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**Prognostic influence of the treatment approach for pulmonary metastasis in patients with soft tissue sarcoma**

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**Abbreviations:** STS, soft tissue sarcoma; UPS, undifferentiated pleomorphic sarcoma; MFH, malignant fibrous histiocytoma; VATS, video-assisted thoracic surgery.

**Article type:** Original Research

## **Abstract**

Soft tissue sarcomas (STSs) are rare heterogeneous malignancies of mesenchymal origin. Pulmonary metastases develop in approximately 50% of the patients with high-grade STS, being the major cause of mortality in patients with metastatic STS. Pulmonary metastasectomy has been reported to contribute to long-term survival; however, an appropriate treatment has not been established. We aimed to identify factors associated with post-metastasis survival in STS patients with pulmonary metastasis and determine the appropriate treatment for each patient. We retrospectively reviewed the records of metastatic STS patients treated between 2000 and 2017 and analyzed the clinico-pathologic variables to identify factors associated with the survival. The median survival after pulmonary metastasis was 20.6 months, and the 1-, 3-, and 5-year survival rates were 68.6%, 36.0%, and 25.1%, respectively. The survival was significantly greater in patients who underwent pulmonary metastasectomy than in those without surgery (38.9 months vs. 10.5 months;  $p < 0.0001$ ). Among those who did not undergo surgery, the survival was significantly greater in patients who received chemotherapy than in those without chemotherapy (19.1 months vs. 6.3 months,  $p = 0.037$ ). Multivariate analysis identified pulmonary metastasectomy as the most important prognostic factor for post-

metastasis survival (Hazard ratio: 5.623; 95% Confidence Interval: 2.733-11.572;  $p < 0.0001$ ). In conclusion, pulmonary metastasectomy was the most important prognostic factor for post-metastasis survival in patients with metastatic STS. In addition, chemotherapy could prolong survival in patients who were not eligible for pulmonary resection. Although we should carefully weigh the risks and benefits, appropriate treatment for pulmonary metastases could contribute to long-time survival.

**Keywords:** Soft tissue sarcoma, Pulmonary metastasis, Lung, Metastasectomy, Survival

## **Introduction**

Soft tissue sarcomas (STSs) are a rare form of cancer with an incidence of less than 5 per 100,000 persons per year [1, 2]. They have mesenchymal origin, arising from muscles, fat, nerves, and other soft tissues, and occur at various anatomical sites, with the extremities being the most common [3]. Most STSs are clinically aggressive, demonstrating high-grade metastatic behavior in various organs. The lungs are the primary site of distant spread, with pulmonary metastases developing in approximately 50% of the patients with high-grade STS, usually within the first 2 years from primary tumor diagnosis [4, 5]. In 70% of these patients the metastases are limited only to the lungs [6]. Surgical treatment of the primary lesion with an adequate wide margin, with or without radiotherapy, reduces the risk of local recurrence, but has no impact on the development of distant metastases and patient survival [7]. The effects of systemic chemotherapy are also limited, with low response rates, reported to be approximately 25–30% [8, 9]. Multimodal therapy, including surgery, chemotherapy, and radiotherapy has improved the clinical outcomes in patients with STS but not in those with pulmonary metastases; therefore, pulmonary metastases remain a major cause of mortality.

Previous reports have shown prolonged survival after pulmonary metastasectomy in patients with metastatic STS [10-14]. Pulmonary metastasectomy is widely accepted as a

standard treatment approach for lung metastases from STS, and complete resection of the metastatic lesions should be the most effective treatment for long-term survival, or even achieving cure in selected patients [13]. The role of systemic treatments has been reported to be controversial, and chemotherapy has been used as a palliative therapy to improve quality of life in patients with metastatic STS who are not eligible for pulmonary resection [15-17]. Furthermore, the effect of perioperative chemotherapy in patients undergoing pulmonary metastasectomy has not been proven to prolong patient survival [18-21].

The aims of this study were to report the clinical outcomes in STS patients with pulmonary metastasis and to identify prognostic variables that may affect the post-metastasis survival in these patients, focusing on the appropriate treatment for each patient.

## **Patients and methods**

### *Ethical considerations*

This study was approved by the Ethics Review Boards of our institutions. Informed consent was obtained in the form of opt-out. Those who rejected were excluded.

### *Study design and patients*

We identified 113 patients with previously treated STS who had developed pulmonary metastases between January 2000 and December 2017. Fifteen patients who had pulmonary metastases at primary tumor diagnosis were excluded. The remaining 98 patients were included in this study and their medical records were retrospectively analyzed. The following data were collected for each patient: age at primary tumor diagnosis, sex, primary tumor site and depth, tumor size, histological type of the primary tumor, primary tumor grade, primary tumor treatments, local recurrence, metastasis-free interval (MFI), laterality and number of pulmonary metastatic nodules, treatments for pulmonary metastases, presence of metastasis in organs other than the lungs (extrapulmonary metastasis), and post-metastasis survival. Pulmonary metastases were evaluated and confirmed by chest computed tomography (CT)

scans. During the initial assessment and follow-up, all patients were evaluated with chest radiographs, physical examination, magnetic resonance imaging for local recurrence, and chest CT scans as part of metastatic surveillance. Positron emission tomography was not routinely used for all patients because it has been previously reported that lung metastases consisting of small nodules had little to no FDG uptake [22]. Follow-up was performed at 3-month intervals during the first 2 years, then every 6 months for the next 5 years, and every year thereafter. The treatment decision for pulmonary metastases was made after the discussion at a multidisciplinary sarcoma tumor board. The MFI was defined as the time between primary tumor treatment and the diagnosis of pulmonary metastasis. The main outcome was post-metastasis survival, which was calculated as the time from treatment for pulmonary metastasis to the last follow-up. Clinical parameters with potential prognostic effect were analyzed, and uni- and multivariate analyses were used to identify factors associated with the clinical outcomes.

#### *Statistical analysis*

The survival was estimated using Kaplan-Meier survivorship curves, and associations between variables and survival were analyzed using the log-rank test. Categorical variables were analyzed using the Chi-squared test. The variables that were found to be significant on univariate analyses ( $p < 0.05$ ) were evaluated by multivariate analysis using Cox regression hazard models. A probability value ( $p$ ) of less than 0.05 was considered to denote statistical significance. Statistical analyses were performed using XLSTAT Biomed v 19.03 (Addinsoft, Paris, France).

## **Results**

### *Clinical characteristics of the patients and primary tumors*

This study included 62 men and 36 women, with a median age of 60 (range, 15–88) years at diagnosis of the primary lesion. The clinical characteristics of the patients and primary tumors

are listed in Table 1.

Of the 94 patients who underwent surgical treatment for the primary lesion, 59 underwent surgery alone, 23 underwent surgery and chemotherapy (pre-surgery 5, post-surgery 7, both 11), 7 underwent surgery and radiotherapy (post-surgery 7), and 5 patients underwent surgery, chemotherapy, and radiotherapy. A complete R0 resection was achieved in 91 of the 94 patients. Treatments for the primary tumor in patients without surgery were chemotherapy only in 1 patient, heavy particle radiotherapy in 1 patient, and palliative radiotherapy in 1 patient. One patient did not receive any treatment. Local recurrence occurred in 25 of the 94 surgically treated patients (26.6%), and was diagnosed at a mean of 19.4 (range, 2.9–76.2) months after the initial surgery. In 18 (72.0%) of these 25 patients, local recurrence occurred before the diagnosis of pulmonary metastasis. Thirty-six patients (36.7%) developed extrapulmonary metastasis, and the most common site was bone in 12 patients, followed by lymph node (11 patients), skin/soft tissue (8 patients), and liver (3 patients).

The histologic results of the primary tumors are listed in Table 2. The most common subtypes were leiomyosarcoma and undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (UPS/MFH), present in 22 patients (22.4%) each, followed by synovial sarcoma (10 patients, 10.2%) and myxofibrosarcomas (10 patients, 10.2%).

#### *Pulmonary metastasis*

The analyses of pulmonary metastasis are summarized in Table 3. The median MFI in 98 patients was 12.3 (range, 1–98.7) months. Sixty patients (61.2%) had metastatic lesions in the bilateral lungs, and three or more lesions were found in 55 patients (56.1%). Regarding treatments, 41 patients (41.8%) underwent pulmonary metastasectomy; the majority (33 patients, 80.4%) underwent video-assisted thoracic surgery (VATS), and 28 patients (68.3%) underwent partial or wedge resection, followed by segmentectomy in 5 patients and lobectomy in 8 patients. Nineteen (46.3%) of the 41 patients received chemotherapy before or after the pulmonary resections. Of the 57 patients who did not undergo pulmonary metastasectomy, 22

(38.6%) received chemotherapy alone and 35 (61.4%) did not receive any treatment for pulmonary metastasis.

#### *Post-metastasis survival*

The post-metastasis follow-up period in all 98 patients ranged from 0.3 to 175.6 months, and the median post-metastasis survival was 20.6 months. At the time of the final analyses, 16 patients (16.3%) were alive without the disease, 16 (16.3%) were alive with the disease, 61 (62.2%) died of the disease, and 5 patients (5.1%) died from other causes. The 1-, 3-, and 5-year survival rates in all 98 patients were 68.6%, 36.0%, and 25.1%, respectively (Fig. 1).

Univariate analyses revealed the following factors to be significantly correlated with post-metastasis survival: age at diagnosis ( $p=0.046$ ), surgery for primary lesion ( $p=0.001$ ), local recurrence ( $p=0.015$ ), presence of pulmonary metastasis at primary tumor diagnosis ( $p=0.008$ ), MFI ( $p=0.046$ ), laterality ( $p=0.0002$ ), number of metastatic nodules ( $p=0.0002$ ), and pulmonary metastasectomy ( $p<0.0001$ ) (Tables 1 and 3). Sex, site, depth and size of the primary tumor, chemotherapy for the primary tumor, primary tumor histological type, primary tumor grade, and extrapulmonary metastases were not associated with the patient prognosis. In the analysis of laterality and multiplicity of metastatic lesions, bilateral involvement and/or three or more lesions were significant indicators of poor prognosis (Fig. 2); however, there was no significant difference between single and multiple lesions in cases of unilateral involvement.

Patients who underwent pulmonary metastasectomy had longer median post-metastasis survival (38.9 months vs. 10.5 months) and greater 1-, 3-, and 5-year survival rates (89.6%, 67.9%, and 56.5% vs. 53.0%, 12.2%, and 0%, respectively;  $p<0.0001$ ) than those in patients without surgical treatment for pulmonary metastases (Fig. 3). No significant difference in the survival was detected between the surgical approach (open or VATS), among the types of lung resection (partial/wedge resection, segmentectomy, or lobectomy) or in repeated pulmonary metastasectomy. Among postoperative complications, pulmonary fistula (pneumothorax) occurred in two patients (one of each in open and VATS approach); however,

we did not observe any other major complications. Moreover, perioperative chemotherapy did not affect the prognosis in patients who underwent pulmonary metastasectomy (Fig. 4). Among the 57 patients who did not undergo pulmonary metastasectomy, the median post-metastasis survival was significantly longer (19.1 s vs. 6.3 months) and the 1- and 3-year survival rates were significantly greater (68.2% and 19.5% vs. 42.4% and 7.1%, respectively;  $p=0.037$ ) in patients who received chemotherapy than in those without chemotherapy (Fig. 5). There was no significant difference in the survival among the chemotherapy regimens, including doxorubicin plus ifosfamide, gemcitabine plus docetaxel, pazopanib, eribulin, and trabectedin. The comparison of the clinical characteristics among the patients who underwent and those who did not undergo pulmonary metastasectomy is summarized in Table 4. In our series, pulmonary metastasectomy was performed significantly more frequently in patients who were younger at diagnosis ( $< 60$  years), had no extrapulmonary metastasis, and had unilateral lung metastasis and less metastatic nodules (1 or 2 lesions).

Multivariate analysis using the Cox proportional hazard model identified pulmonary metastasectomy as the most important prognostic factor for post-metastasis survival (Hazard ratio: 5.623; 95% Confidence Interval: 2.733-11.572;  $p<0.0001$ ) (Table 5). Primary tumor surgery, age at diagnosis, MFI, number of metastatic nodules, and laterality were not significant prognostic factors in the multivariate analysis.

## **Discussion**

In this study, we retrospectively analyzed factors associated with the post-metastasis survival in STS patients with lung metastases to determine the appropriate treatment for each patient to achieve long-term survival. We demonstrated that patients who underwent pulmonary resection had longer median post-metastasis survival and greater 1-, 3-, and 5-year survival rates than those without surgical treatment for pulmonary metastases. Our results strongly indicate that pulmonary metastasectomy could prolong the survival in these patients.

Treatment for pulmonary metastases is crucial for improving the prognosis in patients with STS; however, multimodal therapies including surgery, chemotherapy, and radiotherapy have not proven to be beneficial to patient survival. The poor prognosis and unfavorable clinical course of the disease require that an appropriate and effective therapeutic strategy to be established [8, 9].

Previous studies have reported prolonged survival in STS patients undergoing pulmonary metastasectomy, with 5-year post-metastasis survival rates ranging from 25 to 50% [4, 7, 10-14]. In this study, the 5-year post-metastasis survival rate was 56.5%, which is significantly more favorable than those shown in the previous studies. Most previously reported studies on patients with metastatic STS included surgically treated patients [23-26], whereas we analyzed both patients who underwent pulmonary metastasectomy and those who did not undergo surgery. Therefore, our data should help elucidate the role of pulmonary metastasectomy compared with other treatment options in the prognosis in these patients. Previous retrospective studies also demonstrated that the type of pulmonary resection [13, 27, 28] and repeated pulmonary resections [11, 14] showed a correlation with patient survival. Chudgar et al. reported that minimally invasive metastasectomy showed better prognosis without increasing the risk of recurrence [13], and Lin et al. showed that open surgery was a negative predictor of the survival and that a minimally invasive approach should be preferable, which allows for faster recovery and repeated operations [28]. In our series, neither the surgical approach, the type of pulmonary metastasectomy, nor repeated surgery showed any significant difference in the survival of patients with metastatic STS.

Furthermore, we have identified positive prognostic factors using univariate analyses, including younger age at diagnosis ( $< 60$  years), resection of primary tumor, no local recurrence, longer MFI ( $\geq 12.3$  months), unilaterality, and less metastatic nodules (1 or 2 lesions). These results were consistent with those shown in previous studies [4, 6-14, 21, 23-26]. In this study, other variables, such as the primary tumor histological type, primary tumor grade, and

extrapulmonary metastases, were not associated with the post-metastasis survival in patients with metastatic STS. The histological type and grade have been reported variably as a prognostic factors for the survival in these patients [27-34]. Frequent STS subtypes metastasizing to the lungs are leiomyosarcoma, UPS/MFH, synovial sarcoma, and liposarcoma [29, 30], and our findings were similar in terms of prognosis. A better prognosis has been reported in patients with leiomyosarcoma [27-29], malignant peripheral nerve sheath tumor [29], and liposarcoma [29, 30]. Regarding tumor grade, an increased frequency in lung metastasis and a worse prognosis have been reported to be associated with increased histologic grade [31, 32]; however, previous studies have not consistently shown a correlation between histology or grade and survival. Moreover, most previous series reported that the existence of extrapulmonary metastasis was associated with unfavorable outcomes in patients with metastatic STS, and was considered a contraindication for pulmonary surgery [23, 25, 26, 29, 35]. However, Blackmon et al. have shown that similar post-metastasis survival to that in patients with isolated resectable lung metastases can be achieved with complete resection of the extrapulmonary metastasis, and they concluded that the existence of extrapulmonary metastasis should no longer be a contraindication for surgical intervention in these patients [27]. Consistent with their findings, we have demonstrated that the existence of extrapulmonary metastasis did not influence the survival in patients with metastatic STS.

The role of chemotherapy for metastatic STS remains controversial. Cytotoxic chemotherapy comprising anthracycline-containing regimens has long been the mainstay of treatment for unresectable and/or metastatic STS; however, previous studies have not proven its effectiveness in patients with STS with pulmonary metastasis [15-21, 23, 36]. Therefore, in patients who are not eligible for pulmonary resection, systemic chemotherapy has been used in palliation to improve their quality of life by reducing their symptoms [15-17]. In this study, chemotherapy could prolong the post-metastasis survival in patients who were not eligible for pulmonary resection but did not influence survival in patients undergoing pulmonary

metastasectomy. In recent years, treatment with second-line agents for advanced STS has been often histology-driven [15, 16], and novel therapeutic agents, such as trabectedin and eribulin, have shown a role in some sarcoma subtypes. Therefore, newly developed agents may expand the treatment options and improve the prognosis of patients with metastatic STS in the near future.

Several limitations exist in this study. First, due to its retrospective design, we cannot exclude the possibility of the selection bias. Second, since STSs are rare cancers, this study lacks the consideration for anatomic and histologic heterogeneity among STSs. Finally, the sample size was relatively small, although it represents an 18-year experience at our institutions. Therefore, multicenter studies with larger sample size, meta-analyses, or systemic reviews should be helpful to elucidate the factors associated with the prognosis and benefit of pulmonary metastasectomy in patients with STS with lung metastases [23].

## **Conclusion**

In this study, we found that patients with metastatic STS who underwent pulmonary resection had longer median post-metastasis survival and greater 1-, 3-, and 5-year survival rates than those without surgical treatment for pulmonary metastases. In addition, chemotherapy could prolong the survival in patients who were not eligible for pulmonary resection. Multivariate analysis identified pulmonary metastasectomy as the only significant prognostic factor for the survival in these patients. Although we should carefully weigh the risks and benefits, an appropriate treatment approach for each patient with pulmonary metastases could be a means of achieving long-time survival.

## **Declarations**

## **Funding**

Not applicable

### **Conflicts of interest**

There are no conflicts of interest to declare.

### **Compliance with Ethical Standards**

Ethics approval for the retrospective data analyses was obtained from the Institutional Review Boards of the Kobe University Hospital and the Hyogo Cancer Center (IRB Number: B190212). Informed consent was obtained in the form of opt-out. Those who rejected were excluded.

### **Authors' contributions**

TK was responsible for the study conception and design, and drafted the manuscript. HH, MM, NF, YK, TT, SF, KaK, SY, TomohiroM, TF, and IF were responsible for acquisition of data. KeK, TomoyukiM, and TakehikoM were responsible for data analyses. TN, RK, and TA helped in correction of the manuscript. All authors contributed to and approved the final version of the manuscript.

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### **Figure legends**

Figure 1. Post-metastasis survival in all of the 113 patients with STS

Figure 2. Kaplan-Meier survival curves according to the number of metastatic nodules (p=0.0002)

Figure 3. Kaplan-Meier survival curves according to pulmonary metastasectomy (p<0.0001)

Figure 4. Kaplan-Meier survival curves according to chemotherapy in 41 patients who underwent pulmonary metastasectomy

Figure 5. Kaplan-Meier survival curves according to chemotherapy in 57 patients who did not undergo pulmonary metastasectomy (p=0.037)

Fig. 1. Post-metastasis survival in all 98 patients with STS

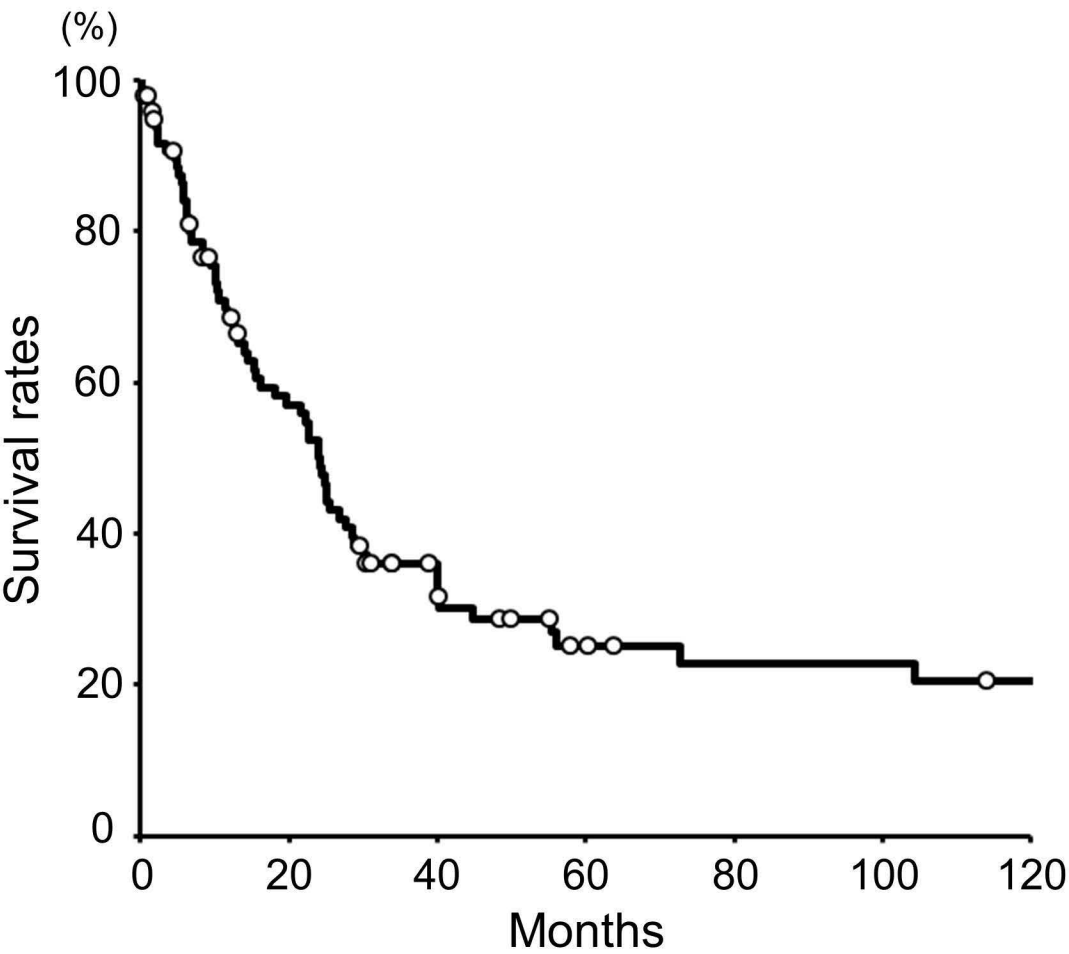


Fig. 2. Kaplan-Meier survival curves according to the number of metastatic nodules

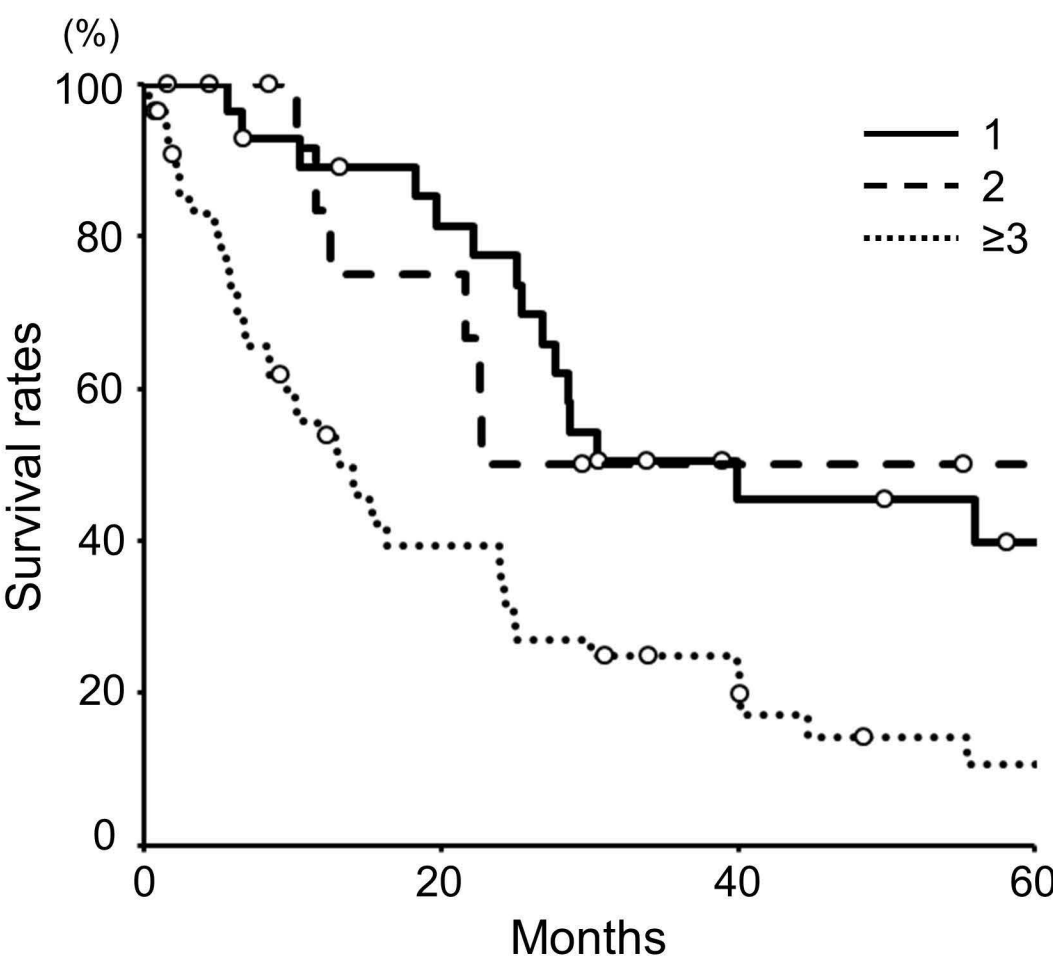


Fig. 3. Kaplan-Meier survival curves according to pulmonary metastasectomy

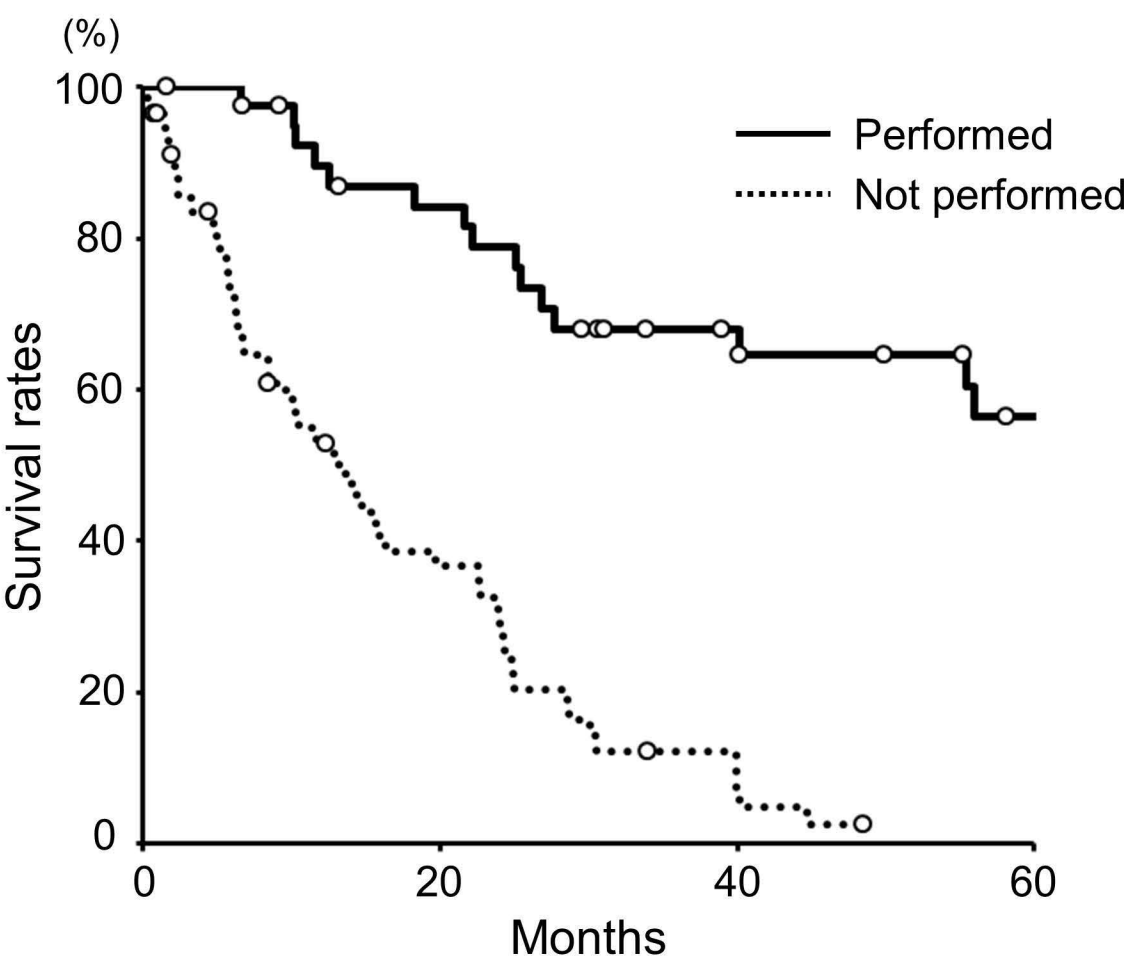


Fig. 4. Kaplan-Meier survival curves according to chemotherapy in 41 patients who underwent pulmonary metastasectomy

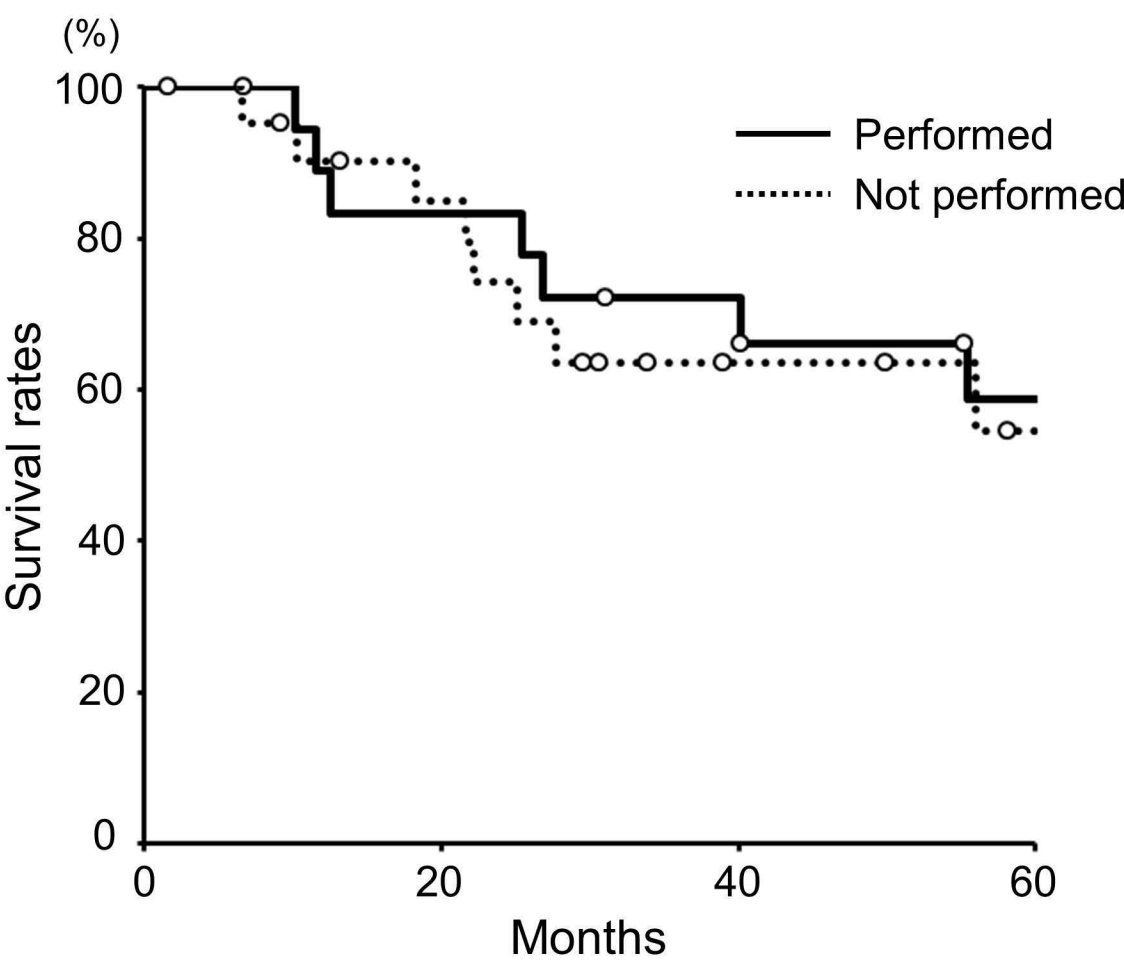


Fig. 5. Kaplan-Meier survival curves according to chemotherapy in 57 patients who did not undergo pulmonary metastasectomy

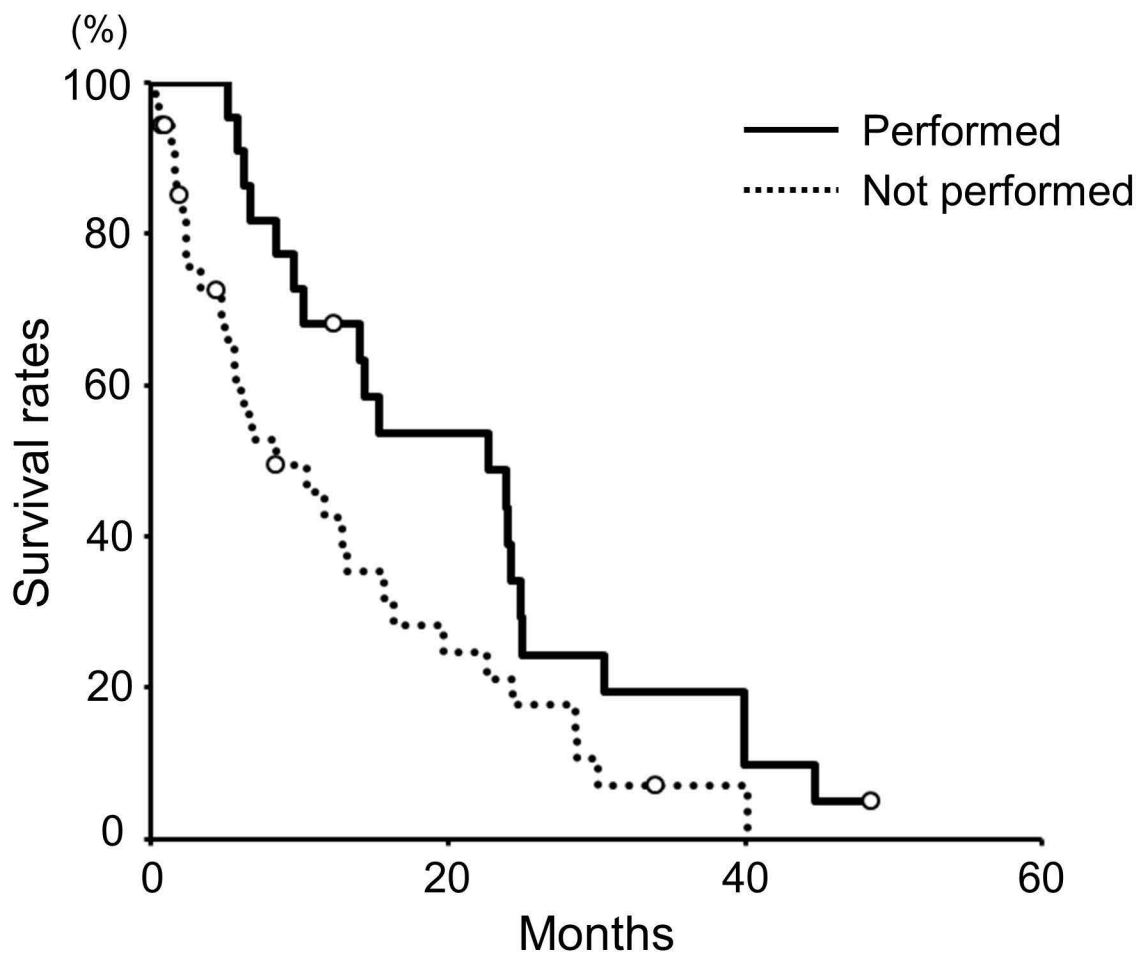


Table 1. Clinical characteristics of the patients and primary tumors

| Variables                         | n (%)     | Median survival<br>(months) | Survival rate (%) |        |        | p value |
|-----------------------------------|-----------|-----------------------------|-------------------|--------|--------|---------|
|                                   |           |                             | 1 year            | 3 year | 5 year |         |
| <b>Age (years)</b>                |           |                             |                   |        |        | 0.046   |
| < 60                              | 49 (50.0) | 24.9                        | 79.0              | 43.9   | 31.3   |         |
| ≥ 60                              | 49 (50.0) | 11.7                        | 57.5              | 27.1   | 16.9   |         |
| <b>Sex</b>                        |           |                             |                   |        |        | 0.341   |
| Male                              | 62 (63.3) | 21.9                        | 71.0              | 35.6   | 33.5   |         |
| Female                            | 36 (36.7) | 19.0                        | 64.4              | 36.6   | 9.1    |         |
| <b>Primary tumor site</b>         |           |                             |                   |        |        | 0.249   |
| Upper extremities                 | 6 (6.1)   | 12.9                        | 66.7              | 25.0   | 25.0   |         |
| Lower extremities                 | 62 (63.3) | 24.0                        | 75.0              | 40.1   | 30.2   |         |
| Trunk                             | 30 (30.6) | 10.4                        | 54.9              | 29.0   | 9.7    |         |
| <b>Primary tumor depth</b>        |           |                             |                   |        |        | 0.719   |
| Superficial                       | 21 (21.4) | 25.1                        | 80.2              | 32.2   | 24.2   |         |
| Deep                              | 77 (78.6) | 15.6                        | 65.4              | 37.1   | 25.3   |         |
| <b>Primary tumor size (mm)</b>    |           |                             |                   |        |        | 0.253   |
| < 91.5                            | 49 (50.0) | 21.9                        | 79.8              | 47.5   | 25.0   |         |
| ≥ 91.5                            | 49 (50.0) | 12.2                        | 58.4              | 26.0   | 23.6   |         |
| <b>Primary tumor grade</b>        |           |                             |                   |        |        | 0.249   |
| Low/Intermediate                  | 10 (10.2) | 36.5                        | 90.0              | 60.0   | 22.5   |         |
| High                              | 88 (89.9) | 17.5                        | 66.0              | 32.9   | 24.6   |         |
| <b>Primary tumor surgery</b>      |           |                             |                   |        |        | 0.001   |
| Performed                         | 94 (95.9) | 22.4                        | 70.9              | 37.2   | 25.9   |         |
| Not Performed                     | 4 (4.1)   | 3.8                         | 0                 | 0      | 0      |         |
| <b>Primary tumor chemotherapy</b> |           |                             |                   |        |        | 0.536   |
| Performed                         | 29 (29.6) | 23.9                        | 72.4              | 31.0   | 21.3   |         |
| Not Performed                     | 69 (70.4) | 16.3                        | 67.0              | 38.8   | 26.9   |         |
| <b>Local recurrence (n=94)</b>    |           |                             |                   |        |        | 0.008   |
| Yes                               | 25 (26.6) | 10.3                        | 48.4              | 26.4   | 7.9    |         |
| No                                | 69 (73.4) | 24.4                        | 78.7              | 40.9   | 32.2   |         |
| <b>Extrapulmonary metastasis</b>  |           |                             |                   |        |        | 0.539   |
| Yes                               | 32 (32.7) | 14.9                        | 67.8              | 38.3   | 19.1   |         |
| No                                | 66 (67.3) | 24.3                        | 69.2              | 34.5   | 29.1   |         |

Table 2. Histological types of primary tumors

| Histological types                  | Number (%) |
|-------------------------------------|------------|
| Leiomyosarcoma                      | 22 (22.5)  |
| UPS/MFH                             | 22 (22.5)  |
| Synovial sarcoma                    | 10 (10.2)  |
| Myxofibrosarcoma                    | 10 (10.2)  |
| Liposarcoma                         | 9 (9.2)    |
| MPNST                               | 7 (7.1)    |
| Ewing/PNET                          | 3 (3.1)    |
| Extraskeletal myxoid chondrosarcoma | 3 (3.1)    |
| Rhabdomyosarcoma                    | 3 (3.1)    |
| Clear cell sarcoma                  | 2 (2.0)    |
| Angiosarcoma                        | 1 (1.0)    |
| Carcinosarcoma                      | 1 (1.0)    |
| Fibrosarcoma                        | 1 (1.0)    |
| Malignant glomus tumor              | 1 (1.0)    |
| Malignant granular cell tumor       | 1 (1.0)    |
| Malignant myoepithelial tumor       | 1 (1.0)    |
| Solitary fibrous tumor              | 1 (1.0)    |
|                                     | 98 (100)   |

UPS/MFH, undifferentiated pleomorphic sarcoma/ malignant fibrous histiocytoma;

MPNST, malignant peripheral nerve sheath tumor;

PNET, primitive neuro ectodermal tumor;

Table 3. Analyses of pulmonary metastasis in STS patients

| Variables                                                                | n (%)     | Median survival<br>(months) | Survival rate (%) |        |        | p value  |
|--------------------------------------------------------------------------|-----------|-----------------------------|-------------------|--------|--------|----------|
|                                                                          |           |                             | 1 year            | 3 year | 5 year |          |
| <b>MFI (months)</b>                                                      |           |                             |                   |        |        | 0.046    |
| < 12.3                                                                   | 48 (49.0) | 15.8                        | 61.4              | 26.0   | 17.1   |          |
| ≥ 12.3                                                                   | 50 (51.0) | 22.7                        | 75.8              | 45.8   | 33.0   |          |
| <b>Laterality</b>                                                        |           |                             |                   |        |        | 0.0002   |
| Unilateral                                                               | 38 (38.8) | 28.6                        | 88.7              | 52.0   | 40.1   |          |
| Bilateral                                                                | 60 (61.2) | 12.1                        | 55.8              | 25.9   | 15.3   |          |
| <b>Number of nodules</b>                                                 |           |                             |                   |        |        | 0.0002   |
| 1 or 2                                                                   | 43 (43.9) | 28.6                        | 87.4              | 50.2   | 43.0   |          |
| ≥ 3                                                                      | 55 (56.1) | 11.7                        | 53.8              | 24.8   | 10.6   |          |
| <b>Pulmonary metastasectomy</b>                                          |           |                             |                   |        |        | < 0.0001 |
| Performed                                                                | 41 (41.8) | 38.9                        | 89.6              | 67.9   | 56.5   |          |
| Not Performed                                                            | 57 (58.2) | 10.5                        | 53.0              | 12.2   | 0      |          |
| <b>Approach of pulmonary metastasectomy (n=41)</b>                       |           |                             |                   |        |        | 0.223    |
| Open                                                                     | 8 (19.6)  | 95.4                        | 100               | 71.4   | 71.4   |          |
| VATS                                                                     | 33 (80.4) | 47.1                        | 87.3              | 67.1   | 51.3   |          |
| <b>Type of pulmonary metastasectomy (n=41)</b>                           |           |                             |                   |        |        | 0.484    |
| Partial/wedge resection                                                  | 28 (68.3) | 40.1                        | 88.0              | 68.0   | 52.9   |          |
| Segmentectomy                                                            | 5 (12.2)  | 27.7                        | 80.0              | 40.0   | 40.0   |          |
| Lobectomy                                                                | 8 (19.5)  | 36.4                        | 100               | 87.5   | 87.5   |          |
| <b>Repeated pulmonary metastasectomy (n=41)</b>                          |           |                             |                   |        |        | 0.492    |
| Performed                                                                | 8 (19.5)  | 47.6                        | 85.7              | 71.4   | 38.1   |          |
| Not Performed                                                            | 33 (80.5) | 33.9                        | 90.4              | 67.0   | 61.8   |          |
| <b>Chemotherapy for patients with pulmonary metastasectomy (n=41)</b>    |           |                             |                   |        |        | 0.341    |
| Performed                                                                | 19 (46.3) | 55.2                        | 88.9              | 72.2   | 58.8   |          |
| Not Performed                                                            | 22 (53.7) | 30.1                        | 90.2              | 63.7   | 54.6   |          |
| <b>Chemotherapy for patients without pulmonary metastasectomy (n=57)</b> |           |                             |                   |        |        | 0.037    |
| Performed                                                                | 22 (38.6) | 19.1                        | 68.2              | 19.5   | 4.9    |          |
| Not Performed                                                            | 35 (61.4) | 6.3                         | 42.4              | 7.1    | 0      |          |

MFI, metastasis-free interval; VATS, video-assisted thoracic surgery

Table 4. Comparison of clinical characteristics of the patients with or without pulmonary metastasectomy

| Variables                                    | n (%)      | Pulmonary metastasectomy |                      | p value  |
|----------------------------------------------|------------|--------------------------|----------------------|----------|
|                                              | All (n=98) | Performed (n=41)         | Not performed (n=57) |          |
| <b>Age (years)</b>                           |            |                          |                      | 0.014    |
| < 60                                         | 49 (50.0)  | 27 (65.9)                | 22 (38.6)            |          |
| ≥ 60                                         | 49 (50.0)  | 14 (34.1)                | 35 (61.4)            |          |
| <b>Primary tumor grade</b>                   |            |                          |                      | 0.831    |
| Low/Intermediate                             | 10 (10.2)  | 4 (9.8)                  | 6 (10.5)             |          |
| High                                         | 88 (89.8)  | 37 (90.2)                | 51 (89.5)            |          |
| <b>Primary tumor surgery</b>                 |            |                          |                      | 0.858    |
| Performed                                    | 94 (95.9)  | 40 (97.6)                | 54 (94.7)            |          |
| Not Performed                                | 4 (4.1)    | 1 (2.4)                  | 3 (5.3)              |          |
| <b>Primary tumor chemotherapy</b>            |            |                          |                      | 0.869    |
| Performed                                    | 29 (29.6)  | 12 (29.3)                | 17 (29.8)            |          |
| Not Performed                                | 69 (70.4)  | 29 (70.7)                | 40 (70.2)            |          |
| <b>Local recurrence (n=94)</b>               |            |                          |                      | 0.313    |
| Yes                                          | 25 (26.6)  | 8 (20.0)                 | 17 (31.5)            |          |
| No                                           | 69 (73.4)  | 32 (80.0)                | 37 (68.5)            |          |
| <b>Extrapulmonary metastasis</b>             |            |                          |                      | 0.033    |
| Yes                                          | 32 (32.7)  | 8 (19.5)                 | 24 (42.1)            |          |
| No                                           | 66 (67.3)  | 33 (80.5)                | 33 (57.9)            |          |
| <b>MFI (months)</b>                          |            |                          |                      | 0.517    |
| < 12.3                                       | 48 (49.0)  | 18 (43.9)                | 30 (52.6)            |          |
| ≥ 12.3                                       | 50 (51.0)  | 23 (56.1)                | 27 (47.4)            |          |
| <b>Laterality</b>                            |            |                          |                      | < 0.0001 |
| Unilateral                                   | 38 (38.8)  | 27 (65.9)                | 11 (19.3)            |          |
| Bilateral                                    | 60 (61.2)  | 14 (34.1)                | 46 (80.7)            |          |
| <b>Number of nodules</b>                     |            |                          |                      | < 0.0001 |
| 1 or 2                                       | 43 (43.9)  | 32 (78.0)                | 11 (19.3)            |          |
| ≥ 3                                          | 55 (56.1)  | 9 (22.0)                 | 46 (80.7)            |          |
| <b>Chemotherapy for pulmonary metastasis</b> |            |                          |                      | 0.576    |
| Performed                                    | 41 (41.8)  | 19 (46.3)                | 22 (38.6)            |          |
| Not Performed                                | 57 (58.2)  | 22 (53.7)                | 35 (61.4)            |          |

MFI, metastasis-free interval

Table 5. Multivariate analysis of the post-metastasis survival

| Variables                        | HR    | 95%CI          | p value  |
|----------------------------------|-------|----------------|----------|
| No pulmonary metastasectomy      | 5.623 | 2.733 - 11.572 | < 0.0001 |
| No primary tumor surgery         | 3.911 | 1.108 – 13.802 | 0.034    |
| Age $\geq$ 60 years              | 1.047 | 0.621 – 1.764  | 0.863    |
| MFI $\geq$ 12.3 months           | 0.744 | 0.447 – 1.238  | 0.255    |
| Number of metastatic nodules < 3 | 0.699 | 0.285 – 1.712  | 0.433    |
| Unilateral involvement           | 0.533 | 0.228 – 1.245  | 0.146    |

HR, hazard ratio; CI, confidence interval; MFI, metastasis-free interval