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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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.
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 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
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
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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