Eur Spine J (2009) 18:1091–1095
DOI 10.1007/s00586-009-0921-0

ORIGINAL ARTICLE

Treatment of nonmetastatic Ewing's sarcoma family tumors of the spine and sacrum: the experience from a single institution

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Received: 7 October 2008 / Accepted: 13 February 2009 / Published online: 11 March 2009

Abstract The objective of this study is to determine the best local treatment combined with neoadjuvant chemotherapy for ESFT of the spine and sacrum, for the best local treatment for Ewing sarcoma family tumors (ESFT) according to the primary site is still unclear. Nowadays surgery is used in local treatment of ESFT, but literature is scarce on the best local treatment in sites where surgery is problematic, such as the spine. This study evaluates the outcome and the rate of local recurrence of ESFT in the spine and sacrum when treated with neoadjuvant chemotherapy, and locally by radiotherapy alone or surgery, followed by reduced doses of radiotherapy. Forty-three patients with nonmetastatic ESFT located in the spine and sacrum were treated at our institution between 1983 and 2000 with neoadjuvant chemotherapy, and locally by radiotherapy alone in 26 cases, and surgery followed by radiotherapy at reduced doses in 17. The 5- and 10-year event-free survival (EFS) was 37 and 30%, and the 5- and 10-year overall survival was (OS) 42 and 32%. The prognosis was unrelated to gender and age, tumor volume, chemotherapy protocol, and local treatment. The outcome seemed worse for patients with primary tumors located in the sacrum than for patients with tumors located in the rest of the spine (5-year EFS = 23 vs. 46%). For these patients the results were significantly worse than for those we achieved with neoadjuvant treatment for ESFT located in other sites. However, no differences were observed between patients locally treated with radiotherapy alone and those treated by radiotherapy followed by surgery. We concluded that regardless of the type of local treatment even when associated with neoadjuvant therapy, ESFT in the spine and sacrum has a poor outcome and prognosis is significantly worse than that of primary ESFT in other sites.

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Keywords Ewing's sarcoma family tumors · Spine and sacrum · Neoadjuvant chemotherapy · Radiotherapy · Surgery

Introduction

Metastases in the spine are very common events in patients who relapse with different types of tumors. The ratio of secondary to primary malignant neoplasms of the spine is 9/1 [10]. Secondary involvement of the spine is also relatively frequent in patients who relapse with primary metastatic Ewing's sarcoma family tumors (ESFT) located outside the spine [5]. However, primary involvement of the column in ESFT is infrequently seen, amounting to 3.5% of these tumors according to Whitehouse and Griffiths [20].

Literature reports few data on ESFT of the spine [8, 11, 17]. The largest series consists of 59 patients enrolled in 20 years in the three international multicenter studies: Cooperative Ewing Sarcoma Study-81 (CESS 81), Cooperative Ewing Sarcoma Study-86 (CESS 86), and European Intergroup Cooperative Ewing's Sarcoma Study Group-92 (EICESS 92) [17].

This paper proposes a retrospective analysis of treatment and outcome in 43 patients with primary nonmetastatic ESFT of the vertebral column treated at our institute between 1983 and 2000.

Patients and methods

Patient selection

During the years between 1983 and 2000, 767 patients with nonmetastatic ESFT were treated at our institute with neoadjuvant chemotherapy. To enter the neoadjuvant trials, when first admitted to our institution, patients had to fulfil the following criteria: (a) histologic diagnosis of Ewing's sarcoma of bone, (b) less than 41 years of age, (c) absence of metastases at diagnosis, (d) no previous treatment, and (e) less than 4-week interval between biopsy and beginning of treatment. We will here consider only the 43 patients with tumors located in the spine and sacrum. None of these patients were lost to follow-up, and all eligible patients entered the study. The patient characteristics are reported in Table 1.

Table 1 Patient characteristics and 5-year EFS

Variable	No. of cases	Percentage	5-year EFS (%)	*P*
Age (years)				
<14	16	37	25	0.8
≥14	27	63	33	
Gender				
Male	23	53	29	0.89
Female	20	47	31	
Volume (ml)				
<150	21	49	30	0.87
≥150	22	51	31	
Site				
Spine	26	61	46	0.01
Sacrum	17	39	6	
Local therapy				
Radiotherapy	26	81	34	0.4
R × T + surgery	17	9	12	

Pretreatment evaluation

The diagnosis of ESFT was made on representative specimens obtained from open biopsies. Standard histologic investigations and immunohistochemistry studies were performed. The histologic diagnosis was based on the presence of small round cell tumors occurring in the bone with no histologic, cytologic, and immunohistochemical features of lymphoma, rhabdomyosarcoma or neuroblastoma. No attempts were made to differentiate ESFT from malignant neuroectodermic tumors. The diagnostic imaging varied reflecting changes that occurred in imaging techniques in the 17 years of the study. The local imaging of primary lesions included X-rays and CT scan in all cases. In 38 patients treated more recently, MRI was also included. Metastases were investigated by total body scintigraphy and CT scan of the chest. The tumor size was estimated by CT scan measures of the three diameters of the lesion and calculated according to the method previously reported [1].

Criteria to determine the choice of local treatment

In all three trials the local treatment was performed after neoadjuvant chemotherapy and consisted of radiation therapy alone or surgery combined with radiation. The choice of local treatment was decided according to the specifics of each patient. Although not randomized because of the scarce cohorts, the group treated with radiotherapy alone was not significantly different for gender, volume, or site from the group treated with surgery followed by radiotherapy. Radiation therapy was preferred when the option offered by surgery could only be a debulking. Surgery (decompressive, excisional, vertebrectomy) was performed in patients in whom wide or marginal resections were feasible or as an upfront treatment, and in patients presenting with symptoms of paraparesis or tetraparesis to allow decompression. On examination of the surgical

specimens, if margins were marginal or intralesional, radiotherapy at reduced doses was added after surgery.

Radiotherapy

For all patients radiotherapy was performed by CT scan centering. High energy was used (60Co and Linear Accelerator) with doses from 4,400 to 6,000 cGy; 4,400–4,800 cGy above the cauda and 5,000–6,000 cGy below. The patients treated by surgery were given reduced doses of radiotherapy (3,000–3,500 cGy). Twelve patients were treated by conventional fractioning between 1983 and 1989 and 31 with fractioning twice daily, 160 cGy × 2, between 1990 and 2000 as reported in detail in another paper [2].

Chemotherapy

Patients were treated by three different neoadjuvant protocols previously reported [1]. Summarizing, the first consisted of vincristine, cyclophosphamide, adriamycin, dactinomycin C, whereas the second and third also included ifosfamide and etoposide.

Follow-up

During and after combined treatment patients were followed by physical check-ups, standard radiographs and CT scan of the chest and spine. Additional studies, including if necessary biopsy, were performed when indicated by clinical and radiological evaluation. Outpatients were followed every 3 months for 4 years and then twice a year for 10 years. For this review, patients were contacted in September 2007 by phone or mail.

Comparison of results with tumors in other locations

As reported in a previous paper [1] and in Table 2, we compared the results achieved in this study with the results obtained in patients with ESFT located outside the spine and sacrum, treated in the same period with the same chemotherapy protocols. From these data it results that the group of patients with ESFT outside the spine was super-imposable to that of the present study for age, tumor volume and serum level of LDH at presentation. Moreover, the group treated by radiotherapy alone or surgery plus radiotherapy as well as the group with tumor located in the spine and sacrum were also super-imposable for these variables (Table 3).

Statistics

The primary end-point of the study was event-free survival (EFS) defined as the period without any adverse events (local or systemic relapse or death as a complication of treatment) from the start of chemotherapy to the most recent follow-up. EFS was correlated with age and gender, tumor volume and site (spine vs. sacrum), type of local treatment, LDH serum values at presentation. The overall survival (OS) was also evaluated, although the results must be considered with some caution because, after relapse, most patients were treated elsewhere. Of these patients we know the final outcome but not the details of the post relapse treatment received. The Kaplan–Meier product limit estimate was used to calculate EFS. Distribution of frequency of different parameters was compared in groups

Table 3 Characteristics of tumors located in the spine and sacrum

Variable	Sacrum (%)	Spine (%)	*P*
No. of cases	17	26	
Gender			
Male	9 (52)	14 (53)	NS
Female	8 (48)	12 (47)	NS
Age			
<14	2 (12)	6 (23)	NS
≥14	15 (88)	20 (77)	
Elevated LDH	7 (41)	7 (26)	NS
Radiotherapy as local therapy	13 (50)	13 (50)	NS
Volume (ml)			
<150	8 (50)	13 (50)	NS
≥150	9 (50)	13(50)	
Time to diagnosis less than 2 months	4 (23)	8 (30)	NS

Table 2 5- and 10-year EFS, relapse after 5 years and local recurrence rate according to primary tumor site in 767 patients with nonmetastatic ESFT treated with neoadjuvant chemotherapy between 1983 and 2000

Site	Cases (%)	5-year EFS (%)	10-year EFS (%)	Relapse after 5 years (%)	Local recurrence (%)	Patients rescued after relapse (%)
Extremities	64	61	55	5	9.3	5
Pelvis	19	46	45	1	24.2	0
Spine-sacrum	5.6	32	32	0	21	0
Spine	3.3	46	46	0	15	0
Sacrum	2.2	0	0	0	29	0
Other sites	11	54	42	13	12.3	6

of patients by means of the χ^2 test. Significance was set at $P < 0.5$.

Results

A total of 43 patients were included in the analysis. As reported in Table 1, 23 were male (53.5%) and 20 female (46.5%). The median age at diagnosis was 17.2 years (range 9–40 years). The primary tumor site was cervical in 2 cases (4.6%), thoracic in 10 (23.3%), lumbar in 14 (32.5%), lumbo-sacral in 4 (9.3%), and sacrum in 13 (30.2%). The initial tumor volume was less than 150 ml in 21 patients (49%) and more than 150 ml in 22 (51%). The mean interval between onset of symptoms and start of treatment was 5 months (range 0.5–36 months). Local therapy was radiotherapy alone in 26 patients (60.5%), decompressive laminectomy in 6 (14%) and excisional resection in 11 (25.5%). In both groups of patients, surgery was followed by radiation therapy at reduced doses. In two patients the first local treatment was radiation therapy and a vertebrectomy was carried out at the end of chemotherapy. Surgical margins in patients surgically treated were intralesional in six, marginal in seven and wide in two. Of these 43 patients, two progressed (locally and at distance) during treatment and died 4 and 6 months later. Of the remaining 41 patients at a mean follow-up of 14 years (range 8–24 years) 14 patients (34%) remained continuously disease-free and 27 relapsed. The mean time to relapse was 28.5 months (range 3–84 months). All relapsed patients died 12–96 months from the beginning of treatment (mean 39.2 months). For the 43 patients, 5- and 10-year EFS was, respectively 37 and 30%, and the 5- and 10-year OS, 42 and 32%. The 5- and 10-year EFS for patients with tumors located in the vertebral column was 46 and 47, and 0% for patients with tumors in the sacrum.

Comparison with nonmetastatic ESFT located in other sites (not vertebral column)

As shown in Table 2 the rate of nonmetastatic EFST located in the vertebral column is only 6% in comparison with 64% of cases located in the extremities, 19% in the pelvis and 11% in other sites. Five-year EFS in patients with tumors in the sacrum and pelvis was lower compared with ESFT located in other sites. None of the patients with spine or sacrum tumors relapsed after 5 years. The rate of relapse after 5 years for tumors located in other sites varies between 5% for the extremities and 13% in other sites. The rate of local recurrence was 21% for tumors of the vertebral column, 24% for tumors located in the pelvis, 12.3% for tumors in other sites and 9% for tumors of the extremities. None of the patients who relapsed in the spine or sacrum group were rescued versus 6% of cases with tumors located in other sites and 5% for cases located in the extremities.

Discussion

The combination of systemic chemotherapy with local treatment, as well as the development of new radiographic techniques (CT scan and MRI) and new methods of surgical reconstruction, have considerably changed the outcome of patients with nonmetastatic ESFT. The 5-year EFS, that was only 10% today has improved to around 70%. In the neoadjuvant chemotherapy era, from literature it is however difficult to understand the exact outcome and the most appropriate local treatment of nonmetastatic ESFT arising in distinct sites. With few exceptions [13, 16, 18] most papers concerning larger series of modern treatment of nonmetastatic ESFT have been written by chemotherapists who report separate data on cases located in the extremities and in the central skeleton, but do not report the single extremity or axial sites. With regards to tumors located in the spine and sacrum, in a series of 32 patients of a multicenter study (IES), reported by Pilepich et al. [15], local control was 83% and 5-year disease-free survival was 66%. In a more recent report on the same topic, considering three multicenter studies (CESS 81, CESS 86, and EICESS 92) Schuck et al. [17] report a 5-year EFS of 55% in 87 patients with nonmetastatic disease of the spine. It must be stressed however that this study excluded tumors of the sacrum.

The EFS of our complete series of 43 cases was 32%. However, it is important to note that tumors primarily located in the sacrum have a much poorer outcome compared to those located in the rest of the spine (0 vs. 53%, $P < 0.0008$). Therefore, if we consider only patients with ESFT of the spine our results are comparable to those reported in the two major multicenter studies: 47% EFS in our series of 26 patients, 33% in the Grub et al. [7] series of 36 cases, and 55% in the Schuck et al. [17] series of 87 patients. However, if we also consider the cases with primary tumors located in the sacrum our 5-year EFS was only 32% and no patients were rescued after recurrence. The main strength of our study is that all patients were treated at the same institution by the same team of doctors and that data concerning their outcome is available for all cases. The main shortcoming is that patients were not randomized for chemotherapy protocols and, more important, for the type of local treatment. In fact, the cases selected for surgery, as referred above, had less extensive tumors than those selected for radiotherapy where tumor invasion was more extensive. Therefore, the possibility of a bias toward surgery as far as prognosis is concerned does exist. Although there were no significant differences in

prognosis between patients treated only by radiotherapy and patients treated by surgery followed by radiotherapy. Prognosis of ESFT located in the vertebral column proved worse than that of patients with ESFT located in other sites. These data are also confirmed by results reported by other authors [14] and more in general by several series where prognosis of axial lesions is much worse compared to that of tumors located in the limbs [3, 4, 9, 12, 14]. Because of neighboring critical structures local treatment in ESFT of the vertebrae is an issue and local failure rate is higher. This is probably due to the fact that wide surgical resections are possible only in very few selected cases and thus tumors located in this site are treated by radiotherapy, necessarily performed with limitations. In fact, high radiation doses to the cervical, thoracic and upper lumbar vertebrae are contraindicated because of the spinal cord. None of our patients had a complete spondylectomy. We do not have any experience with stereotactic radiotherapy that could be another possibility for local treatment in these tumors. However, we found that when feasible, surgery followed by radiotherapy at reduced doses is a valid alternative.

In contrast with the results observed for other locations [4, 6, 7, 9, 12–16, 19], the outcome for our series was unrelated to tumor volume, type of local treatment, histology (ES vs. PNET), LDH serum levels, and neoadjuvant chemotherapy protocols.

We conclude that in spite of neoadjuvant treatments, ESFT located in the spine and sacrum still has a dismal outcome, which remains significantly worse than that of ESFT located in other sites.

Acknowledgments The authors thank Ms. Cristina Ghinelli for her support in preparing the manuscript.

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