Pergamon

European Journal of Cancer, Vol. 35, No. 12, pp. 1698–1704, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00144-6

Original Paper

Local Therapy and Other Factors Influencing Site of Relapse in Patients with Localised Ewing's Sarcoma

A.G. Shankar,[1] C.R. Pinkerton,[1] A. Atra,[1] S. Ashley,[2] I. Lewis,[3] D. Spooner,[4] S. Cannon,[5] R. Grimer,[6] S.J. Cotterill[7] and A.W. Craft[7] on behalf of the United Kingdom Children's Cancer Study Group (UKCCSG)

[1]Paediatric Department; Royal Marsden NHS Trust, Downs Road, Sutton, Surrey SM2 5PT; [2]Computing Department; [3]Children's Day Hospital, Regional Paediatric Oncology Unit, St James's University Hospital, Leeds; [4]Queen Elizabeth Hospital, Edgbaston, Birmingham; [5]Royal National Orthopaedic Hospital, Middlesex; [6]Royal Orthopaedic Hospital, Birmingham; and [7]Department of Child Health, Sir James Spence Institute of Child Health, The Royal Victoria Infirmary, Newcastle upon Tyne, U.K.

Relapse patterns have been documented in 191 children with localised Ewing's sarcoma treated with the United Kingdom Children's Cancer Group (UKCCSG) Ewing's Tumour regimen ET2. All received chemotherapy comprising ifosfamide, vincristine, doxorubicin and actinomycin D. Local treatment modality was excision and or radiotherapy depending on tumour site and response to primary chemotherapy. Although not strictly comparable, due to the clinical indications used for each modality, local relapse rates were very low and were similar, irrespective of the type of local treatment modality: radiotherapy (3/56), surgery (7/114) or a combination (0/20). Combined relapse (local + distant) rates were similarly low irrespective of the type of local therapy: radiotherapy (4/56), surgery (4/114) or a combination (0/20). Overall survival was lower in females ($P=<0.04$), older children ($P=<0.002$) and those with primaries at sites other than long bones ($P=<0.02$). It is concluded that with effective intensive chemotherapy combined with either radiotherapy or surgery, local control in this study was excellent at sites other than the pelvis. Preventing distant relapse, predominantly to lung and bone, remains the major challenge.

Key words: local control, Ewing's sarcoma, chemotherapy, surgery, radiotherapy
Eur J Cancer, Vol. 35, No. 12, pp. 1698–1704, 1999

INTRODUCTION

AGGRESSIVE MULTI-AGENT combination chemotherapy combined with adequate local treatment, surgery and or radiotherapy, has dramatically improved survival in patients with localised Ewing's sarcoma [1, 2]. For many years radiation treatment has been the local treatment of choice especially for inoperable bulky pelvic and spinal tumours. Its role is less clear in the light of advances in orthopaedic surgery and with the use of effective multi-agent chemotherapy. There are conflicting reports in the literature regarding the effectiveness of irradiation in local disease control [3–8]. Another important consideration is the risk of second malignancies within the radiation field for patients with Ewing's sarcoma, [9, 10] although with lower doses and less extensive irradiation fields the incidence is likely to be lower than reported in the past [11].

Surgery is increasingly the preferred modality of local treatment in Ewing's sarcoma with many reports in the literature suggesting improved local control and survival [12–14]. It must be recognised, however, that those patients undergoing surgical resection tend to have smaller tumours and/or have shown a good response to chemotherapy, both factors which could account for the favourable outcome.

In this study, we examined the impact of local treatment modality on local control, overall relapse pattern and survival in an unselected, national series of patients with localised

Professor C.R. Pinkerton, e-mail: rossp@icr.ac.uk
Received 17 Feb. 1999; revised 30 Apr. 1999; accepted 31 May 1999.

Ewing's sarcoma treated on a standardised ifosfamide-based chemotherapy protocol combined with surgery and/or radiotherapy.

PATIENTS AND METHODS

From January 1987 to November 1993, 201 patients with localised Ewing's sarcoma of the bone were registered on the Ewing's Tumour Study-2 (ET-2) of the United Kingdom's Children's Cancer Study Group (UKCCSG). 10 patients were excluded due to major protocol violations ($n = 7$) or due to insufficient clinical details ($n = 3$). Hence 191 patients were available for analysis. For this analysis the median follow-up period was 5.5 years (range 2 months–10 years). Of the 139 living patients, 114 had been seen within the last 2 years.

All patients had biopsy proven Ewing's sarcoma of bone with no prior local treatment or chemotherapy. Staging investigations included bilateral bone marrow aspirate and trephine biopsies; posterior–anterior and lateral chest X-ray (CXR), computed tomography (CT) scan and/or magnetic resonance imaging (MRI) Scan of primary and CT scan of chest. Precise tumour volume at diagnosis was not formally documented in this study.

Additional investigations prior to and during treatment have been previously reported [15]. Prior to a decision regarding local therapy, the primary tumour was examined with CT or MRI. Whether surgery, radiotherapy or both were used was at the discretion of individual investigators.

Chemotherapy

Chemotherapy combined ifosfamide (I) with vincristine (V), and doxorubicin (D) or actinomycin-D (A). Dosages, routes and schedules of chemotherapy administration are shown in Table 1. All patients received four courses of the combination chemotherapy IVAD-3 within 4 weeks of histological diagnosis. Treatment was administered at 3–4 weekly intervals dependent on recovery of blood counts.

After surgery or radiotherapy all patients continued treatment with IVAD-2 which was similar to IVAD-3 but without the third day of ifosfamide infusion and doxorubicin was given at 30 mg/m^2 on days 1 and 2 only. IVAD-2 was also administered at 3–4 weekly intervals dependent on recovery of blood counts. After three courses of IVAD-2, chemotherapy was changed to IVA (ifosfamide, vincristine and actinomycin-D), administered at 3–4 weekly intervals for the remainder of 1 year from the start of chemotherapy.

A reduction of dose in the next and subsequent courses of chemotherapy was recommended where there was repeated neutropenic sepsis. In the event of ifosfamide-related encephalopathy or severe renal toxicity, ifosfamide was replaced with cyclophosphamide. Doxorubicin dose was reduced in the next and subsequent courses of chemotherapy if there was severe mucositis or oesophagitis. Actinomycin-D was substituted for doxorubicin if there was any clinical evidence of left ventricular dysfunction. Dose reduction of vincristine was considered for patients with severe neurotoxicity such as foot drop, ileus or severe paraesthesia. All patients received Co-trimoxazole three days per week as prophylaxis against *pneumocystis carinii*.

Table 1. *ET-2 chemotherapy regimen*

			IVAD 3	IVAD 2	IVA
Ifosfamide	3 g/m^2	i.v. infusion	×3 days	×2 days	×2 days
MESNA	3 g/m^2	i.v. infusion	×3 days	×2 days	×2 days
Vincristine	2 mg/m^2	i.v. push	×1 day	×1 day	×1 day
Doxorubicin	20 mg/m^2	i.v. infusion	×3 days	*	—
Actinomycin-D	1.5 mg/m^2	i.v. push	—	—	×1 day

*Doxorubicin in IVAD 2 30 mg/m^2×2 days. i.v., intravenous.

Surgery

Surgery was considered after four courses of IVAD-3 chemotherapy at approximately 12 weeks from diagnosis. In a proportion of patients surgery was delayed, either electively or due to unavoidable reasons. Surgery was deemed to be complete or incomplete based on the histopathology report of the resected specimen and surgical notes of the operating surgeon. Definitive surgery was defined as tumour excision or amputation as the sole modality of local treatment.

Radiotherapy

'Primary' radiotherapy was used in bulky, inoperable tumours. 'Postoperative' radiotherapy was recommended when surgery was incomplete with gross macroscopic or microscopic disease. Primary radiotherapy was defined as irradiation being the exclusive modality of local treatment. Radiotherapy was either given with conventional fractionation or split course and hyperfactionation. Treatment was delivered using megavoltage equipment.

Conventional fractionation. Once daily fractions with 5 fractions per week and a dose per fraction of 180–200 CGy was used. Total dose ranged from 40 Gy to 60 Gy for those patients undergoing definitive irradiation and 35–55 Gy for those patients receiving postoperative radiotherapy.

Split course hyperfractionation radiotherapy. The scheme was identical to that used in the CESS-86 study [16]. Two courses of 22.4 Gy (two fractions of 160 CGy/day) i.e. total dose 44.8 Gy for postoperative radiotherapy or three courses of 22.4, 22.4 and 16 Gy, respectively, for definitive radiotherapy. The objective of hyperfractionated radiotherapy was to continue radiation treatment without interruption or alteration of systemic chemotherapy. Total dose and overall treatment time were identical for both types of treatment.

Chemotherapy during radiotherapy. During conventionally fractionated radiotherapy vincristine 1.5 mg/m^2 and cyclophosphamide 300 mg/m^2 were administered concurrently at weekly intervals during the radiation treatment. Patients undergoing pelvic irradiation had cyclophosphamide omitted completely.

Relapse was documented by unequivocal clinical evidence of either local recurrence or metastatic disease supported by radiological evidence of disease by plain X-ray, CT scan/MRI scan or isotope bone scan. Histological proof was not mandatory.

Statistical methods

Survival, relapse-free survival and local control were calculated by the life-table method of Kaplan and Meier [17] and differences between groups were assessed by the logrank test [18]. In calculating the local control, the data were censored at the time of first relapse. Subsequent relapses were not evaluated. Since the choice of local treatment is likely to have been based on patient and disease factors (e.g. age, site of disease) a multivariate analysis was used to investigate the independent effect of variables on survival. Cox's proportional hazards model [19] was employed using the method of maximum likelihood in a step-up procedure. Relative risks were calculated for the different patient groups.

Table 2. Patient characteristics and method of local treatment

Total number	191
Median age (range)	12 (1–27) years
Sex	
Male	106
Female	85
Site	
Long bones	96
Pelvis	34
Spine	8
Flat bones	44
Small bones	9
Local treatment	
Surgery	114 (60%)
Definitive radiotherapy	56 (29%)
Surgery + radiotherapy	20 (10%)
No treatment	1 (<1%)

Table 3. Relapses according to site of primary tumour

Primary site	Local treatment		Surgery + radiotherapy
	Radiotherapy	Surgery	
Long bones ($n = 96$)	1/14	22/75	3/7
Pelvis ($n = 34$*)	13/25	3/7	0/1
Spine ($n = 8$)	2/7	0	0/1
Others ($n = 53$)	2/10	15/32	0/11
Total	18/56 (32%)	40/114† (35%)	3/20 (15%)

Long bones = 26, pelvis = 16, spine = 2, others = 17. *One patient did not receive any form of local treatment. †4/40 patients who relapsed had incomplete surgical excision.

RESULTS

Patients characteristics for the entire group are listed in Table 2.

Definitive surgery

114 patients had surgery alone as local treatment. There was complete surgical excision of tumour with clear margins on histopathological examination in 107 (including 10 amputations), whilst 7 had incomplete resection. The sites of resected primary tumours were long bones 75, pelvis 7, rib 16, skull 2, others 14. The interval between the last course of chemotherapy prior to surgery and resumption after surgery, in 111 evaluable patients, was 47 days (range 33–97 days). In 69 patients chemotherapy was recommenced within 21 days of surgery and a further 33 patients resumed it within 30 days. 9 patients had a delay in excess of 30 days for recommencement of chemotherapy.

Primary radiotherapy

56 patients had radiotherapy alone as local treatment. The sites of the primary tumour were pelvis 25, spine 7, long bone 14, and other sites 10. One patient was treated by brachytherapy for a pelvic tumour. Chemotherapy details prior to definitive radiotherapy were available in 53 patients; 34 patients had four cycles and 15 patients received five cycles. In 4 patients it was delayed beyond five cycles.

In the majority of patients chemotherapy was modified to vincristine + cyclophosphamide or vincristine alone during radiotherapy. One patient had no local treatment.

Postoperative radiotherapy

20 patients were given postoperative radiotherapy of whom 17 had undergone incomplete surgical excision of the primary tumour, whilst 3 patients had postoperative radiotherapy despite complete excision on clinician preference. The primary sites treated were long bones 7, pelvis 2, rib 4, spine 1, other sites 6.

Of the 134 patients who had surgery (definitive surgery $n = 114$ and postoperative radiotherapy ($n = 20$), 93 patients had it after 4 cycles of IVAD-3 chemotherapy and 25 after five cycles. Surgery was delayed beyond five cycles in 8 patients. Details were not available for 8 patients.

Outcome

Relapse. 61 patients relapsed. Table 3 shows that pelvic primary tumours had the highest incidence of relapse, irrespective of the type of local treatment—13/25 after irradiation and 3/7 after definitive surgery.

Relapses were separated into (1) local recurrence alone; (2) local recurrence and synchronous systemic relapse (combined); and (3) systemic relapse alone (Table 4). Table 5 shows the relapse sites according to site of primary and local treatment. There was no significant difference in local, systemic or combined relapse rates either after surgery, radiotherapy or a combination of both. Time interval to relapse in relation to local treatment is shown in (Figure 1). The site of relapse did not affect survival after relapse (Figure 2a), but a longer interval from diagnosis to relapse did give a better prognosis (Figure 2b). No difference in the local control was apparent whether or not surgery was complete (Figure 3a) and similarly local control was identical for the group receiving radiotherapy or not (Figure 3b, Table 6). There was a small group of 8 patients whose tumours were incompletely resected but who did not receive local irradiation. 3 of those had a local relapse and 1 a metastatic recurrence. Statistical analysis is not appropriate with these small numbers. Local control was significantly better when the primary was in the long bones (the wide confidence interval (CI) is the result of very few local relapses in the long bone group, long bones, relative risk (RR) = 1, other sites RR = 8.6, 95% CI 1.97–37.32, $P = 0.0003$).

There was no significant difference in the interval (in days) between the last course of chemotherapy prior to surgery and

Table 4. Relapse pattern according to local treatment

Local treatment	Local (%)	Systematic (%)	Combined (%)	Total (%)
Radiotherapy ($n = 56$)	3 (5)	11 (20)	4 (7)	18/56 (32)
Surgery ($n = 114$)	7 (6)	29 (25)	4 (4)	40/114 (35)
Surgery + postoperative radiotherapy ($n = 20$)	0 (0)	3 (15)	0	3/20 (15)
Total ($n = 190$)	10/61 (16)	43/61 (70)	8/61 (13)	

Table 5. Relapse sites according to site of primary and local treatment

Site	XRT	Surgery	Surgery + XRT	Local relapse	Systemic relapse	Combined relapse
Long bones ($n = 96$) (R = 26)	14	75	7	1	24	1
Pelvis* ($n = 34$) (R = 16)	25	7	1	4	8	4
Spine ($n = 8$) (R = 2)	7	0	1	0	1	1
Other sites ($n = 53$) (R = 17)	10	32	11	5	10	2
Total ($n = 191$)	56	114	20	10	43	8

*One patient did not receive any form of local treatment. XRT, radiotherapy; R, relapses.

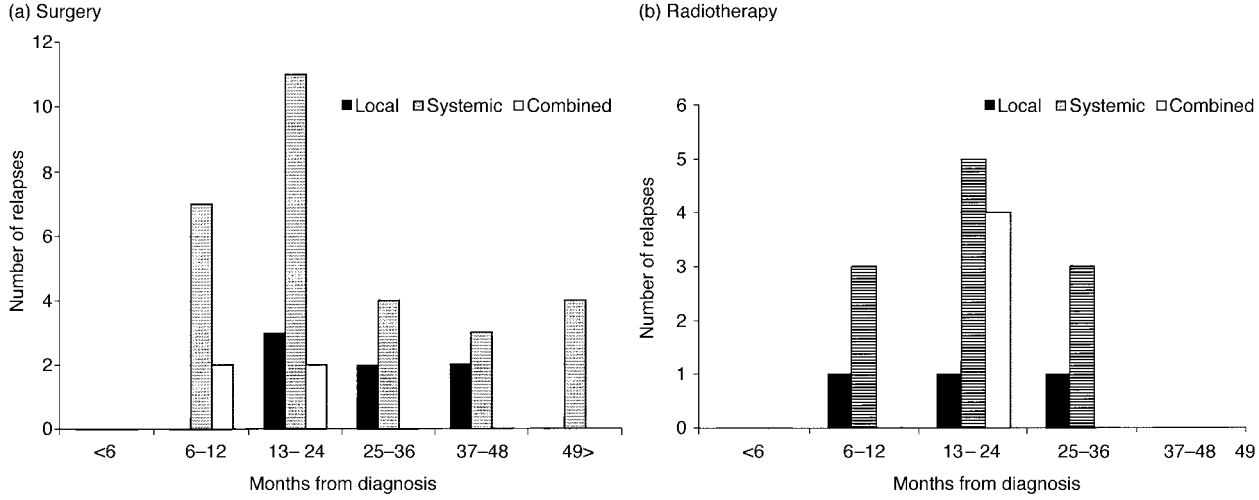

Figure 1. Time interval (months) from diagnosis to relapse after (a) surgery; (b) primary radiotherapy.

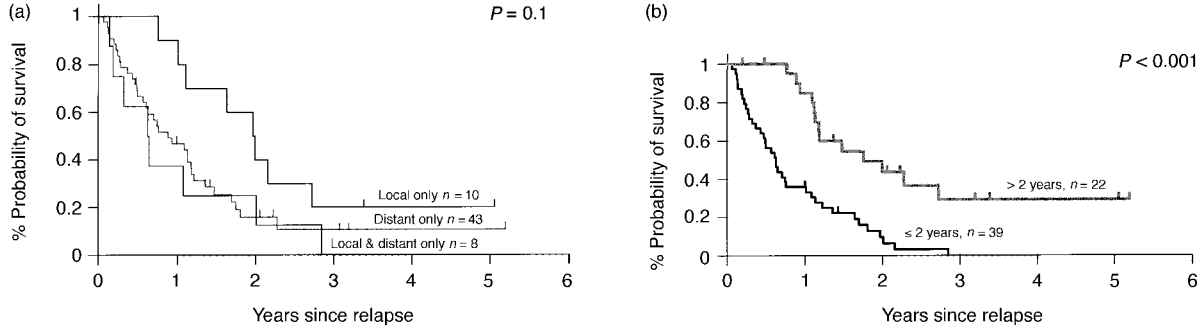

Figure 2. Survival after relapse according to (a) site of relapse; (b) interval from diagnosis.

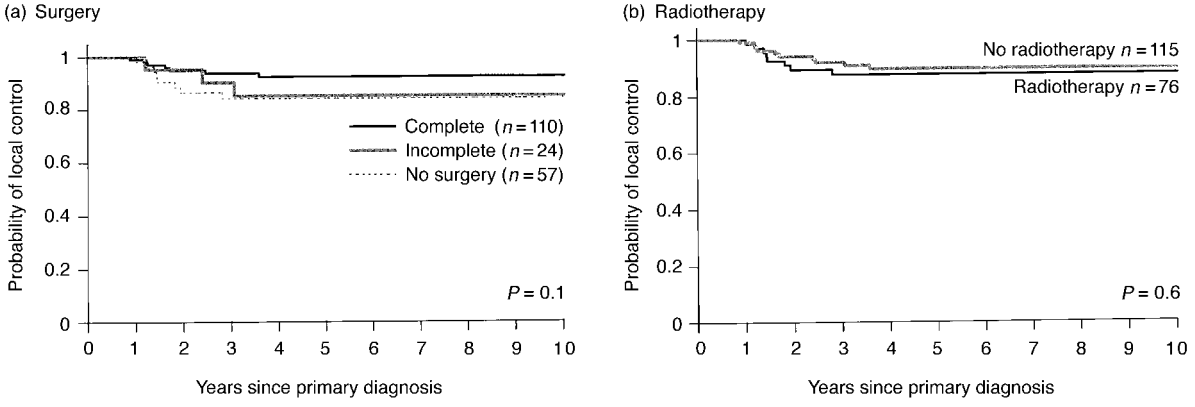

Figure 3. Local control in relation to (a) extent of surgery; (b) with or without radiotherapy.

Table 6. Local control

	Patients	Relapse	% Local control at 5 years (95% CI)	Significance
All cases	191	18	89 (83–93)	
Male	106	9	90 (81–95)	$P = 0.4$
Female	85	9	87 (77–93)	
Age (years)				
0–4	11	0	100	$P = 0.3$
5–9	36	4	88 (72–96)	(Trend test)
10–14	76	6	91 (81–96)	
15+	68	8	85 (71–92)	
Site				
Long bones	96	2	98 (91–99)	
Pelvis	34	8	72 (52–85)	
Spine	8	1	88 (39–98)	Long bone versus rest
Other	53	7	84 (70–92)	$P = 0.0006$
Surgery				
None	57	8	84 (71–92)	$P = 0.1$
Incomplete	24	3	85 (61–95)	(Trend test)
Complete	110	7	92 (85–96)	
Radiotherapy				
Yes	76	8	88 (77-94)	$P = 0.6$
No	115	10	90 (82–94)	

CI, confidence interval.

the resumption after surgery between the patients who relapsed and those who did not relapse.

Mortality

52 patients died, 50 (96%) due to progressive disease following relapse. One child died because of transfusion-associated, biopsy-proven, graft versus host disease and another from *pneumocystis carini* pneumonia. 23% (14/61) of those with recurrent disease died within 6 months from the date of relapse and 54% (33/61) died within 1 year.

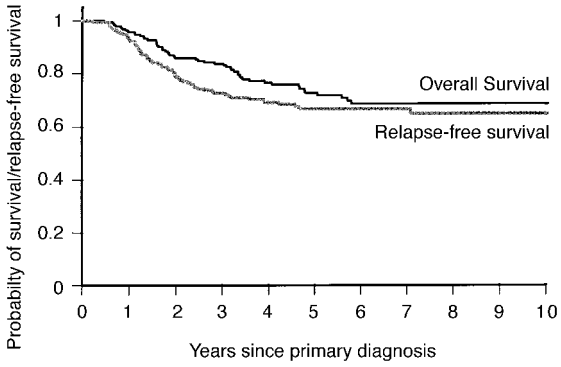

Figure 4. Overall survival and relapse-free survival.

Overall and relapse-free survival

The 10-year overall survival (OS) for the entire cohort was 69% (Figure 4) and Table 7 shows OS according to age, sex, primary site and local treatment modality. The 5-year relapse-free survival (RFS) for the entire cohort was 67% (Figure 4). The 5-year RFS for patients who underwent definitive surgery, definitive radiotherapy and postoperative radiotherapy were 62, 67 and 78% respectively ($P = 0.6$) (Figure 5).

DISCUSSION

This study has evaluated a number of factors which could contribute to local control in patients with Ewing's tumour. Tumour bulk rather than site (although these are often related) was not documented consistently in this trial. Similarly, histological response to preoperative chemotherapy, which

Table 7. Overall survival

	Patients	Deaths	% Alive at (95% CI) 5 years	% Alive at (95% CI) 10 years	Significance
All cases	191	52	73 (66–79)	69 (61–76)	
Male	106	23	79 (69–86)	75 (64–83)	$P = 0.04$
Female	85	29	65 (54–75)	61 (49–72)	
Age (years)					
0–4	11	0	100	100	$P = 0.002$
5–9	36	4	92 (76–97)	87 (68–95)	(Trend test)
10–14	76	25	66 (54–76)	64 (51–74)	
15+	68	23	65 (51–76)	59 (43–71)	
Site					
Long bones	96	18	81 (71–88)	79 (69–87)	
Pelvis, sacrum	34	15	53 (34–69		Long bone versus all others $P = 0.02$
Spine	8	2	73 (28–93)		
Other	53	17	72 (57–82)		
Surgery					
None	57	17	67 (52–78)	67 (52–78)	$P = 0.7$ (Trend test)
Incomplete	24	6	77 (53–90)	68 (41–85)	
Complete	110	29	75 (65–82)	70 (59–78)	
Radiotherapy					
Yes	76	21	70 (57–79)	70 (57–79)	$P = 0.7$
No	115	31	75 (65–82)	68 (57–77)	

CI, confidence interval.

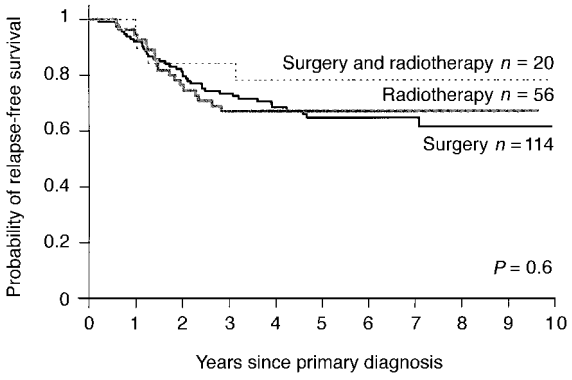

Figure 5. Relapse-free survival in relation to local treatment.

has been shown to correlate with event-free survival, was not available for inclusion in the analysis.

These results show that using a four-drug ifosfamide-based chemotherapy regimen and applying a relatively conservative radiotherapy policy, the overall prognosis for localised Ewing's sarcoma is encouraging with a 5-year RFS of 67% and 10-year OS of 69%. These results compare favourably with published reports [1, 2, 16, 20], in particular, when compared with ET-1 study in which the overall local relapse rate was 17% (33% for those treated with radiotherapy). The 5-year OS of all evaluable patients including those with metastatic disease at diagnosis in the ET-2 study was 62% [15].

Pelvic tumours continue to have a poorer prognosis, [21–23] irrespective of the type of local treatment given. There was no clear difference between surgery and radiotherapy for treatment of pelvic Ewing's demonstrated in this small series. Neither group did particularly well. This poor outcome, in part, reflects the adverse prognostic significance of tumour bulk [24–26], although with more intensive chemotherapy regimens—especially those that are ifosfamide based—tumour volume may be less of a risk factor [13, 27]. In the present study, 8/16 (50%) patients with pelvic primaries who relapsed did so at distant sites only whilst 4 (25%) had local recurrence alone. The high incidence of systemic relapse in patients with pelvic tumours undergoing definitive radiotherapy may reflect inadequate systemic treatment that these patients received during the radiation treatment which had to extend over 5 to 6 weeks. During this period chemotherapy was limited to cyclophosphamide and vincristine and in many cases cyclophosphamide was omitted so as to reduce bladder toxicity when combined with pelvic irradiation. Patients undergoing definitive surgery usually resume intensive combination chemotherapy within 3 weeks of surgery.

The Cooperative Ewing's Sarcoma Study (CESS) 81 and 86 trials have reported a higher incidence of systemic recurrence in patients undergoing surgery as local treatment [13, 28]. This finding was not observed in the present study (Table 4). In both the CESS trials, neoadjuvant chemotherapy consisted of the four drug regimen—VACA (vincristine, actinomycin-D, cyclophosphamide and doxorubicin). The more intensive—VAIA regimen (vincristine, actinomycin-D, ifosfamide and doxorubicin) was restricted to high risk patients (tumour volume >100 ml and tumours of central origin) in the CESS 86 trial. VACA is less intensive than the IVAD/IVA regimen which may have contributed to the higher systemic relapse rate. There is continued debate regarding the relative efficacy of cyclosphamide and ifosfamide [29–31]. It would seem likely that the use of ifosfamide in place of cyclophosphamide contributed to the improved OS in ET-2, although published reports suggest that equivalent results may be obtained using escalated dose-intensive cyclophosphamide-based chemotherapy regimens [20]. Improved results have also been obtained after dose intensification of doxorubicin in the IESS-II trial [32].

Where surgical resection is impossible, it is clear that local irradiation is an effective alternative. In this study, the combination of local irradiation and chemotherapy resulted in exceptionally low local recurrence rates. It seems unlikely that local irradiation is required where there has been a complete resection of the tumour, irrespective of the extent of chemotherapy-induced necrosis. In the ET-2 study, unlike the current EICESS (European Intergroup Cooperative Ewing's Sarcoma Study) study, no irradiation was given in this situation and there was no adverse effect on local control.

A recent report from the CESS group has shown that the addition of postoperative radiation after incomplete surgical excision did not significantly reduce the local relapse rate [13]. Of the 63 patients reported who had incomplete surgery, only 49 had additional postoperative radiotherapy to the primary site. The local combined relapse rate in this group was 12% (6/49); the local or combined relapse rate in the unirradiated group was 14% (2/14). By contrast, in the present study, 38% of those who did not receive additional postoperative radiation had local recurrences. The addition of postoperative radiotherapy to patients who have less than complete surgery thus seemed to achieve better local control (Table 4). The conclusion would seem to be that at present, radiation is indicated. With accrual of information on children who for various reasons did not receive radiotherapy i.e. concern about the adverse effects on growth in the younger child, it may become clearer whether there are some circumstances where a more conservative approach is possible. Other factors such as initial tumour size or the degree of tumour necrosis may also have to be taken into account. This possible benefit must be weighed against the risk of second malignancies and growth impairment. It is clear from the low local failure rate in the large number of patients who did not receive any radiotherapy (approximately 60% of the study population) that intensive chemotherapy and surgery are sufficient for most cases. In this trial approximately 70% of patients had their definitive surgery in one of two specialised orthopaedic surgical centres. Nevertheless, it is difficult to assess the impact of this centralisation of surgery as a critical factor in the very low relapse rates reported in the study, as local therapy in the earlier ET-1 study was radiotherapy [33]. However, in other tumour types, particularly in breast cancer, centralisation of surgery to specialist centres has been demonstrated to have a significant influence in outcome [34, 35]. At the time of analysis, local recurrences have not occurred beyond 48 months from diagnosis, irrespective of the local treatment modality. Systemic relapses continued to occur beyond 5 years from diagnosis but only in patients who had surgery.

Distant bone metastases were as common as pulmonary metastases as sites of distant relapse. Other sites included bone marrow, spinal cord and liver. The high incidence of distant bone metastases probably explains the very poor salvage rate after recurrent disease. With improved local control rates using surgery and/or radiotherapy, more effective means for control of distant metastases are urgently needed. It is

important to identify those patients at high risk of development of recurrent disease in whom chemotherapy dose intensification, perhaps including myeloablative therapy with autologous haematopoietic rescue should be considered [36–38]. Chemotherapy-induced tumour necrosis is considered an important prognostic factor in predicting clinical outcome, and in conjunction with tumour volume may help in identifying high-risk patients who might benefit from more intensive chemotherapy treatment [13, 25, 39, 40].

The optimal timing of local treatment, the value of chemotherapy dose intensification and the identification of poor prognostic factors are outstanding issues which must be addressed in order to make further improvements in OS and RFS in Ewing's sarcoma. This can be only done via cooperative multi-institutional and multinational trials.

1. Marcus RB, Springfield DS, Pole G Jr, Heare TC, Enneking WF, Million RR. Late follow-up of a short term intensive regimen for Ewing's sarcoma. *Am J Clin Oncol* 1991, **14**, 446–450.
2. Burgert EO Jr, Nesbit ME, Garnsey LA, *et al.* Multimodal therapy for management of non-pelvic localised Ewing's sarcoma of bone: intergroup study IESS-II. *J Clin Oncol* 1990, **8**, 1514–1524.
3. Brown AP, Fixen JA, Plowman PN. Local control of Ewing's sarcoma: an analysis of 67 patients. *Br J Radiat* 1987, **60**, 261–268.
4. Terek RM, Brien EW, Marcove RC, Meyers PA, Lane JM, Healey JH. Treatment of femoral Ewing's sarcoma. *Cancer* 1996, **78**, 70–78.
5. Bacci G, Picci P, Gherlinzoni F, *et al.* Localised Ewing's sarcoma of bone ten years experience at the Instituto Orthopedico Rizzoli in 124 cases treated with multimodal therapy. *Eur J Cancer Clin Oncol* 1985, **21**, 163–173.
6. Bolek TW, Marcus RB Jr, Mendenhall NP, Scarborough MT, Graham-Pole J. Local control and functional results after twice daily radiotherapy for Ewing's sarcoma of the extremities. *Int J Radiat Oncol Biol Phys* 1996, **35**, 687–692.
7. Evans RG, Nesbit ME, Gehan EA, *et al.* Multimodal therapy for the management of localised Ewing's sarcoma of pelvic and sacral bones: a report from the second intergroup study. *J Clin Oncol* 1991, **9**, 1173–1180.
8. Kinsella TJ, Lichter AS, Miser J, Gerber L, Glatstein E. Local treatment of Ewing's sarcoma: Radiation therapy versus surgery. *Cancer Treat Rep* 1984, **68**, 695–701.
9. Tucker MA, D'Angio GJ, Boice JD, *et al.* Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 1987, **317**, 588–593.
10. Gasparini M, Lombardi F, Ballerini F, *et al.* Long term outcome of patients with mono-ostotic Ewing's sarcoma treated with combined modality. *Med Ped Oncol* 1994, **23**, 406–412.
11. Strong LC, Herson J, Osborn BM, *et al.* Risk of radiation related subsequent malignant tumours in survivors of Ewing's sarcoma. *J Natl Cancer Inst* 1979, **62**, 1401–1406.
12. Bacci G, Toni A, Avella M, *et al.* Long term results in 14.4 localised Ewing's sarcoma patients treated with combined therapy. *Cancer* 1989, **63**, 1477–1486.
13. Ozaki T, Hilmann A, Hoffmann C, *et al.* Significance of surgical margin on the prognosis of patients with Ewing's sarcoma. *Cancer* 1996, **78**, 892–900.
14. Wilkins RM, Pritchard DJ, Burgert EO Jr, Unni KK. Ewing's sarcoma of bone: experience with 140 patients. *Cancer* 1986, **58**, 2552–2555.
15. Craft AW, Cotterill SJ, Malcolm AJ, *et al.* Ifosfamide containing chemotherapy in Ewing's sarcoma: The second United Kingdom Children's Cancer Study Group and Medical Research Council Ewing's Tumour Study (ET-2). *J Clin Oncol* 1998, **16**, 3628–3633.
16. Dunst J, Jurgens H, Sauer R, *et al.* Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. *Int J Radiat Oncol Biol Phys* 1995, **32**, 919–930.
17. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958, **53**, 457–481.
18. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation for each patient: II. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
19. Cox DR. Regression models and life tables. *J R Stat Soc* 1972, **34**, 187–202.
20. Kushner BH, Meyers PA, Gerald WL, *et al.* Very high dose short-term chemotherapy for poor risk peripheral primitive neuro ectodermal tumours, including Ewing's sarcoma in children and young adults. *J Clin Oncol* 1995, **13**, 2796–2804.
21. Scully SP, Temple HT, O'Keefe RJ, Scarborough MT, Mankin HJ, Gebhart MC. Role of surgical resection in Pelvic Ewing's sarcoma. *J Clin Oncol* 1995, **13**, 2336–2341.
22. 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.
23. Evans RG, Nesbit M, Askin F. Local recurrence, rate of 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 pelvic bones. *Int J Radiat Oncol Biol Phys* 1985, **11**, 120–136.
24. Gobel V, Jurgens H, Etspuler G, *et al.* Prognostic significance of tumour volume in localized Ewing's sarcoma of bone in children and adolescents. *J Can Res Clin Oncol* 1987, **113**, 187–191.
25. Jurgens H, Exner U, Gadner H, *et al.* Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6 year experience of a European co-operative trial. *Cancer* 1988, **61**, 23–32.
26. Barbieri E, Emiliani E, Zingi G, *et al.* Combined therapy of localized Ewing's sarcoma of bone: analysis of results in 100 patients. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1165–1170.
27. Jurgens H, Treuner J, Winkler K, Gobel U. Ifosfamide in paediatric malignancies. *Semin Oncol* 1989, **16**, 46–50.
28. Dunst J, Sauer R, Burgers JMV, *et al.* Radiation therapy as local treatment in Ewing's sarcoma. Results of the co-operative Ewing's sarcoma studies—CESS 81 and CESS 86. *Cancer* 1991, **67**, 2818–2825.
29. Craft AW, Cotterill S, Imeson J. Improvement in survival for Ewing's sarcoma by substitution of ifosfamide for cyclophosphamide—A UKCCSG/MRC study. *Am J Ped Hemat Oncol* 1993, **15**, 31–35.
30. Berger DP, Frebig HH, Winterhalter BR, Wallbrecher E, Henss H. Pre clinical phase II study of Ifosfamide in human tumour xenografts *in vivo*. *Cancer Chemother Pharmacol* 1990, **26**(Suppl.), S7–111.
31. Goldin A. Ifosfamide in experimental tumors systems. *Semin Oncol* 1982, **9**, 14–23.
32. Smith MA, Ungerleider RS, Horowitz ME, Simon R. Influence of doxorubicin dose intensity on response and outcome for patients with osteogenic sarcoma and Ewing's sarcoma. *J Natl Cancer Inst* 1991, **83**, 1460–1469.
33. Craft AW, Cotterill SJ, Bullimore JA, *et al.* Long term results from the First UKCCSG Ewing's Tumour Study (ET-1). *Eur J Cancer* 1997, **33**, 1061–1069.
34. Sainsbury R, Howard B, Rider L, *et al.* Influence of clinician work load and patterns of treatment on survival from breast cancer. *Lancet* 1995, **345**, 1265–1270.
35. Blair SL, O'Shea KE, Orr KK. Surgeon variablity in treating non-palpable breast cancer: surgical oncology as a value added speciality. *Ann Surg Oncol* 1998, **5**, 28–32.
36. Atra A, Whelan JS, Cakvagna V, *et al.* High-dose busulphan/melphalan with autologous stem cell rescue in Ewing's sarcoma. *Bone Marrow Transplant* 1997, **20**, 843–846.
37. Meadows AT, Baum E, Fossati-Bellani F, *et al.* Second malignant neoplasms in children: an update from the late effects study group. *J Clin Oncol* 1985, **3**, 532–538.
38. Burdach S, Jurgens H, Peters C, *et al.* Myeloablative radiochemotherapy and haemopoietic stem cell rescue in poor prognosis Ewing's sarcoma. *J Clin Oncol* 1993, **11**, 1483–1488.
39. Van der Woude HJ, Bloem JL, Taminian AH, Nooy MA, Hogendoorn PC. Classification of histopathologic changes following chemotherapy in Ewing's sarcoma of bone. *Skeletal Radiol* 1994, **23**, 501–507.
40. Picci P, Bohling T, Bacci G, *et al.* Chemotherapy induced tumour necrosis as a prognostic factor in localised Ewing's sarcoma of the extremities. *J Clin Oncol* 1997, **15**, 1553–1559.

Acknowledgements—On behalf of the joint UKCCSG and MRC Bone Tumour Working Party. The UKCCSG and CRP are supported by the Cancer Research Campaign. We would like to thank all clinicians and patients who participated in the study. We also thank Ms Jane Neil for her secretarial support.