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Excision of pulmonary metastases of osteogenic sarcoma of the limbs ☆

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Abstract

Objective: The combination of surgery and chemotherapy improves the prognosis of patients with osteogenic sarcoma of the limbs without detectable metastases at presentation. However, lung metastases are a frequent complication. To evaluate the role of the resection of pulmonary metastases of osteogenic sarcoma of the limbs, we have reviewed our experience with this type of surgery, combined with a multidrug chemotherapy protocol. **Patients and methods**: From January 89 to December 97, 198 patients operated on for osteogenic sarcomas of the limbs were followed in our centre. Of these, 31 patients (15.7%), with a mean age of 25 years (range 10–54 years), developed lung metastases and had undergone 45 thoracotomies. All patients received chemotherapy, followed by resection of metastatic lesions and additional chemotherapy. The mean time interval between resection of the primary tumour and the diagnosis of lung metastases was 22 months (4–122 months). Eight patients (25.8%) needed more than one (2–4) thoracotomy. The mean time interval between the first and second thoracic surgeries was 9.2 months (2–14 months). **Results**: There was no operative mortality or major morbidity. During the 45 thoracotomies, five lobectomies and 40 wedge resections were necessary. The mean number of metastases resected per thoracotomy was 3.4 (range 1–10). The degree of necrosis was evaluated by seriated sections for a histologic study. In the end the mean necrotic volume was calculated. A strong correlation was found between the degree of necrosis of the metastases and the need for reoperation for new metastatic lesions, because all the patients who needed more than one operation had less than 80% of necrosis of metastases. The patients were followed for a mean period of 28 months (6–72 months). Ten patients (32.2%) died of related causes at a mean of 19.4 months after thoracic surgery, three of whom had more than one operation. The 3-year survival after metastasectomy was 61%. Patients without pulmonary metastases had a 3-year survival of 79%. **Conclusions**: In patients with lung metastases of an osteogenic sarcoma, the combination of chemotherapy and surgery improves the outcome. In our series the mortality was not influenced by the number or thoracotomies required.

Keywords: Osteogenic sarcoma; Metastases; Surgery; Chemotherapy

1. Introduction

The lung is the most common site of metastisation of malignant tumours with the exception of those occurring in organs that drain to the portal venous system [1]. Pulmonary metastases occur in approximately 30% of all malignant tumours and in up to 60% of patients with sarcoma of the limbs treated surgically. The development of pulmonary metastases is a factor of very poor prognosis, the majority of untreated patients dying within 6 months of diagnosis.

The role of surgery in the treatment of pulmonary metastases has evolved with time, also influenced by advances in the knowledge of tumoural biology and by better understanding of the natural history of malignant tumours. Early resection of pulmonary metastases improves survival markedly [2–5]. The 5-year survival may reach 50%, although true cure is extremely rare, the majority of patients eventually dying of the disease.

Multiple metastases, unilateral or bilateral, and further metastisation are frequent, obliging to multiple resection, bilateral approach and repeated thoracotomies [6]. However, the number of metastases, bilaterality and further surgery do not appear to influence survival significantly. Currently, the number of metastases that can be resected is only limited by the capacity to eliminate all the metastatic disease, but leaving enough pulmonary parenchyma to guarantee a reasonable functional respiratory capacity.

Chemotherapy appears to further improve prognosis by its effect on micrometastases [7]. The association of multiagent chemotherapy and of surgery of both primary and secondary tumours has improved the 3-year survival up to 70%.

We have reviewed our recent experience in the treatment

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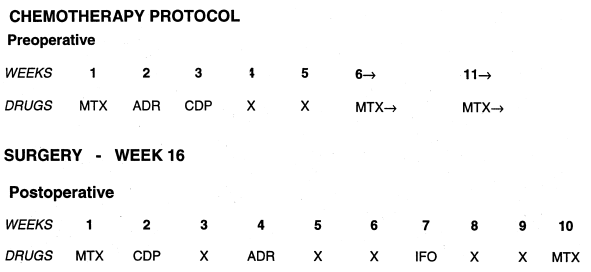

Fig. 1. Chemotherapy protocol utilised pre and postoperatively in 31 patients subjected to surgical excision of pulmonary metastases of osteogenic sarcoma of the limbs (see explanation in the text).

of patients who developed pulmonary metastases after surgical treatment of osteogenic sarcoma of the limbs.

2. Patients and methods

2.1. Patients

In the 9-year period from January 1989 to December 1997, 198 patients with osteogenic sarcoma of the limbs were operated on in our hospital. Of this group, 31 patients (15.7%), with a mean age of 25 years (range 10–54 years), developed pulmonary metastases. There were 21 males and 10 females, and nine patients (29.0%) were under 15 years of age at the time of the initial operation. The primary tumour had been located in the femur in 11 patients (35.5%), in the tibia in 10 (32.3%), in the humerus in four (12.9%) and in other sites in six (19.4%). Following the excision of the primary tumour, all patients had CT scans every 3–6 months until 2 years free of disease had elapsed. A complete clinical, laboratorial and imagiologic workout was undertaken to identify or exclude the presence of metastases in other organs and systems. Magnetic resonance imaging was performed in some patients but none had high resolution spiral thoracic CT because it is not available to us. All 31 patients were evaluated by CT scan before thoracic exploration, in order to determine the number and localisation of metastases present in each lung. No comment on specificity can be made, however, as specific roentgenographic abnormalities were not correlated with individually resected metastases.

Table 1
Localisation of the metastases

Right lung	
Superior lobe	13
Middle lobe	6
Inferior lobe	31 (+n)[a]
Left lung	
Superior lobe	31
Inferior lobe	32 (+n)[a]

[a] In two patients who had lobectomies, the total number of metastases in the resected lobes is unknown.

Patients were selected for resection of pulmonary metastases if they met the following criteria: (1) primary tumour completely eradicated and without local recurrence; (2) no recognisable metastases in other organs besides the lung; and (3) all pulmonary metastases resectable with a low operative risk and an adequate residual pulmonary function. Factors such as the number of metastases, unilateral versus bilateral involvement, disease-free interval and duplication time of the osteogenic sarcoma were not factors of exclusion. There were another 27 patients (14%) who developed lung metastases but were not included in this group because they did not meet these criteria.

2.2. Chemotherapy

The therapeutic control for patients with lung metastases of osteogenic sarcoma was based on the combination of chemotherapy and surgery, as indicated in Fig. 1. This was initiated by three cycles of pre-operative chemotherapy with methotrexate (MTX) 12 g/m^2, adriamycin (ADR) 90 mg/m^2, cisplatinium (CDP) 160 mg/m^2. The chemotherapy course was repeated in the sixth and eleventh week with 2-week intervals. During the 16th week, the patients were submitted to surgery and chemotherapy was reinitiated on the 10th post-operative day, following a protocol identical to the pre-operative one with the single difference that on the 21st day, after administration of adriamycin, ifofosfamide (IFO) 10 g/m^2 was initiated. In patients over 40 years, methotrexate was not used and was replaced by adriamycim 75 mg/m^2. Three identical therapeutic cycles were completed, after which the patient was re-evaluated from a clinical, laboratorial and radiological stand point.

2.3. Surgery

All operations were performed through a lateral thoracotomy, but bilateral metastases were removed through a median sternotomy in one patient. Thorough palpation of the lung was carried out to detect metastases not identified by the chest X-ray or CT scan. Palpable abnormalities that did not appear to be obvious granulomas were excised by wedge resection, segmental resection of formal pulmonary resection, and were subjected to thoracotomy for removal of these lesions. Resection of the metastases was as conservative of the lung parenchyma as possible. Enucleations or wedge resections were performed in the majority of the cases. When this was not possible, a lobectomy was performed. The mean time interval between the resection of the primary tumour and the occurrence of pulmonary metastases was 22 months (range 4–122 months). Table 1 indicates the localisation of metastases. In four patients there was bilateral involvement. In one of these the metastases were removed through a median sternotomy and in the other three through sequential thoracotomies. Resected metastases were sent for histologic study. The degree of necrosis was evaluated from seriated sections. At the end, the mean necrotic volume was calculated.

3. Results

In this group of 31 patients, 45 thoracotomies were performed. Eight patients required more than one thoracotomy, four required two thoracotomies, two required three thoracotomies and two required four thoracotomies. In these cases, the interval between surgeries was lower than that between resection of the primary tumour and first thoracotomy (22 months): 9.2 months (range 2–14 months) between first and second thoracotomies and 14.8 months (6–24 months) between second and subsequent thoracotomies. Enucleations or wedge resections were performed on 40 occasions and five patients had lobectomies.

The mean number of metastases diagnosed by CT scan was 3.2 (range 1–8). The mean number of metastases resected in each surgery was 3.4 (range 1–10). Only metastases <1 cm in size accounted for the discrepancy. In patients subjected to more than one thoracotomy the mean number of metastases resected was 5.7 (2–10). The extent of necrosis varied between 60 and 95% but in all patients subjected to more than one thoracotomy, pathological examination showed an extent of necrosis of the metastases lower than 80%, as observed by seriated sections in the histologic study.

There was no operative mortality or major morbidity, but one patient required ventilation for 48 h.

All patients were followed for a mean period of 28 months (range 6–72 months) after the first thoracotomy. Ten patients (32.2%) died of related causes, at a mean of 19.4 months after thoracic surgery (6–30 months) and 8–130 months after treatment of the primary tumour. All but one died of uncontrollable pulmonary metastisation. Three of the 10 had more than one thoracotomy.

The 3-year survival was 61% for the patients with pulmonary metastases. By comparison, a 3-year survival of 79% was recorded for patients with osteosarcoma without metastases treated at our institution during the same period of time. Five of the eight patients with more than one thoracotomy (62%) are alive. There did not appear to be a correlation between survival and the number and localisation of the metastases. All patients with metastases not resected died.

4. Discussion

It is thought that 40–60% of all primary sarcomas of the limbs treated surgically develop pulmonary metastases within 3 years. If not resected, the mean survival of patients is around 6 months [15]. Because the dissemination of osteogenic sarcoma is through the haematogenous route, the tumour cells are trapped in the pulmonary capillary bed. Hence the lungs are, by far, the most frequent location for distant metastases in these tumours.

The first intentional resection of a pulmonary metastasis, secondary to a renal tumour, was performed in 1939 by Barney and Churchill [8]. Other surgeons followed this example and in 1947 Alexander and Haight [9] found that 24 patients had been operated on for resection of pulmonary metastases. However, this surgery was then performed only in very selected patients, all having a single pulmonary metastasis and with a recurrence-free interval of at least 2 years.

Martini et al. [6] and Morton et al. [10] compared the survival of patients with unilateral and bilateral pulmonary resection and concluded that the survival was identical. Thereafter, the surgical attitude towards resection of pulmonary metastases has been more aggressive, especially after the studies of Morrow et al. [11] demonstrated almost identical survival for patients with a single metastasis and those with multiple metastases (27% and 22% survival, respectively).

Surgery for resection of pulmonary metastases is usually simple and carries low mortality risk, even when multiple lesions are present, provided that the amount of pulmonary parenchyma removed does not significantly compromise global pulmonary function. Resection must be as conservative for parenchyma as possible and patients with sarcoma of the limbs are usually young and have a normal respiratory function. We did not have mortality in this series and there were no significant respiratory complications.

Carter et al. [12] found, as did we in this series, that patients who had resection of pulmonary metastases had a better prognosis than those who, for any reason, had not. But they did not find a significant relationship between survival and the number and bilaterality of metastases. However, these authors found that patients with metastases localised to a single lobe had a longer survival than patients with metastases in more than one lobe.

On the other hand, Girard et al. [13] found that in patients with resectable pulmonary metastases from sarcoma and carcinoma, the number of metastases had little influence in the surgical decision. They advised delaying the decision to thoracotomy in patients with several metastases until a significant interval has shown that metastatic disease remains resectable and confined to lungs.

Resection of pulmonary metastases results in 50–70% 3-year survival and 30–50% 5-year survival. Patients with solitary metastases should have the best prognosis. However, several authors were able to obtain similar results in patients with several and bilateral lesions [14–15]. But the long-term prognosis is dependent on the ability to achieve complete surgical resection of pulmonary metastases. Goorin et al. [16] found that 82% of patients who could be made free of disease were long-term survivors, as compared to 13% of those who could not. But even with an aggressive surgical approach to the pulmonary lesion, only 42% of their patients could be made free of disease.

A significant number of patients in our series required additional thoracotomies for resection of metastases not present or not detected during the initial thoracotomy. This did not appear to affect survival negatively. However,

the time between 1st and 2nd thoracotomies and between 2nd and subsequent thoracotomies was significantly shorter than that between the operation for removal of the primary tumour and the first thoracotomy. Beattie et al. [17] reported survival of up to 22 years after multiple resection of pulmonary metastases. In their series of 22 patients treated surgically, before the chemotherapy era, there were six 10-year, five 15-year and four 19-year survivors. But of concern was the finding that 50% of the 10-year survivors developed second primary malignant tumours during their second decade of follow-up.

We could not find a correlation between length of survival and the number, localisation and bilaterality of metastases but there appeared to be a direct relationship with the degree of necrosis of the metastases. However, Inoue et al. [18] found the disease-free interval to be a significant prognostic factor in a series of 22 patients subjected to 34 thoracotomies during a 15-year period. Repeated thoracotomy for removal of additional metastases is, therefore, beneficial, which justifies close follow-up of the patients, with frequent diagnostic imaging.

Based on the fact that occult contralateral metastases are present in 20% of the cases, Pastorino et al. [15] used median sternotomy routinely for the treatment of lung metastases. In their experience with 68 patients treated during a 4-year period, about one third of the patients clinically with unilateral lesions were found to have contralateral lesions that were resected through the median sternotomy. Nonetheless, they observed relapses in 21 patients, mostly within 6 months from the sternotomy.

Chemotherapy has been used as an adjuvant or neoadjuvant therapy in the treatment of both primary and metastatic malignant tumours. Markedly improved survival rates have been reported [19]. Chemotherapy aims at destruction of residual malignant cells after surgical excision of the tumour or metastases. Besides, preoperative chemotherapy improves the resectability rate of pulmonary metastases, which was 86% in the experience of Eilber et al. [20], as compared to only 45% in patients who did not receive chemotherapy.

Chemotherapy is utilised in the form of multi-drug protocols administrated both pre and post surgery. Bacci et al. [21] have demonstrated improved results in patients who had metastatic disease at the time of the initial diagnosis and who underwent simultaneous resection of the primary tumour and of the pulmonary metastases. In these authors' experience, some of the metastases completely disappeared after chemotherapy. Marina et al. [22] also found improved outcomes in patients with metastatic pulmonary disease at the time of the initial diagnosis in the new era of multi-agent drug therapy, when compared with patients treated earlier with single-agent or two-agent therapy. But it is important to note that a much more aggressive surgical approach to the lung metastases was also used in the patients treated in the most recent period.

However, the majority of authors have used chemotherapy as adjuvant therapy in association with surgery for resection of metastases that have appeared later after surgery to the primary tumours, with additional benefits over those obtained with excision of metastases alone. In our series, patients who had pulmonary metastases resected surgically in association with chemotherapy had a lower medium-term survival than those who did not have pulmonary metastases. Nonetheless, the 3-year survival of 61% is clearly an improvement over that commonly observed in patients without either form of therapy.

In conclusion, aggressive surgery for removal of pulmonary metastases associated with multi-agent chemotherapy significantly improves survival of patients with osteogenic sarcoma of the limbs. Repeated thoracotomy, if further metastases appear, is compatible with long-term survival. Hence, close follow-up for early diagnosis of relapses is essential in these patients.

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Appendix A. Conference discussion

Dr Grodzki (*Szczecin, Poland*): I would like to discuss one of your selection criteria, because I think that excluding patients with metastases to other organs, despite lungs, is not justified, and other centers try to treat them surgically with good results.

Dr Antunes: Well, I apologize, I may have not expressed myself correctly. I excluded these from this study. They were not excluded from surgical treatment, when that was felt appropriate.

Dr Athanassiadi (*Athens, Greece*): If I understood correctly, your surgical approach of choice is thoracotomy. I wonder why not a median sternotomy. Pulmonary metastases after osteosarcoma can be missed on a CT scan, especially when their diameters are smaller than 1 cm. Through a median sternotomy you have always the opportunity to inspect the other lung.

Dr Antunes: Yes, you're quite right and I agree with you. A median sternotomy is a very good mode of access for bilateral lesions. In our circumstances, though, of the four patients who had bilateral involvement, three of them had bilateral involvement treated sequentially rather than synchronously. And in the one who had metastases on X-ray or CT scan (we do both at one time) we did a median sternotomy, but we didn't find more in this instance. I think you're correct.

Dr Lerut (*Leuven, Belgium*): If you evaluate your patients after three cycles and you see that they respond, do you continue your chemotherapy until completed and subsequently go for surgery, or do you perform surgery systematically after the three cycles? And if they respond, do you perform chemotherapy after the surgery as well, after resection?

Dr Antunes: Yes, we will give chemotherapy after the surgery irrespective of what the results are and what the preoperative status was. But I may not be entirely sure about all this, because, obviously, the excision of the primary tumour is done in another department, and the chemotherapy is done by yet another different department, so I'm not entirely sure of whether all the patients who came to us were in fact the ones that did not respond completely. That is, I'm not sure if there were patients who responded completely and the metastases disappeared and, therefore, were not referred to surgery. As you know very well, there are cases like that, described in the literature, of complete remission of metastases after chemotherapy. This is just the cohort of the patients who had thoracotomies for resection of metastases.

Dr End (*Vienna, Austria*): You mentioned that postoperative morbidity is very low, of course.

Dr Antunes: These were young patients.

Dr End: Could you comment on your complications in detail, if there are any?

Dr Antunes: There was only one patient who had prolonged ventilation. None of the other 30 patients required ventilation in the ward. They were extubated on the table. But one patient who had a previous resection already and probably was marginal in his lung function, because he had one lobectomy done previously, now followed by another lobectomy, required ventilation for a little bit more than 24 h.