Long-term results after resection for bone sarcoma pulmonary metastases

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Abstract

Background: Pulmonary metastases from bone sarcomas occur in approximately 40% of the cases. The combination of both chemotherapy and surgical resection is currently the standard treatment options for these patients. We aim to study the influence of different prognostic factors on long-term survival. Methods: We reviewed the prognostic factors and survival rate in 52 consecutive patients with pulmonary metastases from bone sarcomas. All of them were previously treated with chemotherapy and submitted to metastasectomy at our institution from 1996 to 2006. Clinical and demographic variables, related to the primary tumour as well as to the pulmonary metastases, and treatment procedures were registered. Univariate (log-rank) and multivariate (Cox regression) analysis were carried out to identify significant prognostic factors related to overall survival. Five-year survival rates were estimated using Kaplan–Meier methods. Results: Median follow-up was 28 months. Follow-up duration ranged 7—148 months; the median survival was 27 months. As many as 31% of the patients were alive without disease, 3% were alive with disease, 64% died of disease while 2% died from other causes. Complete resection was achieved in 49 cases (94%). The overall 3- and 5-year survival rates were 43% and 31%, respectively. Univariate analysis showed (1) disease-free interval between treatment of the primary bone tumour and first lung metastasectomy (DFI) and (2) disease-free interval between first and second lung surgery (DFI2) as prognostic factors. Gender, primary site, histology of primary tumour, surgical approach, number of lung nodules, type of lung resection and re-do lung surgery did not have a significant impact on survival. Conclusion: The long-term survival after bone sarcoma lung metastasectomy is encouraging. In our series, DFI and DFI2 were identified as the only prognostic factors.

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1. Introduction

Pulmonary metastases occur in approximately 40% of the patients with bone sarcomas. Although the 5-year survival has reached 40—70% for bone sarcomas, only 20—40% of those found to have pulmonary metastases would survive 5 years [1—3]. The development of pulmonary metastases is a factor of poor prognosis and most of untreated patients died within 6 months of diagnosis [4].

Surgical resection has proved to be effective to prolong survival among patients with pulmonary metastases [3,5]. Indications for pulmonary metastasectomy have evolved due to a better understanding of the natural history of malignant tumours and the improvements in surgical techniques. Nevertheless, prognostic factors associated with improved survival after resection of pulmonary metastases are still unclear [1,6].

Chemotherapy seems to improve survival as a result of its effect on micrometastases [7]. The association of chemotherapy and surgery is currently the standard treatment options for patients with pulmonary metastases [7—9]. This study is a retrospective review of our experience with bone sarcoma patients whose lung metastases were managed surgically. We tried to identify the tumour characteristics that were associated with improved survival.

2. Material and methods

After obtaining IRB approval a comprehensive search on our database was conducted to identify patients with resected STS lung metastases. We managed to identify 52
consecutive patients treated surgically for pulmonary metastases, at CUF, from December 1996 to December 2006.

At the time of surgery all of these patients met the following criteria: (1) had their primary STS under control, (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.

Therapeutic control for patients with lung metastases was based on surgery in combination with pre- and postoperative multi-agent chemotherapy. Detailed regimens of chemotherapy were different among patients; however, cisplatin, adriamycin, etoposide, methotrexate and ifosfamide were the most common agents used.

The following variables were considered: (1) age, (2) gender, (3) primary site, (4) histopathologic type, (5) disease-free interval between treatment of the primary bone tumour and first lung metastasectomy (DFI), (6) disease-free interval between first and second lung surgery (DFI2), (7) thoracic approach and type of lung resection, (8) number of lung metastases, (9) complete resection of lung metastases and (10) re-do surgery for oncological purposes.

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical calculations. Survival rates were calculated starting from the date of first lung metastasectomy and the time to death was modelled using the Kaplan-Meier method [7]. The correlation of the above-mentioned factors with survival was analysed by log-rank model (for univariate analysis) and the Cox model (for multivariate analysis). In multivariate analysis, forward and backward stepwise procedures were used to determine the combination of factors essential in predicting survival. In all statistical analyses, p < 0.05 was considered significant.

## 3. Results

In this group of 52 patients, the age ranged from 5 to 74 years (median 20 years); 31 patients were male (61%) and 21 female (39%). The histologies of the primary tumour were osteosarcoma in 31 patients (60%), Ewing sarcoma in 12 (23%), chondrosarcoma in 12 (23%), undifferentiated sarcoma in two (4%), fibrosarcoma, neuroectodermic tumour, leymiosarcoma, adamantine and fusocellular tumour in one patient each (9% in total) (Table 1). The primary sites of bone sarcoma were femur in 19 cases (36%), tibia in 11 (21%), humerus in five (9%), pelvis in four (8%), fibula in four (8%), foot bones in three (6%), ribs in two (4%), scapula in two (4%) and other locations in two patients (4%) (Table 2). The DFI ranged from 5 to 189 months (median 20 months). The disease-free interval between first and second lung surgery (DFI2) ranged from 6 to 126 months (median 9.5 months). The surgical thoracic approaches were thoracotomy in 30 patients (58%), sequential bilateral thoracotomy in seven (13%), video-assisted thoracic surgery (VATS) in 10 (19%) and clamshell approach in five patients (9%). The types of lung resection performed were: wedge resection in 44 patients (85%), lobectomy in six (11%) and exploratory thoracotomies in two (4%). Chemotherapy lung perfusion was used in one patient and intra-operative radiotherapy was implemented in another case. Cardiopulmonary bypass was necessary in one patient. Complete removal of lung metastases (R0) at the time of first surgery was achieved in 49 patients (94% of cases). Re-do surgery due to recurrent lung metastases was performed in 16 patients (31%); nine of these patients (17%) went through a third surgery for removal of recurrent lung disease. There was no operative mortality. Major morbidity occurred in four patients: one patient required mechanical ventilation for more than 24 h due to ARDS, two patients had pneumonia of the operated lung and two suffered persistent air leaks (>7 days).

The follow-up period for this group of patients ranged from 7 to 148 months: median follow-up was 28 months. Median survival was 27 months and 31% of the patients were alive without disease, 3% were alive with disease, 64% died of disease, while 2% died from other causes. Complete resection was achieved in 49 cases (94%). The overall 3-, 5- and 10-year survival rates were 43% and 31% each, respectively (Fig. 1).

The log-rank analysis showed a DFI exceeding 20 months (p = 0.03) and DFI2 exceeding 9 months (p = 0.001) as prognostic factors (Figs. 2 and 3). Age (p = 0.28), sex (p = 0.49), site (p = 0.62) and histology of primary tumour (p = 0.36), surgical approach (p = 0.72), number of lung nodules (p = 0.59), type of lung resection (p = 0.57), re-do lung surgery (p = 0.61) and complete resection of lung metastases (p = 0.59) did not have any significant impact on survival (Table 2).

No independent prognostic factors were obtained when studying aforementioned variables with multivariate analysis (using the Cox model), perhaps due to the size of the series.

## 4. Discussion

This series of patients represents a single-institution 10-year experience in the surgical management of bone sarcoma lung metastases. These metastases occur due to bone sarcoma...
primary tumour cells that travel through a haematogenous route and get easily trapped in the pulmonary capillary bed. Hence the lungs are, by far, the most frequent location for distant metastases in these tumours.

The first resection of pulmonary metastases, originated from renal cancer, was performed in 1939 by Barney and Churchill [11]. In 1947, Alexander and Haight [12] reported their results on 24 selected patients with pulmonary metastases. In the 1970s Martini et al. [13] and Morton et al. [14] compared the survival rates of patients with unilateral and bilateral pulmonary resections and concluded that their rates were identical. However, until the 1980s, after the studies of Morrow et al. [15], this surgery was mainly performed in selected patients with few metastases. Morrow et al. obtained very similar survival rates for patients with single or multiple metastases.

Just 3 decades ago, the development of pulmonary metastases from bone sarcoma virtually ensured early death [5,10]. Advances in chemotherapy strategies and the refinements of surgical indications and approaches have significantly improved the prognosis of these patients. As our series have shown, after undergoing chemotherapy regimens and resection of pulmonary metastases, overall survival rates of 40—70% for 3 years and 30—50% for 5 years can be achieved [3,7]. Lung metastasectomies have low morbidity and mortality rates. This is basically because (1) patients with bone sarcoma lung metastases usually have normal cardiopulmonary function tests and (2) lung resections are conservative operations, being re-do lung surgery for recurrent disease, quite frequent in these patients (31% of patients in our series). Various studies have demonstrated that repeated pulmonary resections enable controlling the disease for an extended period [16—18].

Various prognostic factors such as number of pulmonary metastases [1,19], disease-free interval [5,19,20] and complete removal of metastases [7,21] have been consistently reviewed in several different series. In our series, we did not find the number of lung metastases nor complete removal of metastases to be significant prognostic factors. In the last case probably because all patients, except three, were R0; therefore we believe this small group did not have enough power to be appropriately compared with the other 49 patients. However, DFI longer than 20 months and DFI2 longer than 9 months were favourable prognostic factors. We emphasise that DFI2 should be considered as a relevant prognostic factor. In our series, re-do surgery was performed in nearly a third of the patients, DFI2 being as important in their prognosis as DFI. DFI2 is not always studied when dealing with lung metastases surgical series, but we would stress upon its importance. Furthermore, it is noteworthy that of the 16 patients who were alive without disease at the end of the study period, six (38%) had undergone re-do surgery. However, in our study, re-do surgery was not a prognostic factor ($p = 0.61$); nevertheless, it is well known that patients who can be completely re-resected have better outcomes than those incompletely resected [9,16—18,20].

VATS was performed in 10 patients (19%) without differences in long-term survival compared with open procedures. Use of VATS for pulmonary metastasectomy has been controversial, basically because palpation is crucial.
in identifying lung nodules and is problematic with VATS. However, some studies have suggested that it can be used safely to remove a small number of peripheral nodules [22]. The accuracy of modern multi-slice CT in showing lung nodules is quite high and becomes very useful when planning surgical resections.

In the 1980s, perioperative chemotherapy was proved to be effective, increasing survival rates and resectability in these patients [23]. Bacci et al. [24] demonstrated better results using preoperative chemotherapy in patients with metastatic diseases, at the time of diagnosis, who underwent simultaneous resection of the primary tumour and lung metastases. Most authors advocate using adjuvant therapy in association with surgery for resection of metastases that have shown up after treatment of the primary tumour, as survival rates are usually better than when undertaking surgery alone. Keeping all this in mind, in our series, we used pre- and postoperative chemotherapy regimens to control any possible systemic dissemination.

Our analysis has several limitations such as (1) the retrospective design of study, (2) chemotherapy regimens are highly individualised based on unique patient and tumour characteristics and (3) the results are based on a relatively small number of patients operated in a single institution. Prospective multi-institutional large-scale studies are needed to confirm our present provisional results.

5. Conclusion

Long-term survival is encouraging after bone sarcoma lung metastasectomy, with a 5-year survival rate of 31%. In our series, DFI and DF2 showed to be prognostic factors, none of the other variables studied had an influence on survival. Redo surgery, although not found to be a key prognostic factor, was highly significant in long-term survivors.

References