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Original Paper

Ewing's Sarcoma of the Ribs. A Report from the Cooperative Ewing's Sarcoma Study

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31 patients with primary Ewing's sarcoma of the ribs were treated according to the protocols of CESS 81, CESS 86P and CESS 86. The results of treatment were reviewed and analysed. 24 patients presented with localised disease and 7 with regional disease. 20 of 24 localised cases and 6 of 7 regional cases underwent tumour resection. All but 2 localised cases received irradiation. The cumulative relapse-free survival (RFS) rate of 31 patients was 61% at 12.8 years. Patients with poor prognosis had tumour of the upper ribs ($P = 0.0338$), the posterior component of the ribs ($P = 0.0597$), or regional disease ($P = 0.0001$). Tumour size, existence of pleural effusion, type of the surgical margin and response to chemotherapy were not significant prognostic factors. Most of the localised cases could be controlled by combined treatment, but in regional cases prognosis remained poor.

Key words: bone, neoplasms, malignant, Ewing's sarcoma, PNET, rib, therapy, relapse
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INTRODUCTION

EWING'S SARCOMA is a high grade malignant bone tumour with a predilection for the long bones and the pelvis. The ribs are the third most frequent site with approximately 10–25% of all cases [1, 2]. In 1981, the first Cooperative Ewing's Sarcoma Study (CESS) was initiated by the German Society of Paediatric Oncology and Haematology (GPOH) [3]. 674 patients were registered to the CESS 81, 86P and 86 protocols; 84 (12.5%) patients had primary rib lesions.

Based on recent pathological criteria, there is another subgroup other than the typical "Ewing's sarcoma": primitive neuroectodermal tumour (PNET) [4, 5]. A chromosomal translocation t(11; 22)(q24;q12) is found in both entities [6, 7]. The expression of at least two neuronal markers and/or the presence of Homer–Wright rosettes are detected in the PNET [4]. Most of the PNETs were located in the thoracopulmonary region [4, 5]. According to some reports, patients with PNET have a worse prognosis than those with Ewing's sarcoma [4, 5, 8, 9]. There have been several reports on patients with Ewing's sarcoma of the ribs, but questions remain concerning the prognostic factors, adequate surgical margins and modalities of optimal treatment [10–16]. This report is a review of recent experiences of treatment for patients with Ewing's sarcoma of the rib in the CESS trials.

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PATIENTS AND METHODS

Patients' characteristics

380 patients with primary Ewing's sarcoma were treated according to the CESS 81, CESS 86P or CESS 86 studies [3, 17]. Protocol patients included in this study were defined as patients without pretreatment or primary local treatment, with less than 3 weeks from biopsy to start of therapy, enrolment less than 6 weeks after start of therapy, and an age not above 25 years. Radiologically, these patients were without visible metastases on chest X-ray and/or computed tomography (CT) and bone scan at diagnosis and had received treatment according to the protocol. Information about the patients were gathered by the CESS trial office in Münster, Germany. The follow-up periods ranged from 9 to 154 months (median: 61 months).

In the analysed group of 31 patients with rib tumours, there were 17 male and 14 female patients, ranging in age from 3 to 25 years (median: 13 years) (Table 1). The patients registered in the study included 25 Ewing's sarcomas and 6 PNETs. All cases belonged to Enneking's stage IIB [18]. During the treatment, the location of all primary tumours could be identified. The rib tumours were classified into two groups according to the level: the upper ribs (1st to 4th) and the middle or lower ribs (5th to

Table 1. Relapse-free survival by variables

Variable	No.	No. of relapse			10-years relapse-free survival (%)	P^*
		Loc.	Loc. & Syst.	Syst.		
Sex						
Male	17	2	1	2	63	—
Female	14	3	1	1	57	NS
Histology						
Ewing's sarcoma	25	4	2	2	60	—
PNET	6	1	0	1	67	NS
Tumour level						
Upper (1st–4th)	11	2	1	3	34	—
Middle or Lower (5th–12th)	20	3	1	0	75	0.0338
Rib component						
Ant. or Lat.	16	2	1	0	75	—
Post.	15	3	1	3	46	0.0597
Size (ml)						
<100	7	2	0	1	43	—
≥ 100	22	2	2	2	67	NS
Preural effusion						
Positive	19	2	2	2	57	—
Negative	12	3	0	1	67	NS
Tumour extension						
Localised	24	3	1	2	74	—
Regional	7	2	1	1	14	0.0001
Surgical margin						
Tumour-negative	15	2	1	2	60	—
Tumour-positive	8	1	1	1	62	NS
Histological response						
Good	18	3	1	2	61	—
Poor	5	1	0	1	60	NS

Loc: local relapse, Sys: systemic relapse; NS: not significant ($P > 0.06$).

12th). According to CT imaging, the component of the ribs in which the primary tumour occurred was classified into three groups: anterior (Ant.), lateral (Lat.) and posterior (Post.). The definition of the posterior component was "more posteriorly located segment of the ribs to the tangent line at the anterior edge of the spinal body". The remaining component was defined as anterior or lateral. The 12th ribs have only a posterior component. Tumour volume was calculated according to the method described by Göbel and associates [19]. A tumour volume above or equal to 100 ml was defined as a large tumour, below 100 ml as a small tumour. Radiological pleural effusion was noted in 19 of 31 patients. Regional disease was defined as tumour spreading into the pleural space, manifested both by the presence of a large amount of pleural effusion or gross tumour involvement of the pleural space and the cytopathological examination of the pleural fluid (tumour-positive). According to this definition, 24 patients presented with localised and 7 patients with regional disease.

Chemotherapy

The CESS 81 trial has a four drug combination chemotherapy composed of vincristine, dactinomycin, cyclophosphamide and doxorubicin [3]. The trial CESS 86P was a preceding pilot-phase to the CESS 86 trial. In CESS 86, patients with a large (volume ≥ 100 ml) or central tumour (rib, pelvis, spine and skull) received a special regimen where conventionally dosed cyclophosphamide was replaced by high dose ifosfamide [17]. These regimens lasted 40 weeks. These protocols have been previously described in detail [3, 17]. 8, 2 and 21 patients were treated according to the trials CESS 81, CESS 86P and CESS 86, respectively. Although differences among these protocols are apparent, there were not enough patients with primary rib tumours in this series to detect any significant differences. In this report, therefore, the two protocols and the pilot trial CESS 86P were analysed together.

Local treatment

2 patients underwent definitive surgery, 5 patients definitive irradiation and 24 patients a combined local therapy (Figure 1). All surgical margins were classified in the tumour-negative margin (wide or marginal) and the tumour-positive margin (intralesional) according to Enneking's criteria [18]. After surgery, the surgical specimens were examined histologically and classified into two categories of regression grades according to the criteria published by Salzer-Kuntschik and associates [20]: good (grade 1–3) and poor response (grade 4–6) (Table 1). In the group of irradiated patients, doses ranged between 22.4 and 60.8 Gy (median: 44.8 Gy). For central tumours, the recommended total dose in postoperative irradiation was 36 Gy in CESS 81 and 44.8 Gy in CESS 86 [21]. Due to disease progression, 1 patient received less than 35 Gy. The total dose of definitive irradiation for central tumours was 50–60 Gy in CESS 81 and 60 Gy in CESS 86. Irradiation to the ipsilateral hemithorax including the ipsilateral lung was recommended in addition to irradiation of the local tumour. 2 patients with regional disease were treated with pre-operative irradiation: 1

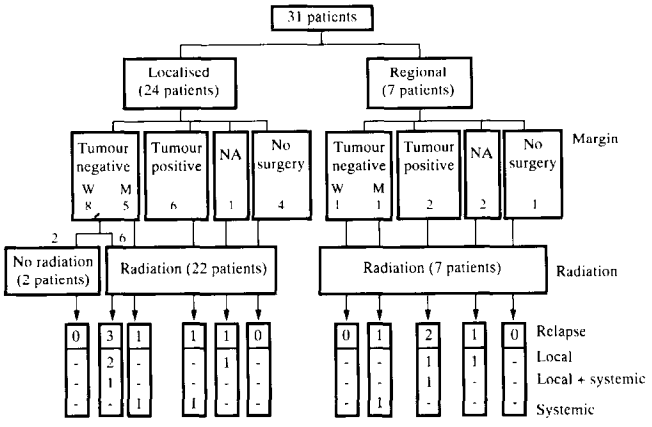

Figure 1. Tumour extension, local therapy and pattern of relapse. W: wide margin, M: marginal margin; NA: information of the margin was not available. 2 patients with regional disease and "M and NA" resection underwent surgery after preoperative irradiation.

with only pre-operative irradiation and the other with pre- and postoperative irradiation.

Statistical analysis

The cumulative probability of relapse-free survival (RFS) was calculated by the Kaplan–Meier method. Tests of the difference between or among survival curves were carried out using log-rank tests. The date of this analysis was January 1995.

RESULTS

Relapse-free survival

The cumulative RFS in 31 patients with Ewing's sarcoma of the ribs was 61% at 12.8 years and that of 277 patients with Ewing's sarcoma of the other sites was 56% at 13.1 years. According to histological diagnosis, the RFS of 25 patients with Ewing's sarcoma was 60% at 12.8 years and that of 6 patients with PNET was 67% at 11.6 years (Table 1). Tumours originated in the superior ribs (P = 0.0338), the posterior component of the ribs (P = 0.0597), and tumours that extended to regional disease (P = 0.0001) had a worse RFS (Figure 2). Size and existence of the pleural effusion were not important in predicting prognosis.

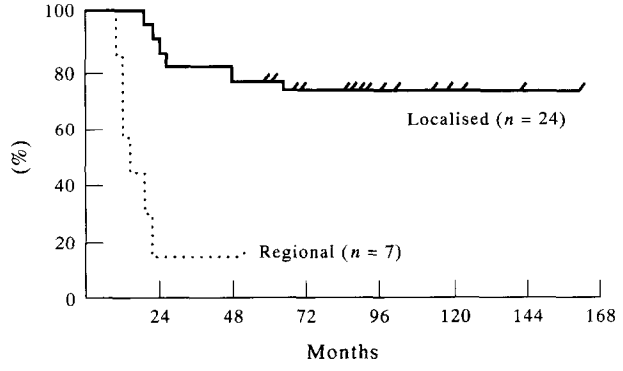

Figure 2. Kaplan–Meier life-table analysis of survival rate according to disease extension. The estimated RFS of patients with localised disease is 74% at 12.8 years and that of patients with regional disease is 14% at 3.9 years (P = 0.0001).

Relapse patterns according to tumour extension and local therapy

Relapse patterns according to tumour extension and local therapy are summarised in Figure 1. In 24 patients with localised disease, 4 patients received definitive irradiation and 2 patients definitive surgery. 18 patients had a combined local therapy. Local recurrences developed in 3 of the 6 patients who underwent wide resection in combination with irradiation and in 1 patient with combined local therapy and no information on the margin. These 4 recurrent tumours occurred not in the ribs but in the pleural tissues and the chest wall around the tumours. The other 20 patients developed no local failures. Distant metastases appeared in 3 patients.

In 7 patients with regional disease, 1 patient received definitive irradiation and 6 patients combined local therapy. One patient underwent wide resection, one marginal. Two tumours were resected with the tumour positive margin and in 2 cases, information about the margin was not available. Local recurrences were registered in 3 patients: in 2 patients with tumour-positive margin and in 1 patient with no information about the margin. Two recurrent tumours occurred in the pleural tissues around the tumour and one in the rib stump. Although 1 patient did not develop a relapse after definitive irradiation, he could not be induced in remission. Distant metastases appeared in 2 patients.

The cumulative 10-year RFS in patients with Ewing's sarcoma who underwent surgery was 60% for 15 patients with tumour-negative margins and 62% for 8 patients with tumour-positive margins (not significant) (Table 1).

Histological response to chemotherapy

The relation between histological response and relapse could be examined in 23 patients (Table 1). There was no significant difference of survival curves between the good and the poor response groups.

Complications

In 1 patient, scoliosis was recognised following resection of the 11th rib and 60 Gy irradiation. After chest wall irradiation, 1 patient developed pulmonary fibrosis. Twenty months after the end of the treatment of the primary tumour, 1 patient died of an acute myelogenous leukaemia as second malignancy. No patients with clinically significant cardiomyopathy have been recorded to date.

DISCUSSION

Ewing's sarcoma is the most common malignant chest wall tumour in children [22, 23]. This tumour tends to penetrate the bone cortex rapidly resulting in formation of a large soft tissue mass which sometimes infiltrates the lung, spine, diaphragm or adjacent viscera. In recent years, combination chemotherapy with surgery and/or irradiation has become standard regimen in the treatment of patients with Ewing's sarcoma. Although the standard surgical approach for rib tumours is to encompass the soft tissue mass with a wide resection, excision with an adequate margin is often difficult to achieve [22]. If patients undergo surgery with tumour-positive margin, postoperative irradiation becomes necessary. In this series, the pleural cavity was considered contaminated through biopsy or definitive surgery and therefore postoperative irradiation was recommended. However, there is a difference in opinion regarding whether definitive irradiation or surgery is effective for local control with modern intensive neoadjuvant chemotherapy [12]. The number of reports on Ewing's sarcoma of the ribs is limited. Not only

prognostic factors but also the optimal treatment modalities are unknown [10–15].

In several series, the survival rate of the patients with Ewing's sarcoma of the ribs have been reported to be between 48 and 53% for relapse-free and overall survival [10, 12, 14, 15]. Patients with Ewing's sarcoma located in the ribs, spine, skull, facial bones and distal portions of the limbs have been reported to have a better prognosis than those of the other sites (1, 6, 24, 25]. In this study, the 12.8 year RFS of 31 patients with tumour of the ribs (61%) was not significantly different from that of the 277 patients with Ewing's sarcoma of other sites after 13.1 years (56%). Although patients with Ewing's sarcoma have been reported to have a significantly better survival than patients with PNET [4, 5], there was no significant difference in the survival rate between these two groups for the patients with rib tumours.

As the tumours of the upper ribs are anatomically close to the brachial plexus and infiltrate into surrounding tissues, they would have the characteristics of the superior sulcus tumour for which destruction of the first to third or fourth rib is indicated on X-ray [26–29]. This was the reason for the classification of the tumour location according to the rib level. 3 patients with the tumour of the upper ribs developed local relapses and another patient failed to achieve remission. The patients with the tumour in the posterior component of the 1st to 12th rib had a tendency to worse prognosis than those of the anteriorly located components. Two of 15 tumours located in the posterior component infiltrated into the vertebral body. The anatomical characteristics of the posterior tumours, such as nearness to the neurovascular band or the thoracic important organs, may be related to this result. Additionally, 5 of the 7 regional cases occurred in patients with a posterior tumour. Not only local but also systemic failures affected the RFS of patients with upper or posterior tumour of the rib. As the number of patients is quite small, the conclusion that this may also be related to the surgical procedures cannot be drawn from these data. If chest wall tumours involved the epidural space, patients have a worse prognosis than those of the soft tissue tumours located in the paravertebral region [5]. However, epidural growth was not noted in our series.

The prognosis of patients with tumour equal or greater than 100 ml was worse than those with smaller volumes [19]. Since initiation of the CESS 86 series, patients with centrally located tumours, including rib tumours, received a special regimen where conventionally dosed cyclophosphamide was replaced by high dose ifosfamide [17]. The size of the lesion seems less significant than tumour site, presence of neurovascular bundle invasion and presence of metastases or regional disease at the time of diagnosis [25]. In the Intergroup Ewing's Sarcoma Study (IESS) report, local recurrences were observed in 4 of 8 patients with regional disease and the other 4 patients with regional disease remained alive and continuously relapse-free [10]. Brown and associates reported a 53% local control rate of rib tumours in 4 patients with local and 14 patients with regional diseases [11]. In our series, only 2 of 7 patients with regional disease continued relapse-free but 1 died of a second malignancy. Regional disease tends to be extensive and close to important organs, and tumour cells disseminate into the pleural space. The RFS of these patients was significantly worse than that of patients with localised disease ($P = 0.0001$).

The histological response to chemotherapy was reported to be a significant prognostic factor in patients of CESS 81 [3]. In this study, histological response to chemotherapy did not affect prognosis (Table 1). 23 of 31 patients (74%) were treated according to the CESS 86 or 86P protocol. The rate of histological response obtained in high risk patients of CESS 86 was higher than that obtained in the high risk patients of CESS 81 [17], but the RFS of the good response group in CESS 86 slightly decreased and that of the poor response group increased as compared to that in CESS 81 (data not shown). This may be due to the effect of the risk stratified therapy of CESS 86 including ifosfamide and must be carefully studied in future trials.

As larger lesions in the thorax or pelvis have a higher risk of local failure, surgery should be considered as an additional local treatment to definitive irradiation [21]. For malignant chest wall tumours, surgical excision with adequate margins is an important determinant of the incidence of local recurrence and survival [30]. Excision of the high grade tumours with 4-cm margin on all sides would be adequate [30]. On posteriorly located rib lesions, the rib is excised from its head to approximately the costochondral junction [12]. In anteriorly placed lesions, the entire cartilaginous portion of the rib is excised, extending to the posterior axillary line [12]. 4 localised cases remained relapse-free after definitive irradiation, so did 2 localised cases after definitive surgery. The number of the patients is too small to allow statistical tests and to decide optimal treatment modalities, but in some localised cases either definitive surgery or irradiation may be appropriate.

A tumour-positive margin was obtained in 8 of 26 patients who underwent chest wall resection in this series, but margin tumour involvement did not significantly affect survival. This is thought to be because of the beneficial effect of postoperative irradiation. 4 patients with localised disease relapsed locally in the tissues around the tumour but not in the stump of the rib. 3 patients had a wide resection and in 1 case the information about the margin was not available. The reason for the local recurrence is thought to be the dissemination of the tumour cells during biopsy or the existence of small tumours at the periphery or around the main tumour. These tumours were not eradicated by postoperative irradiation. A careful incisional biopsy and an exact preoperative evaluation of the tumour location are important. All regional cases with local relapses underwent postoperative irradiation. For improvement of the resectability of the tumour, preoperative irradiation may be useful, since the tumour bearing compartment and satellite lesions of the patients with localised disease, and the disseminated tumour cells of patients with regional disease would get sterilised. The benefits and disadvantages of the preoperative radiation therapy must be carefully studied in future trials.

In summary, favourable results can be obtained in cases with localised Ewing's sarcoma of the rib. Prognosis of the patients was influenced by the tumour site and extension. The prognosis of patients with regional Ewing's sarcoma remains very poor.

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