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Preoperative Chemotherapy and Irradiation in the Treatment of Soft Tissue Sarcomas of the Lower Extremities: Preliminary Report of Experience at Henry Ford Hospital

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The development of effective chemotherapy and improved techniques of radiation therapy offer the possibility of managing soft tissue sarcomas so that surgery may need to be less radical than in the past and amputation can be avoided. The low rates of local-regional and systemic recurrence that have resulted from using innovative combinations of chemotherapy, radiation therapy, and conservative surgery encouraged us to use preoperative intraarterial adriamycin (doxorubicin) with or without radiation therapy for three cases of soft tissue sarcomas of the lower extremities. The rationale for this therapy is also discussed.

Soft tissue sarcomas (STS) consist of at least 55 different types of malignant tumors that originate from the common connective tissues of the body (1,2). These are rare tumors, and only about 4,500 new cases are treated each year in the United States (3). Traditionally, the primary form of therapy for STS has been surgical removal, ranging from local excision through radical amputations (4,5).

At present, controversy exists about the optimal therapy to control local regional disease in STS (6-9). Local recurrences occur in 80-100% of cases after excision biopsy, 50% after wide exision, 10-20% after radical local resection, and about 5% after amputation (5,10). For this reason, amputation is a commonly practiced surgical procedure. Soft tissue sarcomas recur locally because they spread by continuity through nerve fibers, muscle bundles, fascial planes, and along blood vessels. They also invade locally and directly into surrounding structures. Lymph node metastases occur in about 6% of cases (11). Local recurrence after earlier surgery is a poor prognostic factor, since about one third of patients with local recurrences have concomitant systemic recurrence (12).

The high incidence of local recurrence after surgery for sarcomas of the extremities has stimulated the use of innovative approaches that combine multimodality therapy with surgery (7-9). The combination of preoperative radiation and/or chemotherapy (13) has several advantages. It may add to local control by reducing the size of the primary tumor so that previously inoperable lesions can be excised surgically. However, before this type of therapy is undertaken, the probability of producing tumor regression must be high. Such preoperative therapy may also increase the local-regional control rate by retarding the growth of malignant cells that are shed during surgery (9). The disadvantage of adjuvant therapy that begins after surgical resection is that it attacks relatively avascular cells that have been shed into a large wound during surgical resection. Therefore, these cells may not be as susceptible to radiotherapy and/or chemotherapy.

Recently developed approaches to preoperative chemotherapy have been equally concerned with the implications of blood borne metastatic disease in STS (7,9). Patients with sarcomas finally fail and die not because local control of the disease fails, but rather because systemic control fails. It is therefore appropriate that systemic control should receive the highest priority and should not be compromised by local control approaches. Golde calculated that spontaneous mutation to drug resistance may occur over relatively few generation times in micrometastases that contain 10% cells or more (14). It is probable, though uncertain, that the kinetic aggressiveness of micrometastases is greater than that of macrometastases. Therefore, the several months of delay in providing systemic treatment that sometimes occurs because of the time needed for surgery and recuperation may permit drug resistance to develop. Surgery and radiotherapy have major systemic effects that may compromise subsequent chemotherapy.

Another advantage of preoperative multimodality therapy is that the responsiveness of the tumor to chemotherapy and radiation therapy is established while the tumor is in

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vivo. Studies both in head and neck cancer, and more definitively in osteogenic sarcoma, suggest that the responsiveness of the tumor during the initial preoperative treatment period may predict the responsiveness of microscopic disease to chemotherapy treatment given after surgical excision (15).

A number of centers are currently addressing the problem of multimodality therapy for STS (7,9,15). The center at the University of California at Los Angeles (UCLA) has used intraarterial doxorubicin followed by radiation of the tumor, which is followed by resection and adjuvant systemic chemotherapy, since 1974 (17). Not only has this therapy improved the local and regional control rates (16), but it has also permitted limbs to be saved. In this way the major psychosocial complications of amputation are avoided. Moreover, compared to amputation alone, this approach has not adversely affected the prognosis (16). It has been effective both for primary and recurrent soft tissue sarcomas in the extremities (16).

Based on the UCLA experience, we have initiated a protocol at Henry Ford Hospital to treat soft tissue sarcomas of the extremities. We modified the radiation dose after the UCLA center reported four long bone fractures following radiation therapy with 3,500 rads (17). We treated three cases with preoperative radiation and/or chemotherapy. Each was treated differently because of special individual considerations.

Case Reports

Case 1

A 17-year-old black girl presented with a painless enlarging left thigh mass that had been present for about 20 months. The mass, which occupied the anterior and medial compartments of the thigh, measured 33 x 23 cm. It was firm, nontender, and not attached to underlying bone. A CAT scan (Fig. 1) revealed a large, soft tissue mass of varying tissue density which obliterated fascial planes between muscle groups. The mass involved the rectus femoris, sartorius, vastus medialis, and the adductor group, and it extended to within 8 cm of the knee joint and within 5 cm of the inguinal ligament. An arteriogram (Fig. 2) demonstrated a hypervascular mass with displacement of the femoral artery. An incision biopsy revealed a malignant hemangiopericytoma (Fig. 3).

The patient was treated with preoperative chemotherapy that consisted of intraarterial doxorubicin (30 mg per day) by continuous infusion for 72 hours. She also received systemic vincristine, actinomycin D, and cytoxan. The tumor diminished by about 20% over the next month. At that time, a wide excision of the tumor was performed, including the gracilis, the adductor

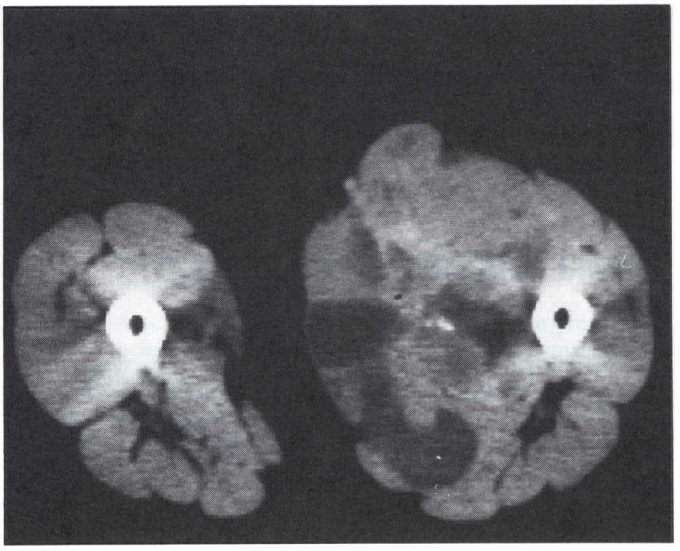

Fig. 1. Case 1
CAT scan through the middle of the tumor in the left thigh demonstrating extensive involvement of the medial and anterior compartments.

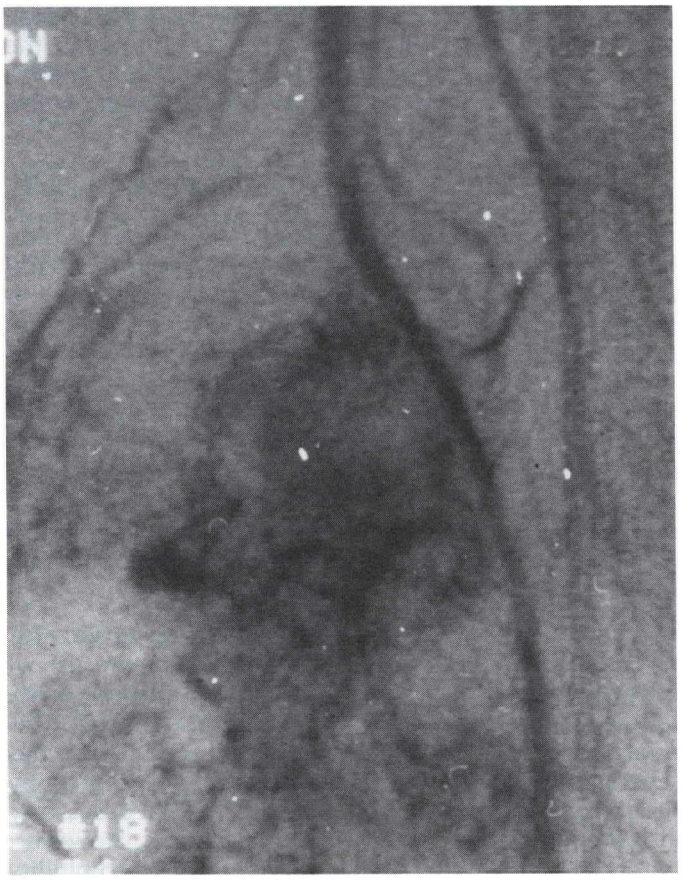

Fig. 2. Case 1
Digital subtraction angiogram (DSA) demonstrating displacement of the superficial femoral artery and marked vascularity of the tumor.

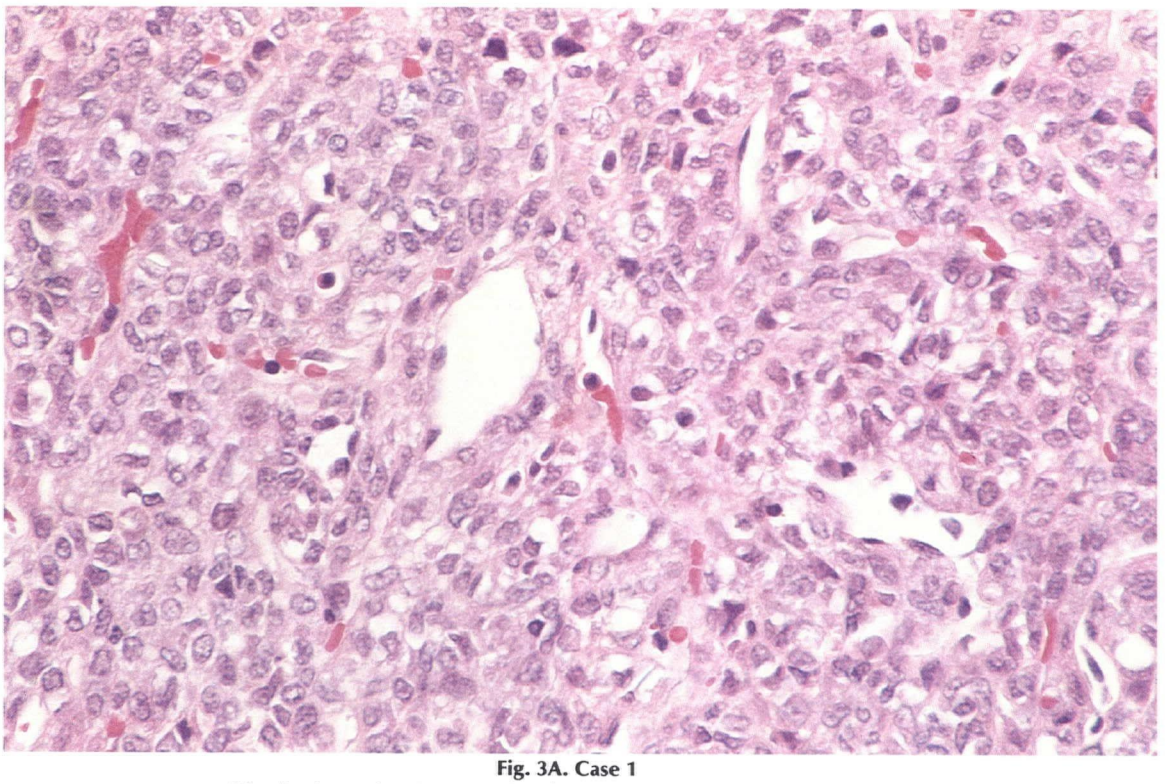

Fig. 3A. Case 1
Histologic section (H + E stain) demonstrating many vascular spaces interspersed with spindle-shaped tumor cells consistent with malignant hemangiopericytoma.

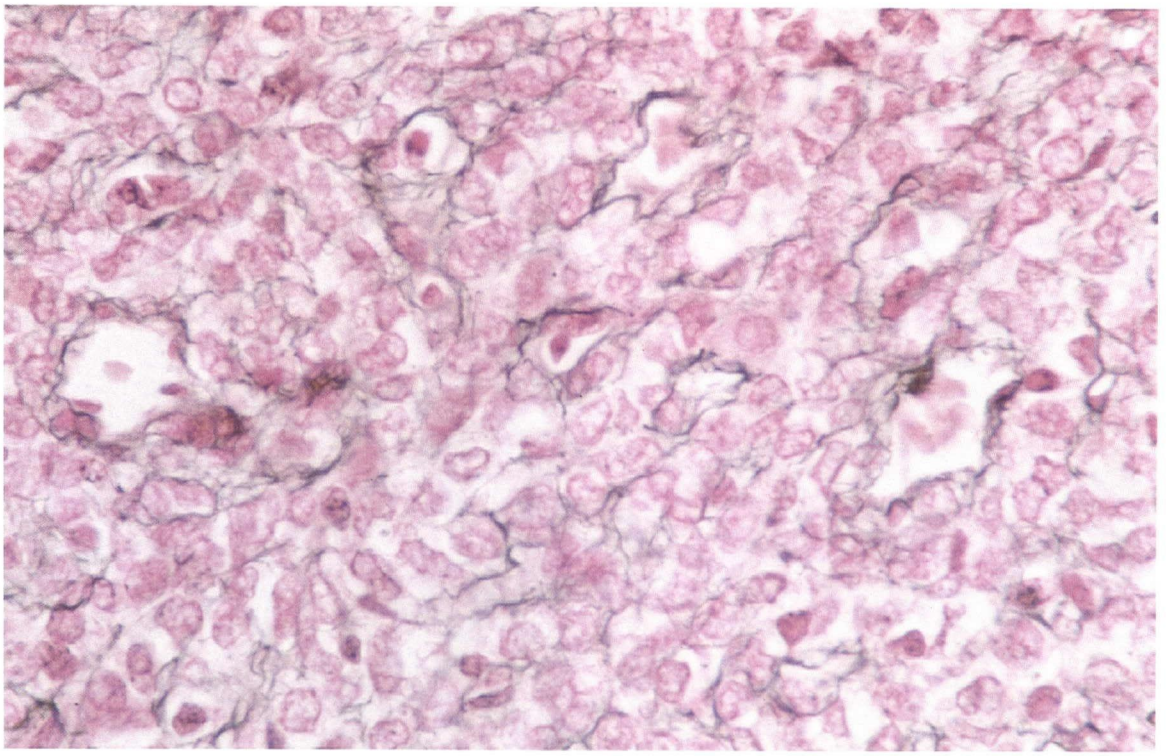

Fig. 3B. Case 1
Histologic section (reticulin stain) demonstrating hemangiopericytoma.

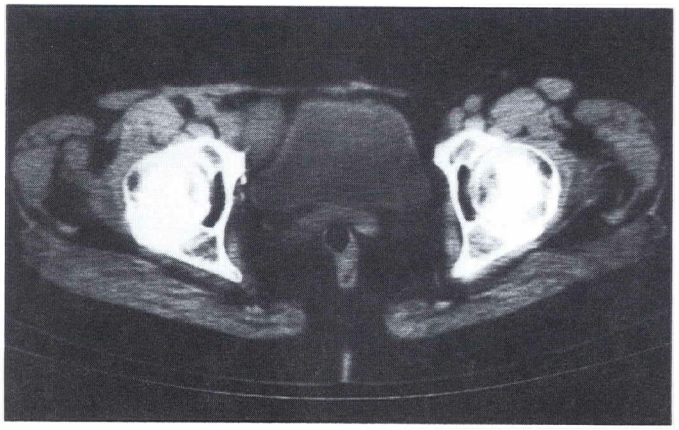

Fig. 4. Case 2
CAT scan of the pelvis demonstrating large tumor adjacent to the pubic bone compressing the bladder.

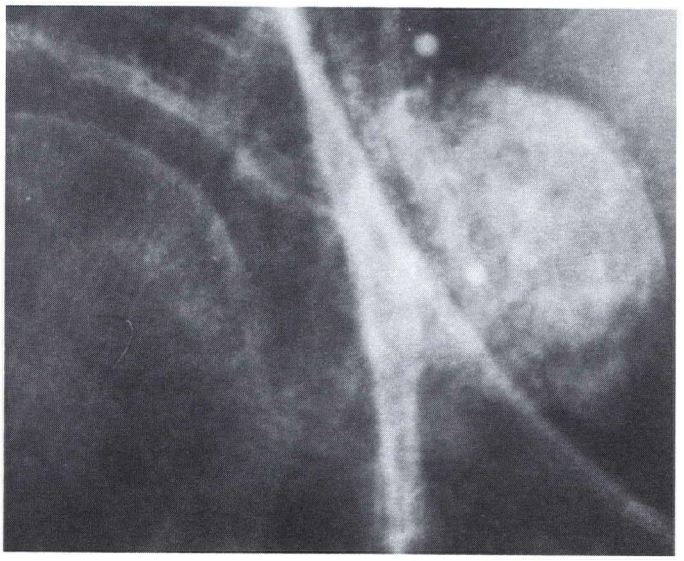

Fig. 5. Case 2
Pretreatment arteriogram demonstrating vascular mass adjacent to the wall of the true pelvis.

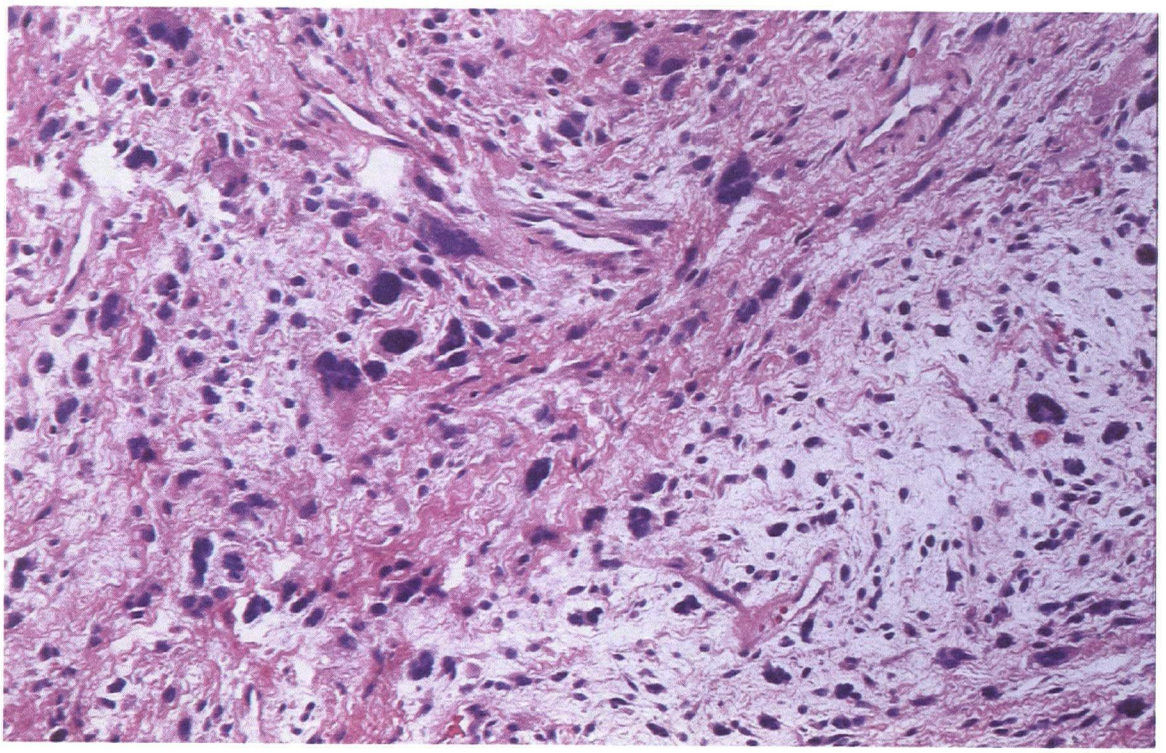

Fig. 8. Case 3
Histologic section (H & E stain) demonstrating a histiocytic tumor. Some areas appear myxoid.

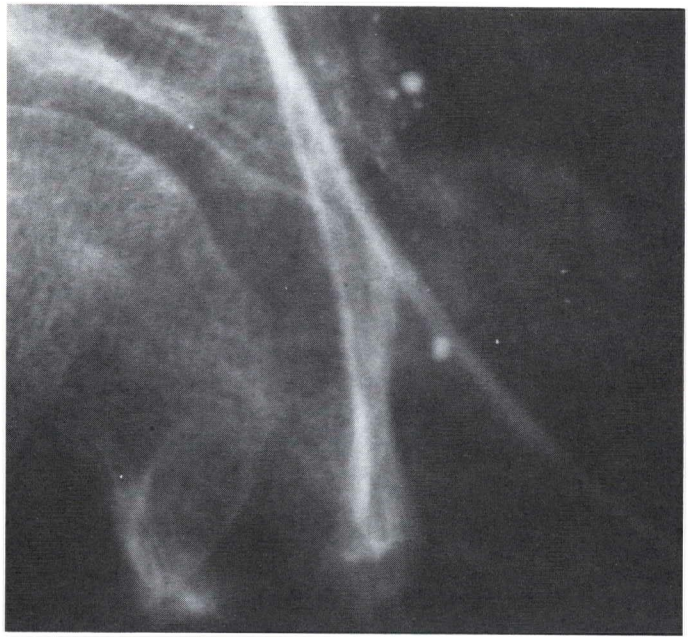

Fig. 6. Case 2
Arteriogram four weeks after intraarterial adriamycin was administered demonstrating decreased size and vascularity of the tumor.

compartment, sartorius, the vastus medialis, and the rectus femoris. The vastus lateralis, which was at least one fascial plane distant from the tumor, was left intact to stabilize the patella. The patella was also stabilized medially by suturing the tendon of the semimembranous muscle anteriorly to its superior border. One inch of the femoral artery was removed, and a primary end-to-end anastomosis was performed.

The patient's postoperative course was complicated by a major skin slough which required three months of dressings and skin grafts. She received 5,400 rads of radiation in six weeks. Six months later, bilateral pulmonary metastases were noted, and systemic chemotherapy consisting of doxorubicin and cytoxan produced a partial response. The metastases were excised by staged bilateral thoracotomies eight and 12 months after primary tumor resection. No local recurrence has been found 15 months after the patient's initial presentation, and she is walking unaided.

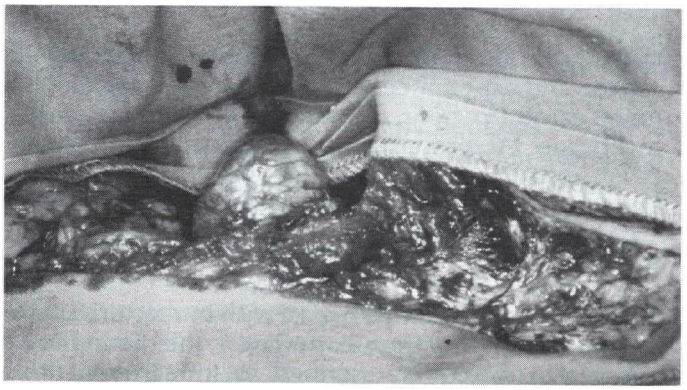

Fig. 7. Case 2
Macroscopic appearance of the hemangiopericytoma at the time of operation.

Case 2

A 70-year-old white woman presented with a recurrent hemangiopericytoma in the right groin. This tumor, first resected in 1970, had recurred in 1979. At that time the mass was excised, and she received 5,600 rads of radiation postoperatively.

She returned in October 1982 because of symptoms of obturator nerve compression. A 3 cm mass was found on CAT scan (Fig. 4). Arteriogram revealed a vascular tumor (Fig. 5) closely associated with the external iliac vessels on the right, but apparently supplied primarily by the branches of the internal iliac vessels. Intraarterial doxorubicin was administered through a catheter placed in the left axillary artery and ending just proximal to the right internal iliac artery. She received 85 mg of doxorubicin over three days by continuous infusion. One month later the patient was readmitted, and the arteriogram was repeated (Fig. 6). The vascularity of the tumor had diminished markedly, and it was about 40% smaller. Previous radiation precluded further radiotherapy. In January 1983 the tumor was excised locally (Fig. 7). Internal hemipelvectomy and vascular reconstruction were rejected because of the patient's age and because of the relatively slow growing nature of this tumor. For similar reasons, postoperative adjuvant chemotherapy was also rejected.

No evidence of recurrence has been found by clinical examination or CAT scan 13 months later.

Case 3

A 39-year-old white woman presented with pain and discomfort in the left thigh of four months' duration. When she was examined, a large tumor mass approximately 15 cm in diameter was found to occupy the medial upper aspect of the left thigh. Incision biopsy demonstrated a high-grade fibrous histiocytoma (Fig. 8), which by CAT scan was located in the adductor compartment (Fig. 9). Arteriogram disclosed a hypervascular tumor (Fig. 10).

The patient was treated with 90 mg of doxorubicin by continuous intraarterial route over 72 hours, with the tip of the catheter placed in the external iliac artery. This therapy was followed by 1,750 rads of radiation to the thigh given for two weeks. The patient had noticeable

relief of her symptoms, and the tumor diminished by 20% within three weeks.

The tumor was then resected with clear margins, including the entire adductor compartment with obturator nerve and arteries. The tumor was not attached to the bone and could be resected with a margin from the femoral vessels. An incontinuity lymph node dissection was also done.

Histology of the tumor showed some necrosis. The patient had an uneventful recovery from the procedure and has completed adjuvant systemic chemotherapy with doxorubicin and cytoxan. No evidence of local or systemic recurrence of the tumor has been found 12 months after the patient's initial presentation.

Discussion

The three cases discussed represent our preliminary experience with a combination of preoperative radiation and/or chemotherapy to treat soft tissue sarcomas at Henry Ford Hospital. Despite the wound complication in Case 1, intraarterial doxorubicin was tolerated well in all three patients. Following the early UCLA experience (9), we placed the tip of the catheter in large arteries proximal to the tumor and avoided placing it close to small branches. The major disadvantage of this technique is that a large bolus of chemotherapy might be delivered to a small area of skin, subcutaneous tissue, muscle, and other normal tissues, which might result in tissue necrosis (9). To obviate this complication, catheters placed carefully at the time of arteriography are secured by sutures in the skin at the point of entry into the vessel. Even so, because the tip of the catheter may migrate for a few centimeters, we inject fluorescein into the catheter every six hours. We also examine the skin with a Woods lamp to ensure that no excessive staining of skin occurs in the distribution of small blood vessels branching from the artery that contains the tip of the indwelling catheter. On one occasion with Case 1 we had to reposition the catheter.

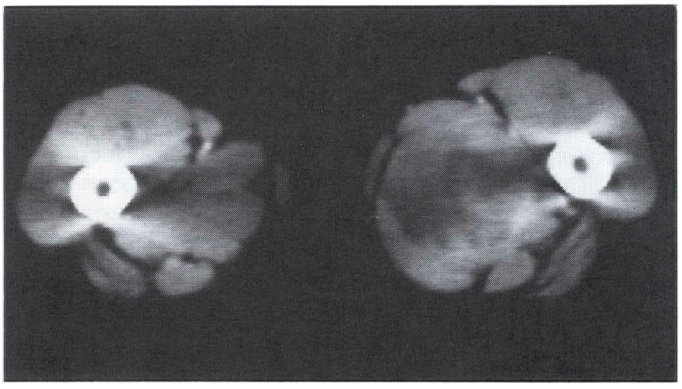

Fig. 9. Case 3
CAT scan of the thigh demonstrating a tumor in the adductor compartment on the left.

Doxorubicin (adriamycin) is effective in soft tissue sarcomas (18). Used as a single agent or in regimens that combine chemotherapeutic agents, the overall response rate for disseminated soft tissue sarcomas has been reported to be 34%. Other drugs, used as single agents with limited efficacy against soft tissue sarcomas, have been added to doxorubicin in sequential, nonrandomized studies, with moderate improvement in the response rates and the length of survival (18). Because doxorubicin is beneficial in disseminated STS when used systemically, intraarterial techniques using this agent have been reexamined (9,19). Theoretically, this route of administration can minimize systemic toxicity and maximize local tumor destruction. Many neoplasms have been treated by intraarterial infusion of drugs, either alone or as an adjunct to surgery or radiation therapy (20,21).

We selected intraarterial doxorubicin because of its known efficacy by the intravenous route, because metabolism of the drug may not be required for its antitumor effect (22), and because pharmacokinetic data in animals suggest that clearance rates following intravenous administration may vary considerably. Since doxorubicin binds avidly to DNA and causes disordered DNA function, it is possible that even a single arterial transit of the drug through tumor tissue would result in substantial DNA binding, possibly many times greater than after intravenous administration.

Studies with intraarterial doxorubicin (23) suggest that these theoretical advantages may in fact justify its clinical use. Although good responses may have been achieved in STS using intravenous doxorubicin preoperatively, some investigators suggest that such good responses to intravenous administration are unusual (23).

The toxicity of intraarterial doxorubicin has been tolerable and similar to that reported with intravenous doxorubicin. Skin necrosis, such as occurred in our first patient, has also been reported. However, with increasing use and experience, this problem can be avoided by more careful patient selection and improved surgical technique. At present, optimal doses of intraarterial doxorubicin are uncertain. The dose of 60-90 mg/m^2 given over three days, selected from previously reported experience with intravenous doxorubicin, is tolerable and effective (23).

All three of our patients treated with intraarterial doxorubicin had some response. In Case 1, the diminution in tumor size cannot be ascribed to intraarterial doxorubicin alone since the patient received vincristine, actinomycin D, and cytoxan as well. In Case 2, both the vascularity and the size of the tumor diminished. In Case

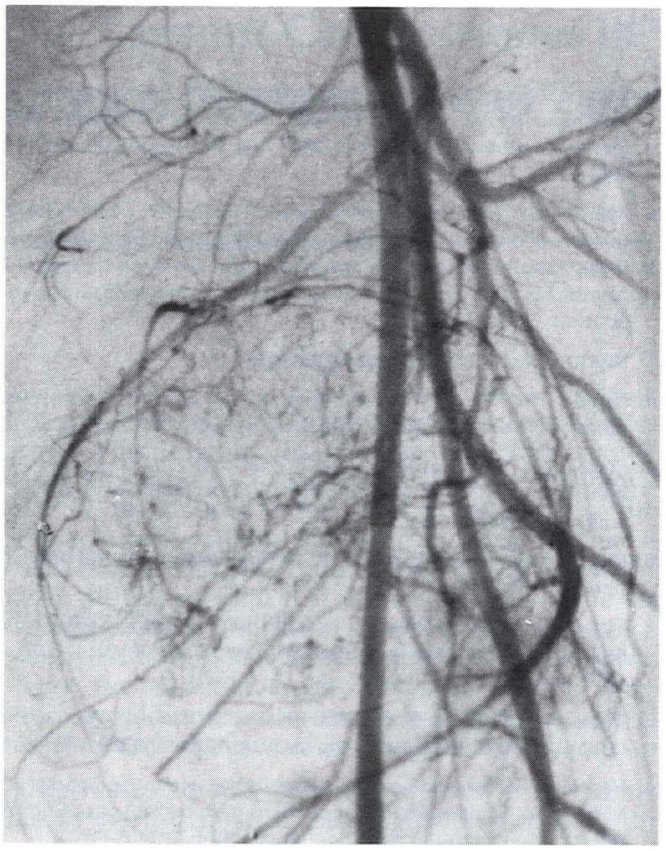

Fig. 10. Case 3
Arteriogram demonstrating a hypervascular tumor supplied mainly by branches of the profunda femoris artery on the left.

3, the dramatic symptomatic improvement may well have been due to a combination of the intraarterial doxorubicin and radiation therapy. Systemic effects, seen in all three patients, included alopecia and leukopenia. None of the three complained of nausea or vomiting, and none had mucositis or gastrointestinal side effects.

Radiation is a potent form of therapy for soft tissue sarcomas. When radiation was combined with limited surgery, the local control rate was better than 85% at the M.D. Anderson Hospital (24). Also, the incidence of local recurrence after radiation therapy depends somewhat on the site; it is higher for proximal thigh and upper arm lesions than for those of the forearm and leg (24). The local recurrence rate also depends on the size of the tumor and is higher for tumors over 5 cm in diameter. Used alone, radiation provides local control in about 60% of cases (25). When preoperative radiation was administered before surgery (7,9), the excised tumor was smaller, surrounded by a relatively dense pseudocapsule, and partially or totally necrotic. The local recurrence rate has been minimal when preoperative radiation therapy was followed by wide excisional surgery (11).

The classical treatment of STS is amputation or radical excision. Even with apparently adequate surgery, local recurrence rates are high (5,10), and approximately 80% of patients die of systemic disease, usually from pulmonary metastasis (2-4,6). As chemotherapy for widely metastatic sarcoma developed successfully, the use of preoperative chemotherapy to treat STS began to appear possible, in the same way that preoperative chemotherapy is used to treat breast carcinoma (26). Although it is too soon to state whether or not preoperative systemic chemotherapy is of value for STS, initial studies suggest that it is beneficial (7,9,16). While each of three major therapeutic modalities used against STS is effective, none is capable of eradicating the disease completely. Accordingly, all three treatments in combination should be used. Initial results show an improved survival rate with a very small local recurrence rate (9,16). However, the optimal timing and dose of chemotherapy and radiation as well as the best form of surgery have not yet been fully determined.

The major benefits of preoperative multimodality therapy combined with limb salvage surgery are the functional advantage of retaining a useful limb and the psychosocial advantage of not having to confront a major amputation. Management of body disfigurement is always a major problem for both physician and patient. Of course, the primary concern is to cure disease even at the expense of incurring undesirable physical changes. With the combination of therapy used in our three cases, major disfigurement was avoided, and ultimate control of the disease was certainly no worse than would be anticipated with conventional therapy. In addition, our patients' rehabilitation improved considerably because they had functional use of their limbs (16).

Patients with STS may now be offered a regimen of preoperative radiation and/or chemotherapy and limb salvage procedures as an alternative to radical amputation. Continued study of the advantages and disadvantages of both approaches is much needed.

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