Pergamon

European Journal of Cancer Vol. 33, No. 7, pp. 1061–1069, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00043-9

Original Paper

Long-term Results from the First UKCCSG Ewing's Tumour Study (ET-1)

A.W. Craft,[1] S.J. Cotterill,[1] J.A. Bullimore[2] and D. Pearson[3] on behalf of the United Kingdom Children's Cancer Study Group (UKCCSG) and the Medical Research Council Bone Sarcoma Working Party

[1]Department of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP; [2]The Royal Hospital for Sick Children, Bristol; and [3]The Christie Hospital, Manchester, U.K.

The aim of this study was to evaluate multimodal chemotherapy and radiotherapy in patients with Ewing's sarcoma. 142 (74 male, 68 female) patients were entered into the ET-1 study between 1978 and 1986. They were treated with vincristine, doxorubicin, actinomycin D, and cyclophosphamide with radiotherapy plus or minus surgery to the primary tumour. Of the 120 who had no metastases at diagnosis, 45 remain alive with a median follow-up of 11.2 years. Only 2 of those with metastases at diagnosis remain alive. The major prognostic factor was site of disease, but age and serum lactic dehydrogenase at diagnosis also had an influence on outcome. 45 of the 61 patients who survived 4 years or more had late effects documented. The type and extent were dependent on tumour site, type of local therapy, volume and dose of radiotherapy. 4 patients had second malignancies. Prospects for long-term survival have improved in patients treated for Ewing's sarcoma. However, late sequelae are present in the majority of patients. © **1997 Elsevier Science Ltd.**

Key words: Ewing's sarcoma, late effects

Eur J Cancer, Vol. 33, No. 7, pp. 1061–1069, 1997

INTRODUCTION

In 1978 the first national Ewing's Tumour Study (ET-1) commenced in the U.K. under the auspices of the United Kingdom Children's Cancer Study Group. Initially it involved only patients treated at paediatric oncology centres, but later was extended to include adult patients under the remit of the Medical Research Council Bone Sarcoma Working Party. It was designed as a non-randomised study with the aim of utilising the four most effective drugs and radiotherapy to maximum potential. It was based on the preliminary data from the first Intergroup study in the United States [1] who have more recently reported on their long-term follow-up results [2]. Preliminary results of ET-1 have been reported [3]. The purpose of this paper is to report in more detail the results of the study along with late follow-up including the long-term sequelae of treatment.

Correspondence to A.W. Craft.
Received 23 May 1996; revised 9 Jan. 1997; accepted 13 Jan. 1997.

PATIENTS AND METHODS

Protocol description

The protocol was designed to utilise what was considered to be at that time the maximum tolerated doses of chemotherapy and radiotherapy. There was no separate protocol for patients with metastatic disease at presentation. Initial investigations included biopsy of the primary tumour for which central review was undertaken. An X-ray of the primary tumour, chest X-ray, whole lung tomography or CT scan, and whole body isotope bone scan were recommended.

Induction chemotherapy (Figure 1) commenced with vincristine, doxorubicin and cyclophosphamide, with additional vincristine on days 8 and 15. At the discretion of the physician, a second course was administered prior to local therapy for patients considered to have a good response to the first course of chemotherapy.

Radiotherapy recommendations depended on primary site, although it was recognised that complete standardisation was not possible. Radiotherapy was scheduled over a three-week period. Guidelines were 45 Gy for tumours of

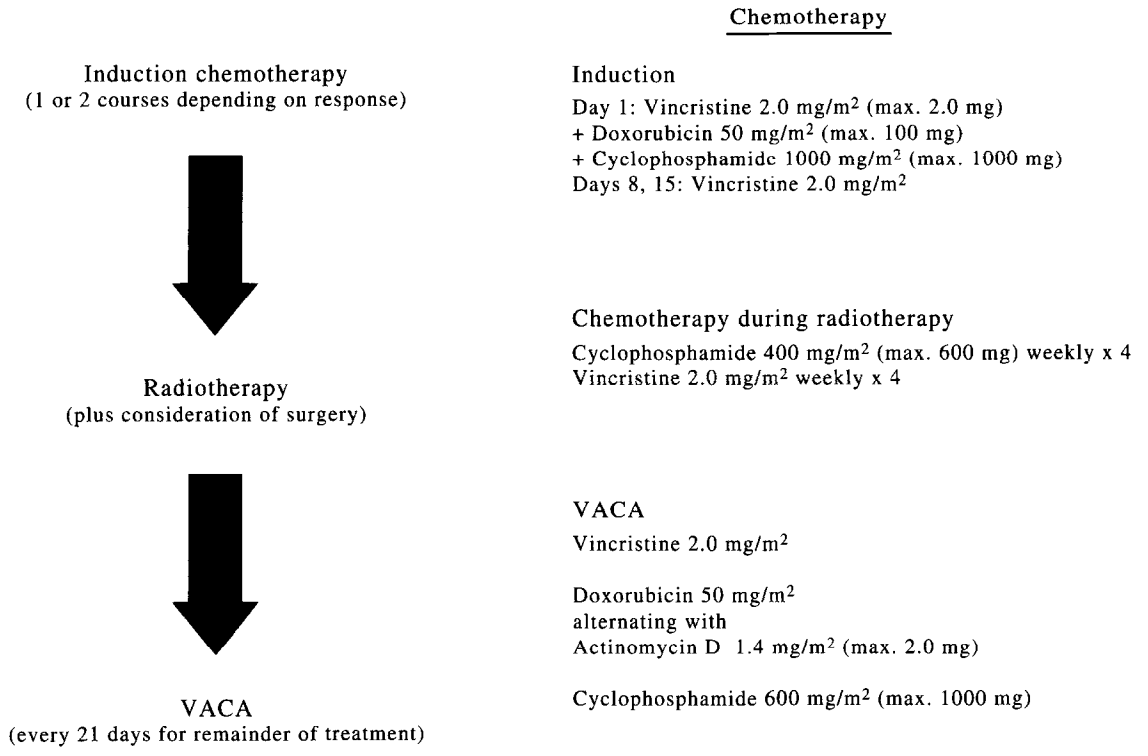

Figure 1. Summary of treatment.

the long bones to include the whole bone, and 25 Gy for rib primaries. Pelvic tumours were to receive 30 Gy with fields covering the hemipelvis and whole sacrum where appropriate. For all tumours, an additional boost of 10–15 Gy to the tumour site was recommended. Doses for primary tumours of the spine depended on the length of the field, 40 Gy were recommended for fields of less than 15 cm, and 32.5 Gy for fields of 15 cm or more, both given over 3 weeks. The field was to cover an uninvolved vertebra above and below the tumour-bearing area. Surgery to the primary tumour was considered where clinically indicated, depending upon the site and age of the patient. When there was definitive surgery to the primary tumour, local radiotherapy could also be given, or withheld at the discretion of the physician.

During radiotherapy, vincristine and cyclophosphamide were given weekly. Following local therapy, chemotherapy with vincristine, doxorubicin and cyclophosphamide was alternated every three weeks with vincristine, actinomycin D and cyclophosphamide. After the cumulative dose of doxorubicin reached 300 mg/m^2, it was omitted from further courses. Chemotherapy was initially planned for two years but was reduced to one year during the course of the study.

Patients

Patients less than 40 years of age with previously untreated biopsy-proven Ewing's tumour of bone were eli-

Table 1. *Survival by primary site and presence of detectable metastases at diagnosis*

Primary site		No metastases		Metastases		Total	
		n	alive	*n*	alive	*n*	alive
Pelvis	Pelvis	23	3	6	1	29	4
Other axial	Spine	15	8	3	0	18	8
	Rib	15	5	4	0	19	5
	Skull	4	1	–	–	4	1
	Scapula	3	0	1	0	4	0
	Clavicle	2	0	–	–	2	0
Extremities	Femur	22	11	3	0	25	11
	Fibula	14	5	2	0	16	5
	Tibia	13	7	1	0	14	7
	Humerus	5	3	–	–	5	3
	Foot	4	2	1	0	5	2
	Hand	–	–	1	1	1	1
All sites	Total	120	45	22	2	142	47

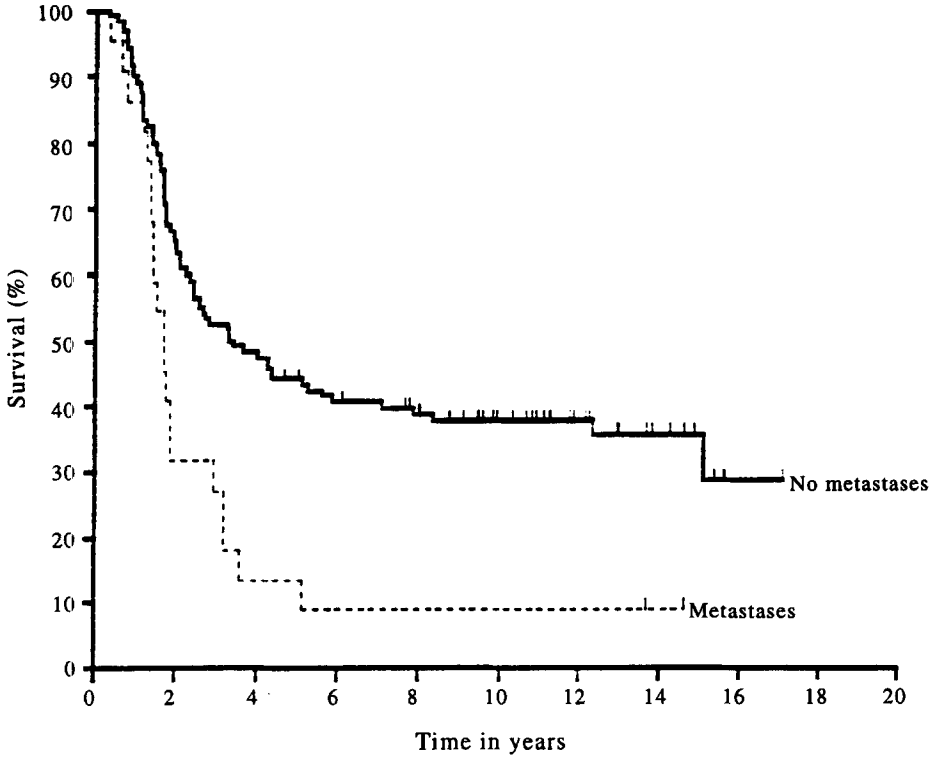

Figure 2. Survival by metastases at diagnosis.

gible for the study. Between 1978 and 1986, 142 patients (74 male, 68 female) were entered into the study. The ages at diagnosis ranged from 1 to 33 years (median 12 years), 25 patients were aged 16 years or more. The length of symptoms prior to biopsy ranged from 2 weeks to 3 years (median 3 months). The primary site and presence or otherwise of metastases is shown in Table 1. Of those patients with metastases at diagnosis, 10 had lung metastases only, 7 bone only, 1 liver, 1 kidney, the remaining 3 had a combination of sites.

Anaylsis was performed on an intention to treat basis. Survival and relapse-free survival were calculated using

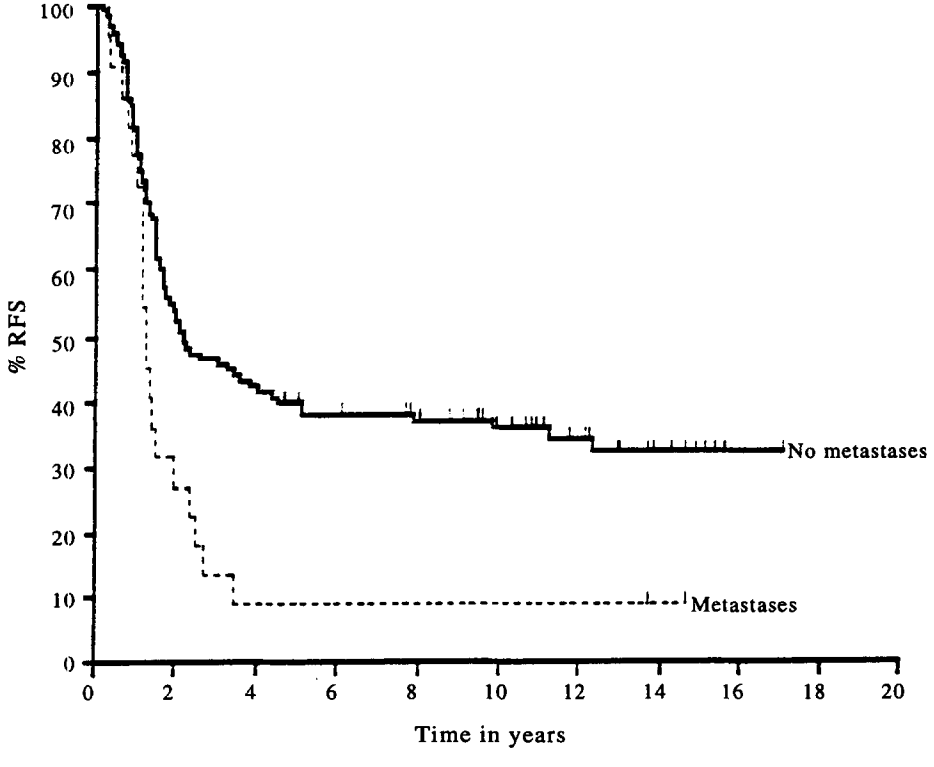

Figure 3. Relapse-free survival by metastases at diagnosis.

Table 2. Key survival and relapse-free survival results with 95% confidence limits

Group	*n*	5 year survival %	10 year survival %	5 year RFS %	10 year RFS %
All patients	142	39 (31–47)	33 (26–41)	36 (28–44)	33 (25–41)
Metastatic	22	14 (0–28)	9 (0–21)	9 (0–21)	9 (0–21)
No metastases	120	44 (35–53)	38 (29–47)	41 (32–49)	37 (29–46)
Pelvic	23	17 (2–33)	13 (0–27)	13 (0–27)	13 (0–27)
Other axial	39	46 (31–62)	37 (22–53)	38 (23–54)	36 (21–51)
Extremities	58	53 (41–66)	50 (37–62)	52 (39–65)	48 (35–61)

Kaplan–Meier estimation [4], and multivariate analysis was carried out using a proportional hazards model [5] taking 0.05 as the level of significance.

RESULTS

Of the 142 patients entered into the study, 45 of the 120 who had no metastases at diagnosis remain alive with a median follow-up of 11.2 years (range 4.7–17 years). Of the 22 who had metastatic disease, 2 are still alive. Of these the first was a 12 year old girl with a primary in the left thumb and lung metastases who remains disease free at 13 years after diagnosis. The second was an 11 year old boy with a pelvic primary and a kidney metastasis who remains disease free at 14 years after diagnosis. 8 patients had bone metastases at diagnosis, none of whom survived beyond 38 months from diagnosis. Survival (S) and relapse-free survival (RFS) are shown in Figures 2 and 3 for patients who were metastatic and non-metastatic at diagnosis. The key results are tabulated in Table 2. In a proportional hazards analysis of patients without metastases at diagnosis, site and, to a lesser extent, age had a significant influence on outcome. Sex and length of symptoms before diagnosis were not significant. In particular, pelvic sites had a poor prognosis with only 3 of 23 surviving ($p = 0.02$). Age was marginally significant, those aged over 16 had a poorer prognosis compared with younger patients (5 year RFS 43% versus 24%). Further analysis using the log-rank test, comparing those under or over 10 years, showed RFS was identical ($p = 0.9$). There was a non-significant trend for better survival for those under 10 years with limb tumours (RFS 64% versus 44%, $p = 0.2$) but this was balanced by a superior outcome for older patients with axial tumours (RFS 35% versus 18%, $p = 0.2$). There was no significant difference in RFS with regard to gender (female 34%, male 47%, $p = 0.3$).

There were 5 treatment-related deaths. 4 patients died during chemotherapy, 3 from pneumonia at 4, 10, and 13 months, respectively, and 1 following left ventricular failure at 15 months. There was also a death at 12 years from the original diagnosis due to a secondary osteosarcoma which was thought to be radiation induced. In addition, there were two deaths due to other causes, one as a result of a swimming accident in a young man aged 19 years who was originally diagnosed with a tibial primary at 12 years old. The other was a 12 year old girl who died 11 months after diagnosis of a vertebral primary from hyperviscosity syndrome related to secondary AML (acute myeloid leukaemia). The original diagnosis of Ewing's sarcoma was confirmed with immunohistochemical tests that excluded a myeloid origin of the initial vertebral tumour.

Induction chemotherapy

The number of courses of "Induction" chemotherapy given prior to local therapy was recorded for 122 patients. 46 patients had one course, 60 had two courses, and 15 went on to have more than 2 courses, 1 patient received radiotherapy prior to any chemotherapy because of a 3 year history of symptoms. A proportional hazard analysis showed that, for all patients, the number of induction courses had no significant effect on outcome. For those without metastases having one course compared to those having two courses, the 10 year RFS was 37% versus 39% ($p = 0.9$). However, those patients with axial primary tumours who had two courses had a better 10 year RFS than those with one, 35% versus 9%, but this did not reach statistical sig-

Table 3. Type of local therapy by primary site

Local therapy	RT alone	RT + Surgery	Surgery alone	Total
Metastases at diagnosis	20	2	–	22
Met. free	88	24	8	120
Pelvis	22	1	–	23
Spine	14	1	–	15
Rib	7	7	1	15
Skull	3	1	–	4
Scapula	3	–	–	3
Clavicle	1	1	–	2
Femur	16	5	1	22
Tibia	9	2	2	13
Fibula	8	3	3	14
Humerus	3	2	–	5
Other extremity	2	1	1	4
Total	108	26	8	142

Table 4. Event-free survival with 95% CI by local therapy for patients free of metastases at diagnosis

	RT alone			Surgery ± RT		
Group	*n*	5 year RFS %	10 year RFS %	*n*	5 year RFS %	10 year RFS %
Axial sites	50	30 (17–43)	26 (14–38)	12	25 (1–50)	25 (1–50)
Other sites	38	47 (31–63)	42 (26–57)	20	65 (44–86)	65 (44–86)
All sites	88	38 (27–48)	33 (23–43)	32	50 (33–67)	50 (33–67)

nificance ($p = 0.5$). For non-axial tumours, there was no difference (45% versus 45%, $p = 0.9$).

Local therapy

The type of local therapy according to site is shown in Table 3. Three patients had amputations, two with tibia and one with fibula primaries. The relapse-free survival according to local therapy and site for patients free of metastases at diagnosis is shown in Table 4. The type of first relapse according to site of local therapy is shown in Table 5. In addition, 17 patients had second relapses, of which 3 were local (1 pelvis, 2 femur), while the remainder were systemic. 36 (33%) of the 108 patients who had radiotherapy alone had a local relapse compared with only 3 of 31 (10%) who had a resection with or without radiotherapy ($\chi^2 = 5.6$, 1df, $p < 0.02$). Of those with axial disease, the local relapse rate was 38% (24/63) for radiotherapy alone compared with 8% (1/13) for those who had a resection. For all other sites, it was 27% (12/45) for radiotherapy alone and 11% (3/31) for resection.

76 patients had metastic relapse. Only 2 remain alive and both of these had late relapses at 9 and 11 years from diagnosis.

There was no difference to RFS for patients free of metastases at diagnosis according to whether they were diagnosed in the first or second half of the study period, i.e. up to 1981 or 1982 and later. The duration of chemotherapy was reduced from two years in the first period to one year in the second period. There was no significant difference between the two periods (10 year RFS 37% versus 35%, $p = 0.9$). Out of 22 patients with metastases, there were 2 survivors, both of whom were diagnosed prior to 1982.

Levels of lactic dehydrogenase (LDH) were recorded at diagnosis for 98 patients who were free of metastases. There was no significant difference between patients with LDH levels in the normal age-related range compared to those with elevated levels (5 year RFS 37% versus 37%). There was a suggestion that patients with extremely elevated levels had a poorer prognosis. There were 11 patients with levels of >600 IU, and 87 <600 IU (5 year RFS 18% versus 43%, $p = 0.04$).

Late effects of treatment

Details of late effects of treatment were requested during regular follow-ups. 45 out of 61 patients surviving beyond 4 years had late effects documented, and those are detailed in Appendix 1. A summary of the late effects is given in Table 6.

The type and extent of late effects may depend on the tumour site, the type of surgery, volume and dose of radiotherapy, and the patient's age during treatment [6]. 28 patients with tumours of the lower extremities who survived for 4 years or more were assessed for leg function using a scheme based on that developed by Jentzch and associates [7]. Out of the 28, there were 5 patients following radiotherapy who were classed as having severe grade 4 problems (greater than 4 cm length discrepancy or complications requiring surgery). 6 had moderate, grade 2 (shortening up to 2.5 cm), and 12 had only minimal or no late effects (grade 1). Two had amputations and no information was available for 3 patients.

4 patients have had second malignancies. The first was a 14 year old girl with a tibia primary at diagnosis who developed an osteosarcoma 10 years after the original diagnosis. This was in the tibia distal to the original tumour site on the margin of the radiotherapy field. She is alive and well 17 months after diagnosis of osteosarcoma. The second was a 5 year old boy with a humerus primary, who developed an osteosarcoma in the radiation field. This was discovered 11 years after the original diagnosis, and the patient died a year later. The third patient was a 12 year old girl with a femur primary who after 13 years had a pleomorphic rhabdomyosarcoma arising within the radiation field. This was excised, but recurred a year later. After a further excision and treatment with combination chemotherapy she remains alive and well. The fourth had secondary AML and died 11 months after diagnosis of the primary tumour.

DISCUSSION

The ET-1 protocol was designed as the first standardised protocol of therapy for use throughout the U.K. There had been single institutional or limited multicentre reports, in particular, those from the London Children's Solid Tumour Group. There had been previous reports from the United States, and those by Rosen and his colleagues from the

Table 5. Site of first relapse by local therapy

Group	Relapse free	Local relapse	Systemic relapse	Combined local + systemic	Total
Radiotherapy alone	38	23	37	10	108
Resection (no RT)	2	1	2	0	5
Amputation (no RT)	2	–	1	–	3
Surgery + RT	12	2	11	0	25
RT + surgery + RT	0	0	1	0	1
Total	54	26	52	10	142

Table 6. Summary of late effects reported in 61 patients surviving >4 years

Late sequelae	Number	% of total
Cardiomyopathy	5	8.2
Gonadal injury	4	6.6
Second malignancies	3	4.9
Atrophy/shortening/wasting	27	44.3
Limited joint movement	5	8.2
Other problems	17	27.8
All patients with late sequelae	45	73.4

Memorial Sloan Kettering Hospital in New York were notable in defining that the best drugs available for Ewing's tumour were vincristine, doxorubicin, actinomycin D and cyclophosphamide [8]. In planning the ET-1 study, we had access to the preliminary results of the Intergroup Ewing's Sarcoma Study which had shown that the addition of doxorubicin or lung irradiation to the other three standard drugs produced better survival than when these agents were not given [1]. Because of the probable late effects of radiotherapy on lung function, we opted to use all four drugs and no lung irradiation for ET-1. The results of ET-1 confirm that multimodal therapy is effective treatment for patients with Ewing's sarcoma. For patients with no detectable metastases, the significant prognostic factor of site of disease was also confirmed with pelvis quite clearly being the worst, with non-pelvic axial sites and limb primary tumours having a more favourable outlook. Those of 16 years and older fared less well. The toxic death rate in this study of 3.5% is comparable to other similar intensive chemotherapy regimens given during the same period. The reduction of total treatment from 2 years to 1 year did not appear to reduce the overall survival. In general, in paediatric oncology there is a trend towards shorter treatment, and these results lend support to this.

One of the initial aims had been to study the possibility that more than one course of "induction" therapy prior to local therapy might be beneficial. Overall, a second or even more courses were not beneficial, but for pelvic tumours there was a trend towards better survival (9% versus 35%), although because of small numbers this did not reach significance. However, it would be logical for this subgroup to benefit from intensified induction chemotherapy given that pelvic tumours are generally the larger tumours with both the highest rate of local as well as distant relapse. The treatment of Ewing's tumour is a combination of both optimal local and systemic therapy, and it is important that a balance is achieved to ensure that the treatment of local disease does not compromise that of the systemic component, and vice versa. The lack of survivors after systemic relapse makes it clear that optimum initial systemic treatment needs to be given. When ET-1 commenced, the optimal local therapy was thought to be a maximally tolerated dose of radiotherapy. However, it was accepted that surgery was possible, but initially it was envisaged only for "expendable" bones such as fibula and clavicle. During the course of the study from 1978 to 1986, endoprosthetic surgery began to be performed. There were potential advantages of endoprosthetic surgery over the conventional surgery, i.e. amputation and over local radiotherapy. The endoprosthetic surgery was cosmetically better than amputation and it was hoped that function might also be improved. Radiotherapy was known, even in the 1970s, to cause late effects such as limb shortening and later fracture through the involved bone. It was, therefore, on the basis of function, appearance

Table 7. Comparison of studies: non-metastatic Ewing's sarcoma

	IESS-1 [1]	Bologna [11]	ET-1	CESS-81 [12]
Recruitment period	1973–1978	1972–1982	1978–1986	1981–1985
Multicentre	y	n	y	y
Randomised	y	n	n	n
Additional eligibility criteria	–	–	age < 35	age < 25 excludes PNET
Number of patients	331	144	120	93
Percentage pelvic	19%	20.8%	19.2%	15.8%
M:F	1.64:1	1.52:1	1.26:1	1.43:1
Median age (range)	13	13*	12 (1–33)	13 (2–23)
Protocol 1	VACA	VACA	VACA	VACA
Protocol 2	VActC	VAdrC	–	–
Protocol 3	VAC + lung RT	–	–	–
Radiotherapy alone	79%†	60%	73%	34%
Surgery ± RT	21%	40%	27%	66%
Median FU at publication	6 years	9 years (5–16)	11.2 (4.7–12)	9 years (1–11)§
RFS (VACA only)	60% (5 years)	54% (CDF)	41% (5 years)	54% (5 years)
Toxic deaths	0	n.s.	5	0
Second malignancies	n.s.	4	4	n.s.
Significant prognostic factors	VACA arm Non-pelvic age‡	VACA arm Non-axial surgery	Non-pelvic	T. Vol < 100 Distal sites Surgery Hist response
Local relapse rate				
RT alone	n.s.	36%	32%	47%
Surgery ± RT	n.s.	8%	6%	12%

*Estimated (75 are below age 14 years and 69 are over 14 years).
†There was a greater use of surgery on VACA arm (68% RT alone versus 32% surgery).
‡At the initial publication, sex and time between symptoms and diagnosis were significant.
§At time of interim analysis, 1 July 1995.
n.s., not stated; FU, follow-up; RFS, relapse-free survival.

Table 8. Comparison of studies: prognostic factors for non-metastatic Ewing's sarcoma

	IESS-1 [1]	Bologna [11]	ET-1	CESS-81
	Protocols 1 and 3 only			
Analysis	5 year RFS %	Actual CDF %	5 year RFS %	5 year RFS‖ %
Male	52	38	34	50
Female	56	45	57	59
Age <15	41*	40†	43	62
Age 15+	43	42	31	38
Age <10	66		44	66
Age 10–15	50	n.s.	44‡	56
Age >15	43		24	38
Axial	50*		29	50
Proximal	48	n.s.	56	45
Distal	67		48	62
Pelvis	23	23	14	40
Other	39*	46	45	56
Axial	50*	32	29	50
Other	58*	47	52	56
Radiotherapy alone	n.s.	28	36	44
Surgery ± RT§		60	50	60
Time from symptoms to diagnosis				
<1 month	63		13¶	
1–3 months	57	n.s.	44	n.s.
>3 months	46		39	

*Based on (relapses/no. of patients), not Kaplan–Meier estimates.
†For age <14 versus >14.
‡10 year RFS for ages <10, 10–15, >15 are 44%, 34%, 24%, respectively.
§Tumours that are more amenable to surgery are associated with favourable sites and smaller tumour volumes.
¶Based on only 8 patients.
‖Interim analysis, 1 July 1995.
n.s., not stated; CDF, continuously disease free.

and possible late effects that surgery was progressively introduced into the therapy of Ewing's sarcoma. It was not expected to make any difference to disease outcome or survival. A quarter of the patients in the ET-1 study had surgery and, although the local relapse rate was lower and survival better for those that had surgery, this cannot be inferred to mean that surgery in itself confers a survival advantage. Surgery is not possible for all tumours. Those that are amenable to surgery are the smaller and more accessible tumours and these inherently have the best prognosis. It would need a randomised trial of surgery against radiotherapy to evaluate any survival benefit from one or the other. The optimum method of local treatment remains uncertain. The re-emerging role of surgery has been reviewed by O'Connor and Pritchard [9], and they emphasise the various factors which need to be considered, i.e. optimum local disease control, risk of late effects (pathological fracture and second malignancy) and functional outcome. The Bologna group have also considered optimum local treatment and emphasise the benefit of surgery as a means of assessing response to initial local therapy [10].

Concurrent studies utilising almost identical protocols were undertaken in the U.S.A [1], Bologna [11], and in a German multi-institutional co-operative group (CESS) [12]. Tables 7 and 8 compare the findings of ET-1 with these three other studies. A single institutional report from Milan [13] used only three drugs, omitting actinomycin D, and the results are therefore not included in the tables.

There are no clear-cut explanations as to why there should be differences in survival using very similar regimens in different countries, but it may reflect differences in clinical practice, experience of supportive care, or differences in dose intensity of chemotherapy. The CESS group significantly improved survival in their studies both over time, indicating greater clinical experience, and by the use of centralised radiotherapy planning. It is unlikely that the latter was a reason for the differences in survival of ET-1 and CESS-81 as the local relapse rate, clearly dependent on quality of radiotherapy, was higher in the German than the U.K. study. Also dose intensities differed between protocols; the cyclophosphamide dose in the IESS-1 was 500 mg/m^2 for the first 6 weeks; in the Bologna study it varied between 600 and 1000 mg/m^2 depending on the patient subgroup; in ET-1 600 mg/m^2, and in CESS-81 1200 mg/m^2. The doxorubicin dose was also higher in the CESS-81 study and this, in particular, may be responsible for the inferior survival of patients with lung metastases at diagnosis in ET-1. These variations in survival may potentially relate to differing dose intensities. Smith and associates [14] reviewed published trial data on Ewing's sarcoma and concluded that doxorubicin dose intensity was a very important predictor of outcome. Over one third of the patients in ET-1 had a single dose of doxorubicin followed by an extended break from this drug during definitive treatment of the primary. However, it is not possible to distinguish between this and other potential differences such as those in clinical practice and supportive care, patient selection, length of follow-up and other factors. These differing results once again emphasise the need for randomised studies to determine differences in outcome.

The median follow-up for survivors in the present report of ET-1 is 11 years and this is longer than any of the other reported studies. As can be seen from the RFS and survival data, late relapses and deaths are an issue in Ewing's

tumour. In addition, the late events of second malignancies and deaths from cardiac disease must also be considered when looking at the overall survival from this disease.

The late effects of treatment of childhood cancer are being increasingly recognised and the ET-1 study gives an ideal opportunity to report on such effects in children and young people who have received multimodal therapy. Only 27% of the long-term survivors had no late sequelae reported. Appendix 1 gives a catalogue of problems, many of which are not unique to Ewing's tumour, but are inevitable consequences of multimodal cancer therapy, although the late orthopaedic complications are unique to bone and soft tissue tumours of the extremities. As can be seen, many of the survivors suffered from serious late sequelae requiring further surgery and occasional amputation. Of the 22 patients with primary tumours of the lower limb, over a third had clinically important late effects according to the classification of Jentzch and associates [7]. Late cardiotoxicity was seen in 12% of the 5 year survivors, presumably as a result of doxorubicin therapy, although this may have been compounded by both cyclophosphamide treatment as well as local radiotherapy. These longitudinal data are based on reporting of late effects requested on periodic follow-up forms; it is possible that a more systemic cross-sectional study might reveal a higher incidence of cardiotoxicity and gonadal injury.

Second malignancies have so far occurred in 4 patients, 3 of them sarcomas in the irradiated field. This is a well-recognised late effect and is one for which both the incidence and the mortality may well not be as yet fully determined. The most recent report from the Late Effects Study Group shows a continually increasing incidence of second primary tumours even 30 years or more after the initial treatment [15]. Alkylating agents, in this case cyclophosphamide, are also a risk factor both for sarcoma and AML.

The ET-1 study has confirmed the importance of chemotherapy and radiotherapy in the management of Ewing's sarcoma. However, at best, only approximately half the patients can be expected to be long-term survivors when treated with the four drugs used and radiotherapy with or without surgery. Better chemotherapy is needed if more patients are to survive, and over the past 10 years better supportive care has allowed an increase in dose intensity, and cyclophosphamide has been replaced with ifosfamide. More recent results do show improvements in survival even though follow-up is short [3]. The study has also shown a disturbingly high incidence of late effects. Very few patients are surviving with little or no sequelae. In future studies, the possible late effects need to be contemplated and anticipated during the planning phase and every measure taken to minimise them. Infusion of doxorubicin may be less cardiotoxic than bolus injection [16] and cardioprotective agents are being actively pursued. The increased use of endoprosthetic surgery may minimise the use of radiotherapy and hence the late functional sequelae of the latter and second primary tumours, but such surgery brings with it its own complications [17]. Whether or not such surgery is superior to amputation would be worthy of a randomised trial, but given the current enthusiasm by surgeons, oncologists and patients alike such a trial is unlikely to be undertaken in the foreseeable future.

Future studies require improvement in survival with less cost

1. Nesbit ME, Perez CA, Tefft M, *et al.* Multimodal therapy for the management of primary, non-metastatic Ewing's sarcoma: An Intergroup Study. *NCI Monograph* 1981, **56**, 255–262.
2. 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.
3. Craft AW, Cotterill S, Imeson J. Improvement in survival for Ewing's sarcoma by substitution of ifosfamide for cyclophosphamide. *Am J Pediatr Hematol* (Suppl A) 1993, **15**, S31–S35.
4. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
5. Cox DR, Oakes D . *Analysis of Survival Data* London, Chapman and Hall, 1984.
6. Potter R, Kuhnen C, Ritter J, *et al.* Side-effects after combination therapy for Ewing's sarcoma. *Recent Results Cancer Res* 1993, **130**, 251–258.
7. Jentzsch K, *et al.* Leg Function after Radiotherapy for Ewing's Sarcoma. *Cancer* 1981, **47**, 1267–1278.
8. Rosen G, Caparros B, Mosende C, *et al.* Curability of Ewing's sarcoma and consideration for therapeutic trials. *Cancer* 1978, **41**, 888–899.
9. O'Connor MI, Pritchard DJ. Ewing's sarcoma. Prognostic factors, disease control and the re-emerging role of surgical treatment. *Clin Orthop Rel Res* 1991, **262**, 78–87.
10. Picci P, Rougraff BT, Bacci G, *et al.* Prognostic significance of histological response to chemotherapy in non metastatic Ewing's sarcoma of the extremities. *J Clin Oncol* 1993, **11**, 1763–1769.
11. Bacci G, Toni A, Avella M, *et al.* Long-term results in 144 localised Ewing's sarcoma patients treated with combined therapy. *Cancer* 1989, **63**, 1477–1486.
12. Jurgens H, Exner U, Gadner H, *et al.* Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6 year experience of a European cooperative trial. *Cancer* 1988, **61**, 23–32.
13. Gasparini M, Lombardini F, Gianni C, Fossati-Bellani F. Localised Ewing's sarcoma: results of integrated therapy and analysis of failures. *Eur J Cancer Clin Oncol* 1981, **17**, 1205–1209.
14. Smith MA. The impact of doxorubicin dose intensity on survival of patients with Ewing's sarcoma. *J Clin Oncol* 1991, **9**, 889–891.
15. Robison L. Survivors of childhood cancer and risk of a second tumour. *J Nat Cancer Inst* 1993, **85**, 1102–1103.
16. Casper ES, Gaynor JJ, Haidu SI, *et al.* A prospective randomised trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. *Cancer* 1991, **68**, 1221–1229.
17. Craft AW. Prosthetic replacement surgery for bone tumours—cure at less cost? *Br J Cancer* 1991, **63**, 173–175.

Acknowledgements—We acknowledge the Cancer Reasearch Campaign support of the UKCCSG. The following clinicians entered patients into the study and we are grateful for their co-operation: C. Bailey (Leeds), F. Breatnach (Dublin), V.A. Broadbent (Cambridge), J.A. Bullimore (Bristol), A.W. Craft (Newcastle), S. Dempsey (Belfast), J. Lilleyman (Sheffield), J. Martin (Liverpool), D. Pearson (Manchester), J. Pritchard (Great Ormond Street), M. Radford (Southampton), P. Salaman (Cardiff), R. Shannon (Leicester), M. Stevens (Birmingham) and M. Sokal (Nottingham).

APPENDIX 1

Details of reported late effects ordered by primary site for patients surviving 4 years or more

Age at diagnosis	Site	Local therapy	Late effects
21	femur	RT	Sterile, early menopause, hormone replacement therapy.
10	femur	RT	Shortening of leg by 3.8 cm, stiff knee, peripheral weakness—wasting of thigh.
12	femur	RT	Minimal wasting of thigh. 2nd malignancy in RT field—Pleomorphic rhabomyosarcoma excised 13 years after ET diagnosis.
10	femur	RT	Shortening, growth damage to femur.
13	femur	RT	Ovarian failure, shortened right leg later required disarticulation at 3 years—phantom pains. Hindquarter amputation at 7 years. Needed psychologist support.
4	femur	RT	Shortening of leg by 4 cm.
5	femur	RT	Post-RT fracture. Shortening, muscle wasting, required below knee amputation.
8	femur	RT + S	Problems with endoprosthesis: still chronic infection at 12 years.
9	femur	RT + S	Persistent haematuria, muscle wasting, restricted knee movement.
7	femur	RT + S	Hypoplasia, mild cardiotoxicity.
15	femur	RT + S	Transient problem with dislocation of prosthesis.
6	femur	RT	Shortening of leg by 2.5 cm.
26	tibia	RT	Sterile, amennorhea.
9	tibia	RT	Minor leg deformity, short leg (fracture of tibia at 15 years).
12	tibia	S	Osteomyelitis, amputation.
8	tibia	RT	Chronic osteomyelitis.
6	tibia	RT + S	Shortening of leg, multiple fractures of bone graft, psychological problems.
14	tibia	RT	Footdrop, 2nd malignancy osteosarcoma at 11 years distal to original site.
12	tibia	RT	Shortening and necrosis. Required surgery at 5 years.
20	tibia	RT	Minor mobility problem due to ankle torsion.
7	fibula	S	Persistent ulceration of stump after amputation.
10	fibula	RT	Shortening of leg by 5 cm required surgery. Stress fracture.
9	fibula	RT + S	Shortening of leg by 3.8 cm, needed calliper but mobile. Later required below knee amputation 11 years after diagnosis.
9	fibula	RT	Severe footdrop and shortening, required amputation.
7	rib	RT + S	Cardiotoxicity, fibrosis of lung, mild elevation of liver enzymes (heart, lung + liver in RT field).
12	rib	RT	Mild scoliosis.
12	rib	RT	Moderate chest deformity.
13	chest	RT	Reduced breast development.
8	chest	RT	Mild chest wall deformity.
11	spine	RT	Residual footdrop, requires stick. Severe cardiotoxicity (heart failure at age 27 year).
10	spine	RT	Scoliosis.
12	spine	RT	Leg shortening plus muscle wasting.
6	spine	RT	RT damage to spine.
12	spine	RT	Paraplegic.
11	spine	RT	Footdrop and hip dysfunction.
11	pelvis	RT	Due to have leg lengthening at 12 years after treatment.
10	pelvis	RT	Hypogonadism, requiring testosterone therapy.
13	pelvis	RT	Developed Guillain Barre syndrome. Mild cardiotoxicity.
12	mandible	RT	Facial palsy and deafness.
5	humerus	RT	Radiation induced osteosarcoma at 12 years.
5	humerus	RT	Cardiotoxicity.
12	humerus	RT	Hypoplasia: shortened arm, post RT fracture, limited movement of shoulder.
9	humerus	RT + S	Considerable shortening requiring surgery. Limited shoulder movement.
15	clavicle	RT	Nerve palsy and footdrop
8	phalange	RT	Chest hypoplasia, bilateral breast prosthesis (RT to chest).

RT, radiotherapy; S, surgery; ET, Ewing's tumour.