Leukaemia–Lymphoma Incidence Study (ECLIS). *Eur J Cancer* 1993, **29A**, 87–95.
12. Ruccione K, Waskerwitz M, Buckley J, Perrin G. What caused my child's cancer? Parents' responses to epidemiology studies of childhood cancer. *J Pediatr Oncol Nurs* 1990, **4**, 50–51.

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Metachronous Pulmonary Metastases Resection in Patients With Ewing's Sarcoma Initially Treated With Adjuvant or Neoadjuvant Chemotherapy

G. Bacci, A. Briccoli, P. Picci and S. Ferrari

55 patients with Ewing's sarcoma of bone, treated at our Institution with adjuvant or neoadjuvant chemotherapy between 1972 and 1990, relapsed with pulmonary metastases alone. 12 of these patients—selected according to their long disease-free interval before relapse, monolaterality of the lesions, small numbers of metastatic nodules, resectability and refusal to undergo further chemotherapic treatments—were treated with surgical resection of the metastatic lesions and with no additional radio- or chemotherapy. At a follow-up ranging between 3 and 14 years (mean 9 years), 5 of these 12 patients (42%), were continuously free of disease, whereas the remaining 7 patients died with uncontrolled disease 12–39 months (mean 22 months) after thoracotomy. These results seem to indicate that an aggressive surgical approach should be considered for a selected group of Ewing's sarcoma patients who relapse with only lung metastases.

Key words: Ewing's sarcoma, pulmonary metastases, surgery, survival
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INTRODUCTION

ADJUVANT AND neoadjuvant chemotherapy have dramatically improved the prognosis for patients with Ewing's sarcoma of bone. However, approximately 40% of these patients eventually develop metastases, which in almost half the cases are initially located only in the lung [1–3].

Several treatments have recently been attempted for these patients: a combination of cytotoxic drugs [4, 5], a high dose of melphalan associated with bone marrow transplantation [6], and half-body irradiation [7]. Although some of these therapies gave an initial response, very few patients (less than 10%) were eventually cured. The role of surgery in the treatment of pulmonary metastases from Ewing's sarcoma has so far, been neglected. We are aware of only one paper in which 19 cases were retrospectively evaluated [8].

The purpose of this paper is to report the results achieved at our Institution between 1979 and 1991 in 12 selected patients who, after having been initially treated with adjuvant or neoadjuvant chemotherapy for a Ewing's sarcoma of bone, relapsed with lung metastases alone and were treated with surgical resection of the pulmonary lesions.

MATERIALS AND METHODS

Among the 316 patients with Ewing's sarcoma of bone treated at the Rizzoli Institute between 1972 and 1990 with adjuvant (144 cases) or neoadjuvant (172 cases) chemotherapy [9, 10], 125 relapsed with metastatic disease, which in 45 cases was located only in the lung. 12 of these patients were treated with pulmonary resections, whereas the remaining 33 received additional chemotherapy, in 10 cases associated with radiotherapy. No attempt was made to differentiate Ewing's sarcoma from primary neuroectodermal tumour (PNET).

The decision to perform surgical treatment instead of chemo-

Correspondence S. Ferrari.
S. Ferrari and G. Bacci are at the Sezione di Chemioterapia dei Tumori Ossei, Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna; A. Briccoli is at the Patologia Chirurgica dell'Università di Modena; and P. Picci is at the Laboratorio Ricerca Oncologica cell'Istituto Rizzoli, Italy.
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or radiotherapy in these 12 patients was based on the following criteria: (1) potentially resectable pulmonary metastases considered on X-rays in the first 2 cases and on computed tomography scans in the remaining 10 cases; (2) well-controlled primary tumour and no other detectable sites of metastatic disease. Moreover, these patients had been previously treated for 12–18 months with chemotherapy and would have accepted no more.

Before 1982, lung surgery was performed only in those patients who had monolateral lesions and a disease-free interval of more than 3 years. After 1983, thoracotomy was performed also in those with bilateral lesions and a shorter disease-free interval. In all cases after lung surgery, no additional treatments were given unless the patient had a further relapse.

The clinical characteristics of the 12 patients considered in this report are shown in Table 1. The criteria for histological diagnosis of Ewing's sarcoma as well as the examinations performed for the staging and the follow-up controls have been reported previously [9, 10].

The surgical approach was always an axillary thoracotomy. The lungs were sequentially deflated after intubation with a double lumen endotracheal tube and examined thoroughly by palpation. The chest wall, mediastinum, hilar lymph nodes and diaphragm were also examined, and all gross disease was removed when possible. In 10 cases, the lung metastases were resected with a wedge resection and in 2 cases with lobectomy.

RESULTS

Twenty-one pulmonary nodules were visible on X-rays, whereas at operation 59 nodules were found (Table 1). Six of the resected nodules were non-metastic lesions. 10 of the 12 patients were rendered disease-free at operation. A mean of 3.6 pulmonary nodules (range one to nine) were resected. The remaining 2 patients, in spite of the removal of more than 10 nodules, were not rendered disease-free, respectively, for unresectable mediastinal lymph node disease and hilar disease necessitating pneumectomy for resection.

5 of the 10 patients successfully rendered disease-free at operation remained continuously free of disease from 3 to 14 years after thoracotomy (mean 9.5 years). The remaining 5 patients, as well as the 2 patients not rendered free of disease at operation, developed new metastases in 4–18 months, initially located in the lungs in 4 cases and in other sites in 3 cases. These patients received several types of treatment: chemotherapy, radiotherapy, surgery for bone lesions, but none were reoperated upon in the lungs. All these patients died of uncontrolled disease 12–39 months after the thoracotomy (mean 22 months).

Of the 33 patients who relapsed with pulmonary metastases alone and were treated with chemotherapy and radiotherapy, only 1 is alive and free of disease 6 years after relapse, whereas the remaining 32 died of uncontrolled disease 6–48 months after relapse (mean 16 months). It must be stressed that these 33 patients, compared to the 12 patients treated with surgery, had a shorter disease-free interval (19 versus 41 months), a higher percentage of bilateral lesions (75 versus 25%) and a higher number of metastatic nodules (mean on standard X-rays: 6 versus 1.6). In 8 of these patients, the nodules were located in sites where a radical resection of the pulmonary lesion was not feasible. This group also had a higher percentage (36 versus 8%) of primary tumours located in sites (pelvis or spine) where Ewing's sarcoma usually has a worse prognosis (Table 2).

Table 2. Patients with Ewing's sarcoma who relapsed—after adjuvant or neoadjuvant chemotherapy—with metastases initially located only in the lungs. Comparison between patients treated with surgery alone and patients who received other treatments (chemotherapy and radiotherapy)

	Lung surgery	Other treatments
No. of cases	12	33
Mean number of metastatic nodules	1.6	6.2
Mean time to relapse after primary treatment (months)	41	19
Patients alive and free of disease after treatment of the metastatic lesions	5	1
Mean survival after initial relapse in the patient who died (months)	22	16
Site of the primary lesion		
Extremity	9 (75%)	14 (42%)
Pelvis and spine	1 (8%)	12 (36%)
Other sites	2 (17%)	7 (21%)

Table 1. Patients' characteristics

Patient	Year*	Age (years)	Sex	Site of primary tumour	Chemotherapy	Time of relapse† (months)	No. of metastatic nodules On standard X-ray	No. of metastatic nodules At operation	Pulmonary surgery	Results‡
1	1972, 1979	30	F	Scapula	Adjuvant	85	1	1	MWR	DF at 14 years
2	1973, 1978	21	M	Clavicle	Adjuvant	72	1	2	Lobectomy	DF at 13 years
3	1979, 1982	22	M	Humerus	Adjuvant	42	1	4	MWR	DF at 9 years
4	1983, 1986	10	F	Fibula	Neoadjuvant	34	1	3	MWR	DR at 8 years
5	1983, 1984	19	M	Humerus	Adjuvant	18	2	9	BWR	Died at 14 months
6§	1985, 1987	30	F	Radius	Neoadjuvant	62	2	12	BWR	Died at 38 months
7§	1985, 1990	10	M	Metacarpus	Neoadjuvant	64	5	11	MWR	Died at 12 months
8	1986, 1991	39	F	Humerus	Neoadjuvant	23	2	2	MWR	Died at 24 months
9	1987, 1989	14	M	Metatarsus	Neoadjuvant	25	1	1	MWR	DF at 3 years
10	1987, 1988	21	M	Femur	Neoadjuvant	18	1	3	MWR	Died at 19 months
11	1988, 1990	17	F	Tibia	Neoadjuvant	24	1	4	BWR	Died at 39 months
12	1989, 1991	31	M	Spine	Neoadjuvant	30	3	7	Lobectomy	Died at 12 months

*Year of the primary treatment and year of resection of pulmonary metastases. †From the beginning of treatment. ‡Time from thoracotomy. §Patients not rendered free of disease at the operation. MWR, monolateral wedge resection; BWR, bilateral wedge resection; DF, free of disease.

There were no major surgical complications and the average hospital stay for lung surgery was 9 days.

DISCUSSION

Numerous reports have documented a significant advantage in survival for patients with metastatic osteosarcoma and soft tissue sarcomas after resection of pulmonary metastases [11–13], but the applicability of these findings to Ewing's sarcoma has been poorly investigated. The only report we are aware of [8] evaluated retrospectively 19 patients with synchronous or metachronous lung metastases, and concluded that an aggressive surgical approach may improve survival. It must be emphasised, however, that all but 1 of these patients also received chemo- and/or radiotherapy treatment in addition to lung surgery.

In our patients, the number of pulmonary nodules found at operation was higher than in the presurgical staging. In 2 patients, the hilar location of the nodules and mediastinal lymph nodes involvement did not allow a complete resection of the metastases. In our study 5 of the 12 patients treated with thoracic surgery alone remained continuously free of disease for 3–14 years, whereas only 1 of the 33 patients treated with chemo- and radiotherapy remained free of disease for 6 years. Although the two groups were not completely comparable, being quite different for disease-free interval before relapse, number and sites of pulmonary metastases and site of the primary tumour, our results seem to confirm the usefulness of surgery in Ewing's sarcoma with metachronous metastases only in the lung. This does not mean that Ewing's sarcoma relapsing with metastases only in the lungs must always be treated surgically. In fact, 12 cases treated over a period of more than 10 years are little more than an anecdotal experience, and our patients were a very selected group with very favourable characteristics, i.e. a long disease-free interval after initial treatment, relatively few metastatic nodules located in well resectable sites, and primary tumours in favourable sites. However, even considering these limitations, our results seem to indicate that a surgical resection of metastatic lesions should be considered for selected patients with Ewing's sarcoma who, after the initial treatment, relapse with lung metastases alone.

1. Burgert EO, Nesbit ME, Garnsey LA, *et al.* Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. *J Clin Oncol* 1990, **8**, 1514–1524.
2. Jurghens H, Exner U, Gadner H, *et al.* Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6-year experience of a European cooperative trial. *Cancer* 1988, **61**, 23–32.
3. Nesbit ME, Gehan EA, Burgert OE, *et al.* Multimodal therapy for the management of primary nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the first intergroup study. *J Clin Oncol* 1990, **8**, 1664–1674.
4. Hayes FA, Thomson EI, Hustu HO, Kumar M, Carbun T, Webber B. The response of Ewing's sarcoma to sequential cyclophosphamide and adriamycin induction therapy. *J Clin Oncol* 1983, **1**, 45–51.
5. Pipelich MV, Vietti TI, Nesbit ME, *et al.* Radiotherapy and combination chemotherapy in advanced Ewing's sarcoma. *Cancer* 1981, **47**, 1930–1936.
6. Cornbleet MA, Corrigham RE, Prentic HG, Boesen EM, McElwain TJ. Treatment of Ewing's sarcoma with high-dose melphalan and autologous bone marrow transplantation. *Cancer Treat Rep* 1981, **65**, 241–244.
7. Lombardi F, Lattuada A, Gasparrini M, Gianni C, Marchesini R. Sequential half-body irradiation as systemic treatment of progressive Ewing's sarcoma. *Int J Radiat Oncol Biol Phys* 1982, **8**, 1679–1682.
8. Lanza AA, Miser JS, Pass HI, Roth JA. The role of resection in the treatment of pulmonary metastases from Ewing's sarcoma. *J Thor Cardiovasc Surg* 1987, **94**, 1679–1682.
9. Bacci G, Toni A, Avella M, *et al.* Long-term results in 144 localized Ewing's sarcoma patients treated with combined therapy. *Cancer* 1989, **63**, 1477–1486.
10. Bacci G, Picci P, Ruggieri P, *et al.* No advantages in the addition of Ifosfamide and VP-16 to the standard four-drug regimen in the maintenance phase of neoadjuvant chemotherapy of Ewing's sarcoma of bone. Results of two sequential studies. *J Chemother* 1993, **4**, 247–257.
11. Creagan ET, Fleming TR, Edmondson JH, Pairolero PC. Pulmonary resection for metastatic osteogenicsarcoma. *Cancer* 1979, **44**, 1908–1012.
12. Roth JA, Putnam JB, Wesley MN, Rosemberg SA. Different determinants of prognosis following resection of pulmonary metastases from osteogenic and soft tissue sarcoma patients. *Cancer* 1985, 55, 361–366.
13. Rodgers BM, Talbert JL, Alexander JA. Pulmonary metastases in children sarcoma. *Ann Thor Surg* 1980, **29**, 410–414.

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