoid carcinoma of the lung, targetable mutations of the classical genes (*EGFR*, anaplastic lymphoma kinase) are uncommon; on the other hand, frequent overexpression of programmed death ligand-1 (PD-L1) has been observed [36–38]. Based on these reports, some researchers have explored the probability of immune checkpoint inhibitors (ICIs) as adjuvant therapy in patients with resected sarcomatoid carcinoma of the lung [39, 40].

Interestingly, immunotherapy is a new treatment choice for NSCLC. However, owing to the lower morbidity of sarcomatoid carcinoma of the lung, large-scale prospective studies of ICIs in sarcomatoid carcinoma of the lung have seldom been performed. Some small-scale studies have demonstrated improved prognosis with ICIs. Therefore, patients with a high PD-L1 expression may show a good response to ICIs. Although immunotherapy is a desired therapy, no patient received ICIs in this study.

Our study has certain limitations. First, this was a retrospective study, and the cases were accumulated from many hospitals, resulting in possible heterogeneity in

the management with surgery and perioperative care. Second, a central review of pathological information, which includes histology of sarcomatoid carcinoma of the lung, vascular invasion, lymphatic permeation, and pleural invasion, was not performed. Third, postoperative follow-up was not uniform and might have affected the detection of recurrence. Lastly, selection bias for chemotherapy and insufficient information on the chemotherapy regimens may exist as this was a database study. Although younger patients receiving chemotherapy could affect the interpretation of our results, this factor was controlled in the multivariate analyses.

Nevertheless, to our knowledge, this is the largest study to demonstrate the clinicopathological characteristics and prognostic factors of patients with surgically resected sarcomatoid carcinoma of the lung in Japan.

Conclusion

This nationwide database study demonstrated the clinicopathological characteristics and prognostic factors of surgically resected sarcomatoid carcinoma of the lung. The prognosis of surgically resected sarcomatoid carcinoma of the lung was worse than that of other NSCLCs. Moreover, adjuvant chemotherapy is associated with improved survival in patients with completely resected pathological stages II–III sarcomatoid carcinoma of the lung. Therefore, these data might reinforce adjuvant chemotherapy use in patients with pathological stages II–III resected sarcomatoid carcinoma of the lung, which may also be helpful for considering future adjuvant therapies, including emerging immunotherapy.

Abbreviations

CI	Confidence interval
EGFR	Epidermal growth factor receptor
HR	Hazard ratio
ICIs	Immune checkpoint inhibitors
JJCLCR	Japanese Joint Committee of Lung Cancer Registry
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD-L1	Programmed death ligand-1
RFS	Recurrence-free survival
TNM	Tumor-node-metastasis
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1: Supplementary Table 1. Clinicopathological characteristics of sarcomatoid carcinoma according to the histological subtype. Supplementary Table 2. Clinicopathological characteristics of completely resected sarcomatoid carcinoma according to whether or not adjuvant chemotherapy was administered. Supplementary Table 3. Comparison of adjuvant chemotherapy agents in patients with completely resected sarcomatoid carcinoma according to the pathological stage

Supplementary Material 2: Supplementary Figure 1. Survival curves for overall survival (A) and recurrence-free survival (B), according to the histological type in pathological stage I cases. Supplementary Figure 2. Survival curves for overall survival (A) and recurrence-free survival (B), according to the histological type in pathological stage II-III cases. Supplementary Figure 3. Survival curves for overall survival (A) and recurrence-free survival (B), according to the histological subtype in the sarcomatoid carcinoma group.

Authors' contributions

"K.K. made contributions to the conception, design of the work, interpretation of data and wrote main manuscript. S.Y. made contributions to the data analysis. K.A., J.O., S.T., Y.S., S.W., M.C., H.S., E.M., I.Y., and H.D. made substantial contributions to the interpretation of data and analysis. All authors reviewed the manuscript". The author(s) read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the Japanese Joint Committee of Lung Cancer Registry Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Japanese Joint Committee of Lung Cancer Registry Database.

Declarations

Ethics approval and consent to participate

We confirmed all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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