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Chemotherapy Influences the Pseudocapsule Composition in Soft Tissue Sarcomas

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Abstract

Background Soft tissue sarcomas are a heterogeneous group of malignant tumors. Standard treatment for soft tissue sarcoma of the extremity is surgical excision and adjuvant therapy; however, the role of neoadjuvant chemotherapy is controversial.

Questions/purposes We sought to (1) define the histologic characteristics of the pseudocapsule in soft tissue sarcomas; (2) compare the appearance of this structure in chemotherapy-treated versus untreated soft tissue sarcomas; and (3) evaluate the effect of chemotherapy on the presence and viability of tumor cells at the host-sarcoma interface.

Methods Twenty-eight patients with biopsy-proven, deep, high-grade extremity soft tissue sarcomas greater than 5 cm (AJCC stage III) treated with chemotherapy and surgical excision were compared histologically with 47 matched control subjects treated with surgery alone.

Results A pseudocapsule was identifiable in the majority of tumors and consisted of two identifiable layers, each with specific histological characteristics suggesting the biologic processes occurring in these layers are different. The pseudocapsule was more frequently observed in the group treated with chemotherapy and it was more frequently continuous, thicker, and better developed in this group. Chemotherapy decreased the number of tumors with malignant cells identified within and beyond the pseudocapsule.

Conclusions Neoadjuvant chemotherapy contributed to the development of a pseudocapsule and decreased the number of tumors with malignant cells identified within and beyond the pseudocapsule.

Clinical Relevance These findings may provide a histological explanation for the clinical effect of chemotherapy in soft tissue sarcoma.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant tumors. Standard treatment for STS of the

extremity is surgical excision and adjuvant therapy. Adjuvant radiotherapy has been shown to decrease rates of local recurrence; however, the role of adjuvant chemotherapy has been less clear [1, 4–6, 13, 17]. Local and distant control of certain histological subtypes of STS improves with chemotherapy; however, there are conflicting results regarding the applicability of chemotherapy to STS as a whole [3–5, 14].

Local growth of STS occurs in a radial fashion, compressing surrounding tissue and forming a "pseudocapsule" around the tumor. Because viable tumor cells can be found extending beyond the pseudocapsule, resection achieving a marginal surgical margin should be supplemented with radiation treatment to decrease local recurrence [2, 6, 8, 15]. Since the original description of the STS pseudocapsule in a rat model, there have been several histological descriptions of the pseudocapsule in treated or untreated human STS and its response to adjuvant chemotherapy [9–12].

The purposes of this study were to (1) define the histologic characteristics of the pseudocapsule in soft tissue sarcomas; (2) compare the appearance of this structure in chemotherapy-treated versus untreated STSs; and (3) evaluate the effect of chemotherapy on the presence and viability of tumor cells at the host-sarcoma interface.

Patients and Methods

Patients and Specimens

Seventy-four patients with biopsy-proven, deep, high-grade extremity STS greater than 5 cm (AJCC stage III) were identified from our institutional review board-approved prospective database of 9364 patients collected over 26 years (Table 1). Patients with metastatic disease were excluded from study inclusion. Two cohorts of patients were evaluated; one underwent resection without previous neoadjuvant chemotherapy and the other was treated with neoadjuvant chemotherapy before resection. Neoadjuvant chemotherapy consisted of four cycles of ifosfamide/doxorubicin. If a patient's medical comorbidities precluded chemotherapy or if the patient declined chemotherapy, then it was not given. Patients included in the neoadjuvant chemotherapy cohort were also enrolled in a National Cancer Institute-registered prospective clinical trial assessing PET-CT treatment response in STS (NCT00346125). No patients in either treatment arm received radiation therapy before surgical excision.

In the group operated on before neoadjuvant chemotherapy, there were 46 patients, 25 females and 21 males, whose ages ranged from 17 to 91 years (mean, 59 years). The pathologic diagnoses included undifferentiated pleomorphic sarcoma ("malignant fibrous histiocytoma"), liposarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma, leiomyosarcoma, angiosarcoma, and hemangiopericytoma.

In the group treated with neoadjuvant chemotherapy (Group 2) before surgery, there were 28 patients, 12 females and 16 males, with ages ranging from 22 to 81 years (mean, 51 years). The pathologic diagnoses included undifferentiated pleomorphic sarcoma, liposarcoma, fibrosarcoma, leiomyosarcoma, synovial sarcoma, and epithelioid sarcoma. All tumors studied in both groups were high-grade (Grade 2 in two-tiered system; Grade 3 in three-tiered system).

Table 1. Patient and tumor-specific details of the two treatment groups

Patient and tumor-specific details of the groups	Group	
	1	2
Number of patients	46	28
Mean age (years)	59	51
Proportion male (%)	42	57
Depth		
Superficial	0	0
Deep	46	28
Grade of tumor		
1	0	0
2	46	28
Mean tumor diameter (cm)	10	11
American Joint Committee on Cancer stage		
I	0	0
II	0	0
III	46	28
IV	0	0
Mean resected specimen (cm)	16	16
Number of amputations	4	0
Histologic type		
Undifferentiated pleomorphic sarcoma	21	13
Synovial sarcoma	1	6
Liposarcoma	8	3
Fibrosarcoma	4	2
Angiosarcoma	2	0
Leiomyosarcoma	3	1
Other	7	3
	46	28
Margin status		
Negative	41	26
Positive	5	2

Group 1 consisted of patients treated with surgery alone. Group 2 consisted of patients treated with neoadjuvant chemotherapy before surgery.

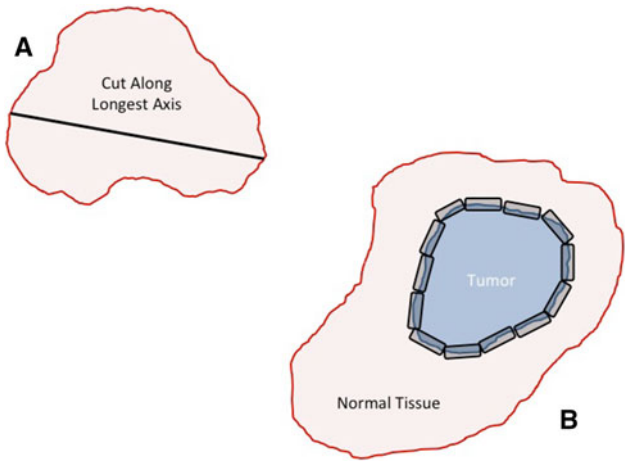

Fig. 1A–B A cartoon that shows the handling and analysis of the pathological specimens. (**A**) Specimens were sectioned along the longest axis. (**B**) The complete tumor-normal tissue interface in this slice was submitted for histologic evaluation.

Histological Evaluation

Specimens were sectioned along the largest tumor diameter; a slice from the central area was photographed, fixed in 10% buffered formalin, mapped, and processed completely for histologic examination. A diagram indicating the source of each block of tissue was constructed and identified the relation between the periphery of the tumor along its circumference and adjacent normal tissues (Fig. 1). This approach permitted microscopic examination of the entire interface among the tumor, pseudocapsule, and the adjacent nontumorous tissue in this plane. Tumor sectioning was done prospectively at the time of initial processing as per the previously described protocol. The largest specimen diameter and largest tumor dimension were measured in each case and averaged for each group. Other steps followed in the gross-room handling of these tumors (photographs, inking of margins, weighing, etc) were those routinely followed for pathological processing of STS. Average tumor pseudocapsule thickness was recorded for each case. Microscopic examination was performed on hematoxylin and eosin-stained slides using an Olympus BX40 microscope (Olympus Optical Co Ltd, Tokyo, Japan). All slides of the pseudocapsule were analyzed microscopically to evaluate its thickness, completeness, structure, and for the presence or absence of tumor cells in it or beyond. A pathologist with experience in soft tissue tumors (JCM) carried out all pathologic assessments.

Statistical Analysis

Data analysis was performed using SAS Version 9.2 computer software (SAS Institute Inc, Cary, NC, USA). Probability values for comparison to no agreement were generated from a Fisher's exact test and Student's t-test. All p values were two-sided and any p values < 0.05 were considered statistically significant. Statistical analysis of the pseudocapsule thickness was not performed, because these measurements were an average of the thickness of the pseudocapsule measured on sections of the central slice on each case for each group.

Results

Histologic Characteristics of the Pseudocapsule

Examination of treated (Fig. 2) and untreated tumors (Fig. 3) revealed a variably developed pseudocapsule. The pseudocapsule when present was composed of histologically distinct inner and outer layers (Fig. 3). The outer layer was composed of preexisting normal, compressed connective tissue, often including adipose tissue and skeletal muscle; this layer contained fibroblasts and frequent macrophages with abundant foamy cytoplasm or hemosiderin granules (Fig. 4). The fibroblasts in the outer layer were more delicate, smaller, more numerous, and appeared less active when compared with those in the inner layer. Collagen fibers in the outer layer were delicate and fibrillary; perivascular inflammatory aggregates were noted; venules, with well-developed muscular walls, were present. The inner layer, when present, consisted primarily of hyalinized collagen. Fibroblasts in the inner layer were less numerous, larger, plumper, and appeared to be more active than those in the outer layer. The inner layer collagen fibers were generally coarse and hyalinized. Blood vessels present in the inner layer consisted mostly of dilated capillaries without a muscular coat (Fig. 3).

Pseudocapsule in Treated versus Untreated Tumors

The pseudocapsule in STSs that was treated with chemotherapy was, in general, thicker and better defined than in those tumors that were not treated with chemotherapy. All treated tumors (28 of 28) had a distinct pseudocapsule compared with 42 of 46 untreated tumors (91%) ($p = 0.29$). In four untreated tumors, no pseudocapsule was grossly or microscopically apparent (Fig. 5). The pseudocapsule completely surrounded the entire tumor perimeter in 20 of 28 treated tumors (71%) compared with only 11 of 42 untreated tumors (26%) ($p = 0.06$). The average thickness of the pseudocapsule in treated versus untreated tumors was 3.45 mm versus 1.13 mm (Statistical analysis of the pseudocapsule thickness was not

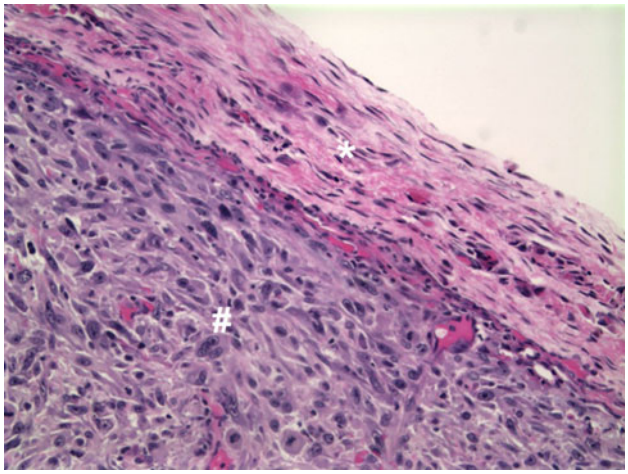

Fig. 2 Undifferentiated pleomorphic sarcoma without neoadjuvant chemotherapy. The tumor (lower left, #) is surrounded by a delicate outer layer of pseudocapsule (*). Please note the absence of the inner layer (Stain, hematoxylin and eosin; original magnification, × 200).

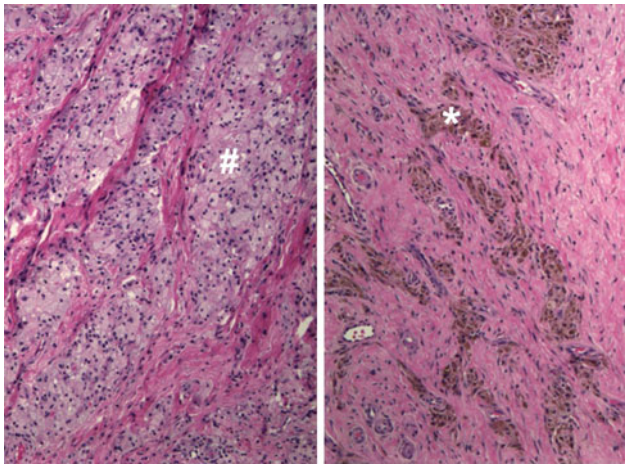

Fig. 4 Synovial sarcoma after neoadjuvant chemotherapy; the external pseudocapsule layer contains numerous foamy macrophages (left, #). Undifferentiated pleomorphic sarcoma after neoadjuvant chemotherapy; external pseudocapsule layer contains numerous hemosiderin-laden macrophages (right, *) (Stain, hematoxylin and eosin; original magnification, × 100).

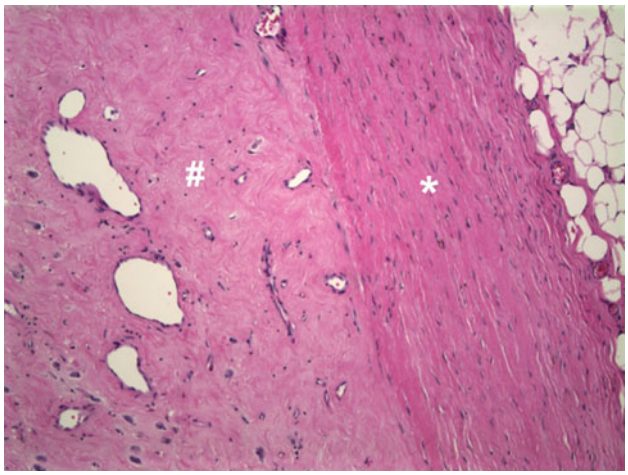

Fig. 3 Pseudocapsule in undifferentiated pleomorphic sarcoma after neoadjuvant chemotherapy. Outer fibroblastic layer is seen at right (*); inner hyalinized hypocellular layer at left (#) contains rare tumor cells with regressive changes and dilated capillaries (Stain, hematoxylin and eosin; original magnification, × 100).

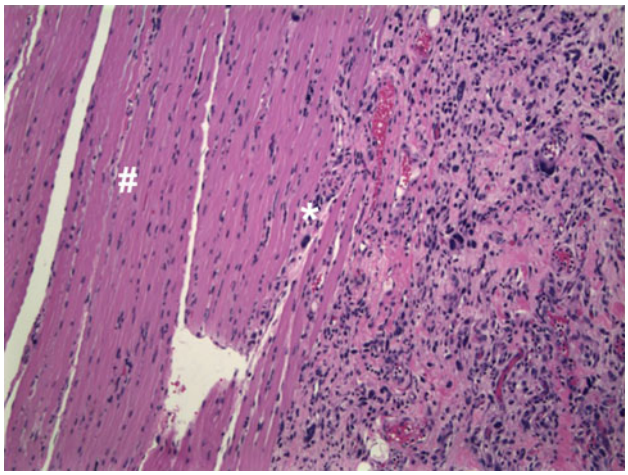

Fig. 5 Undifferentiated pleomorphic sarcoma without neoadjuvant chemotherapy. Tumor (right, *) infiltrates skeletal muscle (left, #); note absence of pseudocapsule (Stain, hematoxylin and eosin; original magnification, × 100).

performed because these measurements were an average of the thickness of the pseudocapsule measured on sections of the central slice on each case for each group.). Treated tumors always had an outer layer of pseudocapsule and were more likely to have a distinct inner layer (Fig. 3). The outer layer of the pseudocapsule was present in all (28 of 28) treated tumors compared with 35 of the 42 untreated tumors with a pseudocapsule (83%) ($p = 0.04$). The inner layer was distinct in 25 of 28 (89%) treated tumors compared with only 16 of 42 (38%) untreated tumors ($p = 0.004$).

Evaluation of Tumor Cells at the Host-Sarcoma Interface

In the absence of a pseudocapsule, or in the presence of an incomplete pseudocapsule, tumor cells infiltrated freely adjacent tissues (Fig. 5); however, with the numbers available, most of the findings on this research question were not different between chemotherapy-treated tumors and those that were not treated. Evaluation of the normal tissue outside the pseudocapsule revealed viable tumor cells beyond the pseudocapsule in 23 of 42 untreated tumors (55%) compared

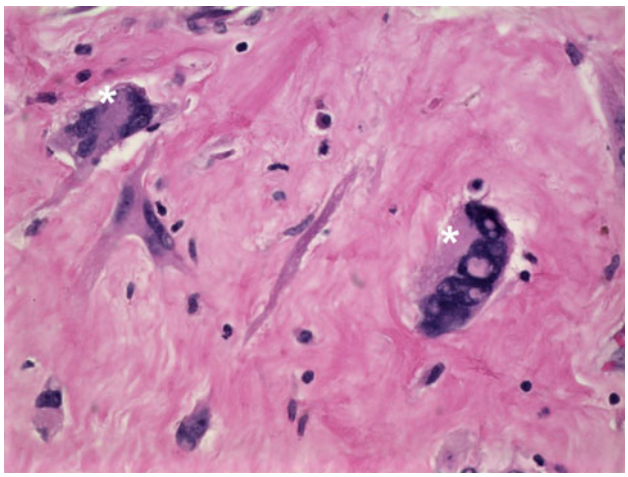

Fig. 6 Fibrosarcoma after neoadjuvant chemotherapy. Residual viable tumor cells (*) in hyalinized inner layer show prominent degenerative changes (Stain, hematoxylin and eosin; original magnification, × 600).

with 11 of 28 treated tumors (39%) ($p = 0.07$). Observation of tumor cells present in or beyond the pseudocapsule varied between treated and untreated groups. Thirty-two of 42 untreated tumors (76%) had viable tumor cells present in the pseudocapsule compared with 17 of 28 treated tumors (61%); with the numbers available, this difference was not significant ($p = 0.33$). After chemotherapy, residual tumor cells in the pseudocapsule frequently had degenerative changes (Fig. 6) ($p = 0.33$). Evaluation of the "normal" tissue outside the pseudocapsule revealed viable tumor cells beyond the pseudocapsule in 23 of 42 untreated tumors (55%) compared with 11 of 28 treated tumors (39%) ($p = 0.07$).

Discussion

The STS pseudocapsule is an infrequently described entity found at the host-sarcoma interface. Because chemotherapy may affect the presence and composition of the pseudocapsule in STSs, we sought to better characterize this structure and its response to chemotherapy. In this study, a pseudocapsule was identifiable in the majority of tumors and consisted of two identifiable layers, each with specific histological characteristics suggesting the biologic processes occurring in these layers are different. The pseudocapsule was more frequently observed in the group treated with chemotherapy and was more continuous, thicker, and better developed in this group. Chemotherapy also decreased the number of tumors with malignant cells identified within and beyond the tumor pseudocapsule.

There are several limitations to this study. First, the study was performed in a retrospective manner and selection bias may exist regarding the use of neoadjuvant chemotherapy in individual patient treatment. Nevertheless, we believe that factors that may have influenced treatment such as patients' choice and the ability to resect individual tumor specimens could also affect overall patient outcome (not the subject of this study). The microscopic effects of chemotherapy on treated or untreated tumors would be similar regardless of the factors or variables that determined why the patients were individually treated. Second, the two cohorts of patients used in this study are relatively small and nonrandomized with only the most commonly represented subtypes of STS. As a result of this limitation, our data may not be representative of all histological subtypes of STS or all patients with these tumors. Although ideally all chemotherapy-treated cases should be matched with untreated control subjects of the same age, evolution, tumor size, location, and histologic type, this approach would be impractical given the rarity of these tumors. Numerous systems have been proposed for the histologic grading of STS. The Musculoskeletal Tumor Society (MSTS) uses the Enneking staging system [7]. This system distinguishes two histologic grades, low grade and high grade (G1 and G2). The two most widely used microscopic grading systems are the French (FNCLCC) and the National Institutes of Health; both are three-grade systems. All cases included in this study were Grade 2 or 3 under either system (so-called high-grade STS). No tumors of "intermediate" or "borderline" malignancy were included. Furthermore, sarcomas known to respond to specific chemotherapy protocols such as rhabdomyosarcoma were not included in this study. As such, although the two patient cohorts presented here are small and nonrandomized, they are controlled in the best method possible to allow for comparison. Finally, issues regarding specimen sampling should be mentioned as a limitation to this study. Although tumors were processed using a standard protocol and examined by a pathologist with experience in the evaluation of STSs, the findings presented here may be subject to random nonrepresentative tumor sampling. We however believe our systematic process for specimen handling and extensive sampling of the pseudocapsule limits this as a potential confounder to the presented data.

The purposes of this study were to (1) define the histologic characteristics of the pseudocapsule in STSs; (2) compare the appearance of this structure in chemotherapy treated versus untreated STSs; and (3) evaluate the effect of chemotherapy on the presence and viability of tumor cells at the host-sarcoma interface. From the data presented here, we first conclude the pseudocapsule consists of preexisting connective tissue peripheral to the tumor, compressed as the tumor expands, but, in addition, is the result of active fibrogenesis induced by the tumor, perhaps through growth factors, but also as a result of

tumor involution. Understanding biologic phenomena that take place in the development of a pseudocapsule is obviously of paramount importance. Far from being an inert "capsule" or "pseudocapsule," the stromal compartment plays an active role in the initiation, growth, and metastatic spread of tumors; it is known to stimulate tumor cell proliferation through provision of various growth factors, hormones, and cytokines. Through autocrine and paracrine networks, these provide survival signals, induce and sustain inflammation and angiogenesis, and facilitate tumor invasion and metastasis. Understanding of these mechanisms will have important implications in the development of novel molecularly targeted therapies; in fact, a number of clinically approved agents target tumor-stromal interactions [16].

Second, comparison of the appearance of the pseudocapsule in chemotherapy-treated versus untreated STSs showed the pseudocapsule was more frequently observed in the group treated with chemotherapy and was more continuous, thicker, and better developed in this group. We conclude therefore that an association exists between the administration of chemotherapy in STS and the histological findings seen regarding the pseudocapsule in this series of patients. Although extrapolation of these histological data to explain the proposed beneficial effect of chemotherapy on STS local recurrence may be enticing, we do not include any such data here for either patient cohort. Therefore, data presented here cannot be used to support or refute the effect of chemotherapy on STS local recurrence or disease-free survival.

Third, although with the numbers available we did not show that neoadjuvant chemotherapy reduced the numbers of viable malignant cells beyond the pseudocapsule, our findings suggest that it is possible that a larger study would show this to be the case, and if so, it may provide one histological explanation for previous reports, which have shown improved local control in STS treated with neoadjuvant versus no chemotherapy [3–5, 13, 14]. However, without clinical data on the patients presented here, we can only hypothesize about this relationship. Studies on the microscopic evaluation of the pseudocapsule of STS are sparse; we believe that the inner and outer layers correspond roughly to the layers described as "fibrous capsule" and "reactive zone" recently [12]. In that study, the integrity of the pseudocapsule in treated cases was comparable to that observed in our series (77% and 71%, respectively). Integrity in untreated patients in that series (35%) was higher than in our study (26%). These differences may be the result of differences in the method of assessment of the pseudocapsule histologically. Our data regarding pseudocapsule presence, thickness, and integrity is based on histological evaluation of the whole periphery of the central slice of tumor, whereas the previous assessment was based on "multiple samples" with a minimum of four, in which only those tumors in which the fibrous capsule and the adjacent reactive zone were clearly visible were included in that study [12]. We believe this method of inclusion confounds the data. It should also be noted that this previous report on the development of the pseudocapsule was in relation to multiple neoadjuvant treatments including chemotherapy, radiotherapy, and isolated limb perfusion [12].

The histological data presented here demonstrate that a tumor pseudocapsule is identifiable in most STSs and that its composition changes with the use of neoadjuvant chemotherapy. Neoadjuvant chemotherapy may make the pseudocapsule a better defined structure when performing surgical resection. Although the presence of a well-defined pseudocapsule may facilitate surgery, the pseudocapsule should not be used as a surgical margin, because tumor cells frequently extend beyond this structure.

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