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Impact of Smoking History on Pulmonary Metastasis-free Survival in Patients With Soft-tissue Sarcoma

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Abstract. *Background/Aim: Although smoking history is predictive of poor pulmonary metastasis-free survival (PMFS) in patients with epithelial tumors, the impact of smoking history on PMFS in those with soft-tissue sarcoma (STS) is not known. Patients and Methods: Patients undergoing treatment for STS at our institutes between 2008 and 2017 were enrolled. Patients were excluded if they had metastatic lesion, or had a histopathological classification demonstrating small round-cell sarcoma. The impact of smoking history on PMFS and overall survival was examined with multivariate analysis using a Cox proportional hazards model. Results: A total of 250 patients were retrospectively reviewed. Patients with smoking history had worse PMFS on multivariate analysis (hazard ratio=2.00, 95% confidence interval=1.12-3.60). On the other hand, smoking history did not significantly affect overall survival (hazard ratio=1.26, 95% confidence interval=0.61-2.58). Conclusion: Patients with STS need to be followed-up by frequent clinical assessments if they have a smoking history.*

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Soft-tissue sarcomas (STSs) are heterogeneous tumor group comprising a variety of histological subtypes that arise in nearly any part of the body. STSs can occur at any age, although the median age is around 60 years, with a peak in the eighth decade (1). Despite progress in medical technology, more than 4,000 Americans will die each year due to STS, with a 5-year overall survival (OS) rate of approximately 50% (2).

Pulmonary metastases are a common manifestation of STS that require special attention (2, 3). Nearly one-quarter of patients will suffer pulmonary metastasis, and the 5-year survival rate in patients with pulmonary metastasis is 15% (4-6). On the other hand, the postoperative clinical outcomes in cases of resectable pulmonary metastasis are relatively favorable, with 3-year survival rates of around 40% after complete resection (7-9). To improve the clinical outcome in patients with STS, identification of factors that modify the microenvironment and enable metastatic colonization or that promote metastatic growth is needed. Although several prognostic factors for pulmonary metastasis-related tumor characteristics have been reported (10), to our knowledge, prognostic factors related to patient characteristics remain unknown.

Tobacco smoking is closely related to the pathogenesis of many kinds of malignant neoplasm and is the main known cause of cancer-related deaths worldwide (11-14). In addition, a smoking history is predictive of poor pulmonary metastasis-free survival (PMFS) in patients with different epithelial tumor types (15-17). Although a smoking history is associated with worse distant metastasis-free survival in patients with STS (18), its influence on PMFS in such patients has not been determined as far as we are aware.

Therefore, we hypothesized that smoking history may influence pulmonary metastasis in patients with STS. To test this hypothesis, we retrospectively reviewed patients with STS treated at our institutes. The final goal of this study was

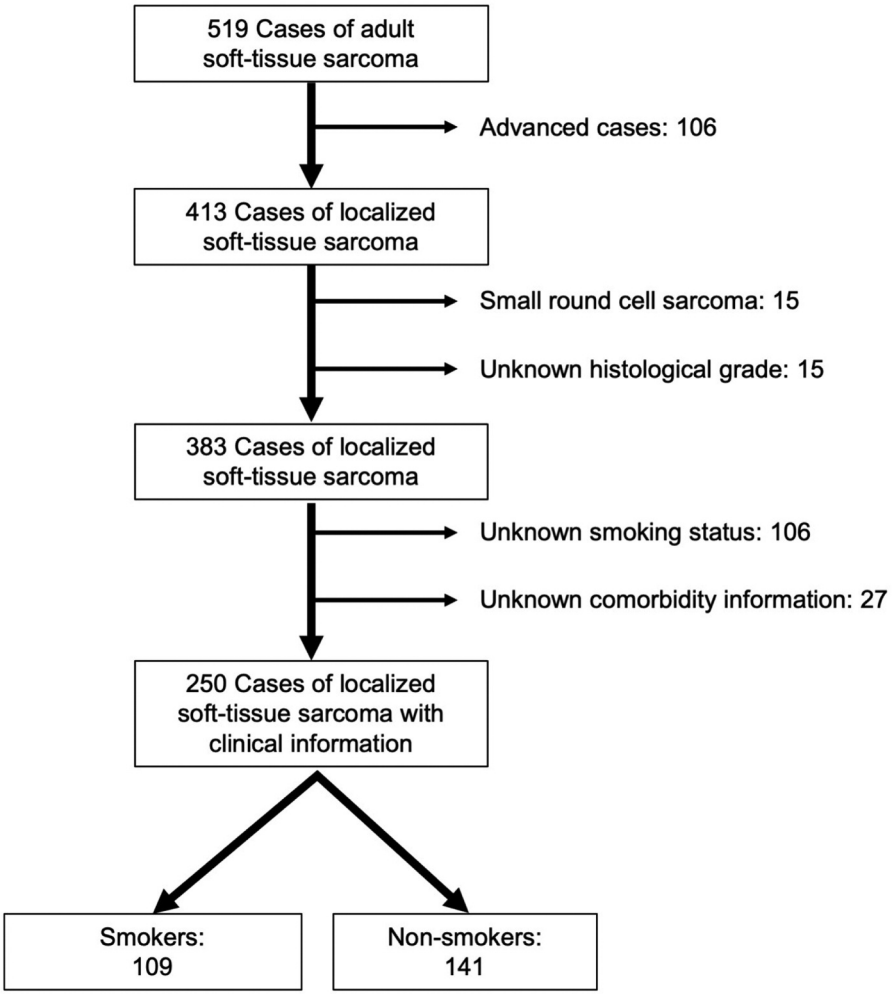

Figure 1. *Flowchart showing the process of including patients in this cohort.*

to investigate the impact of smoking on pulmonary metastasis in patients with STS.

Patients and Methods

Patient characteristics. We retrospectively reviewed and considered 519 adult patients (≥20 years old) undergoing treatment for primary STS at our institutes between 2008 and 2017 for this cohort. We excluded patients who had a metastatic lesion at the initial visit, or had a histopathological classification demonstrating so-called small round-cell sarcoma such as Ewing's sarcoma and rhabdomyosarcoma. Patients who lacked adequate medical records including treatment information, pathological reports, comorbidity information (hypertension, cardiovascular disease, diabetes mellitus, and hyperlipidemia), and smoking history were also excluded (Figure 1). Information on the date of diagnosis, age at diagnosis, tumor size (≥10 cm), depth (deep-seated), French Federation Nationale des Centers de Lutte Contre le Cancer grading (19) (grade 1: low grade; grade 2 and 3: high grade), and smoking history were recorded on an electronic health record system. STSs were histologically classified according to the histological subtypes in the World Health Organization classification (20). Smoking history was self-reported and confirmed by medical staff at the initial visit. Patients with a 5 pack-year history (20 cigarettes per day multiplied by the number of years that the participant smoked) or greater were defined as smokers.

Treatment strategy for STS. The objective of our treatment was to achieve both maximal resection for oncological control and conservation of functional aspects. The tumor was surgically resected through a normal tissue plane with a wide margin that sacrificed tumor-violated soft tissues and neurovascular regions. Vascular surgery and plastic surgery teams were consulted and were involved in cases with a huge defect of the soft tissue or with bypass grafting surgery. Radiation therapy was discussed and offered to the patients when the tumor was closely located to bone or a main neurovascular bundle. Chemotherapy was considered when the patient was younger than 70 years or had a large, deep-seated, high-grade sarcoma.

Table I. *Patient, tumor, and treatment characteristics.*

	Smoker	Non-smoker	*p*-Value
Patients, n			
Total	109	141	
Observation period, months			
Median (range)	36 (1-103)	36 (1-117)	
Age, years			
Median (range)	67 (24-88)	68 (23-95)	
Tumor location, n (%)			
Head and Neck	3 (3%)	2 (1%)	0.52
Trunk	28 (26%)	41 (29%)	
Upper extremity	14 (13%)	25 (18%)	
Lower extremity	64 (59%)	73 (52%)	
Complications, n (%)			
Hypertension	36 (33%)	47 (33%)	0.96
Cardiovascular disease	23 (21%)	17 (12%)	0.053
Diabetes mellitus	17 (16%)	12 (9%)	0.08
Hyperlipidemia	13 (12%)	14 (10%)	0.61
Histological grade, n (%)			
Low	41 (38%)	50 (36%)	0.73
High	68 (62%)	91 (65%)	
Size, n (%)			
<10 cm	53 (49%)	68 (48%)	0.95
≥10 cm	56 (51%)	73 (52%)	
Location, n (%)			
Superficial	9 (8%)	20 (14%)	0.15
Deep	100 (92%)	121 (86%)	
Other therapy, n (%)			
Chemotherapy	14 (13%)	17 (12%)	0.85
Radiation	22 (20%)	31 (22%)	0.73

Pulmonary metastasis. Pulmonary metastasis in patients with STS was defined with the following criteria (21): (i) Pleural effusion formation with morphological carcinomatous evidence; (ii) a single pulmonary nodule on a chest radiograph or computed tomography scan that was confirmed to be a metastatic lesion with pathological examination; and (iii) multiple lung nodules in computed tomography that were interpreted by the musculoskeletal oncologist or radiologist to be metastatic in etiology.

Statistical analyses. The primary outcome of this study was to investigate the impact of smoking history on PMFS. The secondary outcome was to examine the influence of smoking history on OS. PMFS and OS were calculated by the Kaplan–Meier survival analysis. The chi-square test was used for univariate analysis. The impact of smoking history on PMFS and OS was examined with multivariate analysis by a Cox proportional hazards model. Hazard ratios (HRs) were adjusted for tumor diameter (≥10 cm), tumor depth (deep-seated), French Federation Nationale des Centers de Lutte Contre le Cancer grading (high-grade), and comorbid conditions. All statistical tests were two-sided, and statistical significance was set at $p<0.05$. All data were analyzed by the statistical software, JMP Pro 13.1.0 (SAS Institute, Cary, NC, USA).

All experimental protocols were approved by an institutional and licensing committee (Hokkaido Cancer Center Institutional Review Board: protocol 30-109). Informed consent was obtained from all patients and all procedures performed in the study involving human participants were in accordance with the ethical standards of the Hokkaido Cancer Center Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

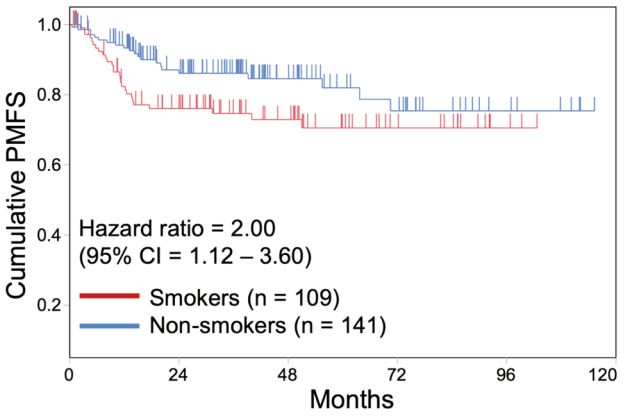

Figure 2. *Relationship between smoking history and pulmonary metastasis-free survival (PMFS) in patients with soft-tissue sarcoma. CI: Confidence interval.*

Results

Patient characteristics. After applying inclusion and exclusion criteria, we retrospectively reviewed 250 patients with available examination points (Figure 1). Overall, 141 patients (56%) were classified as non-smokers, and 109 patients (44%) were classified as smokers. We did not find significant differences in the demographic information between smokers and non-smokers (Table I). The median ages at diagnosis of smokers and non-smokers were 67 and 68 years old, respectively. The corresponding median follow-up periods were 36 and 36 months, respectively. We found no clinically meaningful differences in histological subtypes according to World Health Organization classification (20) (Table II).

Impact of smoking history on PMFS. Pulmonary metastasis developed in 27 smokers (25%) and 21 (15%) of the non-smokers. The 5-year PMFS rates were 71% and 82%, respectively. When the Cox proportional hazards model, adjusted for tumor characteristics and comorbid conditions, was applied to the period of follow-up, development of lung-metastatic tumors and survival as critical events, patients with a smoking history had worse PMFS [adjusted HR=2.00, 95% confidence interval (CI)=1.12-3.60, $p=0.02$; Figure 2].

Influence of smoking history on OS. The 5-year OS rates for smoker and non-smoker groups were 79% and 84%, respectively. Although patients with a smoking history had a

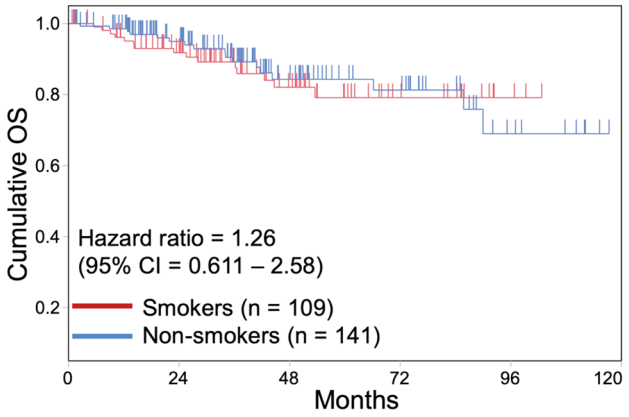

Figure 3. *Relationship between smoking history and overall survival (OS) in patients with soft-tissue sarcoma. CI: Confidence interval.*

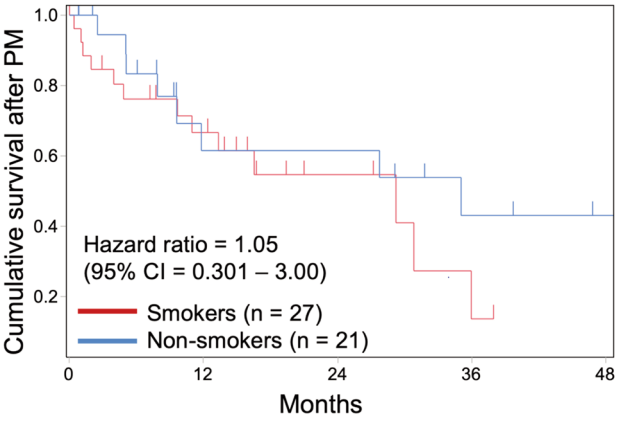

Figure 4. *Relationship between smoking history and the survival rate after a diagnosis of pulmonary metastasis (PM) in patients with soft-tissue sarcoma. CI: Confidence interval.*

Table II. *Histological diagnosis according to World Health Organization classification of patients with soft-tissue sarcoma.*

Histology	Smoker, n (%)	Non-smoker, n (%)	*p*-Value
Adipocytic tumors	41 (38%)	52 (37%)	
Fibroblastic/myofibroblastic tumors	20 (18%)	25 (18%)	
Smooth muscle tumors	7 (6%)	14 (10%)	
Skeletal muscle tumors	3 (3%)	3 (2%)	
Nerve sheath tumors	4 (4%)	5 (4%)	
Tumors of uncertain differentiation	4 (4%)	9 (6%)	
Undifferentiated/unclassified sarcomas	29 (27%)	33 (23%)	
Total	109	141	0.89

worse PMFS, smoking history did not significantly affect OS on multivariate analysis (adjusted HR=1.26, 95% CI=0.611-2.58, p=0.52; Figure 3). We further analyzed the survival rate after pulmonary metastasis. The 2-year OS rates after diagnosis of pulmonary metastasis for smokers and non-smokers were 55% and 62%, respectively (adjusted HR=1.05, 95% CI=0.301-3.00, p=0.93; Figure 4).

Discussion

Data from this cohort indicate that a smoking history may be a specific risk factor for shortened PMFS. This risk in the smoking group was about 2.0-fold higher than in the non-smoking group. In contrast, smoking history did not affect the OS nor survival after the diagnosis of pulmonary metastasis. The ultimate goal of the current study was to investigate whether a smoking history reduced PMFS. Therefore, we did not take into account the impact of pulmonary tumor resection which would affect OS to avoid confusion. The precise relationship between a smoking history in patients with STS and OS will be addressed in future study by different study design and methodology.

The risk factors associated with pulmonary metastasis of STS include histological high-grade tumor, large tumor size, lesion of a lower extremity, and non-round-cell sarcoma (10, 22). Although the risk factors associated with the finding are unknown, an increased risk of reduced metastasis-free survival among patients with a smoking history was reported in Gannon *et al.*'s epidemiological study (18) and may be associated with a higher rate of developing pulmonary metastases among the patients with smoking history; our results are consistent with these observations.

Several prognostic factors for better survival after the development of pulmonary metastasis in patients with STS have been reported, such as complete resection of pulmonary metastasis, longer disease-free survival period, histological low-grade sarcoma, and a small number of pulmonary metastases (2, 23, 24). However, the demographic prognostic

factors related to survival after pulmonary metastasis have not been identified. In the current study, a smoking history affected the occurrence of pulmonary metastasis but not the survival rate after pulmonary metastasis. As we studied a cohort with a modest size, future validation is needed for determining prognostic factors for survival after diagnosis of pulmonary metastasis.

Cigarette smoke has multiple detrimental effects on human health (25, 26). The enormous number of toxic irritants and chemicals in cigarette smoke likely produce lung inflammation, which leads to increased mutation and silencing of tumor-suppressor genes through various stress mechanisms (11). Natural killer (NK) cells, which are critical regulators of host immune defense mechanisms, are responsible for tumor immune surveillance against smoke-induced pulmonary metastases of malignant neoplasms. In response to inflammatory and chemical stimulation, NK cells infiltrate into the lung parenchyma from the bone marrow (27). Cigarette smoke impairs NK cell activation, migration, or viability, without any activating or inhibitory receptor expression system in the lungs (28). We speculate that altered innate immunity and microenvironmental changes that result in NK cell-dependent immune insufficiency may contribute to increasing the risk of pulmonary metastasis in patients with STS.

There are several limitations to the current study that should be considered when interpreting the results. Firstly, as this was a retrospective study, the data may involve selection and observational biases, such as recall, interviewer, and misclassification biases that may have affected the results. Secondly, we did not consider the smoking status after the diagnosis of STS. Ideally, this factor should be included because modification of smoking-related behavior may have affected clinical outcomes in this cohort. Future studies should include this factor. Thirdly, we did not consider the influence of an involuntary history of passive smoking. Second-hand tobacco smoke has several deleterious effects on people who inhale it (11, 29). Exposure to cigarette smoke is known to be a risk factor for several malignancies (30-32). Although the influence of passive smoking history on pulmonary metastasis in patients with malignant neoplasms has not been described, these effects should be examined in future studies.

Conclusion

Our findings that pulmonary metastases developed at a higher incidence among patients with STS with a greater lifetime smoking exposure supports our hypothesis that smoking history may influence pulmonary metastasis in patients with STS. If correct, a smoking history may be a poor predictive factor in patients with STS. To the best of our knowledge, this is the first study to indicate that a smoking history may be a poor predictive factor for lung metastasis of STS. Although further research including prospective studies is needed, clinicians should carefully follow-up patients with STS if they have a smoking history.

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

MM and HH were involved in the design of the study; performed the clinical assessment, analysis, and interpretation of data; and drafted and revised the article. MO, TS, IY and RA assisted with data interpretation and revised the article for important intellectual content. TO, EK, and NI were involved in data acquisition and revised the article critically for important intellectual content. All Authors have read and approved the final article.

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