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ORIGINAL STUDY

Non-Metastatic Pelvic Ewing's Sarcoma : oncologic outcomes and evaluation of prognostic factors

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We are reporting our experience on patients with pelvic Ewing's Sarcoma treated in our unit. We retrospectively reviewed a series of patients with non-metastatic pelvic Ewing's sarcoma treated between 1977 and 2009. Patients were classified into three groups according to the local treatment received : Group 1. radiotherapy-chemo ; Group 2. surgery-chemo and Group 3. radiotherapy-surgery-chemo. Recurrence free and overall survival rates were calculated using the Kaplan-Meier method. Influence of various factors (age at diagnosis, gender, tumour site and size, chemotherapy response, surgical margins and type of treatment) on survival was assessed with a logistic regression model. A total of 85 patients were treated with a mean follow-up of 65.8 months and mean tumour volume of 435ml. The 5-year survival for all patients was 40.7% decreased to 36.2% at 10 years. A significant prognostic factor identified was chemotherapy response only. There was a trend for improved survival and local control rates for patients who had chemotherapy and surgery and the results were apparent for all tumours irrespective of size but not statistically significant. Currently, the optimal management of pelvic Ewing's sarcoma is controversial but our study shows a trend for improved survival for patients treated with chemotherapy and surgery.

Keywords : ewing sarcoma ; pelvis ; treatment, prognostic factors.

INTRODUCTION

Ewing's sarcoma (EWS) has been traditionally treated with chemotherapy and radiotherapy, and surgery also plays an important role. It is of general consensus that in appendicular lesions surgical excision is the optimal modality for local control but the role of surgery in pelvic tumours is still debatable (*2,5,13,23,25*). Ewing's sarcoma of the pelvis still have a poor prognosis, significantly worse compared to tumors located outside the pelvis (*3,6*). This is probably due to the difficulty of achieving local

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control in the pelvis (*7*) and the distant relapses occurring in many patients (*9*).

A randomised trial comparing the two approaches (chemotherapy/radiotherapy and chemotherapy/surgery) is lacking and specific recommendations based on the available literature are limited by selection bias, small study size and mixed results. Many studies fail to reach statistical significance but show a trend favouring surgery in pelvic lesions (*3,12,15,24*).

The aim of our study is to retrospectively review a prospectively registered case series of patients with non-metastatic pelvic EWS, to determine the overall and recurrence free survival, to assess the influence of type of treatment on survival and to identify possible prognostic factors

PATIENTS AND METHODS

One hundred forty six patients were referred to our unit between 1977 and 2009. Forty one patients presented with lung and/or bone metastases and 14 patients were referred for an opinion without follow up data available. There were 6 pelvic soft tissue Ewing's tumours. Thus, 85 patients with non-metastatic skeletal pelvic EWS were eligible for evaluation of possible prognostic factors at diagnosis.

Of the 85 patients, 45 were male and 40 female with a mean age of 18 years (range, 5-60). The mean follow up time was 65.8 months (range, 5-343). The mean tumour volume was 435 mL (range, 2.5-2593). According to Enneking classification the tumour site was as follows : 44 (P1-iliac bone) ; 4 (P2-periacetabulum) ; 20 (P3-pubic bone) ; 5 (P4-hemisacrum) ; 4 (P23-peri-acetabulum & pubic) ; 7 (P14-sacroiliac) ; 1 (P123-hemipelvis).

The 85 patients with data available for evaluation (Table I), were divided into three groups according to the local treatment received : Group 1. radiotherapy-chemo (54 patients) ; Group 2. surgery-chemo (21 patients) and Group 3. radiotherapy-surgery-chemo (10 patients).

Sixteen patients underwent limb-sparing surgery, 10 patients had an endoprosthetic replacement and in 5 patients data was not available.

All patients received neo adjuvant and adjuvant chemotherapy as per the existing national protocol and reflected the most up to date chemotherapeutic regimens.

Local treatment consisted of radiotherapy only, surgery only and surgery followed by radiotherapy. Surgical margins were classified according to Enneking *et al* (*8*) as intralesional, marginal, wide and radical. All resected specimens had a histological assessment of the effectiveness of chemotherapy and surgical margins. More than 90% necrosis was classified as good response. Radiotherapy was added to surgery for close margins or poor necrosis. Measurement of the volume of the tumour was

Table I. — Characteristics of the 85 patients with non-metastatic Pelvic EWS

Gender	Number of cases
Male	45
Female	40
Site (Enneking classification)	
P1	44
P2	4
P3	20
P4	5
P14	7
P23	4
P123	1
Tumour volume[a]	
< 100 ml	12
≥ 100 ml	37
Local treatment	
Surgery	31
No surgery	54
Histologic response[b]	
Good	16
Poor	11
Surgical margin[c]	
Intralesional	3
Marginal	6
Wide	20
Radical	0
Local recurrence	
Yes	21
No	64
Metastases	
Yes	42
No	43

[a]Thirty six cases missing for tumour volume.
[b]Four cases missing for histologic response.
[c]Two cases missing for surgical margins.

independent and blind, without any knowledge of the outcome of the patients and was performed by the first author. Assessment of the intra- and extra osseous component for each patient was made from the extension of the tumour in the longitudinal, lateral and anteroposterior planes. The calculations were as recommended by the CESS depending on whether the soft-tissue component of the tumour was large or discrete (22).

The CT or MRI scans taken before biopsy, were used to measure the volume of the tumour.

Evaluation included history, clinical examination, routine haematological studies, immunohistochemistry tests and bone marrow aspiration/biopsy. All patients had histopathological diagnosis of Ewing's tumour proven and confirmed by at least two pathologists. Radiological assessment used included plain radiographs of pelvis and chest, bone scan (Tc MDP), CT of chest and pelvis and MRI of the pelvis. Systemic and local control of the disease was monitored by routine clinical examination, and appropriate radiographic studies. These tests were carried out every 3 months for the first 2 years, every 6 months for the following 2 years and yearly thereafter for a total of 10 years.

Statistical analysis

Overall survival and recurrence free survival curves were estimated according to the Kaplan-Meier method. The logistic regression model was used to analyze possible factors influencing prognosis. The results of the logistic regression analyses were expressed as odds ratio (OR) and p values of less than 0.05 were considered to be statistically significant. All statistical analyses were carried out using the IBM SPSS 20 package (Armonk, New York, USA).

RESULTS

Fifty one died of the disease, 6 are alive with the disease, 20 are disease free and in 8 no relevant data was available. The 5-year survival for all patients was 40.7%, decreased to 36.2% at 10 years (Fig. 1). In our series, the 5-year survival of the patients who had surgical resection was 44.7% and at 10 years 31.3%.

In patients free of local and distant recurrences the 5-year survival was 74% and the 10-year survival 70%. The 5-year local recurrence free survival was 51.8% and at 10 years it was 42.7%.

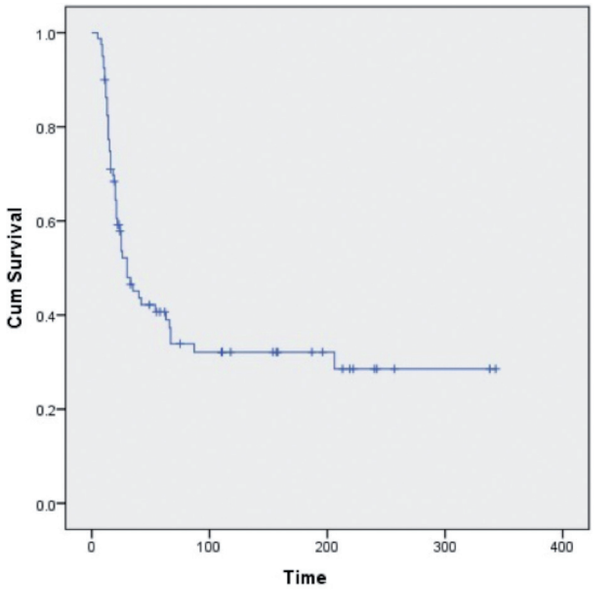

Fig. 1. — Kaplan Meier survival curve for all patients

Regarding overall survival in terms of treatment group, there was a trend for improved survival in the group of chemotherapy and surgery but it was not statistically significant (OR : 0.87, 95% CI 0.27-1.75, p = 0.75) (Fig. 2). For small tumours that received chemotherapy and surgery, there was a trend for improved survival although not statistically significant (OR : 2.43, 95% CI 0.2-28.9, p = 0.48). There was true for large tumours as well (Fig. 3) (OR : 0.81, 95% CI 0.23-2.82, p = 0.74).Of the 21 patients in the surgery only group, 15 wide and 4 marginal surgical margins were achieved. All small tumours were removed with wide margins. Four local recurrences developed in 2 tumours removed with wide margins and in 2 tumours removed with marginal margins.

Twenty six patients developed metastases only, 21 patients had a local recurrence and 16 patients developed both local and distant relapses. Eight patients who had surgery developed local recurrence. Of those patients, 4 had wide, 3 marginal and 1 intralesional surgical margins.

Among patients with small tumors only 3 developed local recurrences, compared with 18 local recurrences within patients with tumors larger than

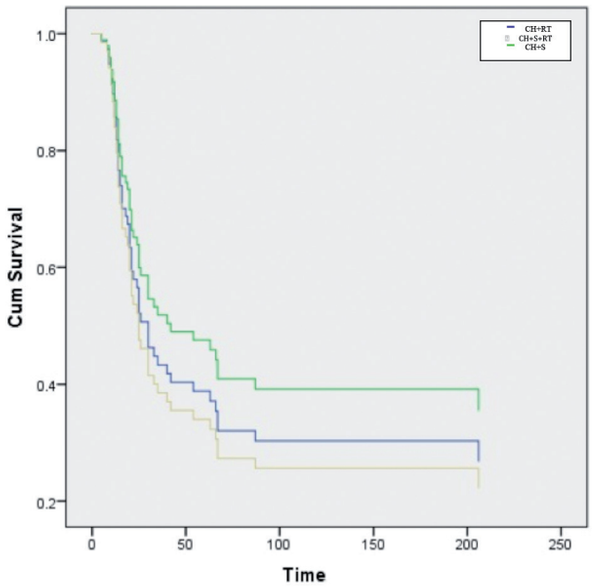

***Fig. 2.* —** Kaplan-Meier survival curve according to treatment group for all patients.

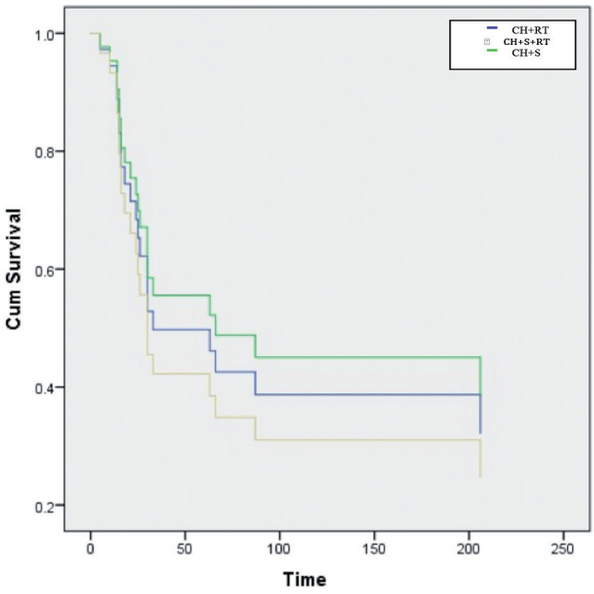

***Fig. 3.* —** Kaplan-Meier survival curve for large tumours according to treatment group.

100 mL. Patients with recurrence had a worst prognosis as expected (Fig. 4).

Logistic regression analysis was performed on those 85 patients. Age, gender, tumour location tumour volume, treatment type and surgical margins were not found to be significant (Table II). The only significant factor identified was adequate response to chemotherapy (necrosis > 90%) (OR : 0.06, p = 0.01).

DISCUSSION

Ewing sarcoma of the pelvis requires particular attention because this site is the second most common primary site and is also associated with a particularly unfavorable prognosis (*15,16,18*).

In our series the 5-year survival for all patients with non-metastatic pelvic EWS was 40.7%, decreased to 36.2% at 10 years. In recurrence free patients, the 5-year survival was 74% and the 10-year survival 70%. Hoffman *et al* (*12*) in their large retrospective study have shown that the overall and event free survival rates for patients without metastases at diagnosis were 45% and 39%, respectively.

Evans *et al* (*10*) reported a 63% 5-year survival in the IESS-II study, Sucato *et al* (*24*) 51.3% , and Rodl *et al* (*20*) 49%. Furthermore, Bacci *et al* (*1*) showed that 5 and 10-year event-free survival rates were 45% and 44% respectively, and the 5 and 10-year overall survival rates were 48% and 44%.

When we look at the overall survival for our patients who had a surgical resection, that was 44.7% at 5 years. Puri *et al* (*19*) showed an overall survival of 72% at 5 years and Carrie *et al* (*3*) an overall survival of 72% in patients with non-metastatic pelvic EWS treated with surgery.

The decision about the selection of the most appropriate local treatment was made combining both aims of the complete local control, associated with the need to retain the highest level of function. Retrospectively, we do not know the exact basis for each decision. The decision about the local treatment was based on careful consideration of patients' characteristics (age, tumour site and size, resect ability, chemotherapy response, and surgical margins) and after discussion with surgeons, oncologists and histopathologists. In general, patients with small tumours had chemotherapy and surgery, as

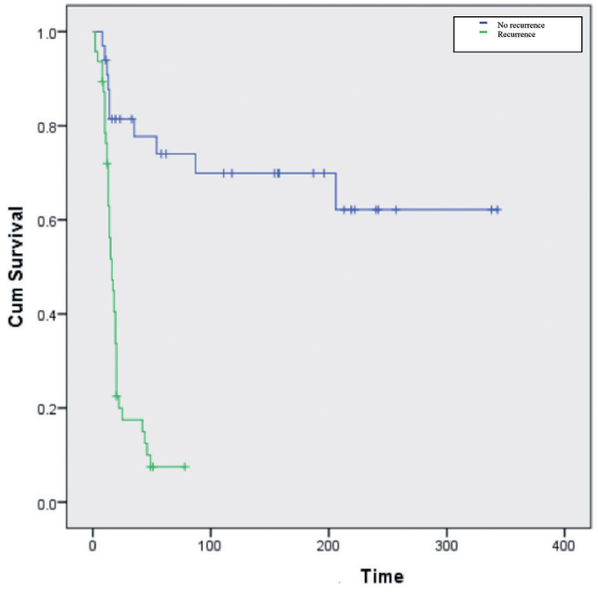

Fig. 4. — Kaplan-Meier survival curve for all patients according to recurrence.

did those with peri-acetabular and pubic tumours. Iliac tumours extending near to acetabulum were usually treated with chemotherapy and radiotherapy. Thirty one of 85 cases (36%) of non-metastatic Ewing's sarcoma of the pelvis underwent surgical resection at our institute. Furthermore, patients with close surgical margins received radiotherapy and therefore they had the worst survival results.

Although several papers seem to indicate a trend of better local control and a higher rate of cure for patients treated surgically (*4,10,11,12,17,21,23*) it is difficult to assess fully the usefulness of surgical treatment. The treatment outcome of pelvic EWS depends on many factors and many of these studies were not randomised, so selection bias might have played an important role in the evaluation of prognostic factors and the assessment of different local treatments. Studies on local control in pelvic EWS are quite rare and usually include a small number of patients. In our series we showed a trend for improved survival for patients treated surgically but it was not statistically significant. Furthermore, we have shown that there was a trend for improved survival for patients treated surgically for all tumours irrespective of size.

Table II. — Logistic regression analysis

Variable	p value	Odds ratio
Tumour volume	0.16	1.0
Chemotherapy response	0.01	0.06
Gender	0.37	0.67
Age	0.06	2.35
Tumour site	0.5	1.01
Treatment type	0 .65	1.15
Surgical margins	0.79	1.15

In this retrospective evaluation we also tried to identify possible prognostic factors which could help determining possible treatment strategies. We identified positive response to chemotherapy as the only significant prognostic factor.

Hoffman *et al* (*12*) showed the only variables that appeared to be statistically relevant were tumour volume and histologic response to initial chemotherapy. Jawad *et al* (*14*) also showed tumour volume as a significant prognostic factor whereas Zang *et al* (*26*) showed resection margin and metastatic disease as independent prognostic factors.

One of the main strengths of our study was the large number of patients treated at a single institution by the same team of surgeons, radiotherapists and oncologists. This grants a uniformity of treatment, especially as regards local control. On the other hand the main weakness was that this was a retrospective study of patients over a 30-year period in which many changes in the chemotherapy protocols, radiation therapy and imaging studies have occurred and influenced the diagnostic approach and treatment of patients with EWS. Furthermore, the iliac bone was the most frequent involved site and this is the reason most of our patients were treated non-surgically. In combination with the fact that some of the data was unavailable, this could have contributed to some of the results being not statistically significant. Finally, there is an element of selection bias as patients with poor surgical margins went over to the surgery plus radiotherapy group.

In conclusion, pelvic Ewing's sarcoma remains a challenge and current available literature stresses the need for a multinational prospective randomised

study that would decide on the best local treatment strategy. However, the favorable results obtained with surgical treatment are encouraging and suggest that a further extension of this strategy might be worthwhile.

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REFERENCES

1. **Bacci G, Ferrari S, Mercuri M *et al.*** Multimodal therapy for the treatment of nonmetastatic Ewing sarcoma of pelvis. *J Pediatr Hematol Oncol* 2003 ; 25 : 118-124.
2. **Bacci G, Ferrari S, Longhi A *et al.*** Role of surgery in local treatment of Ewing's sarcoma of the extremities in patients undergoing adjuvant and neoadjuvant chemotherapy. *Oncol Rep* 2004 ; 11 : 111-120.
3. **Carrie C, Mascard E, Gomez F *et al.*** Nonmetastatic pelvic Ewing sarcoma : report of the French Society of Pediatric Oncology. *Med Pediatr Oncol* 1999 ; 33 : 444-449.
4. **Cotterill SJ, Ahrens S, Paulussen M *et al.*** Prognostic factors in Ewing's tumour of bone : analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol* 2000 ; 18 : 3108-3114.
5. **Donati D, Yin J, Di Bella C *et al.*** Local and distant control in non-metastatic pelvic Ewing's sarcoma patients. *J Surg Oncol* 2007 ; 96 : 19-25.
6. **Dunst J, Sauer R, Burgers JM *et al.*** Radiation therapy as local treatment in Ewing's sarcoma. Results of the Cooperative Ewing's Sarcoma Studies CESS 81 and CESS 86. *Cancer* 1991 ; 67 : 2818-2825.
7. **Elomaa I, Blomqvist CP, Saeter G *et al.*** Five-year results in Ewing's sarcoma. The Scandinavian Sarcoma Group experience with the SSG IX protocol. *Eur J Cancer* 2000 ; 36 : 875-880.
8. **Enneking W, Dunham W, Gebhardt M *et al.*** A system for the classification of skeletal resections. *Chir Organi Mov* 1990 ; 75 (1 Suppl) : 217-240.
9. **Evans R, Nesbit ME, Askin F *et al.*** Local recurrence, rate and sites of metastases, and time to relapse as a function of treatment regimen, size of primary and surgical history in 62 patients presenting with non-metastatic Ewing's sarcoma of the pelvic bones. *Int J Radiat Oncol Biol Phys* 1985 ; 11 : 129-136.
10. **Evans RG, Nesbit ME, Gehan EA *et al.*** Multimodal therapy for the management of localized Ewing's sarcoma of pelvic and sacral bones : a report from the second intergroup study. *J Clin Oncol* 1991 ; 9 : 1173-1180.
11. **Frassica FJ, Frassica DA, Pritchard DJ *et al.*** Ewing sarcoma of the pelvis. Clinicopathological features and treatment. *J Bone Joint Surg [Am]* 1993 ; 75 : 1457-65.
12. **Hoffmann C, Ahrens S, Dunst J *et al.*** Pelvic Ewing sarcoma : a retrospective analysis of 241 cases. *Cancer* 1999 ; 85 : 869-877.
13. **Indelicato DJ, Keole SR, Shahlaee AH *et al.*** Impact of local management on long-term outcomes in Ewing tumors of the pelvis and sacral bones : The University of Florida experience. *Int J Radiat Oncol Biol Phys* 2008 ; 72 : 41-48.
14. **Jawad MU, Haleem AA, Scully SP.** Malignant sarcoma of the pelvic bones : treatment outcomes and prognostic factors vary by histopathology. *Cancer* 2011 ; 117 : 1529-1541.
15. **Li WK, Lane JM, Rosen G *et al.*** Pelvic Ewing's sarcoma : advances in treatment. *J Bone Joint Surg [Br]* 1983 ; 65 : 738-747.
16. **Nesbit ME, Gehan EA, Burgert EO *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.
17. **Perez CA, Tefft M, Nesbit ME *et al.*** Radiation therapy in the multimodal management of Ewing's sarcoma of bone : report of the Intergroup Ewing's Sarcoma Study. *Natl Cancer Inst Monogr* 1981 ; 56 : 263-71.
18. **Pritchard DJ.** Indications for surgical treatment of localized Ewing's sarcoma of bone. *Clin Orthop* 1980 ; 153 : 39-43.
19. **Puri A, Gulia A, Jambhekar NA *et al.*** Results of surgical resection in pelvic Ewing's sarcoma. *J Surg Oncol*. 2012 ; 106 : 417-22.
20. **Rodl RW, Hoffmann C, Gosheger G *et al.*** Ewing's sarcoma of the pelvis : Combined surgery and radiotherapy treatment. *J Surg Oncol*. 2003 ; 83 : 154-160.
21. **Sailer SL, Harmon DC, Mankin HJ *et al.*** Ewing's sarcoma : surgical resection as a prognostic factor. *Int J Radiat Oncol Biol Phys* 1988 ; 15 : 43-52.
22. **Sauer R, Jurgens H, Burgers JM *et al.*** Prognostic factors in the treatment of Ewing's sarcoma : the Ewing's sarcoma study group of the German Society of Paediatric Oncology CESS 81. *Radiother Oncol* 1987 ; 10 : 101-110.
23. **Scully SP, Temple HT, O'Keefe RJ *et al.*** Role of surgical resection in pelvic Ewing's sarcoma. *J Clin Oncol* 1995 ; 13 : 2336-2341.
24. **Sucato DJ, Rougraff B, McGrath BE *et al.*** Ewing's sarcoma of the pelvis. Long-term survival and functional outcome. *Clin Orthop Relat Res*. 2000 ; 373 : 193-201.
25. **Yock TI, Krailo M, Fryer CJ *et al.*** Local control in pelvic Ewing sarcoma : Analysis from INT-0091 – A report from the Children's Oncology Group. *J Clin Oncol* 2006 ; 24 : 3838-3843.
26. **Zang J, Guo W, Qu HY.** Ewing's sarcoma of the pelvis : treatment results of 31 patients. *Zhonghua Wai Ke Za Zhi* 2012 ; 50 : 524-528.