Adjuvant Treatment of Soft Tissue Sarcoma in Children and Adults

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Introduction

Soft tissue sarcomas are a rare group of tumours comprising approximately 1% of all malignant tumours. Conventional management has relied heavily on surgery, but the inadequacy of this approach is reflected by local recurrence rates of 40% – 80% in adult sarcomas and as high as 90% in childhood sarcomas. CANTIN [3] in a review of 784 patients found that 382 had died of sarcoma and 65% had developed metastases concomitantly with local recurrence. The high local relapse rate is due to absence of encapsulation of the tumour, which spreads along fascial planes and nerve trunks and possibly also to a multifocal origin. Thus, more adequate methods of local control and prevention of dissemination are required and these include radiotherapy, chemotherapy and immunotherapy.

Although there is animal data to suggest that the proliferative kinetics of malignant cells in large tumour masses differ considerably from those in small tumours [27], this data has yet to be confirmed for human tumours and it seems sensible, therefore, to use chemotherapy known to be effective in advanced disease.

Whilst some histological types of sarcoma seem to carry a worse prognosis (e. g. rhabdomyosarcomas, leiomyosarcoma), other factors may be more important. SUIT et al. [30] treating 100 patients with localised soft tissue sarcoma using limited surgery and high dose radiation therapy made the following observations:

1. Histological grade affected prognosis (disease-free survivals of 86% for grade I tumours compared to 17% for grade III);
2. size of the primary tumour determined the subsequent local recurrence rate (18% for tumours > 5 cm compared to 8% for those < 5 cm);
3. site of primary tumour was important (local recurrence rate 33% for a proximal site compared with 5% for a distal site).

Therefore, accurate staging is important in sarcomas, both in deciding the most appropriate treatment strategy and in assessing results. A staging system for adult sarcomas has been proposed by RUSSEL et al (26) using the TMN system with the addition of histological grade G, giving four stages (Table 1) that correlate well with survival in 1,215 cases of 13 types of sarcoma (Fig. I). The staging of childhood rhabdomyosarcomas takes into account the resectability of the tumour and the presence or absence of bone marrow involvement (Table 2).

Although bone marrow involvement is said to be rare in adult sarcomas, this may be because it is not looked for. Over the last 18 months, bone marrow aspirates and trephines have been carried out on all patients with locally advanced or metastatic soft tissue sarcoma seen at the Christie Hospital, Manchester, and so far 2 of 23 have been positive — in one pleomorphic rhabdomyosarcoma and in one angiosarcoma of the breast.

Table 1. Staging of adult soft tissue sarcomas

T	Primary tumor	T ₁	5 cm
		T ₂	5 cm
		T ₃	Any size invading bone, major vessel or nerve
N	Regional nodes	N ₀	Not involved
		N ₁	Histologically verified involved
M	Distant metastases	M ₀	No distant metastases
		M ₁	Distant metastases
G	Histological grading	G ₁	Low
		G ₂	Moderate
		G ₃	High
Stage I	Grade I tumour with no nodal or distant metastases		
	Ia	< 5 cm	
	Ib	> 5 cm	
Stage II	Grade 2 tumour with no nodal or distant metastases		
	IIa	< 5 cm	
	IIb	> 5 cm	
Stage III	Grade 3 tumour with no nodal or distant metastases		
	IIIa	< 5 cm	
	IIIb	> 5 cm	
	IIIc	Tumour of any grade or size with regional lymph nodes involved but without distant metastases	
Stage IV	IVa Tumour of any grade grossly invading bone, major vessel or major nerve with or without nodal metastases but without distant metastases.		
	IVb Tumour with distant metastases		

Adapted from Russel et al., Cancer 40, 1562–1570 (1977).

Fig. 1. Survival curves by steps for 702 cases with complete information for staging: 423 cases with slide review and 279 without. The curve for stage II was not plotted beyond 5 years since at that point the standard error was 5% or higher. RUSSEL et al., Cancer 40, 1562–1570 (1970)

Table 2. Staging of childhood rhabdomyosarcoma

Stage I	Localised disease
Stage II	Regional disease
Stage IIA	Completely resectable
Stage IIB	Non-resectable or only partially resectable
Stage III	Generalised disease
Stage IIIA	Distant metastases with normal bone marrow
Stage IIIB	Distant metastases with bone marrow containing rhabdomyoblasts

Source: Malpas et al. *B. M. J.* **1**, 247–249 (1976).

Childhood Soft Tissue Sarcoma

Rhabdomyosarcomas are the commonest group of soft tissue sarcomas occurring in childhood. These are usually of the embryonal or botryoid type, which tend to occur before the age of 6 years, but occasionally may be alveolar or pleomorphic in type, occurring in an older age group (12–16 years) and having a poorer prognosis. Other sarcomas are rare, including fibrosarcoma, liposarcoma, synovial sarcoma and undifferentiated sarcoma, but seem to have a better prognosis. For example, CHUNG and ENZINGER [4] reviewed 48 cases of infantile fibrosarcoma treated mainly by surgery alone and found 31 (65%) were disease-free and only four (8.3%) had died of disease 5 months – 21 years after treatment. Poor overall survival rates (in the order of 10%–30%) have been reported for rhabdomyosarcoma treated by surgery or radiotherapy alone [7, 14, 29, 31]. However, the addition of adjuvant chemotherapy to primary surgery or radiotherapy has led to considerable improvement in both complete remission rate and disease-free survival. Vincristine, cyclophosphamide and actinomycin D have all been shown to be active as single agents [22, 32, 33] although responses are often transient with rapid emergence of drug resistance. Combination chemotherapy with these three agents in advanced disease has produced superior results in terms of both remission rate and duration [23].

In 1972, PRATT et al. [24] reported 20 children with rhabdomyosarcoma treated with a coordinated programme combining surgery, radiotherapy and combination chemotherapy (Table 3). Eleven of 14 patients with localised tumours achieved a complete remission, seven continuing for 2–39 months from the start of chemotherapy. There were four temporary complete remissions and one partial remission in the six patients with metastatic disease.

DONALDSON, et al. [5] reported a 74% (14 patients) survival for a minimum of 2 years and 89% (17 patients) local control in 19 evaluable patients with rhabdomyosarcoma of the head and neck treated by local excision or biopsy, high dose radiotherapy – 6000 rad in 6 weeks – and combination chemotherapy with VAC (Table 3). Complications, however, were severe and included:

1. One death due to unexplained renal failure during chemotherapy.
2. Five patients with ocular problems. Three required exenteration of the orbit, one as the primary procedure, one for residual disease and the other for radiation keratitis, iritis and conjunctivitis. There was one asymptomatic radiation-induced cataract occurring 27

Table 3. Chemotherapy regimes for paediatric sarcomas

Pratt						
Vinc	1.5 mg/m ²	} IV weekly × 6 concurrent with XRT	Vinc	}	Every 2 weeks for 6 months (for localised disease) or 12 months (regional or metastatic disease)	
Act D	0.4 mg/m ²		Cyclo			
Cyclo	300 mg/m ²					
Donaldson						
Vinc	2 mg/m ² IV weekly × 12		Starting concurrently			
Act D	0.075 mg/kg IV for 5–8 days		with XRT			
	Courses repeated every 3 months to a total of 5					
Cyclo	2.5 mg/kg/day orally continuously for 2 years					
Heyn						
Chemotherapy commencing immediately after completion of XRT						
Act D	0.015 mg/kg/day IV × 5 days	}	Repeated every 9 weeks for 1 year			
	0.075 mg/kg/week IV × 6 doses					
	starting on day 21					
Malpas						
Vinc	1.5 mg/m ²	} IV weekly × 6	}	Then all three drugs every 2–3 weeks for 1 years		
Act D	0.06 mg/m ²					concurrent with
Cyclo	300 mg/m ²					XRT
Voute						
Vinc	2 mg/m ² IV every 2 weeks					
Act D	15 µg/kg IV days 1–5 every 12 weeks					
Cyclo	200 mg/m ² days 1–5 every 6 weeks					

- months after therapy and another patient suffered mild superficial keratitis with early corneal stippling year post therapy.
3. Most patients suffered severe mucositis, often requiring nasogastric feeding or intravenous fluids;
 4. There was one case with probable osteonecrosis of the mandible and another with atrophy of the zygoma.
 5. Severe dental decay occurred in two patients;
 6. Seven episodes of ear infection occurred and one patient required a simple mastoidectomy;
 7. Moderate bone marrows suppression was frequent.

Most of these complications could be attributed to the high dosages of radiation used, sometimes aggravated by actinomycin D.

In 1974, HEYN et al. [13] described a randomised study in 32 patients with rhabdomyosarcoma of all sites. Patients were eligible if the tumour had been completely removed surgically and there was no evidence of metastatic disease. All patients had post-operative radiotherapy to the tumour bed and were then randomised to receive either chemotherapy (Table 3) or no

further treatment. An additional group of 11 patients with residual microscopic disease received post-operative radiotherapy and the same chemotherapy. Fifty-three percent (8/15) of the control group subsequently developed metastatic disease 3–30 months from diagnosis of whom six died. In the comparable treated group, only 17.6% (3/17) developed metastases with one death. The use of adjuvant combination chemotherapy in those patients rendered free of macroscopic tumour by surgery and radiotherapy produced a 2-year disease-free survival of 85.7% (24/28).

Some tumour sites, however, preclude radical surgery. MALPAS et al. [15] treated 11 patients with regional disease primarily with radiotherapy supplemented by adjuvant chemotherapy. After biopsy, radiotherapy (4000–6000 rad over 4–6 weeks) was administered using generous fields to include any local extension and the lymphatic drainage of the tumour. Concurrent weekly chemotherapy (Table 3) was followed by further courses of VAC at 2–3 weekly intervals for 1 year. Occasionally radiotherapy was preceded by several courses of chemotherapy if the tumour was very extensive. All 11 patients achieved a complete remission and in four who were submitted to ‘second look surgery’ for suspected recurrence or residual disease, there was no evidence of viable tumour. Three patients subsequently relapsed and died at 15, 16 and 26 months but the rest were disease-free 4–29 months from the start of treatment, and the median survival for the group has not been reached. A historical control group of 17 patients of similar stage treated by radiotherapy and surgery alone had only one survivor at 18 months and the median survival was 10 months. Analysis in January 1978 showed that no further relapses had occurred, an additional 11 patients had been treated, the total group having disease-free survivals ranging 3–67 months (personal communication).

An alternative approach to management of these tumours is primary chemotherapy, supplemented by adjuvant surgery or radiotherapy. This has the potential advantage that extensive and mutilating surgical procedures may be avoided. Similarly, as marginal recurrence is common, wide radiation fields may be needed to encompass local tissue infiltration, thus limiting the total radiation dose and producing late complications due to local growth retardation. Shrinkage of the tumour by chemotherapy may avoid the necessity for extensive fields and allow local high dose radiotherapy or limited surgery to be used.

The Amsterdam Study Group on Childhood Tumours conducted a study of this type between 1971 and 1975 [21], admitting 18 evaluable patients with tumours occurring in the urogenital tract (8 patients) and ENT region (10 patients). All patients were treated with initial chemo-

Table 4. Rhabdomyosarcoma of the ENT and urogenital tract treated in Amsterdam with chemotherapy and limited adjuvant treatment (October 1972 – November 1975)

Patients entered	26
Previous treatment with surgery or radiotherapy	8
Patients evaluable	18
NED after chemotherapy alone	7
NED after chemotherapy and limited surgery	5
DWD (local recurrence)	3
DWC (local control but cerebral metastases)	3

NED No evidence of disease.
DWD Died with disease.

therapy (Table 3), which was administered over an 18-month period with frequent reassessment of the need for additional surgery or radiotherapy. Results of treatment are shown in Table 4. Seven patients had no evidence of disease after chemotherapy alone 24–26 months from the commencement of treatment (Table 5). Five patients required local treatment for residual disease during chemotherapy and are disease-free 24–60 months later (Table 6). Six patients died with disease. One patient with a bladder tumour completed 18 months chemotherapy but developed a vaginal recurrence 2 months later and succumbed despite further surgery and radiotherapy. There were two local recurrences during chemotherapy in a nasopharyngeal and a maxillary tumour, both of which proved to be resistant to radiotherapy. Three patients with tumours of the maxillary sinus, tonsil and pterygoid fossa all died of cerebral metastases but autopsy in each case showed local tumour control and in one case, resolution off lung metastases.

Although overall survival was not particularly good in this study, quality of life was considered to be important and 12 of the 18 children were spared mutilating treatment. Three children died of cerebral metastasis – a site notoriously resistant to these chemotherapeutic agents. These results have encouraged the International Society of Paediatric Oncology to initiate a European trial starting in October 1975, comparing chemotherapy and chemoradiotherapy in the treatment of rhabdomyosarcomas, additional limited surgery being possible in both groups. Chemotherapy is the VAC regime with the addition of adriamycin during the 10th week, actinomycin D and cyclophosphamide being given every 8 weeks.

Table 5. Rhabdomyosarcoma of ENT and urogenital tract treated in Amsterdam. Patients treated with chemotherapy alone who remain disease free

Primary tumour site	Survival (months from diagnosis)
Palate invading left pteryoid process	60
Tonsillar fossa	39
Bladder with local extension and lung metastases	31
Vagina	27
Paratesticular with local extension	60
Bladder	24
Parotid	36

Table 6. Rhabdomyosarcoma in urogenital tract and ENT region treated in Amsterdam. Patients treated with chemotherapy and surgery, disease-free

Primary tumour site	Type of surgery
Vagina: labia	Labiectomy
Oral tumour — local recurrence in cheek	Excision of cheek recurrence
Bladder: prostate	Hemi-prostatectomy
Bladder with lung metastases	Two pulmonary resections, partial bladder resection
Parotid	Parotidectomy

Adult Soft Tissue Sarcoma

Radiotherapy

The place of radiotherapy as an adjunct to surgery in soft tissue sarcomas is disputed. The degree of radioresponsiveness of soft tissue sarcomas has first to be established. Initial reports often described the use of orthovoltage irradiation in widely varying doses and schedules, usually on large inoperable tumours. Not surprisingly, responses were few and unpredictable and local tissue damage could be severe. Nevertheless, MCNEER, et al. [16], in a review of 653 patients with soft tissue sarcomas of all types treated 1935–1959, reported 58 evaluable patients who had been treated by radiotherapy, alone or pre-operatively. Response (defined as greater than 25% regression) occurred in 42 (72%) and 33% showed histological or biological (i.e. no recurrence on follow-up of more than 5 years) sterilisation of the tumour. These patients were treated with a wide range of doses utilising a variety of techniques and types of equipment. However, WINDEYER [36] treated 22 fibrosarcomas by radiotherapy alone with the object of cure. Most patients received 6000–8500 rad on megavoltage equipment over 6–8 weeks. Fourteen showed complete regression and five partial regression. Six of those with complete responses had a subsequent recurrence but 6/8 given radiotherapy to the primary tumour and 6/10 treated for tumours recurrent after previous surgery were disease-free at 5 years. As there are limitations to the volume of tissue that can be treated with a radical dose of radiation, size of the primary tumour is an important factor when making comparisons between studies. Thus, it seems that soft tissue sarcomas are responsive to radiation but high doses (≥ 6000 rad in 6 weeks) are needed and some histological types (e.g. liposarcomas) are more responsive than others (e.g. pleomorphic rhabdomyosarcomas) [16, 18].

ATKINSON et al. [1] advocated pre-operative radiotherapy — 4500 rad over 4–5 weeks preceding surgery by 4–6 weeks — quoting 15 patients treated in this way with only one local recurrence and no metastases with an average follow-up of 40 months. Forty patients having no pre-operative irradiation experienced 40 episodes of recurrence following 54 local surgical procedures and seven patients developed metastases. However, this latter group was not strictly comparable as surgery was usually carried out at referring institutions and only selected high risk cases may have been referred for further management.

Adjuvant radiotherapy is most frequently administered post-operatively. SUIT et al. [30] using high radiation doses (≥ 6000 rad in 6 weeks) in combination with surgery in 71 primary and 29 recurrent soft tissue sarcomas, achieved local control in 87% with follow-up of 2–12 years. Seventy-five percent of the 89 patients with extremity lesions retained a useful limb that was free from pain and oedema. Despite this, the 2-year survival rate was only 50% with the majority of patients dying of metastatic disease. Thus, although good local control may be achieved with radiation therapy, patients still succumb to metastatic disease.

HELLMAN, et al. [12] added razoxane (ICRF 159), an antimitotic drug that seems to potentiate the effects of radiation, to radiotherapy given with curative intent in a group of inoperable or incompletely excised sarcomas and showed a significant difference in the recurrence rate (26% cf. 64%) in favour of the razoxane-treated group. However, this trial has serious defects in that it was non-random, the numbers evaluable were small [33], the initial size of the tumour was not stated and there were major discrepancies in the histological type and primary site between the two groups.

Chemotherapy

There have been few studies of the use of adjuvant chemotherapy in adult soft tissue sarcoma. TOWNSEND et al. [35] reported 35 patients with localised sarcomas, 16 of whom received adjuvant chemotherapy post-operatively with high dose methotrexate and adriamycin. Eleven (68%) were disease-free at the time of analysis (with mean follow-up of 9.3 months) whereas 14 of 19 patients (77%) treated by surgery alone had developed metastases (mean time to recurrence 7.3 months). However, this study is difficult to interpret as it was non-random, included bone and soft tissue sarcomas and gave no indication of tumour type, size or grade. The same group in Los Angeles [17] used adjuvant therapy in 19 patients with extremity soft tissue sarcoma with the aim of avoiding amputation and retaining a functional pain-free limb. Five patients were submitted to wide excision followed by post-operative irradiation (6000 rad in 6–7 weeks) and there were no recurrences. Six patients had pre-operative perfusion of the limb with intra-arterial adriamycin followed 3 weeks later by radical surgery. In five of the six there was insufficient tumour regression to allow local excision, and amputation was necessary. Eight patients were treated with pre-operative radiotherapy and chemotherapy ± immunotherapy (Table 7). Local surgery was possible in

Table 7. Adjuvant therapy for sarcomas of an extremity

Day 1	Adriamycin 30 mg/m ² /day IA × 3
Day 4	XRT 3500 rad over 10 days
Day 21	Surgery
Day 29	Commencement post-operative chemotherapy Vincristine 1.5 mg/m ² IV followed 1 h later by Methotrexate 100 mg/kg as 4-h infusion 4 h after completion of infusion — ‘rescue’ with IV Leucovorin 12 mg every 6 h for 3 days supplemented if methotrexate serum level at 4, 6, 12, 24 or 48 h exceeded 1 × 10 ⁻⁶ M
Day 43	Adriamycin 45 mg/m ² /day IV bolus × 2 These cycles are repeated every 2 weeks to maximum cumulative dose of adriamycin, 500 mg/m ² when discontinued. Methotrexate given every 4 weeks for a further year. Immunotherapy given as below:

Adjuvant immunotherapy of localised soft tissue sarcoma^a

5 × 10⁸ viable organisms Tice BCG ID. Tine method, both axillae, both groins every week for 3 months, then every 2 weeks for 2 years. Tissue culture vaccine 1 × 10⁸ sarcoma cells, total dose, ID both axillae, both groins and region of primary tumour site on same schedule.

Source: Morton et al., Ann. Surgery 184, 268 (1976).

^a Morton, J.A.M.A. 236, 2187 (1976).

Table 8. Alomad

Day 1	Vincristine	1	mg/m ² IV
	Methotrexate	250	mg/m ² IV infusion over 24 h
Day 2	Leucovorin	50	mg/m ² }
	Adriamycin	40	mg/m ² } IV
	DTIC	500	mg/m ² }
	Leucovorin	5	mg/m ² orally every 8 h × 12
Days 15–29 and 57–71	Chlorambucil	6	mg/m ² /day orally × 14
Days 22 and 64	Actinomycin D	1.2	mg/m ² IV
Day 43	Adriamycin	50	mg/m ² IV

seven and all were free of disease 4–34 months later. Of the 17 patients (including four chondrosarcomas) treated by wide excision alone, 11 had recurred within 2 years. SORDILLO et al. [28] used a complex adjuvant regime ALOMAD (Table 8) in 73 patients following surgery for soft tissue sarcoma. Sixty-one patients were evaluable and were divided into five groups. Group I consisted of 19 patients given adjuvant therapy following removal of a primary tumour and there had been one local recurrence, 18 patients having no evidence of disease 3–34 months (median 15) from surgery. Group II comprised eight patients treated for locally recurrent tumour and there had been one local recurrence and one patient had developed distant metastases, the rest having no evidence of disease 4–33 months (median 16) from surgery. The remaining three groups included patients given post-operative radiotherapy because of inadequate surgical margins (III), pre-operative radiotherapy and adriamycin for large tumours (IV) and chemotherapy administered after resection of pulmonary metastases (V). Taking these three groups together there had been 13 recurrences in 34 patients.

These studies also suffer from the defects that they were non-randomised, numbers in each treatment group were small and in Townsend’s study, the control group were treated inadequately and consequently had a high rate of recurrence. The value of adjuvant radiotherapy and chemotherapy in allowing preservation of a limb can only be assessed by comparison of the disease-free intervals, and survivals of a group given adjuvant treatment with those of a concurrent randomised group treated by radical surgery alone, which in most cases would involve an amputation.

A randomised study comparing amputation with limb-sparing surgery and post-operative radiotherapy, both groups having adjuvant chemotherapy ± immunotherapy (Table 9) has been conducted by ROSENBERG et al. [25] at the NCI May 1975 – June 1977. The value of adjuvant chemotherapy was assessed by comparison to a historical control group of 66 patients treated at the NCI by radical surgery alone. Forty-nine evaluable patients were entered – 23 with lesions of the head, neck and trunk, 26 with extremity tumours – and results of treatment are shown in Table 10. Follow-up ranges from 5–30 months with a median of 16 months. Actuarial analysis of all protocol patients compared with historical controls reveals improvement in disease-free interval ($P < 0.001$) as well as survival ($P < 0.001$) (Figs. 2 and 3). Toxic effects were few. Thirty-four of 49 patients received the maximum permitted escalation of chemotherapy. Three patients refused chemotherapy after 50 mg/m², 160 mg/m² and 210 mg/m² of adriamycin. Two were lost to follow-up 121 days and 114 days after

Table 9. Adjuvant chemotherapy used by ROSENBERG et al.

Chemotherapy started when surgical wound healed, the first dose being given 3 days prior to ensuing radiation.	
Adriamycin	50 mg/m ² IV escalating to 70 mg/m ² depending on toxicity
Cyclophosphamide	500 mg/m ² IV escalating 700 mg/m ²
Courses repeated at 4-weekly intervals until maximum cumulative dose of adriamycin reached, 550 mg/m ² . Patient then switched to high dose methotrexate.	
Methotrexate	50 mg/kg by 6 h infusion followed 2 h after completion by ‘rescue’
Leucovorin	15 mg/m ² IV every 6 h × 8 doses
Hydration and alkalinisation carried out. Additional leucovorin given if 48 h serum level methotrexate 4 × 10 ⁻⁷ M.	
Courses repeated every 28 days × 6 with escalation by 50 mg/kg to maximum 250 mg/kg if no toxicity with previous course.	

Table 10. Results of protocol treatment^a

Extremity	No. of patients	No. recurred	Site of initial recurrence	No. dead
Radical surgery	10	1 ^b	Lungs	1
Limited surgery + radiotherapy	9	1	Lung	0
Limited surgery + radiotherapy + immunotherapy	7	1	Local	1
Historical control	46	26	—	23
Head, neck and trunk				
Surgery + radiotherapy	11	1	Lungs	0
Surgery + radiotherapy + immunotherapy	12	1 ^c	Local	0
Historical control	20	10	—	6

^a All patients received chemotherapy with adriamycin, cyclophosphamide and methotrexate.
^b Left protocol after third adriamycin dose. Recurred 1 year later.
^c Recurred at local site during radiotherapy and underwent local resection. Patient is disease-free at day 372.

randomisation and were disease-free. The third patient relapsed with pulmonary metastases 1 year later. Although the use of historical controls is a criticism of this study, the 5-year survival of the control group parallels the survival curves of 1215 cases from ten institutions reviewed by the Task Force on Soft Tissue Sarcoma of the American Joint Committee for Cancer Staging and

Fig. 2. Soft tissue sarcoma — adjuvant study by ROSENBERG et al. Actuarial analysis of time to first recurrence

Fig. 3. Soft tissue sarcoma — adjuvant study by ROSENBERG et al. Actuarial analysis of survival

End Results [26] and should therefore be representative of surgical results. Nevertheless, there may be important differences between protocol patients and historical control groups. For example, the difficulty of establishing accurately the size of lesions in historical control patients as well as time from onset of symptoms to surgery and the changing pattern of referral of patients to the NCI may all influence the comparison of current protocol patients with historical patients. However, the differences between the two groups in terms of time to first recurrence and survival are both highly significant and the tentative conclusion that adjuvant chemotherapy delays or prevents dissemination of soft tissue sarcomas is possible. Clearly, longer follow-up is needed and randomised prospective trials comparing adjuvant chemotherapy with a control group treated by surgery alone are essential and both the NCI and the EORTC are initiating such trials.

Immunotherapy has been used in many types of tumour and the demonstration of tumour-associated antigens [6] prompted TOWNSEND et al. [34] to study the role of adjuvant immunotherapy with BCG and tumour cell vaccine in sarcomas. Eighteen patients with localised primary or locally recurrent soft tissue sarcomas were submitted to wide resection removing macroscopic tumour. Three to six weeks following operation, they were commenced on immunotherapy (Table 7). This group was compared with 15 patients treated

simultaneously by surgery alone because they had refused immunotherapy. Eleven of 18 (61%) receiving immunotherapy remained free of disease compared with 5/15 (33%) having surgery alone. However, ten recurrences (66%) in the control group within 2 years seems rather high for localised disease, for although CANTIN et al. [3] report a 59% recurrence rate in 784 patients seen at the Memorial Hospital, there was only a 29% recurrence rate when the primary treatment was carried out at Memorial. As this was a non-randomised study involving few patients, the value of immunotherapy remains to be proven.

It would seem logical in an adjuvant trial to use chemotherapy that has been proven to be effective in metastatic disease. Recent studies have shown that several drugs have activity against soft tissue sarcoma. Adriamycin is the most potent drug and GOTTLIEB [9] reviewing the world literature found 96 of 357 responses (27%) although there was a wide variation between individual studies. Response to DTIC seems to be in the order of 16% [11] but there is very little data on other single agent chemotherapy in adult sarcomas. Synergism has been noted in experimental animal models between adriamycin and DTIC [8] and the clinical combination of these two agents appears to be superior to adriamycin alone, both in terms of remission rate and survival [10]. Cyclophosphamide and vincristine have been added to this combination because of their efficacy in childhood sarcomas, although few patients with adult sarcomas have received these drugs as single agents. The combination of these four agents (CYVADIC) has been used in a large number of patients by the South West Oncology Group with an overall response rate of 59% in one trial, and of 52% in a subsequent trial in which a slightly modified version was used [9]. Replacing either DTIC [2] or vincristine [19] by actinomycin D produced increased toxicity and an inferior response. The EORTC is currently conducting a trial in metastatic disease [20] comparing two schedules of CYVADIC. The S_1 regime (Table 11) using all four drugs concurrently but modified to give the same total dose of DTIC over 3 days instead of 5 (Table 11) forms the basis of an adjuvant trial recently initiated by the EORTC (May 1978). This trial will include all patients aged 20–70 with a proven histological diagnosis of soft tissue sarcoma (Table 12) who have had complete macroscopic removal of their tumour less than 13 weeks before entry and have no evidence of metastases. Post-operative radiotherapy, minimum dose 5000 rad in 4 weeks will be given to those cases where there is microscopic residual disease, there are inadequate surgical margins or the tumour has recurred locally. Patients will then be randomised into two groups, one receiving eight cycles of chemotherapy at monthly intervals and a control group receiving no further treatment. The disease-free interval and survival of the two groups will be compared.

Table 11. CYVADIC S_1 regime used in EORTC trial of therapy of metastatic soft tissue sarcoma.

Adriamycin	50 mg/m ²	} IV day 1
Cyclophosphamide	500 mg/m ²	
Vincristine	1.5 mg/m ²	
DTIC	250 mg/m ²	IV days 1-5 repeated every 4 weeks

Modified CYVADIC S_1 regime used in EORTC adjuvant trial

Adriamycin	50 mg/m ²	} IV day 1
Cyclophosphamide	500 mg/m ²	
Vincristine	1.5 mg/m ²	
DTIC	400 mg/m ²	IV days 1–3 repeated every 4 weeks for 8 cycles

Table 12. Histologic types of soft tissue sarcomas eligible for EORTC adjuvant trial

Fibrosarcoma
Liposarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Malignant haemangioendothelioma (angiosarcoma)
Malignant lymphangiopericytoma
Malignant lymphangioendothelioma (lymphangiosarcoma)
Malignant synovioma
Malignant schwannoma (neurofibrosarcoma)
Malignant mesenchymoma
Alveolar soft parts sarcoma
Malignant granular cell tumour
Chondrosarcoma of soft parts
Osteosarcoma of soft parts
Malignant giant cell tumour of soft parts
Malignant fibroxanthoma
Clear cell sarcoma of tendons and aponeuroses

N.B. Cases of fibromatosis and well-differentiated liposarcomas are excluded.

Summary and Conclusions

As sarcomas of soft tissues are unusual tumours with widely ranging natural histories, there has been considerable controversy surrounding their management. The desire to avoid mutilating surgery must be balanced against the known frequency of local recurrence that may be accompanied by dissemination, and past experience has shown that the sole use of even extensive surgery may be inadequate. Several problems still remain to be answered:

1. Will *radiotherapy* eradicate microscopic residual disease and can wide local excision with pre- or post-operative radiotherapy $\pm$ chemoimmunotherapy replace amputation in extremity sarcomas? Although there is suggestive evidence from several studies that this may be so, the numbers of patients treated in this way have been small, duration of follow-up short and no prospective randomised controlled trials have been carried out comparing a group given adjuvant treatment with a group managed by radical surgery alone, and this should be rectified.
2. What *dosage of radiation* should be employed and are the results of radiotherapy or chemotherapy affected by the histological type? High radiation doses (≥ 6000 rad in 6 weeks) have been recommended by most authors, lower doses producing less consistent effects. There does not seem to be any statistically significant difference in the response of various histological types of soft tissue sarcoma to combination chemotherapy or radiotherapy, although some authors have commented on the relative radioresponsiveness of myxoliposarcoma.
3. Which *characteristics of the primary tumour* most influence prognosis? The chances of local recurrence and metastasis seem to depend less on histological type than on initial size, site and grade of the tumour and these factors must be carefully controlled when comparing results of treatment.
4. What is the *most appropriate combination of drugs* and the optimum scheduling and duration of adjuvant chemotherapy? Although adriamycin is undoubtedly effective in adult

sarcomas, adequate phase II studies have not been performed for cyclophosphamide and high dose methotrexate. Many of the studies of adjuvant chemotherapy discussed in this article used drugs and regimes of unproven value in adult soft tissue sarcoma and the use in adjuvant trials of the CYVADIC regime that has been extensively studied in metastatic disease seems more logical. Meanwhile, more thorough investigation of cyclophosphamide, high dose methotrexate and actinomycin D as single agents would be valuable, and phase II trials of newer agents such as cis-platinum are required.

The rarity of soft tissue sarcomas means that despite their inherent problems, large multi-centre collaborative trials will be necessary to accrue sufficient patients to produce reliable information on the efficacy of adjuvant therapy. However, despite the many difficulties, sarcomas seem to be a group of tumours that are responsive to chemotherapy and there is every reason to hope that adjuvant therapy will be of considerable value.

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