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## Sarcomas

# Histologic Alterations from Neoadjuvant Chemotherapy in High-Grade Extremity Soft Tissue Sarcoma: Clinicopathological Correlation

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## LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Use the correlation of all data from clinical, imaging, and histopathologic observations by a multidisciplinary tumor board in the prognosis of patients with soft tissue sarcoma.

2. Interpret the prognostic value of histologic response to chemotherapy in soft tissue sarcoma in contrast to its value in osteosarcoma and Ewing's sarcoma.

3. Evaluate the profound histologic alterations induced by neoadjuvant chemotherapy in soft tissue sarcomas.

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## ABSTRACT

Histologic response to chemotherapy is generally regarded as an independent prognostic variable in bone sarcomas, both osteosarcoma and Ewing's sarcoma. In soft tissue sarcomas, however, descriptions of histologic alterations from chemotherapy and correlative outcome studies are much more limited. Herein we report clinicopathological findings from a homogeneously treated group of 31 patients with tumor stage T2 grade 3 extremity soft tissue sarcomas treated with the same neoadjuvant chemotherapy followed by surgical excision, treated by the same medical oncologist and orthopedic surgeon. Histologic response to therapy was evaluated by multiple parameters using a semiquantitative grading system. Based upon the percentage of post-treatment viable tumor, tumors were arbitrarily categorized similarly to Huvos score as showing excellent (≤5% viability), moderate (6%–49% viability), or poor (≥50% viability) responses. Nineteen percent had excellent, 10% had moderate, and 71% had poor responses. These histologic response groups did not correlate with overall or event-free survival. For example, of

**the 22 patients showing a "poor" response, 13 were cured. Similarly, other histologic parameters, including percentages of necrosis, fibrosis/hyalinization, and cellular degeneration, did not correlate with outcome. Chemotherapy induces profound tissue alterations in soft tissue sarcomas. However, histologic alteration by itself may not be a reliable prognostic variable. Correlation of all data from clinical, imaging, and pathologi-** **cal observations by a multidisciplinary tumor board should have greater prognostic value than histology alone. Finally, although the histologic grading system used in this study could not be validated, the criteria we employed are simple and reproducible and take into account the major histologic patterns seen after therapy, and would be amenable for use in future studies.** *The Oncologist* **2008;13:451–458**

## INTRODUCTION

Chemotherapy, while still controversial, is commonly employed in treating high-grade soft tissue sarcomas. Although studies have shown that the use of adjuvant doxorubicin-based therapy leads to a longer time to local and distant recurrence [1] and a longer overall recurrence-free survival time [1, 2], no statistically significant difference in overall survival was demonstrated in a large meta-analysis [1]. Large, high-grade, localized tumors are treated with neoadjuvant chemotherapy followed by complete surgical excision and postoperative radiotherapy in many sarcoma centers in this country. Important benefits of preoperative chemotherapy include: (a) reducing tumor volume and cellular viability to facilitate limb-salvage surgery [3], (b) putatively eliminating micrometastatic disease, and (c) permitting in vivo assessment of treatment effect both by change in size and/or imaging characteristics of the tumor as well as by histologic response. Histologic response to neoadjuvant chemotherapy has been shown to be an independent prognostic variable in bone sarcomas, both osteosarcoma and Ewing's sarcoma [4–9]. Intriguingly, not all studies have demonstrated a correlation of histology with treatment and survival in osteosarcoma [10, 11], challenging the emphasis placed on histologic response as the key treatment-related predictive factor in osteosarcoma [10]. In soft tissue sarcoma, correlations between histologic alteration and long-term outcome are limited to only a handful of studies with opposing results [12–15]. Also, in two of these studies [13, 14], the patients had preoperative radiotherapy and/or intra-arterial infusions in addition to i.v. chemotherapy, which certainly altered the tissue effects of systemic chemotherapy alone. In order to study the histologic effect of systemic neoadjuvant chemotherapy in soft tissue sarcoma and to see if it might have prognostic value, we analyzed a series of common phenotype, localized, high-grade, extremity, soft tissue sarcomas treated at our institution over a 10-year period by the same medical and orthopedic oncologists.

## MATERIALS AND METHODS

### Case Selection

The study was conducted with approval by the institutional review board at our institution. Search of the pathology database for all sarcoma cases during the years 1994–2003 yielded approximately 3,000 entries. All entries were carefully screened to include only high-grade soft tissue sarcomas of common phenotypes limited to the extremities. We excluded a priori all cases of clear cell sarcoma, Ewing's sarcoma, and pediatric rhabdomyosarcoma in order to maintain a uniform series of conventional adult-type soft tissue sarcomas. We then consulted the clinical database to limit the cases only to patients with primary tumors, localized at the time of diagnosis, >5 cm, and who had been treated with systemic neoadjuvant doxorubicin and ifosfamide (without preoperative radiotherapy) and primary surgical excision at our institution. All surgical operations were performed by Dr. Sybil Biermann and all chemotherapy was supervised by Dr. Laurence Baker.

### Imaging Studies

All patients were studied preoperatively with chest computed tomography (CT) and gadolinium-enhanced magnetic resonance imaging (MRI), imaging the entirety of the compartment in which the tumor was contained. Pre- and post-treatment tumor sizes were tabulated from the radiology records based upon results of imaging studies. Clinical response categories were then determined based upon the Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Assessment of primary response and detection of distant metastasis were done in accordance with National Comprehensive Cancer Center Network soft tissue guidelines.

### Chemotherapy

A standard University of Michigan protocol for sarcoma chemotherapy was followed [17]. All patients were treated in the outpatient clinic and received doxorubicin (60 mg/$m^2$) via continuous i.v. infusion and ifosfamide (2–3 g/$m^2$)

as 2-hour infusions with mesna support. All therapy was administered over 72 hours every 21 days. All patients received postchemotherapy G-CSF. Almost all patients received the intended four cycles of therapy. The planned surgery took place 21–28 days following day 1 of the last cycle of chemotherapy.

## Surgical Technique

Patients underwent wide resection of the tumor bed and excision of biopsy tracts. In selected cases, narrow or microscopically positive margins were accepted to spare neurovascular structures. All cases had all gross tumor resected at a minimum.

## Pathology

### Gross

The specimens were dissected in the conventional manner. Following measurement, the marginal surface was inked and the tumors were serially transected. Gross estimation of percent necrosis was recorded, and multiple sections were taken from the solid areas as well as from the margins. The tumors were sampled with an average of one section per centimeter of the tumor's greatest dimension.

### Histologic Grading of Response

The tumors were systematically evaluated with a semiquantitative grading system. In every case, we determined the percent areas of viable tumor, necrotic tumor, and fibrous/hyalinized stroma such that the sum of these three components was equal to 100%. We estimated the percentage of cells demonstrating degenerative changes, defined by large, bizarre, often multinucleated cells with smudged and/or vacuolated chromatin. In addition, we tabulated the presence or absence of mitotic figures, hemosiderosis, xanthogranulomatous and lymphocytic inflammation, and cystic hemorrhagic spaces, and whether or not the margins were positive. These criteria were tabulated independently by two pathologists (DL, MK), and any differences were resolved by consensus at a two-headed microscope. Based upon the results, the tumors were arbitrarily categorized as having an excellent response when ≤5% viable tumor was present, a moderate response for 6%–49% viable tumor, or a poor response for ≥50% viable tumor.

## Clinical Outcome

All patients had been treated in our sarcoma center, and treatment and follow-up data were attained from the medical records. In selected cases, the social security death index was queried. Negative events defined as metastasis, local recurrence, or death resulting from disease, along with the

time interval from initial diagnosis to the specific event and the date of last follow-up, were tabulated.

## Statistics

Kaplan–Meier survivorship plots were constructed from the data comparing clinical or pathological variables with event-free survival. Statistical comparisons were calculated with the log-rank and Wilcoxon methods. A $p$-value of $<.05$ was regarded as significant.

## Results

## General Data

Thirty-one patients met the eligibility criteria, consisting of 11 women and 20 men with a median age of 57 years (range, 7–76). All tumors were high-grade sarcomas based on a two-scale system of low and high grades. Sixteen were categorized as malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma, five as synovial sarcoma, five as liposarcoma (three pleomorphic, one dedifferentiated and one unclassified liposarcoma), three as leiomyosarcoma, and one each as fibrosarcoma and malignant peripheral nerve sheath tumor. Twenty-three tumors were situated in a lower extremity, with the thigh representing the most common site (14 tumors). Eight occurred in an upper extremity, with the upper arm being the most common site (four tumors).

## Pathology

There was excellent agreement between the two observers regarding histology. There were three major architectural patterns: (a) viable tumor, (b) necrotic tumor, and (c) fibrotic or hyalinized stroma (Fig. 1). Viable tumor varied from seemingly unaffected cells to large, degenerated cells. Nuclear and cytoplasmic expansion, smudged chromatin, intranuclear vacuoles, and multinucleation accounted for treatment-related degenerative changes (Fig. 2). The proportions of degenerated cells varied from ≤5% in 19 tumors, to 6%–49% in eight tumors, and to ≥50% in four tumors. The median amount of fibrotic/hyalinized stroma was 15%, but varied from 0% to 95%. Scattered, degenerated tumors cells were frequently present within these fibrotic/hyalinized areas (Fig. 1C), as were xanthogranulomatous inflammation and hemosiderosis. Mitotic figures were identified in all but four tumors, including within areas showing degenerative atypia. Of note, three of the four tumors without mitotic figures had ≤5% viable tumor. Cystic hemorrhagic spaces were microscopically identified in 12 tumors. Based upon the percentage of viable tumor within the post-treatment resection specimens, 19% were categorized as having an excellent response, 10% were cat-
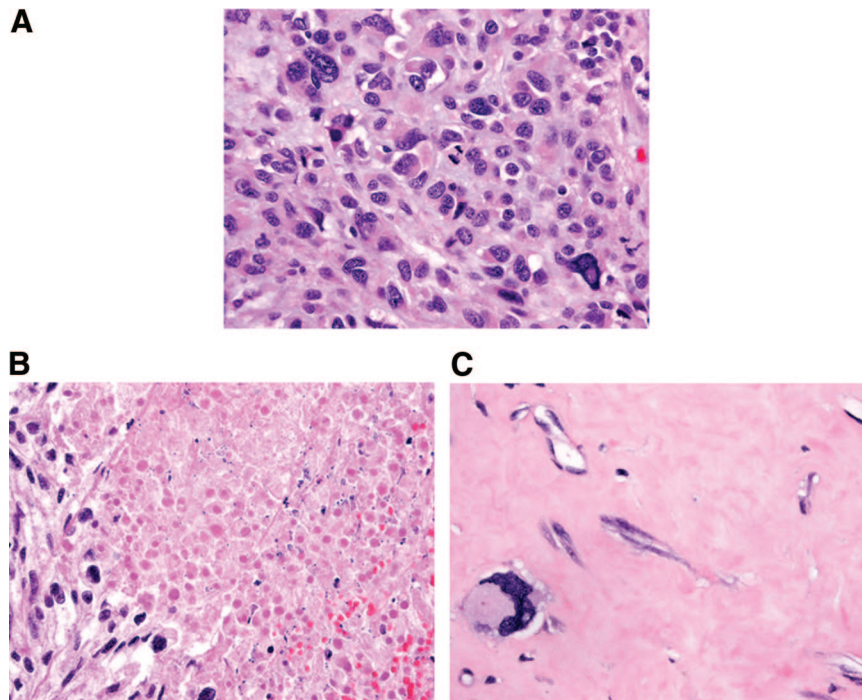
**Figure 1.** Three major architectural patterns were present in sarcomas treated with neoadjuvant chemotherapy: viable tumor **(A)**, necrotic tumor **(B)**, and fibrotic/hyalinized stroma **(C)**. Note the single degenerated cell entrapped within hyalinized stroma. (Hematoxylin and eosin, original magnification ×400.)
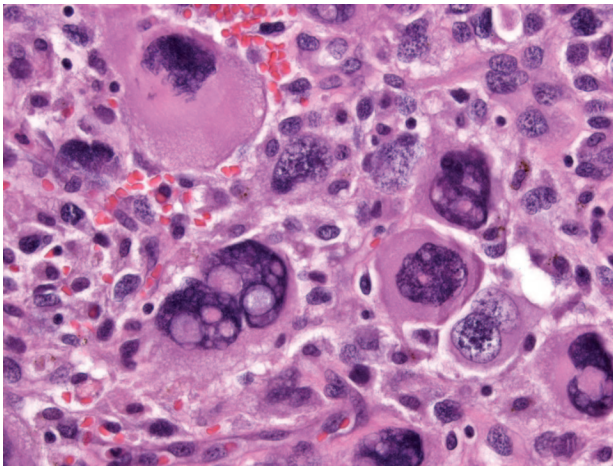


**Figure 2.** Marked degenerative atypia characterized by large, bizarre, often multinucleated cells with smudged and/or vacuolated chromatin was a common finding in tumors treated with chemotherapy. (Hematoxylin and eosin, original magnification ×400.)

egorized as moderate, and 71% were categorized as poor. Ten tumors had microscopically positive margins.

## Imaging Studies

The median pretreatment tumor size was 7.6 cm (range, 5–22). Paired pre- and post-treatment measurements were documented in 21 cases such that clinical response based upon the RECIST could be determined. Among the excel-

lent histologic responders, one (20%) had a partial response and four (80%) had stable disease. The single patient with data who had a moderate histologic response had stable disease, while the poor response group ($n = 15$) showed partial responses in 13%, stable disease in 67%, and progressive disease in 20%. There was no statistical correlation between clinical response by the RECIST and outcome.

## Clinical Outcome

The median follow-up time was 50 months (mean, 52; range, 5–145). Fifteen patients (48%) had a negative event. Nine (29%) had distant metastases, one (3%) had local recurrence only, and five (16%) had both local and distant recurrences. Eleven patients (35%) died of their disease. In the excellent response group, four patients (67%) developed distant metastases, two of whom also had local recurrences. Of these six patients, three died of disease, one was alive with metastatic disease, and two were alive without evidence of disease at last follow-up. In the moderate response group, one patient developed distant metastasis and died of disease, one was alive without disease, and one died (etiology not known by us) 6 months after initial diagnosis. In the poor response group, 10 patients (45%) had a negative event. Nine developed metastases, three of whom also had local recurrences, and one had only a local recurrence. Seven of these 22 patients were dead of disease, one was alive with
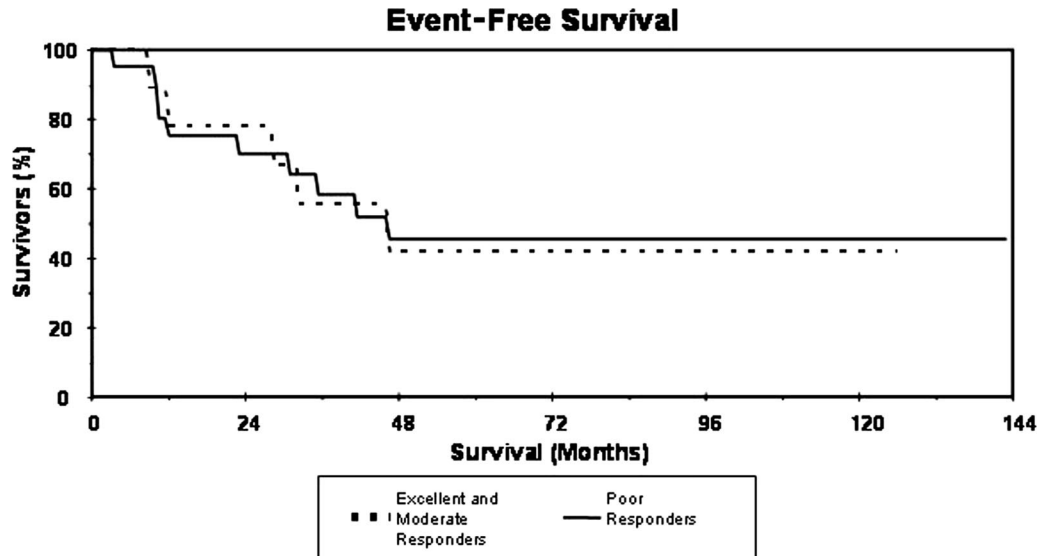
**Figure 3.** Kaplan–Meier event-free survival plot comparing the excellent and moderate histologic response groups with the poor response group. There was no significant difference.

disease, 12 were alive with no evidence of disease, and two were lost to follow-up: one who was alive at 7 years and one who was dead, but of cause unknown to us 2 years after initial diagnosis.

### Statistical Analyses

Utilizing Kaplan–Meier survival plots along with log-rank and Wilcoxon statistics, there were no significant correlations between the histologic response groups (excellent, moderate, and poor) and overall or event-free survival times (Fig. 3). Similarly, necrosis, fibrosis/hyalinization, cellular degeneration, mitotic activity, inflammation, tumor type, pretreatment size, upper versus lower extremity location, age, sex, or clinical response based upon the RECIST had no significant effect upon survival. There were no significant differences in the time to development of a negative event among the three response groups.

### DISCUSSION

The application of neoadjuvant chemotherapy as a treatment modality in cancer derives from animal studies that demonstrate accelerated metastatic tumor growth following surgical excision of the primary tumor, and that chemotherapy is most effective in suppressing residual tumor growth when given preoperatively [18, 19]. Post-treatment tumor necrosis is regarded as a surrogate indicator of the effectiveness of chemotherapy. While well-defined histopathologic criteria for assessing therapy effect in osteosarcoma and Ewing's sarcoma have been devised [7, 20–22], few studies have addressed this in soft tissue sarcoma [12, 13, 15, 23–27]. And, although histologic response to chemotherapy is

generally, but not universally [10, 11], accepted as an important prognostic variable in bone sarcomas [4–9], few studies have addressed this issue in soft tissue sarcomas [12–15, 27]. The aims of this study were therefore two-fold—to describe the histologic findings and develop a grading system for assessing response to therapy and to determine if histologic response would predict clinical outcome. We were able to devise a reproducible grading system based upon our observations.

The study set consisted of a uniquely homogeneous group of patients defined by very specific eligibility criteria. All patients presented with localized, untreated primary tumors limited to the extremities. All were high-grade, common adult-type sarcomas. All patients were treated with neoadjuvant i.v. doxorubicin plus ifosfamide chemotherapy without preoperative radiotherapy. In most of the previous studies, patients had been treated with preoperative radiotherapy and/or intra-arterial infusions in addition to i.v. chemotherapy, which most certainly affected the histology [13, 14, 23, 24], masking the effects of systemic chemotherapy alone. In addition, in our study, all treatments and operations were performed at a single institution by the same orthopedic and medical oncologists, thus providing a uniform treatment group.

By microscopic examination, the post-treatment tumor specimens had three major tissue patterns consisting of viable tumor, necrotic tumor, and stromal fibrosis/hyalinization, which could be roughly quantified as percentages such that the sum was equal to 100%. Based upon the amount of viable tumor, we stratified the cases into excellent, moderate, and poor response groups. We also observed and tabu-

lated a number of other histologic parameters, including cellular degeneration, mitotic activity, inflammation, and hemorrhage. Although response to therapy has traditionally been described in terms of percent tumor necrosis, we, like other investigators [23–25], describe it in terms of percent tumor viability. The advantage to this approach is that it combines necrosis, a common finding in untreated sarcomas, with stromal fibrosis/hyalinization, a more specific pattern associated with treatment effect, as elements of non-viable tumor. Thus, percent viability should be a more accurate portrayal of treatment effect than frank tumor necrosis. Interestingly, mitotic activity was a common finding in treated tumors, identified in all but four of our cases, and was observed occasionally in markedly degenerated cells, suggesting that these degenerated cells are not necessarily terminal forms.

We were not able to demonstrate a correlation between histologic alteration and clinical outcome. In fact, four of the six patients with excellent responses based upon ≤5% tumor viability progressed to distant metastatic disease. By contrast, among the 22 patients with poor responses, 13 seemed to be cured. Similarly, the other histologic features we evaluated, especially percentages of necrosis, fibrosis/hyalinization, and degenerative cellular atypia, showed no correlation with outcome. Nor did clinical response based upon the RECIST, which in our experience have relatively poor performance in the neoadjuvant setting. Although one might intuitively assume that a good histologic response translates into chemosensitivity, conventional histology alone may not be the best indicator of this phenomenon. For example, a given tumor may show an excellent clinical response based upon the reduction in tumor volume, while the histology continues to show mostly viable tumor. In this case, histology would underestimate the level of response. Conversely, a tumor may remain unchanged or even increase in size while showing very little viable tumor. For example, tumors with substantial collagenous or myxoid stroma, and ones that acquire intratumoral hemorrhage or edema during therapy, may show little change in size or even increase in size despite an excellent histologic response. In this case, imaging would underestimate the level of response. Other imaging characteristics beyond simple change in volume, such as decreased fluorodeoxyglucose uptake by positron emission tomography [28], induction of central necrosis with thickening of the pseudocapsule by MRI [13], and reduction in tumor density as evidenced by decreased Hounsfield units by CT [29], may prove to be more accurate ways to assess treatment in vivo.

The percentage of favorable therapy-related histologic responses in our series (19%) is lower than that reported in most other series [12–15, 23–25, 27]. However, most of the previous studies employed preoperative radiotherapy and/or intra-arterial chemotherapy, which most certainly accounted for the enhanced treatment effect. For example, in the largest reported study of 496 patients [14], 52% had either no residual tumor or ≥95% necrosis. In that study, however, all patients had been treated with preoperative radiotherapy and most had also been treated with intra-arterial infusions in addition to systemic chemotherapy. In a smaller study of 33 patients, Henshaw et al. [13] reported 76% of tumors having >95% necrosis. Although none had preoperative radiation, all patients had been treated with intra-arterial cisplatin. Similarly, Schmidt et al. [23] reported a higher percentage of tumors with good responses (defined as <15% viable tumor) present in 44% of their 25 cases, but their patients also had intra-arterial chemotherapy. In a Radiation Therapy Oncology Group trial [24], which employed aggressive preoperative chemo- and radiotherapy, 64% of the tumors showed substantial histologic responses (<25% viable tumor), including 27% with no viable tumor identified. Among studies that employed only systemic chemotherapy without preoperative radiotherapy or intra-arterial chemotherapy, Menendez et al. [12] reported 39% of 82 tumors with ≥95% necrosis, Jimenez et al. [25] reported 21% of 29 tumors with good (≤15% viable tumor) responses, Pezzi et al. [15] reported 48% of 27 patients with "histologic evidence of response," and Casper et al. [27] reported 13% of 29 patients with >90% necrosis.

Among the studies that reported histologic results, we are aware of five that correlated them with long-term follow-up. In the largest study by Eilber et al. [14], ≥95% post-treatment necrosis was associated with a significant survival advantage. Henshaw et al. [13] also reported a longer survival time in patients with ≥95% necrosis. Interestingly however, among the four patients in that study who developed metastatic disease, three had ≥95% necrosis. Among the studies of preoperative systemic chemotherapy alone, only Pezzi et al. [15] reported that histologic response correlated with a significantly longer survival time, while Casper et al. [27] provide less convincing evidence. Similar to our findings, Menendez et al. [12], in a recent study of 82 patients, could not demonstrate a correlation between histologic response and outcome, and concluded that tumor necrosis following chemotherapy has no prognostic value in soft tissue sarcoma.

## CONCLUSIONS AND SUMMARY

We report our experience in a series of patients with stage T2 grade 3 extremity soft tissue sarcomas treated with neoadjuvant chemotherapy. Chemotherapy induced profound tissue changes including necrosis, fibrosis/hyalinization, and marked cytological degeneration, and one fifth of our

cases had an excellent histological response as evidenced by ≤5% viable tumor. As a result of our observations, we devised a semiquantitative grading system based upon percentages of viable tumor, necrotic tumor, and fibrosis/hyalinization. Clinicopathological correlation between histologic response and outcome using these parameters, however, failed to demonstrate a relation. The facts that four of six patients in the excellent response group developed metastases and that 13 of 22 patients in the poor response group were seemingly cured imply that histologic response by itself may not be a reliable predictor of behavior. Although other investigators have proposed including pathological response as a parameter in determining which patients receive additional chemotherapy [15], we cannot recommend this practice based upon histology alone. As in all previous studies that correlated systemic chemotherapy effect on the primary tumor and outcome, ours is limited by inadequate numbers of patients. A much larger cohort, as might be achievable in a multidisciplinary clinical trial, would be required to achieve a more conclusive result. We are prospectively evaluating histologic response in our current neoadjuvant study of doxorubicin plus ifosfamide versus gemcitabine plus docetaxel. Although the grading system we devised—which quantifies the three major patterns of histologic alteration seen after chemotherapy of vi-able tumor, necrotic tumor, and fibrosis/hyalinization such that the sum equals 100%, as well as other parameters such as cellular degeneration— could not be validated, we find it easy to use and reproducible. We propose it as a potentially new way of reporting pathologic tumor response in adult soft tissue sarcomas, acknowledging that future studies may face the same difficulty with validation that we did, especially because there is no definitive proof of the efficacy of chemotherapy in localized tumors. Finally, because histology does not always correlate with clinical response, evaluation of all data by a multidisciplinary tumor board, including clinical, imaging, and histologic data, should provide greater predictive value than histology alone.

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**Final approval of manuscript:** David R. Lucas, Laurence H. Baker

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