1. Introduction

Soft-tissue sarcomas (STS) are rare tumors of mesenchymal origin with a high mortality rate [1]. Sarcoma may arise everywhere, but the extremity is the most common primary site. Isolated pulmonary metastases from STS occur in 20–50% of these patients and, once the metastatic disease develops, the prognosis is typically poor [2], although prolonged survival is possible for a subset of these patients. Three-year actuarial survival rates of 40–50% have been reported for patients whose metastatic disease was completely resected [3–5]. Most authors consider that pulmonary resection, when feasible, remains the established treatment approach in patients with metastatic STS to the lungs. Few data regarding the impact of chemotherapy in patients undergoing pulmonary resection for STS [2, 6] are available, but most patients with pulmonary metastases are treated with chemotherapy at some point in their clinical course.

In this study we reviewed a cohort of consecutive patients who underwent resection for STS pulmonary metastases at our institution. Our main objective was to identify possible prognostic factors and examine their impact in the overall survival. Our goal was also to estimate three- and five-year actuarial survival rates in this group of patients.

2. Patients and methods

After obtaining Institutional Review Board approval, a comprehensive search on our database was conducted to identify patients with resected STS lung metastases. From December 1996 to December 2006, a total of twenty-two patients underwent STS pulmonary metastases resection at our institution. At the time of surgery all of these patients met the following criteria: 1) had their primary STS under control with multimodality treatment, 2) were considered preoperatively to have resectable lung metastases, 3) were deemed eligible for going through lung resection and 4) were free of metastases in other organs. Most patients had received an Ifosfamide-Adriamidine based chemotherapy regimen, either pre or postoperatively: Ifosfamide 6–9 g/m² + Adriamidine 90 mg/m² per cycle. The median number of cycles of preoperative chemotherapy was four (duration approximately three months). Chemotherapy after initial pulmonary resection was administered in four cycles, for a median of four months. Adverse effects from perioperative chemotherapy were assessed regularly, and agents were reduced or discontinued as indicated if toxicity occurred.
The variables studied were: (1) age, (2) gender, (3) primary site, (4) histopathologic type, (5) disease-free interval (DFI), (6) thoracic approach and type of lung resection, (7) complete resection of lung metastases, and (8) re-do surgery for oncological purposes.

Survival rates were calculated starting from the date of surgery of pulmonary metastases, and the time to death was modelled using the method of Kaplan–Meier. The interrelation among survival and the factors mentioned above was analyzed by using the log-rank and the Cox model. In all statistical analyses, $P<0.05$ was considered significant.

3. Results

In this group of twenty-two patients, the age ranged between 13 and 82 years (median 41). Ten patients were male (54.5%) and twelve, female (45.5%). The histologic results of the primary tumor were: Extraskeletal Ewing’s Sarcoma in five patients, Malignant Fibrous Histiocytoma in four patients, Synovial Sarcoma in four patients, Fibrosarcoma in three patients, Leyomiosarcoma and Liposarcoma in two patients, respectively; and Alveolar Sarcoma and Clear Cell Sarcoma in one patient, respectively. Primary sites of the STS were lower limb in 13 cases; upper limb in 5 cases; and other locations in 4 patients (vagina, abdominal wall, pelvis and spine). The DFI ranged between 5 and 84 months (median 18). The surgical thoracic approach was thoracotomy in nineteen patients, video assisted thoracic surgery (VAT S) in two patients and sternotomy in one patient. The types of lung resection performed were wedge resection in nineteen patients, lobectomy in two patients and wedge+lobectomy in one patient. Complete removal of lung metastases at time of first surgery was performed in 20 patients (90% of the cases). Re-do surgery due to recurrent lung metastases was performed in seven patients (31.8%); three of these patients (13.6%) went through a third surgery for removal of recurrent lung disease. There was no operative mortality or major morbidity, except for one patient that required mechanical ventilation for 72 h and another one with a persistent air-leak. Among 18 patients treated perioperatively with Ifosfamine-Adriamycin (A-I) regimen, four were converted to Gemcitabine because of concerns of cardiotoxicity or poor tolerance of A-I.

Four patients (18.2%) were alive without disease, twelve patients (54.5%) died of disease and we lost track of the other six patients (27.3%). We lost complete track of two patients and we could not determine the exact date of death of the other four. These four patients were in fact followed for months or years and all of them were end-stage terminally ill patients at last follow-up date. We assumed that they passed away in the following two months due to their severely poor clinical status. So, all statistical calculations were based upon a total of 20 patients. The follow-up period for this group of patients ranged from 7 to 75 months, with a median of 14 months. The median survival was 19 months and three and five-year overall survival rates were 47.6% and 23.1%, respectively (Fig. 1).

Univariate analysis (using the log-rank test and the Cox model) showed that age ($P=0.17$), gender ($P=0.48$), primary site ($P=0.526$), re-do surgery ($P=0.156$) and complete resection of lung metastases ($P=0.623$) bear no significant relation to survival.

On the other hand, three significant prognostic factors (Figs. 2–4) were identified: first, DFI >1 year was related with longer survival ($P=0.04$); second, if 3 or less nodules...
had been removed the survival rate was better than if 4 or more had been resected \( (P=0.009) \); and third, Ewing sarcoma patients had a poorer prognosis than those suffering non-Ewing sarcomas \( (P=0.01) \).

4. Discussion

The series of patients analyzed show a ten-year experience in the surgical management of lung metastases of STS at our institution. Normally, these metastases show up when STS primary tumor cells travel through a hematogenous route and get trapped in the pulmonary capillary bed. Hence the lungs are, by far, the most frequent location for distant metastases of these tumors.

According to the figures in our study, lung metastases in STS patients have low morbi-mortality rates. This is basically due to two facts: a) patients with STS lung metastases usually have good cardiopulmonary function tests, as they do not normally suffer from COPD or other lung or heart disorders, as for example lung cancer patients many times do, and b) these are conservative operations; we have to take into account that re-do lung surgery for recurrent disease is frequent in these patients \( (31.8\% \text{ of patients in our series}) \). Various studies have demonstrated that repeated pulmonary resections make it possible to control the disease for an extended period of time \( [3, 7, 8] \).

Long-term survival after STS lung metastasectomy has been reported in different research works. A review of sixty-eight patients, treated at the US National Cancer Institute, showed a 35% three-year survival rate vs. a 28% three-year overall survival for all patients (whether or not having gone through lung metastasectomy) \( [15] \), and those who underwent incomplete resection had a median survival of nine months. The European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group, reviewed the collective experience from 11 hospitals, involving 255 patients, who underwent resection of pulmonary metastases. They reported an overall survival rate of 54% at three years and 38% at five years \( [5, 10] \). Other institutions have shown five-year survival rates ranging from 21 to 25% \( [4, 11, 12] \), very close to our own results.

A variety of prognostic factors have been reviewed in a number of different series. The ability to resect metastatic disease completely is consistently the most significant factor in determining postmetastasectomy survival. In our study, however, complete removal of lung metastases was not a significant prognostic factor. Most likely this was due to the fact that two patients remained with lung disease after surgery, one of whom we lost track of, so this small number of patients could not be compared properly with the group of completely resected patients. The other more consistent predictor of survival was an extended DFI \( [4, 9, 13, 14] \), this variable has shown statistical significance in our study. We also examined the number of nodules resected as a prognostic factor, which in fact turned out to be a favorable one if the number of nodules was three or lower. This is consistent with Casson et al. \( [4] \) and Putnam et al. \( [13] \) studies that concluded that patients with three or fewer nodules resected at operation had longer survival rates than patients with four or more nodules. The latter study demonstrated that unilateral versus bilateral disease is not a significant indicator of prognosis.

An interesting conclusion from our study, that we would like to emphasize, is that extaskeletal Ewing’s sarcoma turned out to be an indicator of poor prognosis. In our series the most frequent histologic type was extraskeletal Ewing’s sarcoma, compared to others that in most studies normally take this outstanding place (leymiosarcoma, malignant fibrous histiocytoma or synovial sarcoma) \( [3, 15] \). This rare histologic type had a clearly poorer prognosis compared with the rest of sarcomas. This matter has not been previously reported in the literature and we think it should be borne in mind in borderline surgical cases (e.g patients with multiple and bilateral metastases) where a conservative treatment may be preferable to an operation on these patients, due to their poor survival rate.

As for the four patients who were alive without disease at the end of the period of study, three of them had gone through re-do surgery. We did not find re-do surgery to be a prognostic factor for survival \( (P=0.156) \), nevertheless it is well known that patients who can be completely resected have better outcomes than those incompletely resected \( [8] \).

Some series have suggested that current perioperative chemotherapy has minimal, or no impact, on survival rates of patients undergoing pulmonary resection for metastatic STS \( [2] \). In our study, patients went through both perioperative chemotherapy and surgery, so it was not possible for us to establish the exact role of chemotherapy by itself. Therefore, we think that new series and medical approaches are needed in this setting.

We have found several limitations to our study:

a) The retrospective design;
b) The fact that chemotherapy regimens and surgical thecniqes are highly individualized based on patient and tumor characteristics; and most important of all, c) Results are based on a small number of patients operated in a single institution, and  
d) the most important limitation: we lost track of six patients, at some point in time, during the follow-up period.

Prospective multi-institutional large-scale studies need to be performed in the future to confirm our current results.
5. Conclusion

Long-term survival is possible after resection of pulmonary metastases from STS, although the five-year survival rate is low (23.1%). DFI > 1 year, 3 or less pulmonary metastases and non-Ewing STS are favorable prognostic factors. Re-do lung surgery, although not statistically significant for survival, was present in three of the four patients alive without disease.

References