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Original Paper

Ewing's Sarcoma of the Pelvis: Changes Over 25 Years in Treatment and Results

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The pelvic localisations of Ewing's sarcoma have the worst prognosis due to large size at diagnosis, frequent distant metastases, radiosensitive organs next to the tumour and difficult surgery. The purpose of the present study was to analyse treatment results over a period of 25 years and to investigate the impact of newer chemotherapy schedules, improved radiotherapy techniques and newer surgical methods on the prognosis. 35 children and young adults were identified from 1967 to 1994 for whom diagnosis, presentation, performed treatment and outcome were available. Tumour size, as measured from CT scans, response to chemotherapy and radiotherapy target volume, could be reviewed in the later years. Actuarial 5-year survival for the whole group was 31% and for the 24 non-metastatic patients 40%, with a disease-free interval of 19%. Tumour size could be measured in 27 patients and ranged from 36 to 1540 cm³. There were 12 local recurrences, 1 in the 4 patients treated with surgery. After 1983, 9 out of 17 irradiated patients developed local failure. 3 patients had adequate fields and one a close field which did not cover completely the prechemotherapy extent and 3 of these recurred. All 4 patients with stable disease after neoadjuvant CT failed locally, not withstanding high-dose radiotherapy. The mean length of neoadjuvant CT tended to be shorter in patients without local relapse. There was no significant difference in survival before and after 1983. © 1997 Published by Elsevier Science Ltd.

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INTRODUCTION

SINCE THE introduction of chemotherapy in the 1960s, interest in paediatric oncology has steadily increased. Ewing's sarcoma was considered a very radiosensitive tumour, although many patients succumbed to lung metastases within a short time. Ewing's sarcoma was also found to be chemosensitive. The first European trial which started in 1965, and was run by the EORTC, investigated the value of adding Melphalan and Endoxan to local radiotherapy. No benefit was shown [1].

The Netherlands Cancer Institute with the Children's Hospital Emma Kinderziekenhuis started its Children

Tumour Working Party (WKT) in 1967. One of the first activities was to set up a registry of all patients seen. Treatment results of Ewing's sarcoma including PNET (primitive neuroectodermal tumour) have been reported in an abstract to ESTRO in 1988 and to the yearly SIOP conference in 1989 [2,3]. As reported in the literature, small and distal tumours have the best prognosis. In combination with chemotherapy, either surgery or radiotherapy can be chosen as local primary treatment taking into account the least expected mutilation. At the other end of the spectrum of Ewing's sarcoma are the localisations in the pelvis, which are usually large when first diagnosed. Surgery is difficult and/or highly mutilating, while radiotherapy is limited by sensitive organs such as rectum, bladder, ovary, testis, hip joint and growing bone. Our experience in the pelvic localisations of Ewing's

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sarcoma, treated since 1967, is discussed below, with special emphasis on the role of more intensive chemotherapy, better planning and better tumour delineation in radiotherapy and advances in pelvic surgery.

PATIENTS AND METHODS

Patients

From 1967 to 1994 the Children Tumour Working Party of Amsterdam registered 128 patients with Ewing's sarcoma and 22 patients with PNET. 35 of these (23%) were localised in the pelvis, of whom 4 patients were referred for recurrence and 1 toddler died 3 days after the start of chemotherapy, leaving 30 evaluable patients. During the same period, 5 young adults with Ewing's sarcoma or PNET were registered in the Netherlands Cancer Institute. These 35 patients are presented in this report, with a follow-up ranging between 1 and 20 years. There were 15 boys and 20 girls. Age varied from 3 to 31 years (median 14 years). Patients and treatment factors are listed in Table 1. Tumour localisations were as follows: os ilium 22, os pubis 6, os ischii 5, os sacrum 2. Metastases were found at diagnosis in 11 patients (9 lung, 2 bone). All histological material was reviewed by one of the authors (JFMD).

Staging and tumour evaluation

In the earlier years, standard X-rays of pelvis and chest were available. After establishing the diagnosis with a biopsy, bone marrow aspiration distant from the primary tumour was generally performed. In the 1970s CT scans of variable quality started to be performed. From 1983 onward staging procedures included isotopic bone scans and pelvic CT scans at diagnosis. These procedures were repeated during treatment and follow-up. Since then tumour size and response to chemotherapy could be systematically evaluated. The tumour volume was calculated according to Göbel [4] and could be evaluated in 27 patients, presented in Table 2, in relation to tumour localisation.

Treatment

All patients received chemotherapy, before 1983 either starting concomitant with local treatment or as neoadjuvant treatment for 6 weeks (Table 3). From 1983, the CESS protocols [5, 6] were followed in 21 patients which involved a longer period of neoadjuvant chemotherapy before local treatment (Table 3). In 21 patients, tumour response could be evaluated. The method of the EICESS [7], was chosen: volume reduction (VR) of 75% (near CR), 50% or 25% was scored, or SD (stable disease). Since 1983, surgery has been an option for local treatment, but only 4 of 17 patients received surgery. All other patients (31) were treated with radiotherapy. A dose of 55–60 Gy was given in 6–7 weeks, with generous margins up to 40–45 Gy, followed by a smaller boost field. From 1983, CT-based planning was available and custom-made shielding blocks were used. In case of a good response to neoadjuvant chemotherapy, generally only the remaining soft tissue extension was included with 2 cm margins together with the whole involved bone. Hyperfractionated radiotherapy was used in 5 patients (pts 18, 27, 28, 30, 31) with twice a day fractions of 1.6 Gy, divided over three treatment series, coinciding with three chemotherapy courses (CESS 86 [6]). 3 patients with extensive metastases had a lower dose to the primary area (10, 11, 12).

All patients who presented with lung metastases had whole lung radiation, 15–20 Gy, with a boost on the largest lesions. Before 1983, it was usually given within 1–2 months of diagnosis. In the CESS protocols, it was deferred to the end of all chemotherapy. 1 of 2 patients with bone metastases (32) had local radiotherapy to these lesions followed by high-dose intensive chemotherapy with total body irradiation (TBI) and autologous bone marrow transplantation (ABMT). In patients who developed subsequent metastases, various treatment combinations were given.

To investigate the quality of radiotherapy, especially whether the margins as currently advised and described above, were adhered to, all available CT scans, planning and port films were reviewed. The target volume of the planning CT was compared with the available pretreatment information. The margins were scored as wide (2–5 cm, old instructions), adequate (1–2 cm margin, modern instruction), close (0–1 cm margin, possibly caused by problems with interpretation of imaging material or by pressure to shield normal organs) and inadequate (no margin or cutting through tumour). This evaluation could be performed in 28 patients.

In view of the development of diagnostic and treatment procedures, a comparison was made between 1967 and 1982 (14 patients, of whom 9 non-metastatic (M_0)), treated before 1983, and 1983 to 1994, treated thereafter (21 patients, 15 M_0). For statistical evaluation of the material, the Kaplan–Meier method was used for survival curves and the log-rank test for comparison.

RESULTS

Survival and disease-free survival

For all 35 patients, actuarial survival at 5 years and 10 years was 31% (Figure 1). For the 24 non-metastatic (M_0) patients, progression-free survival at 5 years was 19%, and survival at 5 years 40% (Figure 2). Of these, 17/24 (71%) developed metastases of whom 2 (patients 1 and 3) survived for more than 10 years. The metastatic rate did not differ significantly between 1967 and 1982 and 1983 and 1994, when treatment was according to international guidelines, with more drugs and later local treatment (7/9, 78% and 10/15, 67% respectively). The disease-free interval was different in the first years of follow-up only, with a medium of 9 months in 1967–82 and 21 months in 1983–1994 (Figure 3). Bone metastases seemed more frequent in 1983–1994 (2/9 pt. and 6/15, respectively) (Table 4). An important end point in the present study is local failure, either progression or relapse. Because of the slow repair of bone disease, it is impossible to judge whether a complete remission of the tumour has been reached. Therefore, a distinction between progression or relapse is not possible and both were taken together. In 4 patients (pts 16, 22, 23, 29), local failure occurred before distant metastases and 2 of these patients died of local failure without metastases. Local failure was recorded more frequently in recent years: 2/14 in 1967–1982 and 10/21 in 1983–1994 (Table 4).

Tumour size and site

Most tumours, 22 out of 35 (63%), were localised in the largest bone, the os ilium (including the os pubis) (Table 2). Only 4 patients had a volume less than 100 cm³, while 10 out of 27 patients had a volume between 100 and 300 cm³. Large tumours over 900 cm³ were found in 5 patients, and only 2 of these were in the ilium.

Table 1. Patients' characteristics

Pt. no.	Age	Sex	Localisation	Dimension in cm	Volume in cm ³ *	Chemotherapy schedule†	Interval‡ weeks	Chemotherapy response	RT dose (Gy)	Field adequate§	Local relapse (mo)	Distant relapse (mo)	Follow up (mo or yr)
Non-metastatic patients 1967-1982													
1	8	F	ilium	10×5×?	—	D-act	0	—	57.00	—	—	8 lu	>20 yr
2	7	F	ilium	—	—	E1	0	—	60.00	—	—	—	>20 yr
3	17	M	ilium	12×8×?	—	WKT 1	0	—	60.00	—	—	8 lu	>15 yr
4	10	M	ischium	6×4×?	—	WKT 2	6	—	60.00	—	—	13 lu	15*
5	3	F	ilium	8×7×5	145	WKT 2	6	50% VR	58.25	adequate	—	8 lu, b	10*
6	7	M	ischium	6×6×5	94	WKT 2	6	—	60.00	adequate	—	4 lu	11*
7	6	M	ilium	10×8×8	340	WKT 2	6	25% VR	60.00	close	18	14 lu	21*
8	16	F	pubis	19×13×12	1540	WKT 2	7	75% VR	59.25	close	—	6 b	9*
9	31	F	sacrum	24×12×8	1280	cyvadic [19]	8	50% VR	60.00	wide	—	—	>15 yr
10	13	F	ilium, lu	12×12×?	—	D-act	0	—	34.75	—	—	—	13*
11	15	M	pubis, lu	—	—	WKT 1	2	—	40.25	—	—	—	37*
12	5	M	ischium, lu	5×4×?	—	WKT 1	2	—	40.00	inadequate	18	—	19*
13	10	M	ilium, lu	6×?×?	—	WKT 1	0	—	54.00	adequate	—	—	28*
14	14	M	pubis, lu	15×15×10	1180	WKT 2	23	50% VR	50.00	adequate	—	NED	16**
15	10	M	ilium	11×7×6	240	C 81	19	SD	60.00	adequate	14	14, lu, b	18*
16	16	M	ilium	17×10×10	950	C 81	16	50% VR	60.00	close	20	31, lu	53*
17	11	M	ilium	7×5×2	36	C 81	20	**	surgery	—	—	—	>126
18	15	M	ilium	17×10×10	890	C 86	9	50% VR	60.80††	adequate	18	18, lu	21*
19	14	F	pubis	8×8×6	200	C 86	11	75% VR	60.00	close	—	17, b	21*
20	13	F	ilium	9×8×5	190	C 86	10	75% VR	60.00	adequate	—	—	>72
21	18	F	ilium	12×9×7	395	C 86	13	75% VR	55.80	adequate	—	26, lu	>48††
22	10	F	ilium	10×10×10	520	C 86	20	75% VR	55.80	adequate	13	—	19*
23	13	F	ilium	14×12×10	865	EIC 92	14	75% VR	surgery	—	6	—	29*
24	15	F	ilium	13×8×6	324	EIC 92	10	75% VR	55.80	adequate	28	26, b	>28††
25	9	F	ilium	9×6×6	168	EIC 92	14	75% VR	55.80	adequate	17	17, b	>17††
26	7	M	ilium	9×8×6	210	EIC 92	13	25% VR	55.80	close	—	—	>12††
27	19	M	sacrum	12×10×7	440	C 86	10	25% VR	60.80††	close	—	53, lu, b	71*
28	24	F	ilium	9×6×5	140	C 86	10	SD	60.80††	adequate	23	25, b	27*
29	23	M	ischium, lu	16×11×10	920	EIC 92	11	SD	60.00	adequate	16	20, lu	21*
30	14	F	pubis, lu	9×7×6	380	C 86	10	50% VR	60.80††	adequate	—	—	25*
31	18	F	pubis, lu	11×11×10	640	C 86	11	75% VR	60.80††	adequate	19	—	>85
32	16	M	ilium, b	9×7×5	165	C 86	28	SD	64.80	adequate	—	—	23*
33	16	F	pubis, lu	10×6×4	125	C 86	12	75% VR	surgery	—	—	—	29*
34	3	F	ischium, lu	7×5×5	82	EIC 92	21	25% VR	surgery	—	—	—	>22
35	26	M	ilium, b	8×5×2	42	C 86	12	0	59.75	adequate	—	—	26*

lu = metastases to lung, b = metastases to bone, VR = volume reduction, — = no radiographs available. *According to $a \times b \times c$ 0.52 (ellipsoid) [4]. †For abbreviations see Table 3. ‡Interval in weeks between start of chemotherapy and start of local treatment. §Code see text and Table 6. [19] See reference. ¶Inadequate in comparison with prechemotherapy tumour extent. **No soft tissue component. ††Hyperfractionated RT (CESS 86). ‡‡Alive with disease.

Surgery

Surgery with curative intent was performed in 4 patients where a wide resection could be done with less functional deficit than expected after radiotherapy. Of these 4 patients, 2 survived with no evidence of disease, 10 years and 22 months respectively (patients 17 and 34, the last including treatment for lung metastases). Another patient (pt 33) died due to recurrent lung metastases. The fourth patient (pt 23) with a huge primary tumour had an irradical resection, but was not given postoperative radiotherapy because there was no viable tumour in the resection margin and because of the vulnerability of the bony implant. She succumbed to local failure at 29 months without distant metastases. The size of the

tumour in these patients and response to chemotherapy were 36 cm³ (os ilium, volume reduction (VR) not evaluable—pt 17), 82 cm³ (os ischium, VR 25%—pt 34), 125 cm³ (os pubis, VR 75%—pt 33), and 865 cm³ (os ilium, VR 75%—pt 23), respectively.

Local failure after radiotherapy: patient and treatment factors

Local radiotherapy was given to 31 patients. Local failure, either progression or relapse, developed in 11 patients of whom 2 (2/14) were in 1967–1982 and 9 (9/17) were in 1983–1994 (Table 4). These local failures were diagnosed

Table 2. Site and size of Ewing's sarcoma of the pelvis

	Volume (cm ³)					
	<100	101–300	301–600	601–900	901–1200	>1200
os ilium (n = 17)	2	7	4	2	2	
os pubis (n = 5)		2		1	1	1
os ischii (n = 3)	2		1			
os sacrum (n = 2)		1				1
total* (n = 27)	4	10	5	3	3	2
Local failure† (n = 11)		4	3	2	2	

*According to ellipsoid $a \times b \times c \times 0.52 \text{ cm}^3$ [4]. †Size not available in 8 patients in whom 1 local relapse occurred.

Table 3. Chemotherapy schedules

	n	Neoadjuvant interval* (weeks)	Agents
WKT 1	4	0	Vincristine, D-actinomycin
WKT 2	6	6	Vincristine, cyclophosphamide D-actinomycin, doxorubicin
CESS 81	3	18	Vincristine, cyclophosphamide, D-actinomycin, doxorubicin
CESS 86	12	9	Vincristine, ifosfamide, doxorubicin
EICESS 92	6	12	Vincristine, ifosfamide, doxorubicin, actinomycin-D ± etoposide
Various	3	0	pt. 2—Melphalan, endoxan pts. 1, 10—actinomycin-D pt. 38—Cyvadic†
	1	8	

*Interval between start of chemotherapy and start of local treatment according to protocol. †Ref [19]; cyclophosphamide, vincristine, doxorubicin, dacarbazine.

Table 4. Development of metastases and local recurrence

	1967–1982	1983–1994
M ₀ (n = 24)	7/9	10/15
lungs only	5	4
bone only	1	4
both lung and bone	1	2
M ₀ local failure	1/9	9/15
never metastases	—	2
before metastases	—	2
concurrent or after metastases	1	5
M ₁ (n = 11) Local failure	1/5	1/6

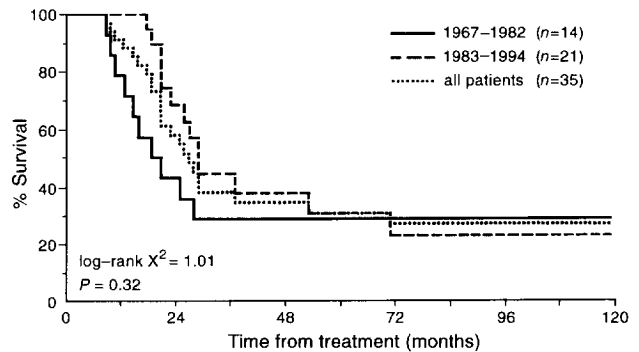


Figure 1. Survival of patients with Ewing's sarcoma 1967–1994 (n = 35).

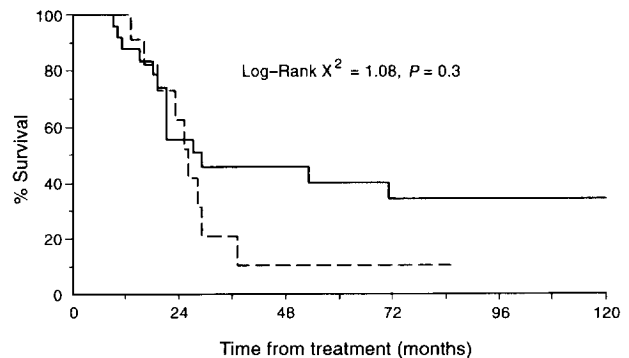


Figure 2. Survival curves of 24 (14 died) non-metastatic patients (M₀) (—) and 11 (9 died) metastatic patients (---).

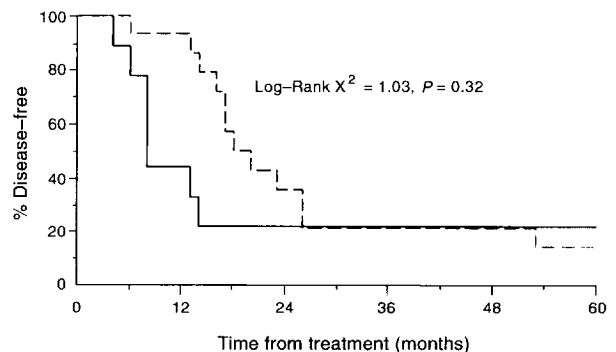


Figure 3. Disease-free survival of non-metastatic patients, 9 (7 died) in 1967–1982 (—) and 15 (12 died) in 1983–1994.

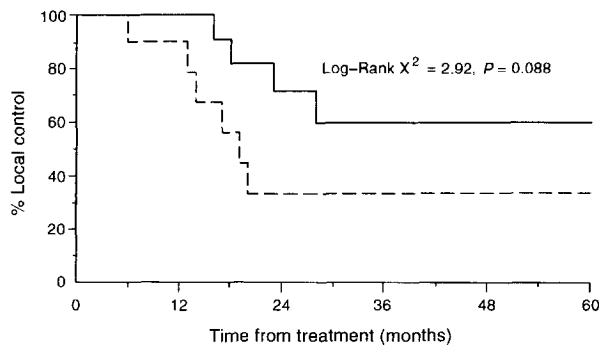


Figure 4. Local control in relation to length of neoadjuvant treatment, for 21 patients in 1983–1994 (15 M₀, 6 M1) ≤ 12 weeks, —, 4/11 relapses; > 12 week - - -, 6/10 local relapses.

6–28 months (median 18 months) after the start of treatment. In 1967–1982, several patients died within 18 months (6/14) and short follow-up might explain the lower rate of local failure. All but one failure were located in the os ilium, independent of tumour size above 100 ml (Table 2).

The interval between start of chemotherapy and start of local treatment was significantly longer in 1983–1994 compared with 1967–1982 on the basis of the protocol used (Table 3). In 4 patients in 1983–1994, neoadjuvant treatment lasted more than 18 weeks before local treatment, 3 had local recurrence and 1 died with no evidence of disease at 16 months (pt 14).

The mean duration of neoadjuvant chemotherapy before local treatment, as used in 1983–1994 was 11 weeks in patients without local relapse and 15 weeks in those with local failure. This trend for a better result after shorter neoadjuvant chemotherapy is shown in Figure 4 taking 12 weeks as a cut-off point, but the difference was not significant ($P = 0.09$).

The relationship between chemotherapy response and local result for 21 patients is shown in Table 5. All 4 patients with stable disease eventually developed local failure as did a third of the other patients. All available port films and planning CT scans were reviewed (28 patients). The target volume in relation to the tumour size at the start of radiotherapy was assessed. The target volume was judged as wide (2–5 cm margin) in 4 patients and adequate (1–2 cm margin) in 17 patients (8 local failures). In 6 patients, the field sizes were close (0–1 cm margin) (2 local failures) and in 1 patient inadequate, cutting through tumour (palliative case) (Table 6). However, comparison with the prechemotherapy CT scan showed that the original volume was covered inadequately in 4 patients, of whom 3 recurred locally.

No correlation could be established between dose of radiation and local failure as most patients had the same

Table 6. Radiotherapy field margins

	Wide	Adequate	Close	Inadequate
Evaluable ($n = 28$)	4	17	6	1
Local failure ($n = 11$)		8†	2‡	1

*wide, 2–5 cm margin; adequate, 1–2 cm margin; close, 0–1 cm margin; inadequate, no margin or cutting through tumour. ‡3 had inadequate prechemotherapy field, 2 recurred. †1 had inadequate prechemotherapy field and recurred.

dose, range 55–60 Gy. Only 3 patients in poor condition due to metastases had 40 Gy and 1 of these developed local failure (pt 12).

Treatment of metastases

Five non-metastatic patients developed lung metastases only. 3 patients had total lung RT, in 2 after metastasectomy and in 1 after chemotherapy, and 2 survived. 2 patients had metastasectomy with further chemotherapy and developed intrathoracic relapse. Of the 9 metastatic patients with lung metastases, who had received radiotherapy to the lungs as part of initial treatment, 3 did not have disease progression. 2 patients presented with bone metastases and died notwithstanding high-dose chemotherapy with ABMT in 1 patient.

Salvage treatment: in case of local relapse

1 patient with local relapse (pt 16) was salvaged by surgery, but he succumbed later to distant metastases. 2 patients died of local relapse without metastases notwithstanding further surgery and/or chemotherapy. Of the other 9 patients, 2 are alive with distant disease and 7 died.

Late effects and tolerance to radiation

Only 12 patients are currently alive, 3 with a follow-up of less than 24 months and 2 with a follow-up of less than 48 and 28 months with disease. Of the other 7 patients, 3 were less than 15 years of age at the time of treatment and 2 had relatively limited late effects: moderate fibrosis and scoliosis or mild leg shortening (2 cm) (pts 1 and 2), while patient 1 had breast hypoplasia, after lung irradiation and pt 2 developed a peroneus paresis. This patient gave birth to a child. Other survivors have little fibrosis and good function. Artificial menopause occurred in the 2 young women (pts 31 and 21). 1 patient developed femoral head necrosis (pt 20). One patient (pt 17, after surgery) had another operation for scoliosis. Short-term tolerance to irradiation was excellent when custom-made blocks for shielding of normal tissues was used. However, in some patients, moist desquamation of the vulva-perineum developed and healed.

DISCUSSION

Pelvic Ewing's sarcomas are known for their large size when diagnosed and for the frequency of metastases both at presentation and during the course of the disease. In the present series, 11/35 patients (31%) had metastases at presentation and subsequent metastases were found in 17/24 (71%). These are comparable to published rates given in recent literature. In our study, 4 of the 27 tumours were less than 10 cm³, which is the usual dividing line between 'small' and 'large' tumours for the CESS and EICESS trials [4]. Other authors refer to the largest diameter: in our cases 18/35 (51%) were 10 cm or more in size.

Table 5. Response to chemotherapy in 21 RT patients

	75% VR*	50% VR	25% VR	SD
Evaluable ($n = 21$)*	8	6	3	4
Local relapse ($n = 10$)	3†	2‡	1	4

*VR: volume reduction. †In 1 of 8 patients, the RT field did not cover prechemotherapy extension and this one recurred. ‡In 3 out of 6 patients, the RT field did not cover prechemotherapy extension and 2 recurred. not evaluable: surgery: 4 patients; no soft tissue component: 1 patient; early local treatment: 9 patients.

The reported survival rates for pelvic Ewing's sarcoma are consistently lower than that of distal or proximal lesions. The present study reports a 5-year survival rate of 31%. For pelvic Ewing's sarcoma, reported figures vary, according to overall survival or disease-free survival and M_0 or M_1 , from 19% to 55% [8, 10–13].

The incidence of local failure, a grave prognostic sign, was 12/35 = 34% in our study. After 1983 it amounted to 10/21 (48%), possibly due to longer observation time in these longer survivors. In the literature, Scully [7] reported 6/39 (15%), Evans (1985) [9] 27%, Capanna [11] 33% and Brown [9] 69%. Scully had the highest rate of surgery (19/39 = 49%), Evans, reporting IESS-I material, used wide, hemipelvis fields and concomitant start of local and systemic treatment. Capanna used concomitant treatment up to 1979 and thereafter neoadjuvant chemotherapy during 5 weeks only. Brown reported an older series, 1973–1984 and mentioned that local relapsing patients had a lower RT dose, 40–55 Gy.

The expectation that treatment results will improve with intensified and sophisticated treatment is only partially confirmed in our report. The applicability for surgery was very limited in our group, although all patients since 1983 were evaluated by the orthopaedic surgeon, the local treatment was radiotherapy in most patients. In view of the small numbers, differences in outcome can hardly reach significance. However, a review of treated patients will teach us where the problems are. This might benefit the approach of a new patient in such a rare localisation of a rare disease. The main differences in treatment between the 14 patients in 1967–1982 and 21 patients in 1983–1994 were the following: more intensive neoadjuvant chemotherapy; a longer interval between start of neoadjuvant chemotherapy and start of local treatment; and sophisticated radiotherapy with sparing of the uninvolved tissues as much as possible.

More intensive, neoadjuvant chemotherapy

In the two groups, the disease-free interval of relapsing patients was different, with a mean of 9 and 21 months, respectively, but the incidence of distant metastases was not different, being 7/9 (78%) and 10/15 (67%), before and after 1983. Therefore, the new chemotherapy was effective at delaying relapse but could not prevent its occurrence (Figure 3).

Longer interval between start of neoadjuvant chemotherapy and start of local treatment

The literature provides very few data on the relationship between duration of neoadjuvant chemotherapy and treatment results. The CESS 81 [5] protocol prescribed 18 weeks, the CESS 86 prescribed 9 weeks and the EICESS 92 [7] prescribed 12 weeks. The best local control was reported in the IESS-1 [14] and IESS-II [15] studies, where local treatment and chemotherapy started concomitantly. Also wide radiotherapy fields were used. In our cases, a shorter duration of neoadjuvant chemotherapy before local treatment showed a trend towards better local control (Figure 4), while very long chemotherapy was not favourable.

A good tumour response as judged by clinical or radiological criteria is a good prognostic sign according to some authors (Oberlin [16]). However, Dunst [6] reported no influence of tumour size or tumour regression after neoadjuvant treatment of 9 weeks in patients treated with radiotherapy. In our cases, all 4 patients with stable disease and 1

of 3 with 25% volume reduction had a local failure. Of 14 patients with 75–50% volume reduction, 5 still had local failure. In 4 patients, the radiotherapy field did not cover the prechemotherapy extension and 3 of these recurred.

Sophisticated radiotherapy with sparing of uninvolved tissues as much as possible

Improvements in radiotherapy techniques aim to increase the normal tissue sparing, for instance by using oblique incident beams, wedges and individualised blocks. These blocks are based on tumour plus margin contouring in each slice of the planning CT scan, which is taken in the treatment position, often prone, shortly before the start of radiotherapy. To delineate the tumour, a comparison is needed 'slice by slice' with the pretreatment CT scan, usually supine and not always of good quality and if available with MRI. Interpretation of tumour soft tissue mass versus normal but displaced structures may not be easy, especially if the pretreatment scan is asymmetrical because the patient could not lie straight due to the tumour bulge or to pain. The usual prescription is to take margins around the prechemotherapy tumour, including the full bone and 5 cm in the length and 2–3 cm horizontally around the soft tissue mass. However, for pelvic and thoracic tumours, it is assumed that these are compressing normal tissues and not infiltrating them and that a 2 cm margin around the postchemotherapy volume is allowed [17]. Such carefully designed treatment volumes excluding as much of the bladder and rectum and gonadal organs as seems justified, certainly create very good tolerance to the irradiation with practically no immediate side-effects during the treatment. The development of fibrosis remains limited if adequate physiotherapy to activate joints and muscles is applied. Growth defects may also be limited particularly as many patients are beyond puberty.

However, in our review of various scans and the actual target volume chosen, we judged 6 patients as having close margins (Table 6). 2 of these patients developed local failure, of whom in one the fields did not cover the prechemotherapy volume (pt 16). No local failure occurred in the 4 patients with wide fields. The general goal was to have an 'adequate' postchemotherapy coverage (1–2 cm margin). However, in this group 8/17 local failures occurred. In 3 of these the radiotherapy field did not cover the prechemotherapy volume and 2 recurred. The 'close' margins are often dictated by shielding of normal structures (e.g. a replaced ovary) or because of difficulties in interpretation of the imaging material. Inadequate coverage of prechemotherapy extension is in agreement with ours and other protocols and results in less acute and late side-effects. The pressure to reduce the treatment volume is therefore high.

Some articles postulate that local relapse occurring 'centrally' in the irradiated area cannot be due to missing the site. We tend to doubt this (Figure 5). If soft tissue masses were infiltrated, invisible tumour remnants around the postchemotherapy volume may persist. The recurrence would only be detectable after reaching a size of several centimetres and then necessarily have extended into the original target volume. It will then be interpreted as a central recurrence inside the irradiated volume. On the basis of our results, we think that 'adequate' postchemotherapy target volumes should have a wider margin taking the prechemotherapy volume and the imaging interpretation problems into account.

Treatment of metastases

Of the 14 patients with lung metastases only, 9 at presentation and 5 later on, 12 had a total lung irradiation in the treatment schedule, and 5 of these survived with no evidence

of disease (42%). This confirms the observation of Dunst [18] that total lung irradiation to at least 18–20 Gy may lead to survival. The 2 patients in our series who had metastasectomy and chemotherapy without irradiation both developed intrathoracic relapse (16, 21). Patients with bone metastases or local relapses have not been salvaged in our cases.

Future developments in local treatment

Our moderate results tend to support the instruction in the modern treatment protocols such as EICESS 92 [7] to combine, if technically possible, radiotherapy and surgery in case of poor response to chemotherapy and not to delay local treatment. The EICESS 92 protocol advocates pre-operative radiotherapy at week 6 in such cases.

There is no definitive proof yet that surgery gives better results than radiation therapy or vice versa. Against the functional loss after surgery one must weigh the long-term functional loss and chance of second malignancies after radiotherapy. However, the incidence of a second malignancy is estimated as relatively low in Ewing's sarcoma (1–5%). In inoperable cases, the addition of hyperthermia to radiation could be explored. On the basis of our review, it seems necessary to increase the margins and cover postchemotherapy volume at least with several centimetres. Any infiltrated muscles or fibrous tissues should be included together with the whole bone.

In conclusion over a period of 27 years, 35 patients with pelvic Ewing sarcoma were treated with a 5-year survival of 31%. Frequency of metastases and large size of primary tumours are the main causes for this limited success. More intensive chemotherapy postponed recurrence, but did not prevent it. Local control tended to be better in patients with a shorter duration of neoadjuvant chemotherapy before local treatment. Response to chemotherapy should be evaluated early and local treatment intensified if possible. Pre-operative radiotherapy in suitable cases, after a short period of neoadjuvant chemotherapy, should be further explored. Modern radiotherapy techniques tend to reduce normal tissue radiation effects with good success, but may lead to sparing of tumour infiltrated tissues, which on CT scans and MRI were not suspected. The patients with very wide local radiation fields and total lung irradiation together with relatively short neoadjuvant chemotherapy did best.

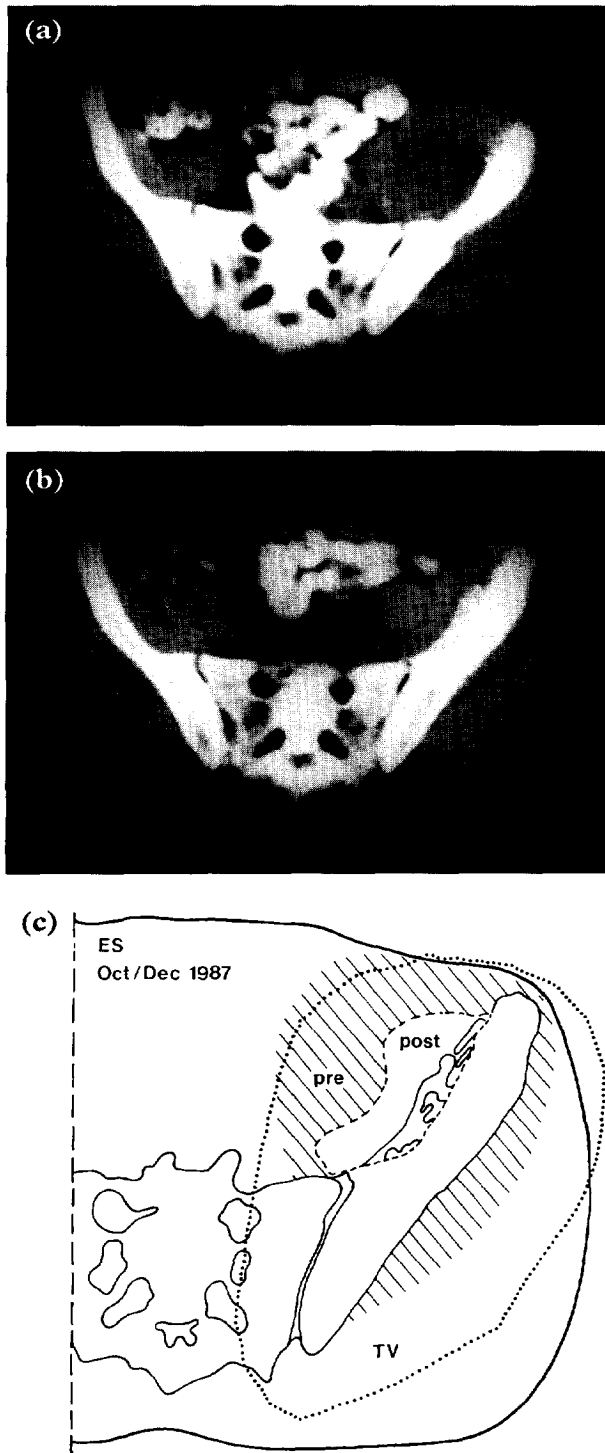


Figure 5. (a) CT scan of patient 18 before chemotherapy. (b) Same level CT scan of patient 18 after neoadjuvant chemotherapy, showing considerable regression of soft tissue component of tumour. (c) Target volume, contoured in treatment CT scan at same level, showing adequate coverage of postchemotherapy volume but not fully including the pre-chemotherapy extent.

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