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Recurrences following primary osteosarcoma in adolescents and adults previously treated with chemotherapy

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Abstract

In this retrospective analysis, we report on the detailed management of 33 recurrent osteosarcoma patients from a population of 81 adolescents and adults previously treated (between November 1979 and November 1998) at the La Timone Adults Hospital, for an extremity-localised osteosarcoma. The site of the first recurrence was limited to the lung in 24 patients (73%), was local in 4 patients (12%), at multiple sites in 4 patients (12%), and limited to the bone for 1 patient (3%). The median interval between the diagnosis of the primary osteosarcoma and the first recurrence was 16 months (range 4–108 months). For all patients, the treatment combined aggressive chemotherapy and surgical resection of the recurrences whenever possible. 19 patients (58%) achieved a second complete remission. The median follow-up time from the first recurrence was 18 months (range 4–150 months). For all patients, the median overall survival from first recurrence was 17 months (95% confidence interval (CI), 11–22 months) and the projected 3- and 5-year survival rates were 31.6 and 23.7%, respectively. Patients with a second complete remission had a better 5-year survival than patients without (44.6% versus 0%, $P=0.001$). The achievement of a second complete remission has an independent significant prognostic value for an improved survival. Aggressive surgery with the removal of recurrence sites combined with multiagent chemotherapy can either cure patients with recurrent osteosarcoma or significantly prolong their survival.
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Keywords: Osteosarcoma recurrence; Chemotherapy; Surgery; Metastasectomy

1. Introduction

With the advent of aggressive chemotherapy, the long-term survival of patients with high-grade osteosarcoma has improved considerably [1–5]. However, despite the success of combined surgical and chemotherapeutic modalities, 30–40% of patients develop lung metastases or local recurrences. Studies on the management of patients who relapse are very limited in number [6–8] and mainly concern patients with pulmonary metastases [9–16]. An aggressive pulmonary metastasectomy is at present an accepted treatment strategy, with good results in patients with metastases confined to the lung [9–16], whereas the value of second-line chemotherapy treatment [7,9,10,14,15] and the best treatment strategy for those patients with recurrences other than in the lung [8,7] are not well defined. Nevertheless, since the introduction of effective chemotherapy for osteosarcoma [17–19], a more aggressive multidisciplinary approach to treat patients with metastatic disease has evolved, and the use of second-line chemotherapy treatment with resection of the recurrence is quite common [6,7,9,10–12,14,15].

We report on a retrospective analysis of 33 adolescent and adult patients who developed metastases or local recurrences from extremity-localised high-grade osteosarcomas. We examine the pattern of recurrence, various treatment methods and results, with particular emphasis on the prognostic impact of previous treatment type,

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salvage surgery ('metastasectomy') and second-line chemotherapy.

2. Patients and methods

2.1. Patients

From November 1979 to November 1998, 81 patients with histologically-proven high-grade osteosarcoma of the extremities were treated at the Oncology Unit of la Timone Adults University Hospital. All were initially free of metastatic disease. There were 51 males and 30 females.

At initial presentation, the absence of metastases at diagnosis was routinely ascertained by bone scans for all patients, conventional lung tomography prior to 1983, and by computed tomography (CT) scans of the chest thereafter.

From 1979 to 1998, three sequential primary treatment protocols have been employed. From 1979 to 1982 (period 1), 19 patients were treated with adjuvant postoperative chemotherapy according to the SO4 78 protocol. This protocol combined two alternative drug combinations and early prophylactic lung irradiation [20]. From 1983 to 1986 (period 2), 16 patients were treated with the SO83 protocol based on cisplatin (100 mg/m^2) and doxorubicin (75 mg/m^2) pre- and postoperatively for a total of six cycles [21]. From 1987 to November 1998, 46 patients were treated with a T-10-derived protocol [22,23].

After the initial treatment, patients were followed with clinical examinations and chest X-rays every 3 months prior to 1983, and then with CT scans of the chest every 3 months, for 3 years after the completion of adjuvant chemotherapy. Then, they were followed in the same way every 6 months until 5 years after the completion of adjuvant chemotherapy. This was followed by clinical examinations and chest X-rays once a year until 10 years after the end of treatment. Bone scintigraphies were performed twice a year for 2 years following the completion of adjuvant chemotherapy and then once a year for 5 years. Of these 81 patients with initially non-metastatic extremity osteosarcomas, 33 (41%) developed a recurrence and are the subjects of this study.

The definitions of response of recurrent disease to treatment, based on the physical examination and medical imaging, were as follows: a complete remission was the disappearance of all signs of tumour, a partial remission was a greater than 50% reduction in the cross-sectional tumour area for all the lesions with no new lesions, an objective effect was the reduction in size from 25 to 50% of all the tumours, and stable disease was a reduction of less than 25%. Progressive disease was defined as an increase in size at any tumour site or the appearance of new lesions. Follow-up periods were defined as the time from the diagnosis or first or last recurrence to the last visit.

2.2. Treatments for recurrence

2.2.1. Surgery

Resection of local recurrence and/or lung metastases was performed whenever they were surgically and functionally resectable with a low operative risk. Criteria for lung metastases resectability were as follows: primary tumour controlled, no evidence of hilar disease, no pleural or pericardial effusion, no metastases in other organs besides the lung, complete resectability leaving adequate residual pulmonary function. Complete surgery was defined as the removal of all evident recurrent disease (local recurrence, lung or other metastases), with no tumour tissue at the resection margins upon histological examination.

2.2.2. Chemotherapy

Three chemotherapy regimens for metastatic disease were used between 1979 and 1998: a two-drug regimen based on ifosfamide-etoposide, a three-drug regimen based on cisplatin–doxorubicin + ifosfamide or high-dose methotrexate (HDMTX), and a four-drug regimen based on cisplatin–doxorubicin–ifosfamide and etoposide. Since 1989, this last regimen has mostly been used pre- and/or postoperatively. Our policy was to treat each patient with an individualised chemotherapy regimen. If metastases occurred early after completion of the postoperative chemotherapy, a change to a different chemotherapeutic regimen was thought to be prudent or additional agents were used. If metastases occurred late, or if the patient's primary tumour had previously demonstrated an excellent response, then retreating with the same agents with fewer modifications was logical and commonly used. Alternatively, if metastases recurred late, but the patient demonstrated a prior poor response, different or additional agents or dose intensities were used.

2.3. Statistical considerations

A univariate analysis was performed on the following variables: age at diagnosis, gender, primary tumour site, first recurrent site, time to first recurrence, number of lung metastases, chemotherapy protocol for primary treatment, the possible complete surgical resection of (all sites of) recurrence, and the possible complete remission status achieved after treatment for first recurrence. Actuarial survival curves were plotted from the time of the first recurrence using the Kaplan–Meier method [24]. Statistical significance was determined using the Student's *t*-test or the log-rank test where appropriate. To assess the relative importance of the

possible prognostic factors for overall survival after the first recurrence, a multivariate analysis was performed. The factors that reached a significance level of $P<0.05$ or lower in the univariate analysis were subjected to a multivariate analysis.

3. Results

3.1. Patterns of recurrence

Patients' characteristics and sites of recurrence are presented in Table 1. 33 patients, 26 males and 7 females, were entered into this study. 7 patients (37%) relapsed after being given period 1 chemotherapy, 8 (50%) relapsed after period 2 (SO83) chemotherapy, and 18 (39%) after completing the T-10-derived protocol; this was not significantly different ($P>0.05$). The median age at the time of diagnosis of the primary tumours was 20 years (range 12–55 years). The median intervals from the diagnosis of the primary osteosarcoma to the first recurrence were 16 months (range 7–44 months), 12 months (range 4–55 months) and 14 months (range 10–51 months) for patients treated with the first, second and the third protocols, respectively again this was not significantly different. The median interval between the first and second recurrences was 8 months (range 3–16 months), and this was 13 months (range 3–23 months) between the second and third recurrences. For the first recurrence, 24 patients (73%) presented with lung recurrences only, 4 patients presented with a local relapse only (12%), and 1 patient presented with a bone relapse (vertebral metastasis) only. Multiple-site recurrences (4 patients) involved the lungs in all cases, and for the first recurrence involved the primary-tumour site (2 cases), bone (multiple vertebral metastases in 1 case), and the liver (1 case).

12 patients presented with a second recurrence. A second recurrence is a new recurrence that occurs after a patient has achieved a (second) complete remission after treatment for the first recurrence.

For the second recurrence, 8 patients (67%) presented with lung recurrences only (5 patients with unilateral metastases and 3 with bilateral metastases), 1 patient (8%) had a bone recurrence, and 1 patient (8%) had a liver and peritoneal relapse. 2 patients presented with multiple-site recurrences: 1 patient with lung and bone metastases, and 1 patient with lung metastases and local relapse. For the third recurrence, the lungs were affected in all cases (3 patients). A third recurrence is a new recurrence that occurs after the patient has achieved a (third) complete remission after treatment for the second recurrence. One patient presented with a single lung metastasis and 2 patients presented with bilateral lung metastases and local recurrence.

Table 1
Patient's characteristics and recurrence sites for the first recurrence

	Primary treatment			
	SO78 ($n=7$)	S083 ($n=8$)	SO87 ($n=18$)	Total ($n=33$)
Median age at diagnosis (in years)	20	19	20	19
Gender ratio (M/F) (n)	7/0	6/2	13/5	26/7
Primary tumour n (%)				
Femur	4	4	10	18 (52)
Tibia	2	2	2	6 (18)
Humerus	1	1	5	7 (24)
Other[a]	0	1	1	2 (6)
Lung metastases n (%)	4	7	17	28 (43)
Bilateral	1	4	7	12 (36)
Median number of metastases (range)	2	3	2	2 (1–10)
Median follow-up from 1st recurrence (in months) (range)				
For all patients	20 (5–30)	8 (4–72)	20 (3–144)	20 (3–144)
For patients who are still alive	No patients	59, 72[b]	38[c] (10–124)	46 (10–124)

pts, patients; M, male; F, female; n, number.

[a] One fibula, one calcaneum, NED: no evidence of disease.

[b] 2 patients alive with NED, lost to follow-up 59 and 72 months after their first metastasis.

[c] 7 patients alive with NED, and 1 patient alive lost to follow-up with NED 46 months after first metastasis.

3.2. Management of the recurrence

3.2.1. Surgery for lung metastases

All of the resections for lung metastases were performed through a lateral thoracotomy, but bilateral metastases were removed through a median sternotomy in 1 patient. Thorough palpation of the lung was carried out to detect metastases that were not identified by the CT scan. Wedge resections were performed for almost all of the resectable lung metastases. A segmentectomy or a lobectomy was performed only when a wedge resection was not possible. There was no operative mortality or major morbidity.

3.2.2. Treatment of the first recurrence

The methods and results of the treatments for the first recurrence are summarised in Table 2 according to the recurrence site. 15 out of 24 patients (63%) with lung metastases only had a surgical resection (13 patients had metastasectomies, 1 patient had a segmentectomy and one a lobectomy). However, for the other 9 patients, lung metastases were considered unresectable for 8 of them (2 because of pleural effusion, 1 because of mediastinal nodes, 1 because of hilar invasion, 1 because of invasion of the diaphragm and 3 because of multiple bilateral metastases), and for 1 patient all lung metastases completely responded to treatment after 3 months of chemotherapy. 14 of the 15 patients with resectable

Table 2
Management of first recurrence and results according to the recurrence site

	Lung	Multiple site	Bone	Local
Surgery alone				
Total	0	0		1
CR2	0	0		1
Prog	0	0		0
R2	0	0		1
Chemotherapy alone				
Total	9	4		0
CR2	1	0		0
Prog	8	2[a] + 2[b]		0
R2	0	0		0
Chemotherapy before and after surgery				
Total	5	0		0
CR2	5	0		0
Prog	0	0		0
R2	4	0		0
Chemotherapy after surgery				
Total	10	0	1[c]	3
CR2	9	0	0	3
Prog	1	0	1	0
R2	5	0	0	2

CR2: second complete remission; R2: second recurrence; Prog: progression.

[a] One patient in progression and 1 patient with stable disease.

[b] The 2 patients benefited from surgery for local relapse only and not for multiple bilateral lung metastases.

[c] The patient benefited from laminectomy followed by radiation therapy and chemotherapy.

lung metastases (93%) had a macroscopically and microscopically complete surgical procedure.

The 4 patients with local recurrence alone received a complete surgical resection (three amputations and one conservative surgery). The 2 patients with concomitant local recurrence and lung metastases received a surgical resection for a local relapse (amputation in 1 case, conservative surgery followed by radiation therapy in 1 case), but not for their lung metastases (1 because of pleural effusion, 1 because of multiple bilateral lung metastases). The patient with a synchronous lung and bone recurrence (bilateral lung metastases and multiple bone metastases to the ribs and spine) received chemotherapy only, as did the patient with a concomitant lung and liver recurrence. The patient with vertebral metastasis only had a surgical resection followed by radiation therapy. 20 out of 33 patients (61%) had a surgical resection of their first recurrence.

All patients with a first recurrence were re-treated aggressively with chemotherapy, with the exception of 1 patient with a local recurrence only. 14 patients had easily resectable recurrences (single or unilateral lung metastases: 10 patients, local recurrence: 3 patients, single spine metastasis: 1 case) and received postoperative adjuvant chemotherapy for 4–6 months. 18 patients received initial chemotherapy followed by surgery in 5 of these 18 (with resectable lung metastases). These 5 patients received preoperative chemotherapy (four cycles) and postoperative chemotherapy (4–5 cycles). Thus, 13 patients received aggressive chemotherapy alone for treatment of their first recurrence. With the exception of 2 patients, all patients progressed after 5–6 cycles. One of these 2 patients had stable disease 29 months after their first recurrence while the other achieved a complete remission after six cycles of the four-drug regimen for lung metastases, and was still alive after 161 months. Thus, 19 out of 33 patients (58%) achieved a second complete remission after treatment for their first recurrence. Of these 19 patients, 12 (63%) presented with a second recurrence.

3.2.3. Treatment of the second and third recurrences

12 patients presented a second recurrence and the lung was affected in 10 cases (83%). 4 out of 10 patients (40%) with lung metastases benefited from metastasectomy and chemotherapy. 3 of them underwent a second thoracotomy and 1 underwent a first thoracotomy. All achieved a complete third remission, but 3 of them relapsed after 13, 18 and 23 months, respectively. 3 patients with unresectable lung metastases benefited from chemotherapy and lung irradiation; all of them progressed and died after 4, 12, and 17 months, respectively. 3 patients received chemotherapy alone (2 patients because of multiple bilateral unresectable lung metastases and 1 because the patient refused a lung metastasectomy); all of the patients progressed and 2 died after 12 and 21 months, respectively. One was still alive 14 months after the second recurrence. 2 patients received an incomplete surgery followed by chemotherapy for vertebral metastases, and for liver and bowel metastases, but they progressed and died after 11 and 4 months, respectively.

3 patients presented with a third recurrence. 2 underwent a third thoracotomy followed by high-dose chemotherapy with peripheral blood stem-cell support. One was still alive in complete remission 47 months after the third recurrence, 1 died 20 months after refusing amputation for a second major local recurrence. One patient received chemotherapy alone for concomitant bilateral lung metastases and local recurrence, but progressed and died after 12 months.

3.3. Follow-up, survival and prognostic factors

The median follow-up times were 42 months (range 10–161 months) from the diagnosis of osteosarcoma, 18 months (range 4–150 months) from the first recurrence and 14 months (range 2–124 months) from the last recurrence. 3 patients were lost to follow-up after 57, 97 and 127 months, respectively. As of 1 June 2002, 7

patients were alive (5 in complete remission, 2 with stable disease) with a median follow-up from the last recurrence of 34 months (range 9–150 months). The median overall survival from the first recurrence for the entire group of 33 patients was 17 months (95% confidence interval (CI) 11–22 months), and projected 3- and 5-year survival rates were 31.6 and 23.7%, respectively (Fig. 1). Median overall survival from the first recurrence for patients achieving a second complete remission was 39 months (95% CI 23–57 months). 10 out of 33 patients (30%) have remained in second complete remission with a median follow-up of 34 months (7 patients alive in complete remission and 3 patients lost to follow-up in complete remission 57, 97 and 127 months after the first recurrence, respectively). For patients with their first recurrence confined to the lung only, the survival rates were 37.7% at 3 years and 28.2% at 5 years. Of these 24 patients, 5 are currently free of disease 8–150 months after their first recurrence, 3 have been lost to follow-up (57, 97 and 127 months after their first recurrence, respectively) and 16 have died from their disease. The number of patients with a first recurrence outside of the lung is too small to plot a survival curve or carry out a statistical comparison. Of the 4 patients with a local recurrence only as their first recurrence, 1 is alive in complete remission 42 months after his recurrence, and all the others have died from their disease. Of the 4 patients with recurrences at multiple sites for their first recurrence, 1 has a stable disease following chemotherapy 28 months after his recurrence, and all the others have died from their disease after 5, 8 and 26 months, respectively.

In univariate analyses (Table 3), there is a significant difference in the 5-year overall survival between patients treated with and those treated without complete surgical resection of their disease at all sites of the first recurrence (37.7% versus 12.5%, $P=0.0001$) (Fig. 2) and between patients with or without a second complete remission (44.6 versus 0%, $P=0.001$) (Fig. 3). Furthermore, the median overall survival for patients relapsing less than 20 months after diagnosis was 10 months (range 6–129 months) and 18 months (range 3–155 months) for patients relapsing $\geqslant 20$ months after diagnosis, although this difference was not significant. In the multivariate analysis, the achievement of a second complete remission had an independent, significant prognostic value for an improved survival.

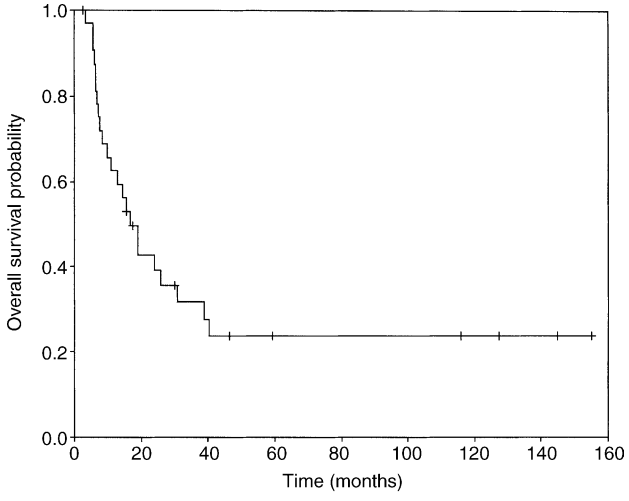

Fig. 1. Overall survival (months) from the first recurrence for the entire group of 33 patients.

Table 3
Effect of patient, tumour and treatment characteristics on overall survival

Variables	No. of patients	OS (%)		
		UvA[a]	*P*	MvA[b]
Age (years)				
<20	23	21.7		
⩾20	10	50	0.75	ND
Gender				
Male	26	26.9		
Female	7	42.8	0.5	ND
Tumour site				
Femur	17	29.4		
Tibia	6	28.6	0.4	ND
Humerus	8	37.5		
Disease-free interval[a]				
<20 months	13	25		
⩾20 months	20	38.4	0.33	ND
First recurrent site[b]				
Lung	24	33.3		
Other	6	16.7	0.5	ND
Treatment protocol				
SO78	7	14.3		
SO83	8	12.5		
T-10-derived	18	44.4	0.11	ND
Lung metastases				
Unilateral	17	41.2		
Bilateral	10	20	0.16	ND
Lung metastases				
Unique	10	60		ND
Multiple	10	30	0.17	
Resection of first recurrence				
Complete	17	47		
Incomplete or no resection	16	12.5	0.0001	NS
Second complete remission				
Yes	17	53		
No	15	0	0.0001	S

ND, not studied in multivariate analysis; NS, not statistically significant; S, statistically significant; OS, overall survival.; Uva, univariate analysis; Mva, multivariate analysis.

[a] Cut-off point with the most significant survival difference in univariate analysis.

[b] Excluding multiple site recurrences (4 patients).

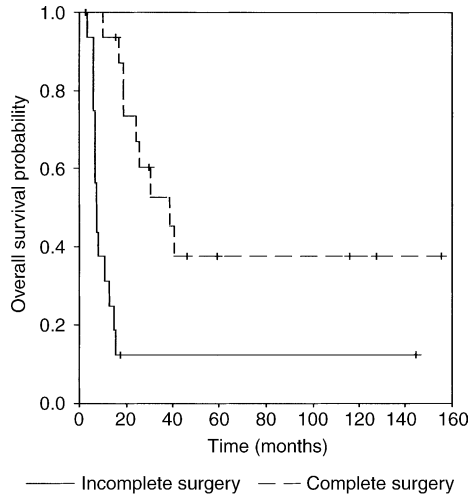

Fig. 2. Overall survival (months) from the first recurrence for patients treated with and without complete surgery.

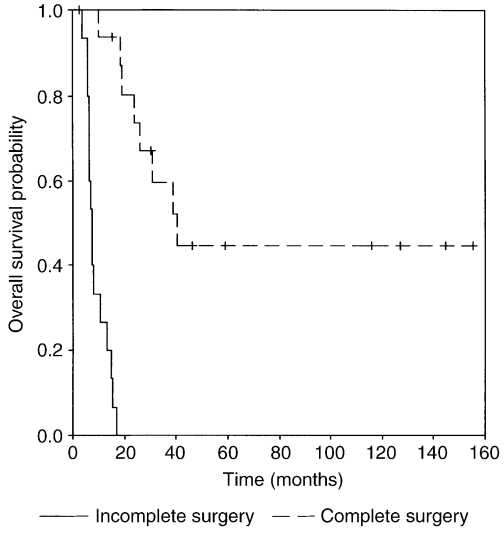

Fig. 3. Overall survival (months) from the first recurrence for patients with or without a second complete remission.

4. Discussion

Before the use of adjuvant chemotherapy, lung metastases appeared in more than 90% of patients 5–8 months after surgical treatment for primary osteosarcoma [15,19,25]. With intensive chemotherapy, the long-term disease-free survival rate for localised high-grade osteosarcoma improved from less than 20% to the 55–75% range [3,5,26–29]. However, 30–40% of patients still relapse, most often with pulmonary metastases, but after a longer median disease-free interval of 10–17 months [15,25,30,31,33].

As in recently published series, we report here that most of the first recurrences remain pulmonary [6,7,9,10]. The finding of a longer disease-free interval (16 months, range 4–108 months) in patients who developed a recurrence could be due to active preoperative and postoperative chemotherapy regimens, and is in accordance with recent studies [6,7,15,33]. Furthermore, as in recent reports [6,7,32], patients with a second or third recurrence often develop metastatic disease to multiple or unusual sites.

To date, only a few studies [6,7] have been published that give a detailed account of the general management of osteosarcoma patients who have relapsed, including those with recurrences outside of the lung. Most published studies concern patients with resectable lung metastases only, treated with surgery alone [8,13,15,16,34,35] or surgery and chemotherapy [9–12,14,36–38]. Our study avoids this selection criteria, since we included all patients with extremity osteosarcomas who received their initial treatment at our institution.

The optimal treatment for recurrent osteosarcoma remains to be determined. An aggressive and even repeated pulmonary metastasectomy is at present an accepted treatment in patients with metastases confined to the lung, and good results have been obtained [7–10,13–16]. Several studies conclude that the completeness of metastasectomy is mandatory for the long-term survival of metastatic osteosarcoma patients [6,7,13,33–35]. However, the best treatment strategy for patients with recurrences outside of the lung is still not well defined. The possibility of a positive impact on overall survival of second-line chemotherapy after systemic recurrence remains undetermined and has never been addressed directly by controlled studies. However, the rarity of the disease and the heterogeneous pattern of relapse make it almost impossible to carry out randomised studies. However, chemotherapy in the setting of known pulmonary metastases aims to destroy residual malignant cells, and hopefully any undetected micrometastases, thereby eliminating the occurrence of new micrometastases [9–11,14,38]. In the 1970s, Beattie and colleagues and Rosen and colleagues were the first to report encouraging results obtained in children with pulmonary metastases treated by combining pulmonary surgical resection and systemic chemotherapy [11,38]. Since then, more studies with combined treatments have been reported, but were too heterogeneous to allow firm conclusions to be drawn [9,13,14,16,33,36,37].

Nevertheless, since the early 1980s, our strategy with recurrent osteosarcoma patients has been to re-treat them aggressively with chemotherapy, in combination with resection of all the recurrence sites (metastases and/or local relapse), whenever surgical resection is possible. This strategy is in agreement with other studies [6,7,9,10,36,37] that used adjuvant chemotherapy in combination with the resection of metastases that have appeared later after surgery to remove the primary

tumour. These studies had additional benefits over those where only excision of metastases was performed. However, these studies are limited in number and there is little in the way of supporting evidence for this treatment strategy. The use of second-line chemotherapy in the treatment of recurrent osteosarcoma still remains an open question. However, on the basis of current knowledge [6,7,9–11,36,37,39] and our experience, our general 'philosophy' for metastatic pulmonary osteosarcoma is as follows: Patients with late solitary nodule(s) found over a year after cessation of adjuvant therapy are candidates for initial thoracotomy followed by 'adjuvant chemotherapy' for approximately 3–4 months. Patients with a few small nodules detected synchronously or within 12–16 months after the cessation of adjuvant chemotherapy, or patients with multiple nodules at any time are treated with aggressive chemotherapy for approximately 3 months before undergoing a pulmonary resection. A change to a different chemotherapy regimen than the one used for treatment of the primary tumour is justified. The drugs to which the patient has not been previously exposed should be used in combination with and at dose intensities that exploit their full therapeutic potential. Following resection of metastases, chemotherapy is continued for approximately 3–4 months.

With this treatment strategy, our 5-year overall survival rates from the first recurrence are encouraging for 23.7% of all of the patients and 37.7% of the patients who underwent complete surgical resection of their first recurrence. These 5-year survival rates are similar to those recently reported by Tabone and colleagues [6] and Saeter and colleagues [7], who observed rates of 24–27% and 42–50%, respectively. Our results indicate that the survival period of patients with recurrent osteosarcoma is longer than previously observed [25,30]. In fact, these survival rates are at least equivalent to the historically reported overall survival rates of patients who presented with non-metastatic osteogenic sarcoma before the use of adjuvant chemotherapy [40,41]. Furthermore, durable remissions can be obtained, even for patients with a second and third recurrence. 10 out of our 33 patients (30%) remained in a second complete remission with a median follow-up of 34 months. This encouraging result is similar to that recently reported by Tabone and colleagues [6], where 13 out of 42 patients (31%) remained in complete remission with a median follow-up of 39 months.

Moreover, as observed in previous studies [6,7,9,13,30,34], the most important prognostic factors for post-relapse overall survival rates are the completeness of the surgical removal of all tumour tissue and, above all, the complete remission achieved after treatment for the recurrence. All patients in complete remission received complete surgery and none of the patients whose lesions were considered unresectable, even after chemotherapy, survived. Moreover, our results support the views of the studies [7–9,13,15,42] that advocate multiple thoracotomies in the event of subsequent relapses. In our study, patients with up to three thoracotomies were among the long-term survivors, and the frequency of re-thoracotomies was 29%. Aggressive surgery with the removal of all tumour tissue at the recurrence sites, combined with multi-agent chemotherapy can either cure patients with recurrent osteosarcoma or significantly prolong their survival, especially for patients with limited pulmonary metastatic disease or with limited local recurrence. Repeated thoracotomies, if further metastases appear, are also compatible with a long-term survival. Therefore, close and long-term follow-up for the early diagnosis of recurrence is essential in osteosarcoma patients. Furthermore, as has been recently reported in patients with osteosarcoma in relapse [43,44], more aggressive treatments such as bone-marrow ablative chemotherapy with peripheral blood stem-cell support may be considered for the treatment of these patients.

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