Original Article

Prognostic factors for sarcomatoid carcinomas of lung: A single-centre experience

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ABSTRACT

Background: Although lung sarcomatoid carcinomas (LSCa) arised from the epithelial tissue, they have very distinctive features than other non-small cell lung carcinomas in terms of histopathology and survival. It constitutes 0.1%–0.4% of all lung cancers. The aim of our study is to evaluate the survival analysis of LSCa in a single thoracic surgery clinic and to determine the prognostic factors. **Materials and Methods:** It was a retrospective cohort study. After the approval of the local ethics committee, a total of 34 patients who were operated in our department between January 2010 and December 2018, whose pathologies were reported as sarcomatoid carcinoma was included in the study. The patients were analyzed by age, gender, presence of necrosis in the histopathological examination, tumor stage, tumor diameter, and tumor location. **Results:** There were 28 males and 6 females. The median age was 60 years (range: 36–80 years). The median survival was 42 months (32.6–52.2 months), and the 5-year overall survival was 33.6%. Significantly negative prognostic factors were tumor diameter and tumor stage (P = 0.003 and 0.001, respectively). Median disease-free interval (DFI) was 38 months (27.3–49.1 months), and 5-year DFI was 32.6%. **Conclusion:** LSCa are highly heterogeneous epithelial malignancies, and it has worse survival than other epithelial cancers. Relatively, satisfactory results can be obtained in these tumors with surgical treatment.

KEY WORDS: Giant cell, pleomorphic carcinoma, sarcomatoid carcinoma, spindle cell

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INTRODUCTION

Lung sarcomatoid carcinomas (LSCa) are highly heterogeneous tumors, which include different carcinomas, and it constitutes 0.1%–0.4% of all lung malignancies.[1] According to the WHO 2015, LSCa were defined as epithelial lung malignancies, which include five different tumor histopathology. These are pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.[2] It has been reported in the literature that LSCa are more common in male and smoker. In spite of its anaplastic characteristics, many cases are surgically complete resectable.[3] Histopathologically, tumor cells are heterogeneous and pleomorphic in LSCa, hence, the diagnosis is difficult with a small biopsy sample, and precise diagnosis can usually be achieved with larger samples or all resected materials.[4] The common opinion in literature is that LSCa have the worst prognosis than other epithelial non-small cell lung cancers.[5] The aim of this study is analyzing the survival of the patients who underwent surgical treatment in our clinic, whose

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histopathologies were reported as LSCa and determined as negative prognostic factors.

MATERIALS AND METHODS

Patient selection

Following the approval of the local ethics committee (Gazi University Ethics Committee), the records of the patients who were operated with the diagnosis of non-small cell lung cancer between January 2011 and December 2018 were examined. Inclusion criteria were as follows: LSCa histopathology (one or combination of these: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma), complete resection (R0), and access to follow-up records (for overall and disease-free survival). Patients who underwent wedge resection and had true mesenchymal sarcoma pathology were not included in the study. Data of patients were analyzed according to the age, gender, tumor stage, tumor diameter, histopathologic subgroup, tumor location, presence of necrosis, visceral pleural invasion, lymph node invasion (hilar/mediastinal), type of resection, and whether given adjuvant therapy.

Statistical analysis

The overall survival (OS) was defined as the length of time as month from surgery to death or the final follow-up. Data of patients were analyzed using SPSS version 20.0 (statistical package for windows manufactured by IBM Corp., Armonk, NY, United States). OS was analyzed with the Kaplan–Meier method with 95% confidence intervals. Survival differences between groups were analyzed using the Log-rank test and Cox regression test. Two-sided *P* values were calculated, and it was considered statistically significant when $P < 0.05$.

RESULTS

The clinico-pathologic features of patients are given in Table 1. A total of 34 patients who fulfilled the mentioned criteria were included in the study. There were 6 females and 28 males. The median age was 60 years (range: 36–80 years). Two patients had carcinosarcoma, nine patients had pure spindle or giant cell carcinoma, and 23 patients had mixed pathology. Mixed histopathologies were as follows: spindle cells accompanied squamous cell carcinoma in five patients, adenocarcinoma in five patients, and large cell carcinoma in two patients. Coexistence of giant cell and adenocarcinoma was detected in seven patients, and a combination of giant cells with squamous cell carcinoma was in one patient. Three patients had three tumor cell combination, including giant cell, spindle cell, and adenocarcinoma. In our series, there was no histopathology of pulmonary blastoma. While 22 patients had no lymph node invasion, there were hilar lymph node invasion (N1) in seven patients and mediastinal lymph node invasion (N2) in five patients. Visceral pleural invasion was detected in 17 patients, and parietal pleural invasion was detected in two patients. The tumor was located in upper zones in 20 cases, lower zones in nine cases, and pulmonary hilum in five cases. Pneumonectomy was performed in

Table 1: Clinicopathologic characteristics of patients

	Study population (*n*=34), *n* (%)
Gender	
Male	28 (82.3)
Female	6 (17.7)
Age, median (range)	60 (36-80)
≤65	26 (76.5)
>65	8 (23.5)
Marital status	
Single	6 (17.7)
Married	28 (82.3)
Tumor diameter (cm), mean±SD (range)	5.5±0.4 (1-10.5)
Histopathology	
Mix (plemorphic carcinoma)	23 (67.6)
Sp + SCC	5 (14.7)
Sp + AdenoCA	5 (14.7)
Sp + LCC	2 (5.8)
G + AdenoCA	7 (20.7)
G + SCC	1 (2.9)
G + Sp + AdenoCA	3 (8.8)
Pure (Sp or G)	9 (18.3)
Carcinosarcoma	2 (5.9)
Tumor stage (8th TNM)	
IA	3 (8.8)
IB	2 (5.9)
IIA	1 (2.9)
IIB	12 (35.3)
IIIA	14 (41.2)
IIIB	2 (5.9)
Tumor diameter (cm)	
≤3	4 (11.7)
3-≤4	6 (17.7)
4-≤5	6 (17.7)
5-≤7	10 (29.4)
>7	8 (23.5)
Occupation	
Retired worker	9 (26.5)
Retired officer	8 (23.5)
Worker	7 (20.6)
Officer	5 (14.8)
Farmer	3 (8.8)
Unemployed	2 (5.8)
Lymph node ınvasion	
N0	22 (64.7)
N1	7 (20.6)
N2	5 (14.7)
Localization	
Upper	20 (58.8)
Centrally	5 (14.7)
Lower	9 (26.5)
Technique	
Lobectomy, segmentectomy	24 (70.6)
Pneumonectomy	4 (11.8)
Extended	6 (17.6)
Pleural invasion	
Nil	15 (44.1)
VPI	17 (50.0)
PPI	2 (5.9)
Necrosis	
Yes	6 (17.6)
Nil	28 (82.4)

AdenoCA: Adenocarcicoma, SCC: Squamous cell carcinoma, Sp: Spindle cell carcinoma, LCC: Large cell carcinoma, G: Giant cell carcinoma, PPI: parietal pleural invasion, VPI: Visceral pleural invasion, SD: Standard deviation, TNM: Tumor, node, and metastasis

four patients, and extended resections (lung resection with chest wall resection or left atrial resection) were performed in six patients, while 24 patients underwent lobectomy (standard or sleeve lobectomy) or segmentectomy operation. Histopathologically, the necrosis was detected in six patient's specimens. Since it is difficult to diagnose sarcomatoid carcinoma in small tissue biopsies, preoperative diagnoses are often given as "nonsmall cell carcinoma" or "malignant epithelial tumor." In our study, 24 of 34 patients (70.5%) had a diagnosis of preoperative malignant tumor, and only two of them diagnosed with pleomorphic carcinoma by transthoracic needle aspiration biopsy. The diagnosis was made in 10 patients (29.5%) as "nonsmall cell carcinoma" with intraoperative frozen section.

The common complaint of patients was cough, followed by shortness of breath. The three patients had pleuritic chest pain. There were no any clinical symptoms in ten patients and their masses were detected incidentally. Postoperative adjuvant chemotherapy was a platinum-based regimen and cisplatin or carboplatin plus docetaxel in 24 patients (70.6%) and cisplatin or carboplatin plus vinorelbine in 7 patients (20.6). Three patients (8.8%) whose tumor stages in stage information architecture according to the 8th tumor, node, and metastasis (TNM) system for non-small cell lung cancer did not receive adjuvant treatment. The median survival was 42 months (32.6–52.2 months), and 5-year OS was 33.6% [Figure 1]. The OS was worse as statistically significant in Stage III patients group according to the 8th TNM staging system than earlier stages (hazard ratio [HR] = 5.02; 95% confidence interval: 1.9–12.3; Figure 2; $P = 0.01$). Patients were grouped according to tumor diameter as ≤ 5 cm, 5–7 cm and >7 cm, the worst median survival was in patients with >7 cm tumor as 13 months (range: 2–23 months), and this correlation was statistically significant (HR = 3.12; 95% confidence interval: 1.9–9.6; Figure 3; $P = 0.02$). When survival analysis was performed according to hilar/mediastinal lymph node invasion, the median survival was 44 months (34.1–55.6) in N0/N1 group and 19 months (3.4–35.3) in N2 group, but there was no statistically significant relationship ($P = 0.10$). Gender, age, and tumor location status had no significant effect on survival. Median disease-free interval (DFI) was 38 months (27.3–49.1), and 5-year DFI was 32.6%. DFI was negatively affected by pleural invasion (visceral and parietal), presence of necrosis, lack of adjuvant chemotherapy, and tumor stage and diameter, but this correlation was not statistically significant ($P > 0.05$).

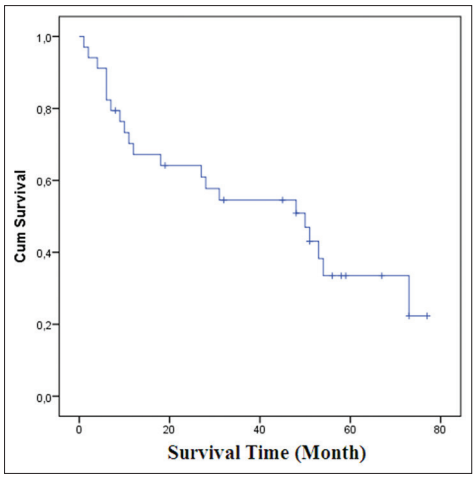

Figure 1: Overall survival curve of patients (Kaplan–Meier method)

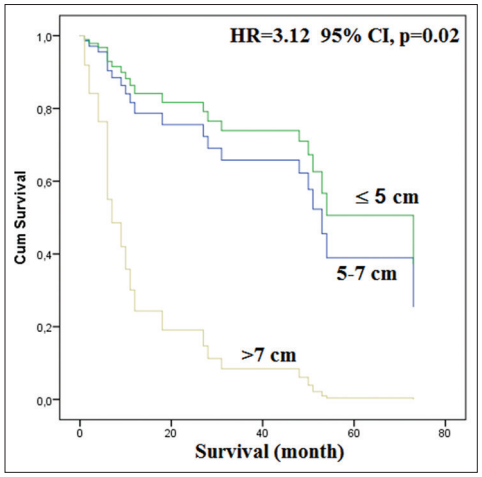

Figure 2: Survival comparison according to tumor diameter (Hazard ratio = 5.02; 95% confidence interval, $P = 0.003$)

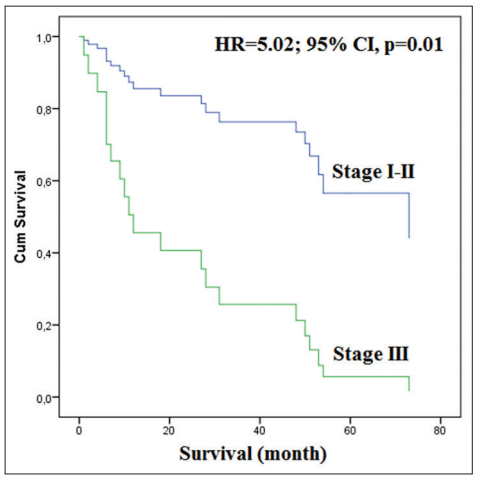

Figure 3: There was a statistically significant correlation between survival and tumor stage (Hazard ratio = 3.12; 95% confidence interval, $P = 0.02$)

DISCUSSION

The sarcomatoid carcinomas of the lung (LSCa) arise from the epithelial tissue are a heterogeneous tumor that constitutes <1% of lung malignancies and have difficulties in both diagnostic and treatment strategies.[6] According to the 4th WHO classification published in 2015, LSCa were divided into five subgroups such as pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. LSCa may be

composed of pure spindle or giant cell carcinoma, and it may also include adenocarcinoma, squamous carcinoma, and large cell carcinoma in different ratios. Diagnosis with small biopsy samples is difficult, and the final diagnosis is often obtained from the whole resected specimens.[2] It was reported that OS and DFI were very poor when compared with other nonsmall cell lung carcinomas, and the median survival was approximately 3 months in metastatic patients.[7] Histopathologically, immunohistochemical methods are frequently used to differentiate LSca from other epithelial, mesenchymal, and mesothelial tumors. The most commonly used immunohistochemical methods for the diagnosis of LSCa in the literature are cytokeratin (CK), transcription factor 1 (TTF1), and epithelial membrane antigen.[8] In our study, CK was found to be positive in 32 patients (94.1%) and TTF 1 in 30 (88.2%) patients. The other immunohistochemical methods used for differential diagnoses were Vimentin, S100, CD56, PanCK, and p63. According to the literature, the majority of LSCa patients are male gender and smokers, and the average age of them is from 60 to 70.[3] However, pulmonary blastoma is seen equally in both gender during the 4th decade.[9] The male-to-female ratio was 4.6, the mean age was 60 years, and the rate of smoking was 88.2% in our study, and these results were consistent with the literature. A total of 30 (88.2%) patients had a history of smoking (active, passive, or ex-smoker). The mean amount of smoking was 39.9 (standard deviation [SD]: 3.2) pack per year. Twenty-two patients (64.7%) were active smokers, six patients (17.6%) were ex-smokers, and the others were passive smokers. The mean exposure time was 41.2 (SD: 4.3). Histopathologically, pulmonary blastoma was not detected in our series. LSCa may be peripheral and central, and it is often located in the upper lobes.[9] In our study, five patients had central, 29 patients had peripheral tumor. Eighteen tumors (53%) were located in the upper zones and in 11 patients (32%) in the lower zones of lungs. The results of previous studies related to surgically treated LSCa are given in Table 2. Venissac *et al*. reported a 5-year survival rate of LSCa was 33%, and they stated that tumor size was an important prognostic factor.[10] Rossi *et al*. reported in their study, which included 75 cases, there were no patients who were living ≥5 years after the operation, the more important prognostic factor was tumor stage, and they no detected any correlation between survival and tumor histopathology.[11] Park *et al*. stated that the 5-year survival was 55%, and tumor stage, tumor diameter, and female gender were negative prognostic factors.[12] Raveglia indicated a median survival was 8 months, and remarkable prognostic factors were mediastinal lymph node invasion and tumor stage.[13] According to another study performed by Mochizuki *et al*. the 5-year survival of LSCa patients was 36.6, and the presence of necrosis, tumor stage, and lymphatic invasion were the worst prognostic factors.[14] Similarly, Nakajima *et al*. suggested negative prognostic factors for survival were tumor stage and lymph node invasion.[15] Lococo found in his study, including 70 patients, the 5-year survival was 12%, and the stage of tumor and the presence of tumor embolism were independent prognostic factors for survival.[16] In our study, the median survival was 41 months, and the 5-year OS was 33.6%. Statistically significant prognostic factors were determined as tumor diameter and tumor stage. Mediastinal lymph node invasions, presence of necrosis, and pure spindle cell or pure giant cell carcinoma histopathology were found to be adversely affected on survival, but these correlations were not statistically significant. There was no significant correlation between survival and tumor location, gender, age, and visceral pleural invasion. It is possible to find both very poor and satisfactory results related to DFI of LSCa in the literature.[4,15-18] Venissac *et al*. found that in the LSCa series, including 39 cases, DFI was worse as 4 months.[10] Mochizuki *et al*. reported 5-year DFI was 40.7%, necrosis and lymphatic spread were associated with recurrence and/or distant metastasis status. Mark reported a 5-year survival as 54.4%; and Martinez reported a mean survival was 49 months in their LSCa series.[5,12] In our study, the median DFI was 38 months (27.3–49.1), and the 5-year DFI was 32.6%. Pleural invasion (visceral and parietal), necrosis, absence of adjuvant chemotherapy, and tumor stage and diameter had a negative effect on DFI, but this was not statistically significant ($P > 0.05$).

Limitations of our study were as follows: it was a single-centered retrospective study, and it has a small number of cases. In this regard, there is a need for multi-centered prospective studies.

CONCLUSION

It has been reported in the literature, LSCa is a highly heterogeneous tumor group, and it has a poor prognosis than other epithelial nonsmall cell lung carcinomas. In our study, we concluded that the results of the surgical

Table 2: Previous studies related to surgically treated pulmonary sarcomatoid carcinoma in the literature

Author	Year	*n*	5-year OS (%)	Median survival (month)	Prognostic factors
Venissac[10]	2007	19	33	11	Diameter
Rossi[11]	2003	75	0	19	Stage
Park[12]	2011	99	55	?	Stage, diameter, female gender
Raveglia[13]	2004	20	0	8	Stage, lymph node invasion
Mochizuki[14]	2008	70	36,6	22,8	Necrosis, stage, lymph node invasion
Nakajma[15]	1999	37	?	10	Stage, lymph node invasion
Lococo[16]	2017	70	12	19	Stage, tumor embolism
Our study	2019	34	33.6	41	Stage, tumor diameter

OS: Overall survival

treatment of LSCa were relative satisfactory in terms of DFI and OS, and significant prognostic factors were tumor diameter and stage.

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Conflicts of interest
There are no conflicts of interest.

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