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Treatment of Soft Tissue Sarcomas

A Combined Modality Approach

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Abstract—*The results obtained in the treatment of* 45 *cases of soft tissue sarcomas are presented. All cases were reviewed and classified according to the modern criteria of malignancy. The treatment schedule comprised:* (1) *Preoperative irradiation: two sessions of* 650 cGy *in* 48 hr—*Target volume: whole limb segment;* (2) *Surgical excision* 48 hr *later with systematic intraoperative histologic verification, until healthy tissue margins are obtained;* (3) *Postoperative irradiation* 3 weeks *later delivering a cumulative total dose of* 5000 cGy *to the preoperative volume and* 6000–7000 cGy *to a reduced volume encompassing the surgical region with protection of vascular axes where possible;* (4) *Chemotherapy: Actinomycin D* 0.3 mg/m^2 *half an hour before the first* 5 *sessions of post-operative irradiation;* (5) *Bilateral lung irradiation:* 4 *sessions of* 375 cGy *in* 7 days *to the whole chest. The results were as follows: Local recurrence rate was* 12% *at* 5 years. *In* 21 *cases in whom surgical excision was deemed histologically adequate, no recurrences were seen at* 2 years (*minimum follow-up*). *Survival at* 5 years *was* 76%. *Deaths were due to metastatic spread, especially to the lungs. These results show an improvement as compared with historical series. New progress should be sought in combining a more aggressive type of chemotherapy for cases with high metastatic risk.*

INTRODUCTION

MALIGNANT tumors of the soft tissues not only present certain difficulties in their clinical and histological diagnosis, but these tumors are particularly problematic when it comes to effective management. Their prognosis has long been considered poor due to the high incidence of local recurrence and metastatic spread.

We have found that a close collaboration between therapists and histopathologists can contribute significantly to improving the survival of these patients.

Although the problem of distant metastases remains a major one, there is hope that the problems raised by local evolution are on the way to being resolved. Until recently, local cure was obtained only at the high price of severe mutilation, which unfortunately often proved fruitless in patients bearing subclinical metastases. In an earlier paper [1], we reported the preliminary results of a combined approach of radiation therapy and conservative surgery; this method has continued to prove its interest. Similar findings have also been reported in other series [2–4].

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We wish, in the present article, to report on our experience with the combined modality approach, and to point out the therapeutic features which appear to have a determining influence.

MATERIALS AND METHODS

Materials

Malignant tumors of the soft tissues are characterized by their great clinical and histological diversity. Similarities in the problems raised with regard to diagnosis, course and prognosis, however, make it possible to group a certain number of these tumors.

For the purposes of the present study, locally malignant tumors (classified as fibromatoses by the World Health Organization) [5] and the sarcoma of Kaposi have been excluded, as have the sarcomas of the orbital, mediastinal, pleural, peritoneal and retriperitoneal organs. Only malignant tumors of the trunk, and the head and neck have been retained. This study is also limited to the so-called "adult" tumors, and does not include the embryonal sarcomas of childhood.

A total of 58 patients with tumors as defined above were treated at the Centre

François Baclesse from July 1972 (date of introduction of new treatment modalities to December 1977. Thirteen of these 58 patients were not retained in the present study. Four were eliminated because the histological diagnosis was not confirmed when the sections were reviewed. The histopathological methods used to review the material have been described elsewhere [6]. Three were excluded because a review of the histopathologic slides was not possible. Six were ineligible for radical treatment: two presented with metastases, three had poor general and local condition precluding inclusion, and one patient refused the treatment.

The present study thus concerns the therapeutic results obtained in a total of 45 cases, all of whom underwent surgery. All the histologic records for these 45 patients were reviewed and the histologic type and malignancy of the tumors were confirmed. There were 24 female patients and 21 males.

The age distribution on our series is classical, and is given in Fig. 1. Distribution according to histologic type is provided in Table 1. It is interesting to note that, after the review of the slides, malignant fibrous hystiocytomas became numerous to the detriment of other types (11 liposarcomas, 4 fibrosarcomas, 1 rhabdomyosarcoma, 1 unclassified malignant (Table 2). Clinical sizes of the primary tumors are provided in Table 1. There was a preponderance of lesions of greater than 5 cm in diameter. Fifteen of the 45 patients had been referred to our Center for treatment of local recurrence. None of the 45 patients had clinical or radiological evidence of metastases at the time of treatment of the primary tumor. Pretherapeutic work-up comprised chest X-ray in all cases and lung tomography only when suspicion of metastases was present. None of the cases were submitted to computerized tomography scan exploration.

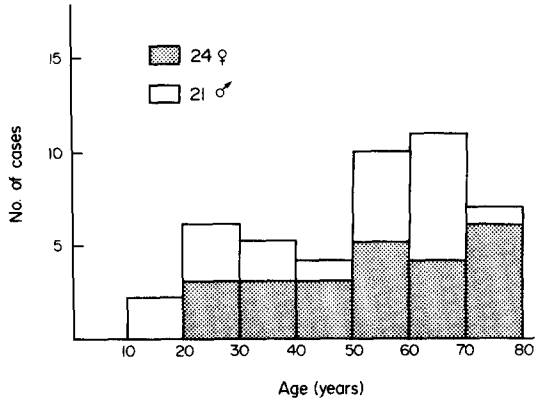

Fig. 1. Age and sex distribution.

Methods

Therapeutic modalities. In July 1972, a new treatment comprising several original features was introduced (Table 3). Basic local treatment comprised a combination of conservative surgical excision and radiation therapy. The essential feature of the surgical procedure was that it was guided throughout by the systematic histopathologic examination of the excised sections. When histologic diagnosis had not been ascertained beforehand, it was obtained immediately on commencement of surgery. Positive diagnosis was then followed by wide excision of the tumor, and the progress of the surgeon was followed closely by the histopathologist until, whenever possible, healthy specimens were obtained.

When the primary tumor had been resected previously, but it was not known whether surgery had been adequate or not (the latter was usually the case), excision was performed again in the above manner until judged satisfactory.

When complete excision of the lesion was found to be impossible, a decision was made either to resort to amputation or to rely on post-operative radiation therapy.

When a histologic diagnosis had been obtained prior to surgery, preoperative radiation therapy was delivered to a large volume including the whole anatomic region of the tumor site (segment of limb, wall of trunk, cervical region) and comprising a safety margin of at least 5 cm around the lesion. Irradiation was delivered in 2 sessions of 650 cGy at 48 hr interval, the second session taking place 48 hr prior to surgery. This irradiation can be considered to be equivalent to 2600 cGy delivered in 2.5 weeks (conventional fractionation) as far as normal tissue tolerance is concerned and according to our clinical experience.

Routine postoperative irradiation, delivered with a conventional fractionation, was performed after healing of the wound (generally 3 weeks after surgery). The total dose, cumulative with the preoperative treatment, was brought to 5000 cGy to the wide volume, i.e. adding a dose of 2400 cGy with a conventional fractionation. In the same way, 6000 cGy was given to the volume encom-

Table 1. *Distribution of cases*

	Site	Tumor diameter			Radiotherapy		Surgical excision ∅			Act. D	B.L.I.	Status	
		⩽5cm	>5cm	Unspecified	Preop.	Postop.	Complete	Uncomplete	Unspecified		§	Alive	Dead
DERMATOFIBROSARCOMA	T W	–	+	–	–	–	+	–	–	–	–	48	–
	T W	–	+	–	–	–	+	–	–	–	–	42	–
(6 cases)	T W	+	–	–	–	+	+	–	–	–	–	70	–
	T W	+	–	–	–	+	+	–	–	–	–	32	–
	T W	+	–	–	+	+	+	–	–	–	+	25	–
	T W	+	–	–	–	–	+	–	–	–	–	31	–
MALIGNANT FIBROUS	U L	+	–	–	+	+	+	–	–	+	+	61	–
HISTIOCYTOMA	U L	–	+	–	+	+	–	+	–	–	–	38	–
	T W	–	+	–	+	+	–	–	+	+	+	29	–
(17 cases)	L L	+	–	–	+	–	+	–	–	–	–	40	–
	T W	+	–	–	–	+	–	–	+	–	–	89	–
	L L	+	–	–	–	+	+	–	–	+	–	28	–
	L L	–	+	–	+	+	–	+	–	–	–	–	9
	T W	–	+	–	–	+	+	–	–	+	+	80	–
	L L	–	+	–	+	+	–	+	–	+	–	–	10
	L L	–	+	–	+	+	+	–	–	+	–	42	–
	U L	–	–	+	+	+	–	–	+	–	–	37	–
	U L	–	+	–	–	+	–	+	–	+	–	–	5
	U L	+	–	–	+	+	–	+	–	+	–	–	73
	L L	–	+	–	+	–	+	–	–	–	–	77	–
	T W	+	–	–	+	+	+	–	–	+	+	66·	–
	U L	+	–	–	–	+	–	–	+	+	–	37	–
	L L	–	+	–	–	+	–	–	+	+	+	73	–
LIPOSARCOMA	L L	–	+	–	–	+	–	–	+	+	+	39	–
	L L	–	+	–	–	+	–	+	–	–	+	–	66
(5 cases)	L L	–	+	–	+	+	–	–	+	+	+	44	–
	L L	–	+	–	–	+	+	–	–	+	+	65	–
	L L	–	+	–	+	+	–	+	–	+	–	46	–
MALIGNANT	U L	–	+	–	+	+	+	–	–	–	+	–	27
HEMANGIOPERICYTOMA	U L	–	+	–	+	#	–	–	+	+	+	69	–
	U L	–	+	–	+	+	–	+	–	–	–	–	30
(4 cases)	L L	–	–	+	+	+	–	+	–	+	+	–	23
LEIMYOSARCOMA	T W	–	+	–	–	+	+	–	–	–	–	28	–
	N	+	–	–	–	+	–	–	+	–	–	57	–
(3 cases)	L L	+	–	–	+	+	+	–	–	–	+	24	–
SYNOVIALOSARCOMA	L L	–	+	–	+	+	–	+	–	+	–	–	28
(2 cases)	U L	–	+	–	+	+	+	–	–	+	+	–	36
UNCLASSIFIED SARCOMA	L L	–	+	–	+	–	+	–	–	–	–	85	–
(2 cases)	U L	+	–	–	+	+	–	+	–	+	+	64	–
MALIGNANT GIANT-CELL TUMOR	U L	–	+	–	+	–	–	+	–	–	–	–	9
EPITHELOID SARCOMA	U L	–	+	–	+	+	–	+	–	+	+	–	8
MALIGNANT SCHWANNOMA	T W	–	–	+	+	+	+	–	–	–	–	55	–
FIBROSARCOMA	L L	–	+	–	–	+	–	+	–	+	–	–	30::
EXTRASK. MYXOID CHONDROSARCOMA	L L	–	+	–	+	+	+	–	–	+	+	39	–
CLEAR CELL SARCOMA	U L	–	–	+	–	+	–	–	+	+	–	71	–
NB OF CASES		14	27	4	27	37	21	14	10	24	18	-	13

T W = trunk walls ; U L = upper limb ; L L = lower limb ; N = neck

∅ Histologically controlled

§ Bilateral lung irradiation

Post operative irradiation to the lymphnode areas only

:: Intercurrent disease

Table 2. Distribution according to tumor site

Head and neck	1
Trunk	12
Upper limb	14
Lower limb	18

Table 3. Treatment scheme

Limited types with no evidence of metastases. Histologic diagnosis confirmed
(1) Preoperative irradiation 2 × 650 cGy 48 hr apart to a wide volume: encompassing at least 5 cm around visible tumor margin. Include whole involved muscular site where possible.
(2) Conservative surgery 48 hr later with intraoperative histologic verification. Excision deemed adequate only when all sections examined found free of disease.
(3) Postoperative irradiation 3 weeks later. 2400 cGy to preoperative volume. 1000 cGy to surgical scar. In case of incomplete excision: 1000 cGy to areas marked by clips.
(4) Actinomycin D (0.3 mg/m^2) 20 min prior to each of first 5 postoperative irradiation sessions.
(5) Systematic early bilateral pulmonary irradiation at end of treatment. 4 sessions of 375 cGy over 7 days.

passing the surgical scar region, and 7000 cGy to the areas of residual neoplasm when excision had been incomplete. These areas were located by clips positioned during surgery.

Actinomycin D was administered by injection at a dose of 0.3 mg/m^2 half an hour prior to each of the first five post-operative radiation therapy sessions.

The regional lymph nodes were not treated. Lymphatic involvement is a rare occurrence in soft tissue sacromas, and the majority of authors concur that systematic treatment of the relevant lymph node areas is not indispensible [7].

The high incidence of pulmonary metastases in this disease led us to prescribe systematic early bilateral lung irradiation [8]. This was delivered in 4 sessions of 375 cGy each over 7 days (870 ret); the irradiation volume encompassed the whole lung and the mediastinum. The presence of air in the lungs was taken into account in the calculation of the doses. The reference point was taken at mid plane in the middle of each lung, as described in a previous paper [9]. Bilateral lung irradiation was only delivered after respiratory function had been tested and found adequate, and the primary tumor had been eradicated or presumably controlled. Pulmonary irradiation for patients with dermatofibrosarcomas was only considered as a possibility in certain specific cases.

Systemic multidrug therapy was, in this period, only envisaged in inoperable or metastatic cases.

Modality of expression of results. Follow-up data (survival, recurrence, metastasis) were calculated from the date of surgery. In order to obtain overall results for the entire series (45 patients), the data were expressed in actuarial curves (method of Kaplan and Meier, [10]) our sample being lower than 50. Results were updated as of December 1979.

RESULTS

Therapeutic modalities

These are summarized in Table 1. The 45 surgical cases in this series comprised 42 limited excisions and 3 amputations (necessitated by the extent of the lesions). Thirty of the operations were performed with intraoperative histopathologic examination. This procedure was not applied in the remaining cases, for a variety of reasons, notably when previous surgery had been deemed adequate (6 cases). In these cases the histological study of the operative specimens had shown a large margin of normal tissue surroundings. But in 20 other cases referred to our Center after a complete macroscopic surgical excision, without histological confirmation, neoplastic microscopic foci were found in 10 of these patients. An extensive analysis of all the histological features is presented in a separate paper [6].

All the patients, with the exception of 3 dermatofibrosarcomas, received a combination of radiation therapy and surgery. Radiation therapy was delivered preoperatively only, in 5 cases, and it was followed by postoperative irradiation in 22 cases. Postoperative radiotherapy was thus delivered to 37 patients, in 24 of whom it was combined with adjuvant Actinomycin D. The final quality of the surgical results could not be ascertained in 10 cases. Total tumor excision was not obtainable in 14 cases (2 of the 3 amputations fell into this category). Excision was considered satisfactory in 21 cases. Eighteen patients received systematic early pulmonary irradiation.

Local control

Recurrences. Three patients developed recurrences, and in all of these, tumor excision had

been deemed inadequate. In one, treatment had been for local recurrence, one developed recurrence at the border of the irradiated field, and the third had persistence of disease after amputation. The actuarial results for the whole series show a recurrence rate of 2% at 2 years, and 12% at 5 years. It is of special interest to note that no local recurrences were found in 21 patients in whom excision was judged to be satisfactory (Fig. 2); all these patients have been followed for at least 2 years.

Metastases

The incidence of metastatic spread in our series was 22% at 2 years, and 28% at 5 years (Fig. 3). Five patients developed metastatic disease within 3 months following excision of the primary tumor. The lungs were involved in 11 of the 12 patients who developed metastases, and in nine, this was the only metastatic site. The histological distribution is of interest, and is given in Table 4. The extreme malignancy of malignant hemangiopericytoma and synovial sarcomas is confirmed here. However, it is noteworthy that metastases, in the whole group of patients, were less frequent in cases having had a complete microscopic surgical excision.

Survival

Survival data are provided in Fig. 4, which shows an overall survival of 87% at 2 years and 76% at 5 years. For patients who had a complete microscopic surgical excision, the 5 year survival was as high as 88%. The status of our patients in December, 1979 was as follows:

13 deceased:
10 succumbed to their metastases, but were free of local recurrence (however, local control was not confirmed in 2 of these cases);
1 died of uncontrolled primary with metastases;

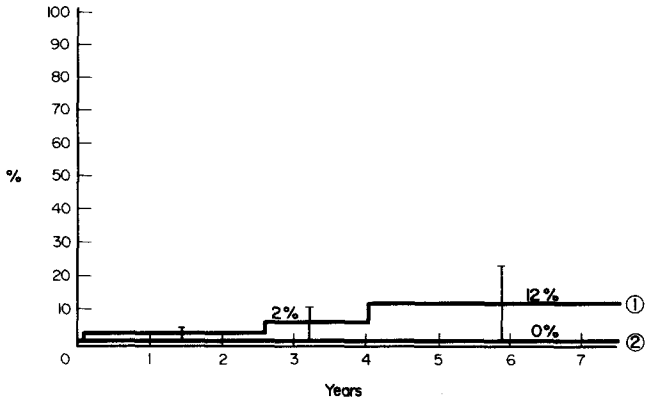

Fig. 2. Incidence of local recurrences (%). 1: *Overall* (45 *cases*). 2: *Cases with complete microscopic surgical excision* (21 *cases*).

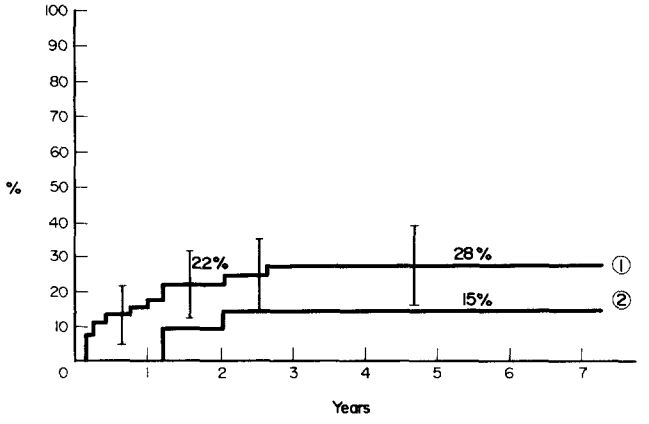

Fig. 3. Incidence of metastases (%). 1: *Overall* (45 *cases*). 2: *Cases with complete microscopic surgical excision* (21 *cases*).

Table 4. Distribution of metastases according to histologic type

Malignant fibrous histiocytoma	4/17
Malignant hemangiopericytoma	3/4
Synovial sarcoma	2/2
Malignant giant-cell tumor	1/1
Liposarcoma	1/5
Epitheloid sarcoma	1/1

1 died of uncontrolled primary;
1 died of other causes (cerebrovascular accident).

32 patients were still alive at the time of study, at least 2 years after surgery. Twelve have been followed for 5 years or more. These 32 patients are living free of disease. One underwent surgery for pulmonary metastases and remains asymptomatic 27 months after these became manifest.

Functional results

These have been evaluated after 2 and 5 years follow up in patients living without evidence of disease. If we except one patient treated by amputation because of the tumor extension at first examination, all others have presented a good functional result, with marked postirradiation sclerosis and/or edema in four of them only.

DISCUSSION

In 1958, Pack and Ariel [11] advocated as treatment of choice in the management of soft tissue sarcomas, an aggressive surgical approach: ablative surgery, involving amputation or disarticulation. Their conclusions were reiterated by Martin *et al.* in 1965 [12] and Cantin *et al.* in 1968 [13]. However, a mutilating surgical procedure is a difficult choice, both for the patient, and for the physician who is aware of the great risk of metastatic spread developing within months of surgery.

Simon *et al.* in 1976 [14] adopted an intermediate attitude in which amputation is only performed when a whole muscle radical excision with resection of insertions and aponeurotic structures is not able to take out all the tumor. Their results showed a marked improvement of long term survival (64% at 5 years) but 54% of their patients were amputated.

Combined radiotherapy and surgery

Soft tissue sarcomas were long believed to be radioresistant due to the fact that they regress slowly after irradiation [15] and that they seldom received sufficient doses to test their curability by this means [7]. Various studies of certain categories of these tumors have, however, established that the role played by radiotherapy is far from negligible [16–20]. While irradiation is not to be considered an alternative to surgery, it does constitute an indispensable adjunct to a conservative surgical treatment, and an important recourse in the case of inoperable tumors. Consequently, a combined approach of radiation therapy and surgery has been advocated by an increasing number of authors for the local control of these tumors [1–4, 21].

Some authors [3] have suggested that radiation therapy delivered immediately after a

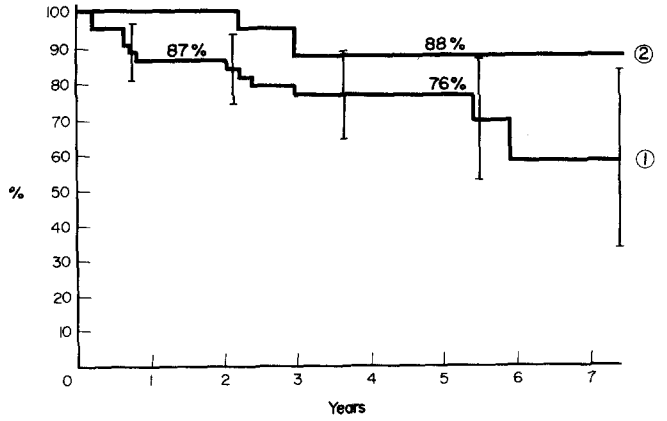

Fig. 4. Survival. 1: Overall (45 cases). 2: Cases with complete microscopic surgical excision (21 cases).

macroscopically satisfactory excision permits the destruction of residual subclinical lesions with relatively moderate doses (5000 cGy to a large volume, then to a reduced volume if the dose is increased). Limb function was spared under these conditions in 80% of the patients. Although these authors report a fairly encouraging recurrence rate of 17.8% for extremity tumors, the overall recurrence rate for all tumor sites was 25% [3].

We believe that the results obtained in our series of 45 patients corroborate the merits of the combined modality approach. However, certain features of our therapeutic sequence merit special attention since they may explain the quality of the results observed.

Intraoperative histologic verification

Intraoperative microscopic confirmation of adequate excision appears to be a determining factor in the local control of the disease, since we found no local recurrences in the 21 patients in our series in whom this was obtained.

These results indicate that the systematic re-excision and the intraoperative histologic verification of the surgical procedure featured in our protocol are justified.

It is now well known that soft tissue sarcomas infiltrate neighboring structures far beyond their pseudocapsule: neoplastic proliferation invades connective tissue layers, and although macroscopically it may appear to the surgeon that wide and total resection of the lesion has been obtained, the margins of the resected specimen are nonetheless frequently found to contain disease. It is of interest to note that, in our series, 20 referrals in whom previous wide excision had been deemed adequate underwent a second operation; neoplastic foci were found in 10 (50%) of these patients. A maximum interval of 2 months lapsed between re-excision and initial surgery.

We would like to emphasize the importance of the intraoperative microscopic verification of the surgical margins (examination of frozen sections). The true value of this method obviously depends on the histopathologist being familiar with this type of tumor and having experience in intra-operative procedure [6]. Frozen section examination is not without its problems, especially in the case of re-excision after simple tumorectomy, when sarcomatous tissues must be differentiated from cicatrical fibrosis. Here it is necessary to remove the entire region of fibrosis since it may contain several tumoral foci. We believe that adequate excision of these tumors can only be obtained in collaboration with the histopathologist, who guides the surgeon by indicating the exact location of the invaded regions and the level to which excision must be pursued. Ideally, surgery is pursued until healthy tissue is reached, and it is only when all the sections obtained are histologically negative that the excision may be deemed adequate. This can be achieved even in some cases in which the tumor invades several anatomical structures without any clearcut macroscopic limits and when a whole muscle excision without histological control cannot be performed satisfactorily.

Radiation therapy

Unfortunately, in some cases proximity to major nerves, vascular or joint structures limits the surgical procedure if functional sacrifice is to be avoided. In these cases, neoplastic foci remain, and the surgeon, under the guidance of the histopathologist, is able to place clips in the involved areas; this is of invaluable aid in postoperative radiation therapy.

We believe this postoperative irradiation to be fully warranted:

(a) although it may be possible to obtain histologically complete resection of the tumor, it remains necessary to take into account the presence of isolated occult neoplastic cells in neighboring tissue. Radiation therapy can have an effective action on these well-oxygenated and radiosensitive cells, and very possibly, at lower doses that those prescribed in our current protocol.

(b) in the case of incomplete excision, radiotherapy is unquestionably indicated. However, local control of the disease is compromised, and it may be necessary to consider the option of ablative surgery in certain cases.

The rationale for preoperative radiation therapy is as follows:

(a) it acts on all the neoplastic cells to decrease the risk of the spread of viable tumor cells;

(b) it acts on tumor cells that may have spread peripherally and avoids their postoperative development. The clinical experience gained with other types of tumor sustains such a concept [22];

(c) the dose and time schedule chosen produces no histologic alteration of the tumor cells that might interfere in the histopathologic examination.

Chemotherapy

Actinomycin D is used essentially as an adjuvant to the radiation therapy in local management. We are unable to assess the systemic effects this chemotherapy may have, and although these seem unlikely given the low dosage, they are perhaps not to be altogether dismissed.

Bilateral pulmonary irradiation

Numerous studies based on modern radiobiologic data together with experience gained have shown that even in the case of reputedly radioresistent tumors, microscopic pulmonary metastases can be sterilized by low dose irradiation [23]. It has been shown that a dose of 2000 cGy (870 ret) which can be effective in 15–20% of these cases, is well tolerated by the lungs. A systematic study of patients receiving this irradiation has confirmed that this dose is not harmful to pulmonary function [9].

This treatment modality was deemed to be of particular interest in the management of soft tissue sarcomas, given the high incidence of pulmonary metastases. The lungs are often the only metastatic site [8]; data from our series confirm this predilection. However, the usefulness of bilateral lung irradiation in this type of disease has still to be proven.

Validity of the material

The therapeutic protocol described here obtained encouraging results in comparison to those observed in our previous series of 31 patients where local recurrence and survival at 5 years were 42 and 52% respectively [24], as well as to those obtained in other published series [2–4, 12–14, 25].

The statistical value of these results (analysed by the method of Kaplan and Meier) is limited due to the small size of the sample. In fact, this type of tumor is a rare one, and the recent literature offers few examples of larger series.

Is our material comparable to that of other published series? Regarding the histologic distribution, the malignant fibrous histiocytomas formed the largest group. This is a category established by Enzinger *et al.* [26, 27] and prior to histologic review and reclassification, this group comprised 11 liposarcomas, 4 unclassified sarcomas, 1 fibrosarcoma, 1 rhabdomyosarcoma. Tumor types that are only malignant locally were excluded from this study, although 6 dermatofibrosarcomas were retained since certain authors have reported metastic spread in some cases [28].

The risk of metastases, however, is low, but if these cases are excluded from the analysis, the survival rate remains encouraging (71% at 5 years). Our series had no particularities with regard to tumor site and size.

CONCLUSION

It seems that there has been unquestionable progress achieved in the local management of these tumors, although prudence is still required in assessing improvements in survival. Although we found an improvement in our overall results, mortality approached 25% at 5 years in our series; death was largely due to metastatic spread, easpecially to the lungs.

The incidence of metastases was particularly high for certain histologic types (malignant hemangiopericytomas, synovial sarcomas ...) and especially when complete excision of the tumor had not been achieved. Consequently, we are currently modifying our protocol to adapt it to the variations found and in treating the above types, we now envisage systematic adjuvant multidrug chemotherapy analogous to that administered to patients with confirmed metastases [29–31]. On the other hand, when microscopically complete surgical excision had been done, the therapeutic modalities could be alleviated, limiting the postoperative irradiation at a moderate dose giving no risk of sclerosis and withdrawing chemotherapy and bilateral lung irradiation in good histologic types.

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