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Non-metastatic Ewing's sarcoma of the ribs: the French Society of Pediatric Oncology Experience

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Abstract

From 1984 to 1997, 57 consecutive patients with non-metastatic Ewing's sarcoma of the ribs were treated according to multimodal French Society of Pediatric Oncology (SFOP) protocols EW 84, EW 88 and EW 93. The results of treatment were reviewed and analysed. Median age was 12 years. 34 patients had large tumours (greatest tumour dimension $\geqslant 8$ cm); pleural effusion was noted in 26. A tumour-positive margin after surgery was noted in 15 patients. Histological response after chemotherapy was assessed in 34 patients. 34 patients received radiation therapy. With a median follow-up of 5 years, the projected overall and relapse-free survival rates were 69 and 62%, respectively. The major site of relapse was local. None of the following was significant in predicting relapse: tumour size, gender, age at diagnosis, existence of pleural effusion, level of rib tumour, rib component, type of local control, surgical margin (positive or negative). Response to chemotherapy was the sole significant prognostic factor ($P = 0.004$). Patients with pleural effusion had a higher percentage of relapse if they were treated without local radiation therapy. Our study confirms the prognostic significance of response to initial chemotherapy. Radiation therapy may be withheld in selected cases, but seems necessary in patients with pleural effusion.

Keywords: Ewing's sarcoma; PNET; Neoplasms; Rib; Children

1. Introduction

Tumours of the Ewing's sarcoma family represent a spectrum of malignant tumours of bone or soft-tissue origin, histologically composed of small, round cells, that include undifferentiated typical Ewing's sarcoma, poorly differentiated atypical Ewing's sarcoma, and differentiated peripheral primitive neuroectodermal tumours [1]. Tumours of the Ewing's sarcoma family are the most common primary malignancy of the bony chest wall in children, and approximately 10% of all cases of these tumours arise in this location [2–5]. Over the past 20 years, the management and prognosis of these tumours have markedly improved with the use of multimodal therapy including adjuvant chemotherapy, surgery and irradiation [4–8]. The rapid response to chemotherapy often obviates the need for extensive local treatment without sacrificing local control or long-term disease-free survival (DFS) [9,10]. Questions remain, however, concerning prognostic factors, adequate surgical margins and optimal treatment modalities [11–13]. This report describes the multicentric experience of the French Society of Pediatric Oncology (SFOP) in the management of 57 patients with non-metastatic Ewing's sarcoma family of the ribs. The aim of this review was to define the characteristics of patients with a rib primary, analyse the results of treatment, and determine the optimal management for patients with a rib primary.

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2. Patients and methods

2.1. Patient characteristics

Between November 1984 and June 1997, the SFOP conducted three consecutive studies on the Ewing's sarcoma family. Patients were eligible if they had not been treated previously and had a histological diagnosis of Ewing's sarcoma, peripheral neuroectodermal tumour, or Askin's tumour. Informed consent was obtained from patients aged $\geqslant$18 years and from parents of younger patients according to the Declaration of Helsinki. The histological material was reviewed by the pathologists of the study committee. Diagnostic procedures to exclude the presence of metastatic disease included complete clinical examination, chest computed tomography (CT), whole-body technetium bone scan, bone marrow aspirates, and biopsy. CT evaluation of the primary tumour included precise tumour localisation, determination of the tumour volume and the presence of any pleural effusion. A large tumour was defined as a neoplasm with a greatest dimension $\geqslant$8 cm. Tumours were classed in two groups according to their level: the upper ribs (1st–4th) and the middle or lower ribs (5th–12th). The rib component in which the primary tumour occurred was classified into three groups: anterior (Ant.), lateral (Lat.) or posterior (Post.). A posterior component was defined as being the 'more posteriorly located segment of the ribs to the tangent line at the anterior edge of the spinal body'.

2.2. Treatment protocols

The multimodal SFOP Ewing (EW) 84, 88, 93 protocols consisting of multi-agent chemotherapy combined with surgery and/or radiation therapy (RT), are described in Figs. 1–3. In the EW 84 protocol, induction chemotherapy consisted of six alternating courses of IVA (ifosfamide, vincristine, actinomycin D) and IVAd (ifosfamide, vincristine, doxorubicin). Induction chemotherapy in both the EW 88 and EW 93 studies was based on five courses of low dose cyclophosphamide and doxorubicin.

All patients were re-evaluated after the completion of the induction chemotherapy. Local therapy (surgery and/or radiation therapy) was given at week 18 in the EW 84 protocol and at week 12 in the EW 88 and EW 93 protocols. Surgery was performed for all patients who had only undergone biopsy at diagnosis. Surgical margins were classified as tumour-negative or tumour-positive. The surgical specimens were examined to determine the histological response according to Huvos's grading system for osteosarcoma [14]. Tumours were assigned to one of the three categories: good response when there was no identifiable viable tumour or less than 5% identifiable residual tumour cells; intermediate response if the specimen contained 5–30% residual tumour cells, and poor response when the surgical specimen contained more than 30% residual tumour cells.

In the EW 84 protocol, after complete surgical resection of the tumour, the dose delivered in the planned volume was 40 Gy. Patients with incompletely resected primary tumours received higher doses (45–60 Gy). In the EW 88 and EW 93 protocols, radiation therapy was omitted after complete resection of tumours containing less than 5% residual tumour cells. In patients with incompletely resected tumours, the radiation dose was similar to the doses given in the EW 84 protocol. In other cases, the percentage of residual tumour cells and patient's age were taken into account when setting the radiation dose (usually 40 Gy). In all three protocols, irradiation to the whole ipsilateral hemithorax was recommended in addition to irradiation of the local tumour in patients with pleural effusion.

In the EW 84 protocol, maintenance chemotherapy was identical for all patients, regardless of the response to induction chemotherapy, and was based on alternating IVA and IVAd cycles for a total treatment duration of 1 year. In the EW 88 protocol, maintenance chemotherapy was also identical regardless of the response to the induction chemotherapy, and consisted of weekly vincristine for 11 weeks and actinomycin D combined with the vincristine every 2 weeks. Subsequent therapy included six additional courses of sequential cyclophosphamide and doxorubicin. The total duration of therapy was approximately 10 months. In the EW 93

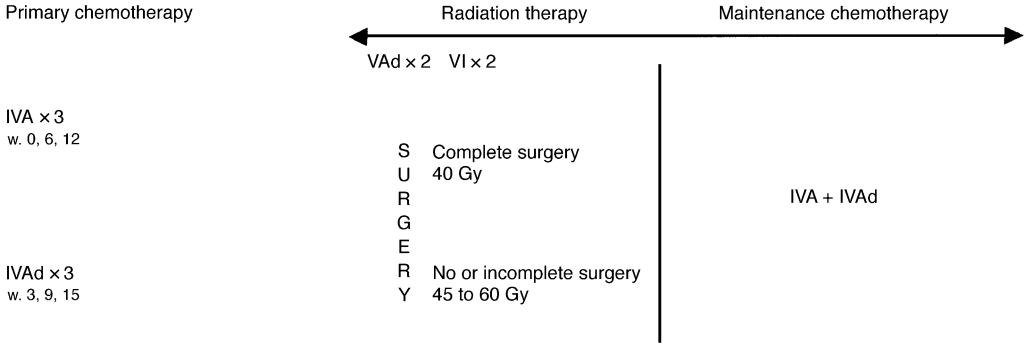

Fig. 1. Protocol EW 84. I, ifosfamide (3 g/m^2); V, vincristine (1.5 mg/m^2); A, actinomycin D (1.5 mg/m^2); Ad, doxorubicin (60 mg/m^2); w, week.

protocol, maintenance chemotherapy was based on the possibility of surgical resection and the histological response to chemotherapy. Good responders or patients with a small unresectable tumour were given the same regimen as in the EW 88 study. Patients with an intermediate histological response or a large unresectable tumour were given six courses of vincristine + actinomycin D, then six courses of etoposide + ifosfamide. Patients with a poor histological response to the induction chemotherapy received two courses of etoposide and ifosfamide, then high-dose chemotherapy with a combination of busulphan and melphalan followed by stem-cell rescue. Patients underwent imaging re-evaluation at the end of all of the chemotherapy and thereafter at least every 6 months during the first 3 years off the therapy.

Relapse-free survival (RFS) was measured from the time of diagnosis to the day of relapse or progression and calculated by the Kaplan–Meier non-parametric method [15]. Risk for relapse was compared across groups defined by treatment or prognostic factors by the two-sided log-rank test [16]. Statistics were performed using the John Macintosh Program (JMP) software (SAS Institute, Cary, NC, USA).

3. Results

Between November 1984 and June 1997, a total of 407 patients from 35 French institutions were entered on the SFOP-Ewing treatment protocols. 10, 25 and 22 patients with a non-metastatic rib primaries were treated in the studies EW 84, EW 88 and EW 93, respectively.

25 patients (44%) were male. Median age was 12 years (range 2–21 years). At diagnosis, 34 patients (60%) had a large tumour (greatest tumour dimension $\geqslant$8 cm). 18 patients (32%) had a small tumour (greatest dimension less than 8 cm). 5 patients were not evaluated. A radiologically visible pleural effusion was noted in 26 (46%) of the 57 patients. Cytopathological examination of the pleural fluid was performed in 15 of these 26 patients, and was positive in 6.

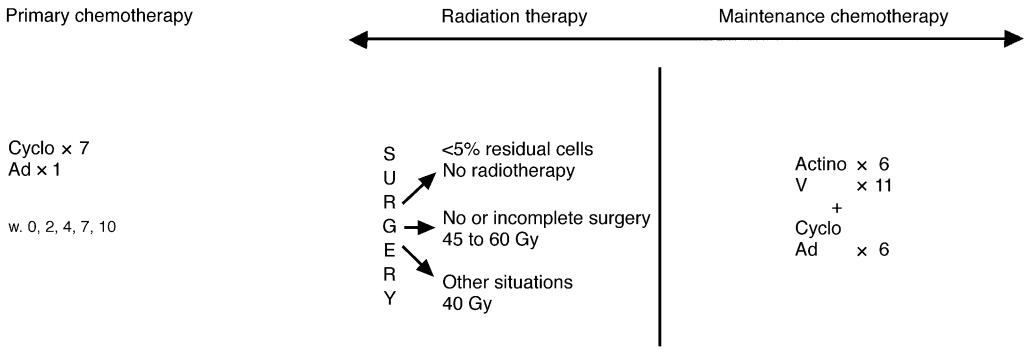

Fig. 2. Protocol EW 88. Cyclo, cyclophosphamide (150 mg/m^2); Ad, doxorubicia (35 mg/m^2); V, vincristine (1.5 mg/m^2); Actino, actinomycin D (1.5 mg/m^2); w, week.

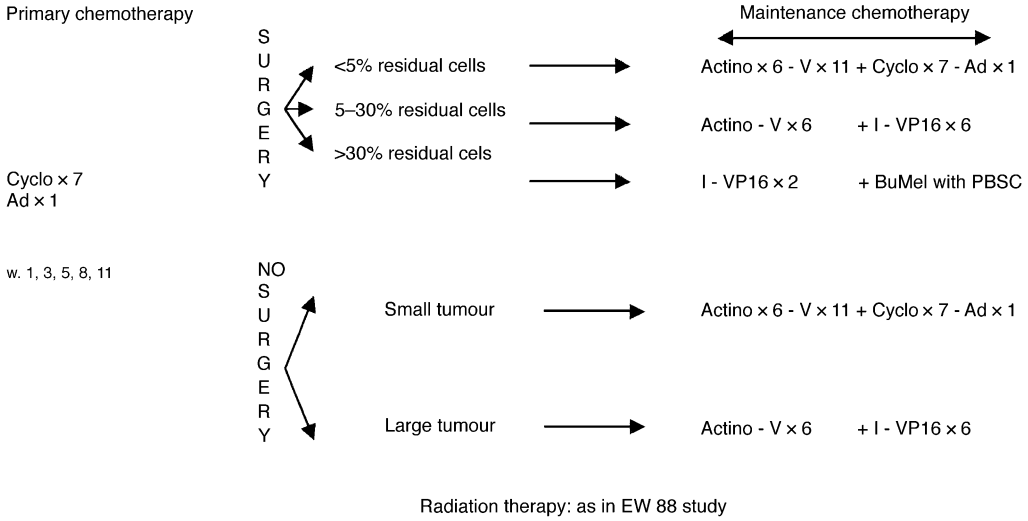

Fig. 3. Maintenance therapy in protocol EW 93. Cyclo, cyclophosphamide (150 mg/m^2); Ad, doxorubicin (35 mg/m^2); V, vincristine (1.5 mg/m^2); Actino, actinomycin D (1.5 mg/m^2); I, Ifosfamide (1.8 g/m^2); VP16, etoposide (100 mg/m^2); BuMel, busulphan 600 mg/m^2 days–melphalan 180 mg/m^2; PBSC, peripheral blood stem cell; w, week.

At diagnosis, 52 patients underwent biopsy only; 5 patients underwent tumour resection, but the procedure was microscopically incomplete in all cases.

After induction chemotherapy, 50 patients underwent surgery. Margins were free in 40 patients, but resection was incomplete or doubtful in 10 (20%). 44 patients were evaluated for a histological response. 27 patients (61%) were good responders (less than 5% residual tumour cells); 6 patients (14%) had an intermediate response (5–30% residual tumour cells) and 11 patients (25%) were poor responders (more than 30% residual tumour cells).

34 patients were given radiation therapy (after surgery in 32). Doses ranged between 25 and 60 Gy (median 40 Gy). Among the 23 who did not receive radiation therapy, 5 had undergone surgery at diagnosis and 16 had undergone complete resection of the primary after induction chemotherapy (with total necrosis of the tumour in 10); 2 patients with pleural effusion were not given radiation therapy because of their young age (both the patients were 4 years old) despite microscopically incomplete surgery.

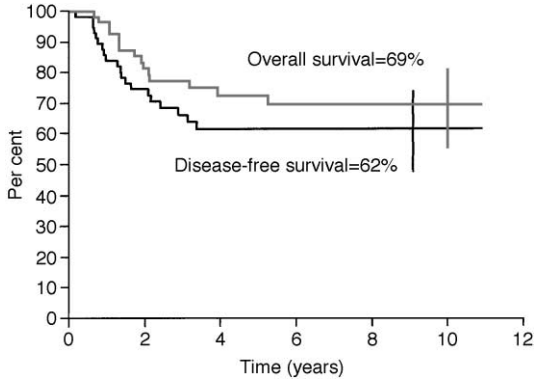

Fig. 4. Overall and disease-free survival of the 57 patients (error bars indicate the 95% Confidence Limits).

3.1. Outcome and survivals

After a median follow-up of 5 years for the survivors, 37 patients were still in their first complete remission at the time of analysis. 2 patients with large tumours progressed under chemotherapy and never achieved first local control. After initial control, 18 patients relapsed. The site of the first relapse was local ($n=7$), both local and distant ($n=5$), or distant only ($n=6$). 13 patients died after relapse. The projected overall survival (OS) at 10 years was 69% (Confidence Limits (CL): 56–82%) and disease-free survival (DFS) was 62% (CL: 49–75%) (Fig. 4).

3.2. Relapse patterns according to pleural effusion and local therapy

Data are summarised in Table 1. Of the 26 patients with pleural effusion at diagnosis, 19 received local combined therapy and 7 were treated by surgery without additional radiotherapy. Only 3 of the 19 patients treated with local combined therapy relapsed locally versus 4 of the 7 patients treated by surgery alone ($P=0.057$, Fisher's Exact test) (Fig. 5).

3.3. Prognostic factors

Patients with large rib lesions were not at an increased risk for an adverse event compared with those with small tumours (DFS 60% versus 78%; $P=0.14$).

As shown in Table 1, univariate analysis revealed that none of the following variables was statistically related to event-free survival (gender, rib component, level of rib tumour, existence of a pleural effusion). The 10-year RFS for patients who underwent surgery was 68% for the 15 patients with a tumour-positive margin and 64% for the 40 patients with a tumour-negative margin (not significant).

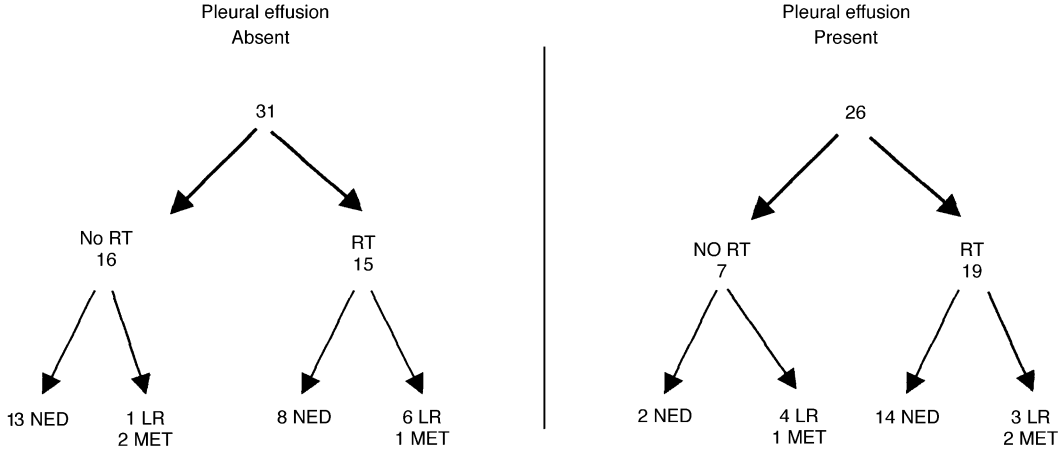

Fig. 5. Impact of pleural effusion and radiation therapy on relapses. NED, no evidence of disease; LR, local relapse; RT, radiotherapy; MET, metastasis.

The histological response to chemotherapy was the only variable strongly correlated to prognosis; the 10-year DFS was 79% for 27 patients with a good histological response versus only 39% for 17 patients with a poor or intermediate response ($P=0.004$) (Fig. 6). The histological response remained an independent prognostic factor in multivariate analysis when modelled with tumour volume and age ($<$ or $\geqslant$15 years) at diagnosis.

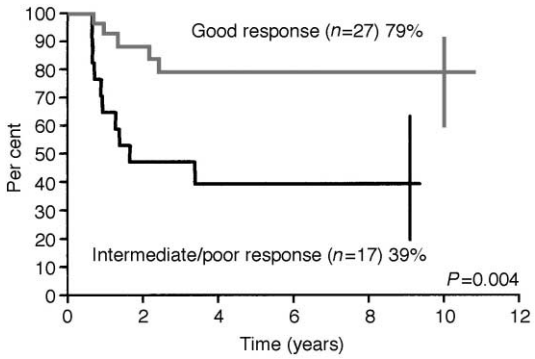

Fig. 6. Disease-free survival according to histological response to chemotherapy (error bars indicate the 95% Confidence Limits).

Table 1
Ten-year disease-free survival (DFS) by prognostic variables (univariate analysis)

Variables	No.	10-year DFS % (CI)	*P* value
Sex			
Boys	25	73 (51–87)	NS
Girls	32	55 (36–71)	
Age at diagnosis			
$<$15 years	39	60 (46–76)	NS
$\geqslant$15 years	18	60 (33–80)	
Tumour size[a]			
$\leqslant$8 cm	18	78 (51–92)	NS
$\geqslant$8 cm	34	60 (43–75)	
Pleural effusion			
No	31	64 (45–79)	NS
Yes	26	59 (39–76)	
Tumour level			
Upper (1st–4th)	18	47 (26–71)	NS
Middle or lower (5th–12th)	39	69 (52–82)	
Rib component[a]			
Anterior or lateral	30	54 (34–73)	
Posterior	26	65 (44–80)	
Quality of surgery[a]			
Complete	40	64 (48–78)	NS
Incomplete	15	68 (41–86)	NS
Histological response to chemotherapy[a]			
Good ($<$5%)	27	79 (59–91)	$P=0.004$
Intermediate or poor ($\geqslant$5%)	17	39 (19–63)	

CI, Confidence Interval; NS, non significant.
[a] Data are not available for all patients.

4. Discussion

The Ewing's sarcoma family is the second most common malignant primary bone tumour of children and adolescents and the most frequent primary malignancy of the bony chest wall. However, the number of reports on Ewing's sarcoma family of the ribs is limited [3,12,13], and optimal local treatment modalities have yet to be defined. Over the past few years, the outcome of patients with localised Ewing's sarcoma family has been significantly improved with the use of multimodal therapy combining chemotherapy with surgery and/or irradiation, and recent studies report event-free survival (EFS) rates at 3 years higher than 60% [17–20]. In our series, the 10-year DFS of 57 patients with a localised tumour of the ribs (62%) confirms that, thanks to recent treatment strategies, their prognosis is similar to that of patients with Ewing's sarcoma family at other sites. Our results are similar to those of the German study, which recently reported a DFS of 61% at 12.8 years in 31 patients with Ewing's sarcoma family of the ribs, and concur with the findings of Shamberger and colleagues reporting on the results of the Pediatric Oncology Group and Children's Cancer Group (EFS at 5 years: 57%). In this last report, the introduction of ifosfamide and etoposide in the therapeutic protocol improved the outcome, with the 5-year EFS reaching 64% versus 51% for the standard four-drug chemotherapy. Probably because of the small number of patients, this difference was not statistically significant ($P=0.02$), but corroborated the analysis of data obtained for all 393 patients randomised to standard chemotherapy versus the same chemotherapy with the addition of ifosfamide and etoposide [20].

We did not find any significant difference in terms of DFS between patients aged $<$15 years and young adults. In contrast, the European Intergroup Cooperative Ewing's Sarcoma Study Group reported that age has an impact on RFS, even in multivariate analysis [21]. Concerning non-metastatic Ewing's sarcoma family of the ribs, the Shamberger study also demonstrated a significant prognostic role in univariate analysis for age at the study entry, but this finding was not evaluated by multivariate analysis [13].

Ozaki and colleagues individualised tumours of the upper ribs (1st–4th) because of the proximity of the brachial plexus and the propensity of these tumours to invade surrounding tissues [12]. Patients with such tumours had a worse prognosis than those with middle or lower level involvement (DFS at 10 years: 34% versus 75%, $P=0.0338$). Our study did not confirm these results. Furthermore, the DFS of patients with a tumour in the posterior rib component (65%) was not significantly different from that of patients with an anteriorly located tumour (54%). By contrast, in the German study, the DFS at 10 years was significantly worse for patients with a posterior tumour (46% versus 75%) ($P=0.0597$) [12].

Tumour size has been an important prognostic factor in certain studies. The Cooperative Ewing Sarcoma

Study (CESS)-81 study first demonstrated that patients with localised Ewing's sarcoma of the bone smaller than 100 cc had a significantly better DFS (80%) than those with tumours larger than 100 cc (31%) [22]. Concerning Ewing's sarcoma family of the ribs, Shamberger and colleagues also demonstrated that increased tumour volume was associated with an elevated risk for adverse events [13]. By contrast, Osaki and colleagues reported that the RFS of patients with regional disease was significantly worse than that of patients with localised disease, as only 2 of their 7 patients with regional disease continued to be relapse-free [12]. Our results do not confirm the value of tumour size as a prognostic factor in Ewing's sarcoma family of the ribs.

Picci and colleagues reported the prognostic value of tumour necrosis in Ewing's sarcoma of the extremities [23]. These results were not confirmed by the German team for rib tumours, where histological response to chemotherapy did not affect prognosis [13]. By contrast, in our study, histological response was the sole prognostic factor. A combined SFOP and Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) analysis performed on a large group of 254 patients treated by surgery after chemotherapy alone revealed that the histopathological response was the only prognostic factor in multivariate analysis (data not shown).

Resection was microscopically incomplete or doubtful in 15 of 55 patients. This did not significantly affect outcome, probably because of the beneficial effect of postoperative irradiation in patients with a tumour-positive margin.

Radiotherapy for local control has several side-effects in Ewing's sarcoma family of the ribs related to the planed treated volume. Postirradiation pneumonitis, and reduction of lung compliance secondary to interstitial fibrosis are commonly reported after doses in excess of conventionally fractionated 20 Gy. Late cardiac side-effects including diffuse myocardial fibrosis and accelerated coronary artery disease add combined toxicity to the damage caused by doxorubicin [1]. Several studies have reported a high risk of second malignant neoplasm after radiation therapy in Ewing's sarcoma [24]. In our study, 23 patients (40%) were not given radiotherapy for local treatment, particularly those with small tumours at diagnosis with complete resection and a good histopathological response to the initial chemotherapy. The rate of local failure was not significantly different after definitive surgery (21%) or after surgery with radiation therapy (22%). The 10-year DFS rates were similar for the different local treatments. Shamberger and colleagues also recently reported that the type of local control measures are not correlated with DFS [13]. Our results confirm that, in selected patients with Ewing's sarcoma family of the ribs, radiation therapy is unnecessary.

Pleural effusion, present in 26 patients in our study, was not a prognostic factor. The main cause of treatment failure in these patients was local recurrence (27% of patients). The frequency of local recurrences was 57% after definitive surgery (100% for patients with a poor histological response) and 11% after local combined therapy. The number of patients is too small to allow statistical tests and define optimal treatment modalities, but radiation therapy appears necessary in patients with pleural effusion, even in those who achieve a good histological response. This important point needs to be explored in other studies that include more patients.

In conclusion, localised Ewing's sarcoma family of the ribs does not represent a disease site with a poor prognosis in the multicentric experience of the SFOP. Histological response to chemotherapy is the sole prognostic factor. Radiotherapy may be withheld in some cases, but it remains necessary in patients with pleural effusion, even those with a good histological response.

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