Pathologic response to neoadjuvant radiotherapy (NRT) as potential prognostic factor in soft tissue sarcomas (STS).

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**Background**
- STS represent a heterogeneous group of tumors that account for greater than 10,000 adult cancers per year in USA.
- Most STS are localized at presentation, with malignancy extent of surgical resection and histology have all been identified as prognostic factors in STS.
- Current experience for high-grade STS includes neoadjuvant radiation therapy (NRT) with surgical resection.
- Several studies have documented the therapeutic efficacy of NRT prior to surgery when compared to preoperative and postoperative radiation.
- The role of pathologic evaluation in STS has been recognized as important for determining response to NRT and selecting appropriate treatment strategies.
- Studies in sarcomas and breast cancers, have shown that extensive chemotherapy-induced necrosis is significantly associated with improved survival rates. This has led many to examine criteria to STS with well conserved and at times conflicting survival studies. A potential cause for this discrepancy is that surgicopathologic community group together the percentage of necrosis and fibrosis/necrosis (i.e. non-viable tumor cells) with the pathologic response to neoadjuvant therapy, reporting both variables under the broader term “necrosis”.

**Materials and Methods**
- **Case selection:** All patients with localized, intermediate or high-grade STS of the extremities or trunk, who underwent preoperative radiotherapy followed by definitive resection at Froedtert Hospital/MCIC from 2001 to 2016 were included.
- Patients with metastases at initial presentation were excluded.
- Specific tumor types, including Rhabdomyosarcoma, Ewing sarcoma/PNET, Kaposi sarcoma and melanomas, were excluded as the basis of different treatment protocols.
- **Treatment protocol:** Preoperative radiation was administered over 25 sessions for a total dose of 50 Gy.
- **Radiologic evaluation:** MRI images before and after preoperative treatment were available in 51 of 89 patients.
- **Statistical analysis:** Demographic data and tumor location, type, depth, size, margin status, recurrence, and survival data were captured.
- **Pathologic evaluation:** All specimens were reviewed by the authors.
- **Pathologic response:** Pathologic response was correlated with clinical response.
- **Pathologic response classification:** Complete Response (CR): Disappearance of all target lesions and a decrease in the sum of the maximum diameter of target lesions by at least 30%.
- **Stromal fibrosis:** Stroma that is normal or hypercellular was scored on a 0-4 scale.
- **Stromal fibrosis/hyalinization:** Stroma that is normal or hyalinized was scored on a 0-4 scale.

**Results**

<table>
<thead>
<tr>
<th>Pathological Response</th>
<th>DFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>CR</td>
<td>0.18</td>
<td>0.011</td>
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<tr>
<td>Part Response (PR)</td>
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<td>0.012</td>
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<tr>
<td>Stable Disease (SD)</td>
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**Discussion**
- We determined the correlation of different morphological variables with histopathologic response to neoadjuvant radiotherapy.
- In our study, patients with higher degree of necrosis had better OS.
- Local tumor size was associated with more necrosis (p<0.001) and less viable tumor (p<0.001). However, this correlation was not significant in DFS.
- Presence of high-grade histology did not impact on the results of histological response to neoadjuvant therapy. Complete necrosis and complete fibrosis were associated with statistically significant improvement in DFS and OS, respectively.
- The study of pathologic responses to neoadjuvant therapy is important to the management of STS.

**Conclusions**
- High percentage of tumor fibrosis (>0%) and low percentage of tumor necrosis (<10%) indicate a better chance for the patient to be alive without disease.
- Patients with fibrosis of greater than 10% were associated with significantly lower OS and DFS.
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**References**

1. Mansson E, Willems J, Aparisi T, et al: Preoperative radiation therapy of high malignancy grade soft tissue sarcoma and angiosarcoma, were excluded on the basis of different treatment protocols.
2. Mansson E, Willems J, Aparisi T, et al: Preoperative radiation therapy of high malignancy grade soft tissue sarcoma and angiosarcoma, were excluded on the basis of different treatment protocols.

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**Figure**

- **Figure 1.** The necrosis is commonly used selectively in the context of evaluating the preoperative therapy in STS. Stromal fibrosis/hyalinization, in which the cellular contours are still visible, but the nucleus and cytoplasm is somewhat blurred and may be accompanied by cellular debris and/or nuclear inflammation (A and B). Soft tissues are commonly lumped together as "reactors."

- **Table 1.** The correlation of different morphological variables with histopathologic response to neoadjuvant radiotherapy.

- **Figure 2.** The necrosis is commonly used selectively in the context of evaluating the preoperative therapy in STS. Stromal fibrosis/hyalinization, in which the cellular contours are still visible, but the nucleus and cytoplasm is somewhat blurred and may be accompanied by cellular debris and/or nuclear inflammation (A and B). Soft tissues are commonly lumped together as "reactors."

- **Table 2.** The correlation of different morphological variables with histopathologic response to neoadjuvant radiotherapy.