# The neutrophil-to-lymphocyte ratio as a novel independent prognostic factor for multiple metastatic lung tumors from various sarcomas

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**Abbreviations:** DFI, disease-free interval; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio

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**Abstract**

**Purpose:** Sarcomas are one of the most refractory malignant tumors and they often recur as pulmonary metastasis. Although the presence of a high neutrophil-to-lymphocyte ratio (NLR) has been associated with the prognosis of several malignancies, the relationship between the NLR and sarcoma with pulmonary metastasis is unclear. We investigated the impact of NLR in patients who underwent surgical resection for metastatic lung tumors from various sarcomas.

**Methods:** The subjects of this retrospective study were 158 patients with metastatic lung tumors from various sarcomas, who underwent initial pulmonary metastasectomy between 2006 and 2015. We examined the clinicopathological variables, including NLR and the characteristics of surgical procedures. Survival was estimated by the Kaplan-Meier method and prognostic factors were evaluated by multivariate analysis.

**Results:** Multivariate analysis revealed significantly better survival of the group with an NLR < 2.26 immediately before the most recent pulmonary metastasectomy, in addition to such factors as the largest resected lesion being < 22 mm, a disease-free interval of > 2 years, and 3 or more pulmonary metastasectomies.

**Conclusion:** The NLR immediately before the most recent pulmonary metastasectomy is a novel independent prognostic factor, which may be helpful when considering repeated

pulmonary metastasectomy.

**Key words:** metastatic lung tumor; sarcoma; metastasectomy; survival rate; neutrophil-to-lymphocyte ratio (NLR)

## Introduction

Sarcoma is a rare malignant tumor that arises from cells of mesenchymal origin [1]. It accounts for approximately 1% of all adult malignancies and is in the heterogeneous group of tumors, divided mainly into soft-tissue sarcoma and bone sarcoma [2, 3]. Soft-tissue sarcoma includes more than 50 different histologic subtypes, the most common being leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma [4]. Common subtypes of bone sarcoma include osteosarcoma, chondrosarcoma, and Ewing sarcoma [5]. Sarcoma is generally a refractory disease and often metastasizes to the lung [6], even after complete resection of the primary lesion [7, 8]. Generally, systemic treatment such as chemotherapy is appropriate for patients with metastatic lung tumors; however, effective chemotherapeutic or molecular-targeted drugs are yet to be developed. Recent reports show promising results with newer cytotoxic agents, including eribulin, trabectedin, and aldoxorubicin [9]. Pazopanib targeting VEGFR has also been approved for sarcomas, although its effectiveness is still being clarified [10]. Despite these encouraging results, the outcome is far from satisfactory. Thus, local therapy such as surgical resection is a therapeutic option for metastatic lung tumors to control the disease. Kondo et al. reported the indications for the surgical resection of metastatic

lung tumors from various solid tumors [11]. Previous reports indicate that pulmonary metastasectomy is an acceptable treatment for metastatic lung tumors from soft-tissue sarcoma and bone sarcoma in selected patients [3, 8, 12-14]. Yet, the clinical benefit of surgical resection for pulmonary metastases from various sarcomas remains controversial. Although a high neutrophil-to-lymphocyte ratio (NLR) has been associated with prognosis of several malignancies [15-17], the relationship between the NLR and sarcoma with pulmonary metastasis is unclear. We investigated the impact of surgical resection for metastatic lung tumors from various sarcomas retrospectively, using a single institution database to identify which patients are more likely to benefit from pulmonary metastasectomy.

## Patients and Methods

### *Patient selection*

This retrospective study was approved by the Institutional Review Board of Okayama University Hospital, Okayama, Japan (approval number: K1612-033) and written informed consent was waived. Between 2006 and 2015, 158 sarcoma patients underwent pulmonary metastasectomy for the first time, with 265 surgical procedures in total performed in the Department of Thoracic Surgery, Okayama University Hospital. Our indication criteria for

surgical resection of metastatic lung tumors from sarcomas are as follows: the performance status should not be significantly deteriorated or impaired by surgery; life-threatening lesions such as those causing hemoptysis need to be removed; and lesions other than the lung metastases can be controlled.

***Data collection***

Clinical data for each patient were collected for the following variables: age at the first pulmonary metastasectomy, sex, the site of the primary lesion, histology, the date of initial surgery for the primary disease, the extent of primary disease at the initial diagnosis (primary localized or metastatic), the date of diagnosis of the first pulmonary metastasis, the extent of pulmonary metastasis at the first pulmonary metastasectomy (unilateral or bilateral), the presence or absence of local recurrence and/or extrapulmonary metastasis with or before the diagnosis of the first pulmonary metastasis, the NLR immediately before the first and most recent pulmonary metastasectomies, operative procedures, the size of the largest resected lesions from all the surgical procedures performed, the maximum number of resected tumors among all the surgical procedures performed, the accomplishment of R0-resection in the operative field at the most recent surgical procedure, postoperative day of chest tube removal, postoperative day of discharge, postoperative complications, frequency of pulmonary

metastasectomy that each patient underwent as of the end of 2018, and disease-free interval (DFI) from the date of the initial surgery for primary disease until the date of diagnosis of the first pulmonary metastasis. If patients had bilateral lung metastases, a two-stage operation for planned sequential pulmonary metastasectomies within a couple of months, or bilaterally simultaneous surgery was selected according to the number of tumors in the bilateral lungs.

***Statistical analyses***

All statistical analyses in this study were performed using the EZR version 1.41.1 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria) [18]. Specifically, the software is a modified version of R commander, designed to add statistical functions frequently used in biostatistics. Kaplan-Meier methods were used for calculating overall survival (OS) from the first pulmonary metastasectomy. The cut off value for continuous variables was defined by receiver operating characteristic (ROC) curve analysis. Cox proportional hazard model was used for multivariate analysis. Selection of explanatory variables was based on previous literature and variables with a $p$-value less than 0.1 in univariate analysis were also included. If it was considered that variables may affect the prognosis, they were also included. A value of $p < 0.05$ was considered significant.

## Results

### *Patient characteristics*

We reviewed 158 consecutive patients with various forms of sarcoma with pulmonary metastases, between 2006 and 2015. Table 1 summarizes their clinical characteristics. There were 36 men and 122 women, with an average age of 53.7 years (range 14-88 years). Leiomyosarcoma was the most common histological subtype (n = 92, 58.2%) and the uterus was the most common location of the primary disease (n = 71, 44.9%). Most of the primary tumors (n = 131, 82.9%) were localized at the time of the initial diagnosis. Pulmonary metastases were spread bilaterally in 63.9% of the patients at the first pulmonary metastasectomy. In 65.2% of the cases, no local recurrence and/or extrapulmonary metastases were found with or before the diagnosis of the first pulmonary metastasis. The mean and median NLR values were 2.59 and 2.30 (range 0.84-10.68), and 2.49 and 2.15 (range 0.70-10.68) immediately before the first and most recent pulmonary metastasectomies, respectively.

### *Surgical interventions*

In total, 1058 metastatic nodules were resected. The average and median number of resected

tumors per intervention was 4.0 and 3.0, respectively (range 1-19). The operative procedures consisted of 202 partial resections, 35 segmentectomies with or without partial resection, 26 lobectomies with or without partial resection, 1 pneumonectomy, and 1 basal segmental auto-transplantation after pneumonectomy. The mean size of the largest resected lesion was 21.1 mm (range 3-110 mm). For bilateral pulmonary metastases, a planned two-stage operation was performed for 52 patients and a simultaneous operation was done for 16 patients. Most of patients had no major postoperative complications. The chest tube was removed by postoperative day (POD) 3 after 86.4% of the procedures, and more than 80% of a cumulative total of 265 patients were discharged within 2 weeks after surgery. About half of the patients had undergone repeated surgery as of the end of 2018, for planned sequential operations or relapse in the lung. The maximum number of pulmonary metastasectomies per patient in our cohort was seven. Table 2 outlines the surgical procedures performed.

***Survival analyses***

To clarify which patients benefit more from surgical resection, we performed a survival analysis using the Kaplan-Meier method. The overall 3-year and 5-year survival rates after the first pulmonary metastasectomy were 50.6% and 32.8%, respectively, with a median follow-up period of 2061 days for censored cases (Fig. 1). Regarding NLR, the cutoff value defined by

receiver operating characteristic (ROC) curve analysis was 2.59 and 2.26 immediately before the first and most recent pulmonary metastasectomy, respectively. The area under the curve (AUC) for the NLR immediately before the first, and the most recent pulmonary metastasectomy, was 0.561 and 0.627, respectively. The NLR values that were less than the cutoff value immediately before the first and most recent pulmonary metastasectomies were both significantly associated with better survival ($p$ = 0.00378 and 0.000121, respectively) (Fig. 2, Table 3). Using the mean and median as the cut-off value, a low NLR value was also associated with better survival (data not shown). Patients with a resected maximum lesion ≥ 22 mm in diameter among all the performed interventions had worse OS than with a resected maximum lesion < 22 mm ($p$ = 0.00000148) (Table 3). The maximum number of resected tumors among all the interventions performed (nine or fewer) was also associated with better 3-year survival ($p$ = 0.0253) (Table 3). A DFI > 2 years was associated with better 3-year survival than a DFI ≤ 2 years ($p$ = 0.00523) (Table 3). Patients who underwent three or more pulmonary metastasectomies had better survival ($p$ = 0.0309) (Table 3). For those who underwent metastasectomy three times or more (n = 36), the number of tumors resected in the third metastasectomy ranged from 1 to 16 (median, 2) and was 5 or less in 31 out of 36 patients. The extent of pulmonary metastasis (unilateral) and R0-resection at the most recent

intervention (accomplishment of R0-resection) was associated with a tendency for better survival ($p < 0.1$). Age, sex, histology, extent of the primary disease at diagnosis, and local recurrence and/or extrapulmonary metastasis were not associated with OS in univariate analysis.

Multivariate analysis for survival included the variables with a $p$-value < 0.1, as well as "histology (leiomyosarcoma or others)", "extent of the primary tumors at the time of diagnosis (primary localized or metastatic)", and "local recurrence and/or extrapulmonary metastasis with or before pulmonary metastasis (Yes or No)" as explanatory variables that could affect the prognosis. Furthermore, "NLR immediately before the first pulmonary metastasectomy" and "NLR immediately before the most recent pulmonary metastasectomy" were possibly confounding. Thus, we set separate two models: either the NLR immediately before the first pulmonary metastasectomy or the NLR immediately before the most recent pulmonary metastasectomy. Ten explanatory variables that were considered to be the maximum number in this cohort [19] were included in separate two models for multivariate analysis. As indicated in Table 4, the size of the largest resected lesion ≥ 22 mm in all the performed procedures [hazard ratio (HR) 2.32, $p = 0.0000619$], the NLR immediately before the most recent pulmonary metastasectomy ≥ 2.26 (HR 1.92, $p = 0.00224$), DFI ≤ 2 years (HR

1.70, $p$ = 0.0367), and frequency of pulmonary metastasectomies > 3 (HR 0.697, $p$ = 0.00552) were significant.

## Discussion

We reviewed, retrospectively, 158 patients with metastatic lung tumors from soft-tissue and bone sarcomas. OS after the first pulmonary metastasectomy was evaluated and the significant factors for better survival, according to multivariate analysis, were an NLR < 2.26 immediately before the most recent pulmonary metastasectomy, the size of the largest resected lesion < 22 mm in all the performed surgical procedures, a DFI of more than 2 years from the date of the initial surgery for primary disease until the date of diagnosis of the first pulmonary metastasis, and the frequency of pulmonary metastasectomy (three times or more). The size of the largest lesion showed the highest hazard ratio.

The NLR is an indicator of systemic inflammation and an elevated NLR is recognized as a poor prognostic factor in various malignancies [15-17]. The mean NLR in the healthy non-geriatric adult population is reported to 1.65 (0.78-3.53) [20]. In this study, we set the cut-off NLR by ROC curve analysis in this cohort, and found that the NLR immediately before the most recent pulmonary metastasectomy was independently correlated with OS. We also set

the cut-off value of the NLR to the mean and median and performed multivariate analysis, respectively, leading to the same significant results. This result may be useful for deciding on the indication for repeated pulmonary metastasectomy. Ultimately, the most recent NLR, and not the initial NLR, affects the prognosis, which means that surgeons need to pay more attention to the very recent status of a patient when planning repeated surgery. To date, there are no reports on the relationship between the NLR and metastatic lung tumors from various sarcomas.

The possibility that previous chemotherapy affected the bone marrow function and NLR prompted us to review the clinical data of chemotherapy in this cohort. Fifty-eight patients received chemotherapy before their first pulmonary metastasecomy. The average and median intervals between the last administration of the chemotherapeutic agent and the pulmonary metastasecomy was 98.9 and 55 days (1-695), respectively. Forty-five patients underwent chemotherapy before their most recent pulmonary metastasectomy. The average and median intervals between the last administration of the chemotherapeutic agent and the pulmonary metastasectomy was 79.3 and 38 days (1-695), respectively. The chemotherapy regimen is detailed in Supplementary Tables 2 and 3. We analyzed the differences in the distribution of the NLR between the group with vs. the group without preoperative chemotherapy.

Supplementary Fig. 1 shows that the distribution of preoperative NLR was not affected by preoperative chemotherapy (Man-Whitney U test) in the first or the most recent pulmonary metastasectomy. The interval between chemotherapy and surgery in this cohort may have been enough for the bone marrow function recovery.

Previous reports on pulmonary metastasectomy for metastatic lung tumors from sarcomas indicate similar results [3, 8, 12-14]. The DFI is reported to be a good prognostic factor of survival after pulmonary metastasectomy, in spite of the different cut-off values. Clinical practice guidelines for soft-tissue sarcomas and bone sarcomas are available from the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the British Sarcoma Group [4, 5, 21-25], who all recommend pulmonary metastasectomy for resectable lung metastases without extrapulmonary disease, if the DFI is significantly long and pulmonary lesions are completely excised, although there is no prospective randomized study proving the effectiveness of pulmonary metastatic surgery for sarcomas [26]. If a significant long DFI is absent, CT scan should be repeated at 3-month intervals and if there are no new lesions and the disease is operable, surgery is usually recommended [23]. Neoadjuvant treatment before pulmonary resection may also be considered for patients with a short DFI [27]. Timing of surgery in pulmonary metastasectomy

is open to debate [26].

Regarding the operative procedures, we usually perform partial resection of the lung as the first choice if the location and number of tumors in the lung field are acceptable, as it is important to preserve lung parenchyma. Because recurrent pulmonary metastases are common after pulmonary metastasectomy in many sarcoma patients [6, 14, 28], selected patients may undergo repeated resections for pulmonary metastases. The typical pattern of relapse for sarcomas is intrathoracic for more than half of all recurrences after pulmonary metastasectomy, which is significantly different from that of other tumors that mainly re-recur as distant metastases. Therefore, the percentage of relapsing patients undergoing a second pulmonary metastasectomy is significantly higher for sarcomas than for any other tumor type [7]. It is essential to preserve respiratory function for patients to undergo repeated pulmonary metastasectomy. In the current study, three or more pulmonary resections was an independent factor for better prognosis according to the multivariate analysis, indicating that more chances for local treatment of metastatic lung tumors from sarcomas can be advantageous to the sarcoma patients. Almost half of the patients in our cohort underwent repeated surgery and perioperative complications were limited, indicating that our procedure to preserve lung parenchyma is successful. As described in the Results, the number of the resected tumors in

the third metastasectomy was 5 or less in most patients undergoing three or more surgeries, although the maximum number of resected tumors was 16 in one patient. If lung metastases recur as numerously multiple tumors, repeated surgery may be difficult.

We preserve the lung parenchyma as much as possible when performing pulmonary metastasectomy. Using a surgical stapler frequently for pulmonary resection results in loss of intact lung parenchyma, compromising pulmonary function; hence, we minimize the surgical margin as much as possible by using an electrocautery scalpel and vessel sealing device, limiting use of the surgical stapler. We reviewed the data on the pulmonary function of patients who underwent resection of 10 or more tumors by partial resection of the lung. Ten to 18 tumors (median, 13) were resected in 22 partial resections of the lung. Both preoperative and postoperative pulmonary function test data were available for 15 of the 22 cases. As for FEV1, the median volume and median rate of decrease were 0.39 L and 15.6%, respectively, measured at different time points (Supplementary Table 1). The postoperative pulmonary function test was performed about 1 month after the pulmonary resection in some patients, and 1 year or more after the surgery in others. Although the number of the cases is limited, it seems that pulmonary function is well preserved, considering that 10 or more tumors were resected in those patients. There may be a concern that stump recurrence could develop with

such a small surgical margin; however, lung recurrence after pulmonary metastasectomy for various sarcomas usually occur in different locations from the previous lesions. As pleural infiltration was reported to be a risk factor for local recurrence, larger margins are needed if there is obvious pleural infiltration [29, 30]. Further verification regarding the surgical margin and local recurrence is needed by the histopathological examination.

In the current study, the largest resected lesion in all the performed surgical procedures being < 22 mm was a good prognostic factor. Although the factor of the largest tumor size is less frequently reported as a prognostic factor [29], our results seems to stand to reason because if the tumor size is smaller, the possibility of curative resection is greater. Regarding R0-resection, it may be difficult to establish complete resection in each procedure . It is difficult to resect a lesion that is too small and located in deep within the lung. In such cases, R0-resection may not affect survival in the immediate future. Therefore, even if resection is incomplete, there may be some cases of a relatively favorable prognosis. There is also the opportunity for other treatments such as chemotherapy and radiofrequency ablation (RFA) [31] after incomplete resection, although detailed information on these treatments is not given in this study.

Our study has several limitations. First, we included sarcomas of various histologic

subtype, making our cohort heterogeneous. Second, there was no control group for comparison, although it would have been difficult to find a group of patients who were just observed. Third, although we focused on surgical resection for lung metastases, some patients in our study may have received other therapies such as chemotherapy and RFA for the lung and/or other metastatic sites in the survey period, and detailed information on this was not included in this study.

In conclusion, we identified the NLR immediately before the most recent pulmonary metastasectomy as a novel independent prognostic factor for patients with various sarcomas who underwent pulmonary metastasectomies. This could be helpful when repeated pulmonary metastasectomy is being considered because the most recent NLR can affect the prognosis even if the patient has undergone pulmonary metastasectomy previously. Although further research to identify potential drugs for sarcomas is needed, pulmonary metastasectomy is still an effective therapeutic option for selected patients with metastatic lung tumors from various sarcomas.

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**Compliance with ethical standards**

**Conflict of interest** We have no conflicts of interest to declare in relation to the present study.

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## Figure legends

**Fig. 1.** Overall survival (OS) of patients with various types of sarcoma after the first pulmonary metastasectomy.

**Fig. 2.** Overall survival (OS) stratified by the neutrophil-to-lymphocyte ratio (NLR) immediately before the most recent pulmonary metastasectomy.

## Supplementary Figure legends

**Supplementary Fig. 1.** Distribution of the neutrophil-to-lymphocyte ratio (NLR) immediately before (A) the first and (B) the most recent pulmonary metastasectomy. The difference in the distribution of NLR between the group with vs. the group without preoperative chemotherapy was analyzed. The Man-Whitney U test was performed.