ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF CLINICALLY LOCALISED EWING'S SARCOMA

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The results are presented of thirty-seven patients with Ewing's sarcoma; ten were treated by a combination of operation, radiotherapy and cyclic chemotherapy, the remainder by radiotherapy and chemotherapy but without operation. The drugs, vincristine, cyclophosphamide and adriamycin were used in combination and were continued for two years. The follow-up ranged from twelve to sixty-two months.

The mortality rate and the incidence of metastases were both markedly lower than in a comparable previous series treated by radiotherapy alone, or by operation plus radiotherapy, but all without chemotherapy. The percentage of local recurrences and of metastases was much higher in the twenty-seven patients who had radiotherapy and adjuvant chemotherapy, than in the ten in whom operation was also performed. It is suggested that on the basis of these results (and on theoretical grounds) treatment should consist of radiotherapy combined with chemotherapy plus, whenever feasible, operative excision of the primary tumour.

In clinically localised Ewing's sarcoma, the results of merely local treatment of the primary tumour have been extremely poor. Falk and Alpert (1967) collected 987 such cases from the literature and found a cure rate after five years of 8 per cent. Since the survival rate of operation does not differ from that of irradiation, the latter is preferred by most authors (Jaffe 1958; Boyer, Brickner and Perry 1967; Phillips and Higinbotham 1967; Pratt 1972; Larson, Boquist and Bergdahl 1973; Lichtenstein 1973; Rosen *et al.* 1974; Pomeroy and Johnson 1975). This preference is reinforced by the fact that the response to radiation is rapid and complete, particularly since the advent of megavoltage radiation therapy.

In 1968 Hustu *et al.* suggested combining systemic chemotherapy with local radiotherapy, assuming that in most cases of apparently localised Ewing's sarcoma tumour cells were already disseminated, even in the absence of clinical or radiological manifestations. The first results of this adjuvant chemotherapy have been very encouraging (Phillips and Higinbotham 1967; Hustu *et al.* 1968; Freeman *et al.* 1972; Fernandez *et al.* 1974; Rosen *et al.* 1974; Bacci *et al.* 1975; Pomeroy and Johnson 1975; Sinks and Shan 1975; Jaffe *et al.* 1976). They show a significant lengthening of disease-free survival and provide real hope of an increase in cure rate. The infrequency of the Ewing's sarcoma, however, makes the number of treated cases too small for accurate statistical evaluation. Moreover, many of the recorded cases have only a short follow-up.

We therefore felt it would be of interest to report the results obtained at the Tumour Centre of our

Institute in thirty-seven consecutive cases of Ewing's sarcoma, in which local treatment of the primary tumour (radiotherapy or wide excision plus radiation) was combined with systemic chemotherapy using vincristine, cyclophosphamide and adriamycin. This adjuvant chemotherapy was continued for two years.

MATERIAL AND METHODS

Thirty-seven consecutive cases of Ewing's sarcoma were treated between January 1972 and June 1976. None had signs of pulmonary or bony metastases on standard radiographs when treatment began. Scintigraphy was not carried out. Age, sex, initial localisation, course and treatment of the primary tumour are reported in Table I.

Diagnosis was based on the histological study of representative sections, using PAS diastase stain for glycogen, and silver stain for reticulum fibres. In some cases (particularly small children) the urinary catecholamine metabolites were investigated to rule out the possibility of metastatic neuroblastoma. A few others had features suggesting a histiocytic lymphoma; if there was genuine diagnostic doubt such cases were excluded from the series and we feel confident that, in the thirty-seven cases reported here, the diagnosis of Ewing's sarcoma was firmly established.

Operation, whether biopsy or excision, was followed immediately by chemotherapy (vincristine 1 mg/m² and cyclophosphamide 500 mg/m² four hours after operation, and cyclophosphamide 500 mg/m² next day).

In ten patients the primary tumour was treated surgically: radical resection in four, scapulectomy in three and subtotal excision in three cases. In all ten the operation was followed by local radiotherapy.

The primary tumour was treated by radiotherapy alone in twenty-seven cases. Radiation was started approximately ten days after the biopsy using caesium-137. The dose, number of fractions, and total time of treatment varied according to the site and volume of the tumour and the age of the patient (Table I). In the majority of the cases the teletherapy was delivered over a period of five to seven weeks with a total dose of 4500 to 5000 rads. The ports were extended to include the entire involved bone and surrounding soft tissues. The concomitant

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Table I. Results of treatment

Case number	Age (years)	Sex	Site of primary tumour	General symptoms	Treatment of primary tumour	Disease-free (months)	Local recurrence (months)	Metastases (months)	Death (months)	Notes
1*	19	M	Clavicle	—	¹³⁷ Cs (4000 rads)	62	—	—	—	—
2	27	F	Scapula	Fever Leucocytosis	Scapulectomy + ¹³⁷ Cs (3000 rads)	62	—	—	—	—
3*	16	F	Ilium	—	¹³⁷ Cs (5000 rads)	—	13	Lung 34 Bone 37	38	Persistent leucopenia after 12th cycle. Treatment continued with reduced doses. Two courses of Cs radiation to local recurrence.
4*	12	M	Rib	—	¹³⁷ Cs (4500 rads)	60	—	Bone 16	24	Chemotherapy modified after metastases: vincristine plus high-dose methotrexate.
5	20	M	Ilium	—	Excision + ¹³⁷ Cs (3000 rads)	60	—	—	—	Chemotherapy interrupted at 20th month because of pulmonary tuberculosis: healed with antibiotics.
6*	18	F	Ilium	Fever High E.S.R. Leucocytosis	¹³⁷ Cs (4000 rads)	—	13	Lung 14 Bone 14	16	Chemotherapy with reduced doses because of marked leucopenia after first cycle.
7*	10	F	Scapula	Fever High E.S.R.	¹³⁷ Cs (3500 rads)	—	—	—	14	Lymphoblastic acute leukaemia at 13th month, death at 14th. Non-apparent local recurrence.
8*	11	F	Scapula	Fever	Scapulectomy + ¹³⁷ Cs (3500 rads)	56	—	—	—	—
9	22	F	Tibia	—	¹³⁷ Cs (5000 rads)	—	8	Lung 42	—	Living at 52 months with metastases and local recurrence. Being treated with vincristine and high-dose methotrexate.
10*	13	M	Tibia	—	¹³⁷ Cs (4500 rads)	48	—	—	—	Radiation ulcer not healed at 48 months.
11	11	F	Scapula	—	¹³⁷ Cs (5000 rads)	—	30	—	—	Local recurrence treated by resection plus radiotherapy 4000 rads. Living with no signs of disease at 44 months.
12	17	F	Ulna	Fever High E.S.R. Leucocytosis	¹³⁷ Cs (5000 rads)	42	—	—	—	Chemotherapy with reduced doses because of marked leucopenia after first cycle.
13	32	F	Radius	—	¹³⁷ Cs (5000 rads)	40	—	—	—	—
14	18	M	Tibia	Fever	¹³⁷ Cs (5500 rads)	37	—	—	—	—
15	17	M	Tibia	—	¹³⁷ Cs (5000 rads)	36	—	—	—	—
16	5	F	Fibula	Fever High E.S.R. Leucocytosis	Resection + ¹³⁷ Cs (4000 rads)	33	—	—	—	—
17	17	M	Femur	Fever Leucocytosis	¹³⁷ Cs (5000 rads)	30	—	—	—	—

	18	7	M	Humerus	Fever Leucocytosis High E.S.R.	¹³⁷ Cs (4000 rads)	8	Lung 19	20	Amputated after local recurrence. Disarticulated after a new recurrence on stump at 17th month.
19	11	F	Metatarsal	—	—	Resection + ¹³⁷ Cs (4000 rads)	—	—	—	—
20	6	F	Scapula	Fever Leucocytosis High E.S.R.	—	¹³⁷ Cs (3500 rads)	—	Lung 5 Bone 5	7	Chemotherapy with reduced doses because of marked leucopenia after first cycle. After metastases, treated by vincristine and high-dose methotrexate.
21	11	M	Tibia	—	26	¹³⁷ Cs (4000 rads)	—	—	—	—
22	9	M	Tibia	—	25	¹³⁷ Cs (4000 rads)	—	—	—	—
23	21	M	Ilium	—	24	Resection + ¹³⁷ Cs (4000 rads)	—	—	—	—
24	17	F	Ilium	Fever Leucocytosis High E.S.R.	—	¹³⁷ Cs (4500 rads)	7	Lung 8 Bone 11	13	After metastases, treated by vincristine and high-dose methotrexate. Herpes zoster at 6th month healed uneventfully.
25	11	M	Ilium	—	18	¹³⁷ Cs (4000 rads)	—	—	—	—
26	26	M	Tibia	—	18	¹³⁷ Cs (5500 rads)	—	—	—	—
27	16	M	Tibia	—	16	Excision + ¹³⁷ Cs (4000 rads)	—	—	—	—
28	18	M	Ilium	Fever Leucocytosis High E.S.R.	—	¹³⁷ Cs (5000 rads)	12	—	14	Local recurrence partially excised. Dead two months later with renal failure and tumour invasion of pelvis.
29	21	M	Femur	—	17	¹³⁷ Cs (5000 rads)	—	—	—	—
30	4	F	Metatarsal	—	15	Resection + ¹³⁷ Cs (3000 rads)	—	—	—	—
31	17	M	Tibia	—	—	¹³⁷ Cs (5000 rads)	6	Bone 11 Lung 12	13	Further course of radiotherapy to local recurrence. Chemotherapy changed after metastases appeared (vincristine and high-dose methotrexate).
32	4	M	Scapula	Fever Leucocytosis	—	Scapulectomy + ¹³⁷ Cs (3000 rads)	—	Lung 8	—	Biopsy elsewhere. Scapulectomy after 15 days. Living with pulmonary metastases at 15 months. After metastases, treated by vincristine and high-dose methotrexate.
33	13	M	Femur	—	14	¹³⁷ Cs (4500 rads)	—	—	—	—
34	17	M	Sacrum	Fever Leucocytosis High E.S.R.	13	¹³⁷ Cs (5000 rads)	—	—	—	—
35	13	M	Tibia	—	—	¹³⁷ Cs (4500 rads)	4	—	—	Another course of radiotherapy to local recurrence. Living with no signs of disease at 13 months.
36	9	M	Femur	—	12	¹³⁷ Cs (4000 rads)	—	—	—	—
37	4	M	Ilium	—	12	Excision + ¹³⁷ Cs (3000 rads)	—	—	—	—

*In these 7 cases the scheme of chemotherapy was slightly different from that indicated in Table II (Bacci *et al.* 1975).

ant administration of chemotherapy decreases the tolerance of normal tissues to radiation (Rosen *et al.* 1974; Tefft *et al.* 1976); consequently the total dose of irradiation was lower than in other reported series (Pratt 1972; Suit *et al.* 1973; Rosen *et al.* 1974). Above 4000 rads, however, there seems to be no definite correlation between the dose of radiation and the local control of the tumour (Suit *et al.* 1973; Fernandez *et al.* 1974; Macintosh, Price and Jeffree 1975). With tumours in the pubis and lower ilium, where irradiation would necessarily involve the bladder, cyclophosphamide (which is a powerful bladder toxin) was omitted during the period of irradiation (Jyalakshamma and Pinkel 1976).

Adjuvant chemotherapy was given as shown in Table II and was continued for two years. In eight cases (Table I) it was started at the end of the radiation course, in the remaining twenty-nine it was concurrent with radiotherapy. The drugs used were those which had proved most effective in treating metastases from Ewing's sarcoma:

Table II. Adjuvant chemotherapy scheme

		Drug	Dose in milligrams per square metre	Notes
Cycle A	Day 1	adriamycin	50	10 consecutive cycles at 21-day intervals
	Day 2	vincristine	1.5	
	Day 3	cyclophosphamide	300	
	Day 4	cyclophosphamide	300	
Cycle B	Both drugs on same day	vincristine plus cyclophosphamide	1	32 consecutive cycles at 14-day intervals, starting 21 days after the end of cycle A
			800	

vincristine (Goepfert, Rochlin and Smart 1967; Sutow 1968; Sutow *et al.* 1971); cyclophosphamide (Sutow and Sullivan 1962; Goepfert *et al.* 1967; Samuels and Howe 1967; Sutow *et al.* 1971); and adriamycin (Oldham and Pomeroy 1972; O'Bryan *et al.* 1973; Gottlieb 1974). Combinations of drugs were used which, both experimentally (Goldman and Fyfe 1973) and clinically (Pouillart *et al.* 1972, 1974), enhanced each other's cytotoxic effect, without having too high a total toxicity. The drugs were administered in such a sequence as to obtain recruitment and synchronisation of the neoplastic cells (Mathé, Schneider and Schwarzenberg 1970; Pouillart *et al.* 1972; Mathé and Kernis 1975). Administration was intermittent in order to minimise the effects of immunodepression and myelodepression (Pouillart *et al.* 1972; Mathé and Kernis 1975).

The interval between the cycles of treatment should be long enough for haematological and immunological recovery. The cycle was not given when the white cell count was less than 3500 or the platelets less than 100 000/mm³. Intermittent treatment also has the advantage of causing a constant and reasonably predictable myelodepression in any given patient (Pouillart *et al.* 1972; Mathé and Kernis 1975). This last point is of great importance, because after the first two cycles in hospital under strict haematological control, treatment continues as an outpatient, and a blood and platelet count is taken the day before the beginning of each cycle.

Blood and platelet counts were done the day before the beginning of each cycle and an electrocardiogram at the end of each cycle that included adriamycin. A stricter haematological control was employed during the first two cycles which were administered in hospital in association with radiotherapy. Every three months radiographs of the primary skeletal lesion and of the chest were taken; radiographic survey of other bones was performed only when clinically indicated.

To evaluate the effect of the adjuvant chemotherapy a comparison was made with a series of consecutive cases of Ewing's sarcoma previously treated in our Institute (1960 to 1970) by operation, by radiotherapy, of by both, but without chemotherapy. These cases matched the present series as regards age, localisation of

the tumour, and type of local treatment (Tables IV and V). Even as far as the radiotherapy is concerned, there were no significant differences between the two series.

RESULTS

Operation plus radiotherapy plus chemotherapy. None of the ten patients who had their primary tumour operated upon had any local recurrence, even when the excision was incomplete. One developed pulmonary metastases eight months after operation; the remaining nine patients had no signs of disease at follow-up varying from twelve to sixty-two months (average thirty-four months) after operation.

Radiotherapy plus chemotherapy. Initially, all twenty-seven patients had apparently complete regression of the tumour. Fifteen were in good health with no signs of disease twelve to sixty-two months (average twenty-nine months) after the beginning of treatment. Distant metastases with no signs of local recurrence were observed in two patients after five and sixteen months respectively; they were noted in the skeleton and lungs in one patient, in the skeleton only in the other, this second patient having signs of cerebral involvement associated with adjacent bone metastases in the skull. These patients died at seven and twenty-four months respectively after the beginning of treatment. We cannot rule out the possibility that, had they lived longer, a local recurrence would have appeared.

Local recurrence occurred in nine instances, at four to forty-eight months (average fifteen months) after the beginning of treatment. In six of these it was associated with metastases. In five cases these appeared at one to twenty-one months after the local recurrence, in one metastases developed six months before the appearance of the local recurrence. Five of these patients died between thirteen and thirty-eight months after the beginning of treatment; one is still living, with multiple metastases, fifty-one months after the beginning of treatment. Of the three patients who had local recurrence without apparent metastases, one died of complications due to the local recurrence. Of the remaining two one had the local recurrence treated by

operation, the other by radiation; both were living with no signs of disease at thirteen and forty-four months respectively after the beginning of the initial treatment. One patient died with an acute lymphoblastic leukaemia which appeared thirteen months after the beginning of treatment; there were no signs of local recurrence.

In contrast to other reports (Marsa and Johnson 1971; Mehta and Hendrickson 1974) no example of cerebral or meningeal involvement was encountered.

TOXICITY AND COMPLICATIONS

On the whole the chemotherapy was well tolerated. The main side-effects are reported in Table III. In addition, there were local complications at the radiation site: transitory oedema and induration of the irradiated limb in three cases; inflammatory reaction at the site of biopsy in three cases; one radiation ulcer; and one fracture of the tibia at the site of biopsy.

Table III. Toxicity and complications

Complications	Number of patients
Leucopenia ($<1000/\text{mm}^3$)	3
Alopecia	34
Infections	1 miliary pulmonary tuberculosis 1 herpes zoster
Severe nausea and vomiting	17
Neurotoxicity	15
Cardiac toxicity—clinical	0
—electrocardiographic	1

A constant but transitory leucopenia was seen with maximum reduction at the tenth to the fourteenth day after the beginning of cycle A. The level usually remained between 1000 and 1500 per cubic millimetre. Only in three cases, after the first two cycles administered during radiotherapy, was leucopenia more pronounced (500 to 800 per cubic millimetre); in these

three treatment was continued with reduced doses. Except in two cases, complete restoration to normal was seen within twenty days from the beginning of cycle A and within fourteen days from the beginning of cycle B. This restoration occurred even after repeated treatment cycles.

Twenty-two of our patients have already finished treatment. In none was there significant reduction of platelets. Two patients had infective complications: one developed miliary pulmonary tuberculosis which healed with antibiotics; the other developed herpes zoster, which also healed. There was constant but reversible alopecia, and moderate to severe nausea and vomiting in two-thirds of the patients. It usually began in the first twelve hours after beginning chemotherapy and persisted for twelve to twenty-four hours. After repeated treatment cycles, there was usually an attenuation of the gastric disturbances.

All patients developed depression or absence of patellar and calcaneal reflexes typical of vincristine neurotoxicity. Notable but transitory numbness was observed in about one third of the patients. Only in one case, at the end of the tenth cycle with adriamycin, did the electrocardiogram show transitory changes of the S-T and T waves.

DISCUSSION

The number of patients was too small to enable a differential prognosis to be made according to site, volume of the tumour and clinical signs. It should be noted, however, that twenty-five patients in the present series could be considered to have a high risk of early metastases, either because of the site of the primary tumour (scapula, ilium, ribs, sacrum) or because of an associated fever, greatly raised sedimentation rate and marked leucocytosis (Falk and Alpert 1967; Lichtenstein 1973; Pomeroy and Johnson 1975).

Our study confirms that, in Ewing's sarcoma, adjuvant chemotherapy is capable of limiting or destroying the micrometastases. The limited number of treated patients with as yet a comparatively short

Table IV. Comparison of disease-free follow-up in patients treated with or without chemotherapy

Number of cases	Treatment of primary tumour	Patients with no signs of disease					Metastases	Local recurrence
		After 1 year	After 2 years	After 3 years	After 4 years	After 5 years		
14	1960–1970 series Operation and radiotherapy	10 of 40	3 of 40	2 of 40	2 of 40	1 of 40	38 of 40	5 of 40
26	Radiotherapy only	(25%)	(7%)	(5%)	(5%)	(2%)	After 8 months (range 3–49)	After 8 months (range 6–14)
10	1972–1976 series Operation, radiotherapy and chemotherapy	25 of 37	15 of 24	9 of 15	5 of 10	3 of 6	9 of 37	9 of 37
27	Radiotherapy and chemotherapy	(62%)	(62%)	(60%)	(50%)	(50%)	After 19 months (range 5–42)	After 15 months (range 4–48)

Table V. Comparison of survival time in patients treated with and without chemotherapy

Number of cases	Treatment of primary tumour	Survivors					Survival time of fatal cases
		After 1 year	After 2 years	After 3 years	After 4 years	After 5 years	
14	<i>1960-1970 series</i> Operation and radiotherapy	18 of 40	7 of 40	4 of 40	3 of 40	2 of 40	38 fatal cases
26	Radiotherapy alone	(45%)	(17%)	(10%)	(7%)	(5%)	Average 10 months survival (range 5-50)
10	<i>1972-1976 series</i> Operation, radiotherapy and chemotherapy	36 of 37	19 of 24	12 of 15	6 of 10	3 of 6	9 fatal cases
27	Radiotherapy and chemotherapy	(98%)	(80%)	(80%)	(60%)	(50%)	Average 17 months survival (range 7-51)

Table VI. Local recurrence in patients treated by radiotherapy to primary site (reports in the literature)

Author	Number of patients*	Local recurrences		Range (months)	Mean (months)
		Number	Per cent		
<i>No chemotherapy</i>					
Boyer, Brickner and Perry (1967)	6	2	33	5-17	11
Marsden and Steward (1968)	22	12	54	?	?
Phillips and Sheline (1969)	20	5	25	?-14	?
Jenkin, Rider and Sonley (1970)	12	6	50	?	?
Freeman <i>et al.</i> (1972)	8	4	50	3- 8	5
Rosen <i>et al.</i> (1974)	16	7	43	6-26	11
Macintosh, Price and Jeffree (1975)	27	14	52	3-23	?
<i>With chemotherapy</i>					
Freeman <i>et al.</i> (1972)	4	3	75	3-15	7
Hustu <i>et al.</i> (1972)	9	1	11	10	10
Suit <i>et al.</i> (1973)	11	1	9	?	?
Rosen <i>et al.</i> (1974)	10	0	—	—	—
Pomeroy and Johnson (1975)	44	3	6	?	?
Jaffe <i>et al.</i> (1976)	8	2	25	?	?

*Only those patients followed up for at least one year have been included.

follow-up does not permit definitive conclusions. There is no doubt, however, that adjuvant chemotherapy increases the period of freedom from disease.

A comparison between the results of treatment with and without adjuvant chemotherapy (Table IV), shows a significant difference in the incidence of metastases at

follow-up. Furthermore the metastases developed later in the patients treated by adjuvant chemotherapy (average nineteen months in comparison with eight months). The length of survival of fatal cases also was longer in the chemotherapy group (average seventeen months against ten months) (Table V).

In our experience, adjuvant chemotherapy did not reduce the high incidence of local recurrence after radiotherapy that has been reported by several authors (Table VI) and appears to be diminished by increasing doses of radiation over 4000 to 4500 rads (Suit *et al.* 1973; Fernandez *et al.* 1974; Macintosh *et al.* 1975). It was hoped that adjuvant chemotherapy would reduce the risk of local recurrences, which usually appear comparatively late in the disease and are almost invariably associated with the appearance of distant metastases (Chabora *et al.* 1976). The first reported results seemed to suggest a lower local recurrence rate (Table VI), though in most cases the follow-up was too short. Our experience, on the contrary, shows a higher incidence in the group treated by adjuvant chemotherapy (nine local recurrences) in comparison with the control group (five local recurrences). This finding could be due to the fact that a high percentage of the patients in the control group died six to eight months after beginning radiation treatment. Local recurrences earlier than this are unusual, so that their figures could give a falsely low impression. In other words, adjuvant chemotherapy, by protracting the course of the disease, might give time for local recurrences to appear.

Local recurrence, as already reported (Suit *et al.* 1973; Fernandez *et al.* 1974), always develops at the site of the primary tumour despite the fact that this site received the maximum dose of radiation. Local recurrence is never seen on the borders of the primary tumour or in the surrounding areas, which received minor doses of radiation. This suggests that the peripheral (and radiologically undetectable) areas of Ewing's sarcoma are destroyed by radiation doses of 4000 to 4500 rads, while the central core of the tumour is not destroyed, even with doses as high as 7000 rads and over. It can be assumed that, as with other neoplasms, in Ewing's sarcoma the central part of the tumour, with its poor blood supply and necrotic areas, contains hypoxic and therefore radioresistant cells. The peripheral areas of the tumour and the micronodes in the medullary spaces,

on the contrary, have a better blood supply and are therefore more radioresponsive. Consequently it seems unlikely that adjuvant chemotherapy could reduce the incidence of local recurrences. Chemotherapeutic agents are in fact unlikely to reach the central, poorly vascularised, areas of the tumour. Even if they did so in a sufficient concentration, their action would probably be minimal on cells which, being hypoxic, are most likely to be mitotically quiescent and therefore resistant to cytotoxic drugs.

This differentiated cytotoxic effect of chemotherapeutic agents on the primary tumour and its micrometastases has been well demonstrated in a number of clinical and animal studies (Schabel 1975; Burchenal 1976) and our study confirms it.

The presence of live tumour cells inside an incompletely controlled primary tumour places the patient at an extreme risk of metastases, which may appear once chemotherapy has been completed. So the question arises whether metastases in Ewing's sarcoma develop from undetected micrometastases already present when treatment commenced, or whether they originate later from a tumour which the local therapy has been unable to control completely. This second possibility appears more likely; thus, of our ten patients whose primary tumours were treated surgically (and were therefore more easily controlled by subsequent radiation), only one developed metastases whereas eight of the twenty-seven patients who had radiotherapy alone developed them.

For these reasons we suggest that the treatment of Ewing's sarcoma should include operation as well as radiotherapy and adjuvant chemotherapy. This conclusion is in agreement with the findings of the Mayo Clinic's orthopaedic oncologists (Pritchard 1978). Operation may consist of amputation, especially for large tumours below the knee; in other cases it merely consists of radical or subtotal excision. The object of these operations is to remove the core of the tumour which is the more radioresistant and chemoresistant portion.

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