A REVIEW OF NEOADJUVANT CHEMORADIATION STRATEGIES IN THE TREATMENT OF EXTREMITY SOFT TISSUE SARCOMAS

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INTRODUCTION

Soft tissue sarcomas are a rare, heterogeneous group of tumors that account for approximately 1% of all adult cancers.1 While they may be found in nearly any site of the body, the upper and lower extremities are the most common locations, accounting for about 50% of all cases. High-risk soft tissue sarcomas of the extremity include those that are large (>5cm) and of intermediate or high-grade. While the mainstay of historical treatment was amputation, current limb sparing surgery approaches combine wide excision with radiation therapy, an approach that yields local control rates of close to 90%.2-5 Despite excellent local control rates and the ability to save the limb in most patients, approximately 50% of patients with high-risk soft tissue sarcomas of the extremity will die from metastatic disease.6 In attempt to improve this outcome, systemic treatment with chemotherapy is often used to eradicate micro-metastatic disease and improve outcome; however, results of adjuvant chemotherapy trials have been mixed and the optimal management of these tumors remains controversial.7

One approach to the treatment of high-risk soft tissue sarcomas of the extremities is the use of combination pre-operative (neoadjuvant) chemotherapy and radiation. In addition to early treatment of micro-metastatic disease, pre-operative chemotherapy may act as a radiation-sensitizing agent to decrease the chance of local recurrence. This review will examine pre-operative chemoradiation strategies in the treatment of soft tissue sarcomas.

PRE-OPERATIVE VS. POST-OPERATIVE RADIATION

The addition of radiation to standard surgical treatment of extremity soft tissue sarcomas has allowed for limb-salvage surgeries to become the norm rather than the exception.2-5 Whether radiotherapy should be administered in the pre- or post-operative setting has been a topic of debate. Advantages to pre-operative radiotherapy include delivery of radiation to well-oxygenated tissue that has not been disturbed. Additionally, lower radiation doses may be used and the field size does not need to be increased to cover a surgical incision.

A randomized trial of 190 patients with extremity soft tissue sarcoma comparing pre-operative (50 Gy in 25 fractions) vs. post-operative radiotherapy (66Gy in 33 fractions) was performed by the Canadian Sarcoma Group.8 The primary endpoint was the rate of wound complications. After a median follow-up of 3.3 years, wound complications were significantly higher in the pre-operative group (35% vs. 17% respectively, p=0.01). There was no difference in local recurrence rate, regional failure rate, distant metastasis rate, or overall survival.9

High-risk soft tissue sarcomas are deep tumors of high pathologic grade and > 5 cm in size. While surgery and radiation are usually effective in eradicating the tumor from the affected limb, their tendency for early, microscopic spread places patients at significant risk for eventual development of metastatic disease.

Dr. Murray Brennan discusses the use of radiation after surgery.
failure rate or progression-free survival. The pre-operative group did have a slightly increased overall survival (85% vs. 72%, p=0.05). Wound complications occurred more frequently in lower extremity (43%) than in upper extremity (6%) tumors.

Limb-sparing surgical approaches usually require the addition of radiation in order to reduce the chance of tumor recurrence in the limb. While the effectiveness in preventing recurrence is the same, side effects may be different depending on whether radiation is given before or after surgery.

A follow-up analysis of this trial reported on late radiation morbidity and found that patients treated with post-operative radiotherapy had a higher rate of grade 2 or greater fibrosis (48.2% vs. 31.5% respectively, p=0.07). Joint stiffness (23.2% vs. 17.8%, NS) and edema (23.2% vs. 15.1%, NS) were also more frequently observed in the post-operative radiotherapy arm as opposed to the pre-operative arm, although these differences were not statistically significant.

Together, these results suggest that pre-operative radiotherapy is associated with more acute wound healing complications in the peri-operative period, but that the higher radiation dose and larger field size of post-operative administration may increase long-term limb complications. Preference for the use pre- vs. post-operative radiation remains institution-dependent, and may be influenced by the location of the tumor given the higher incidence of wound complications in lower extremity tumors.

THE ROLE OF CHEMOTHERAPY

The two most active chemotherapy agents in the treatment of metastatic soft tissue sarcoma are doxorubicin and ifosfamide. Earlier administration of chemotherapy in the course of the disease can theoretically treat micro-metastatic disease and decrease the rate of distant disease and improve overall survival. However, results of studies have been mixed and the use of chemotherapy as an adjunct to surgery and radiation for high-risk tumors remains controversial. The optimal schedule and timing for chemotherapy in this setting remains undefined. Most randomized trials to date have investigated the role of post-operative chemotherapy, and relatively few pre-operative trials have been reported.

Gortzak et al examined neo-adjuvant chemotherapy using doxorubicin and ifosfamide vs. no pre-operative therapy in a small randomized study of patients with high-risk soft tissue sarcomas. This study demonstrated the feasibility of chemotherapy prior to surgical resection without adversely affecting surgery or subsequent radiotherapy. While there was not a statistically different 5-year disease-free or overall survival, this 134-patient study was underpowered to draw definitive conclusions regarding these outcomes.

A multi-institutional, retrospective analysis of patients treated with neo-adjuvant chemotherapy containing doxorubicin/ifosfamide/mesna vs. those treated with surgery alone was reported by Grobmyer et al. Improved 3-year disease specific survival was seen for patients with tumors >10 cm treated with neo-adjuvant chemotherapy vs. those treated with surgery alone (HR 0.45, 95% CI: 0.25-0.83), suggesting a possible benefit for very high-risk tumors.

The effectiveness of chemotherapy in improving survival from high-risk soft tissue sarcomas remains controversial. Some studies have suggested that chemotherapy helps, while others have not. Further studies in patients with high-risk tumors and select sarcoma subtypes are needed.
**Neoadjuvant Chemoradiotherapy**

Theoretical advantages of neoadjuvant chemotherapy together with pre-operative radiation include earlier treatment of micro-metastatic disease and a lower radiation dose requirement. Neoadjuvant chemoradiotherapy may possibly help to downsize the tumor allowing for a more-resectable tumor and possibly less morbid procedure. Additionally, pathologic response determined at the time of surgical resection provides potential prognostic information. While the most important role of neoadjuvant chemotherapy is its potential effect on reducing development of metastatic disease, its activity as a radiosensitizer may help improve local control rates when combined with radiation. While surgery occurs several months later when a neoadjuvant approach is employed, there is no evidence of worse outcome because of what may be perceived as a delay by patients.

Multi-modality approaches using neoadjuvant chemoradiotherapy for high-risk soft tissue sarcomas have been pursued by a number of institutions. Reports of neoadjuvant chemoradiotherapy in this population have consisted of single-arm studies and retrospective analyses (Table 1). As with much other clinical research in sarcoma, the absence of large, randomized trials and Level I evidence limits interpretation of such data. Early strategies employed regional chemotherapy with intra-arterial doxorubicin. Eilber et al reported on consecutive patients treated at UCLA between 1975-1981 with bone and soft tissue sarcomas (n=100) using intra-arterial doxorubicin at 30 mg/day over 24-hours for 3 consecutive days followed by a rapid fractionation radiation plan of 350 cGy/day for 10 treatments (3500 cGy). With a median follow-up of 32-months the local recurrence rate was only 3%. Patients with grade III tumors between 5-10cm had an overall survival of 76% while patients with larger tumors (10-15cm) had 65% overall survival. A subsequent trial reducing the radiation dose (1750 cGy), resulted in an increased local recurrence rate of 20% with only 4% of subjects achieving a complete pathologic response; subsequent trials from this group have used the 2800 cGy dose.

Multiple other reports of pre-operative intra-arterial doxorubicin with high-dose per fraction, short course radiation were subsequently reported. These studies employed similar radiation schemes and reported very low local recurrence and promising disease-free survival rates. The cumbersome and potential toxic effects of intra-arterial chemotherapy were eventually questioned. A randomized trial from the UCLA group demonstrated that there was no difference in local control or complication rates between intra-arterial vs. intravenous doxorubicin combined with radiation (n=112). This trial showed a 6% complete pathologic response, 14% local recurrence rate, and 70% overall survival. Subsequent studies transitioned to the use of intravenous chemotherapy, with similar outcomes reported as with intra-arterial therapy.

More recent studies of neoadjuvant chemoradiotherapy have employed multi-agent chemotherapy. In the metastatic setting, combination chemotherapy has been associated with greater response rates than single-agent doxorubicin, though without clear survival advantage. In the adjunctive, minimal disease setting, it is hoped that potential additional activity of combination treatment may translate into increased clinical benefit. Most recent neoadjuvant regimens have employed anthracycline and ifosfamide combinations.
Table 1. Published Reports of Neoadjuvant Chemoradiotherapy for Soft Tissue Sarcomas

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Chemotherapy Agent</th>
<th>Route of Administration</th>
<th>Radiation Dose, cGy</th>
<th>Local Recurrence (time point)</th>
<th>Overall Survival (time point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eilber</td>
<td>1984</td>
<td>100</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3500</td>
<td>3% (3 y)</td>
<td>76% (3 y)</td>
</tr>
<tr>
<td>Denton</td>
<td>1984</td>
<td>30</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3000</td>
<td>3% (2 y)</td>
<td>68% (3 y)</td>
</tr>
<tr>
<td>Eilber</td>
<td>1984</td>
<td>95</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>1750</td>
<td>20% (NR)</td>
<td>61% (NR)</td>
</tr>
<tr>
<td>Goodnight</td>
<td>1985</td>
<td>17</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3500-4000</td>
<td>0 (2 y)</td>
<td>82% (2 y)</td>
</tr>
<tr>
<td>Eilber</td>
<td>1987</td>
<td>71</td>
<td>Doxorubicin</td>
<td>IA vs. IV</td>
<td>2800</td>
<td>14% (NR)</td>
<td>70% (NR)</td>
</tr>
<tr>
<td>Hoekstra</td>
<td>1989</td>
<td>9</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3500</td>
<td>11% (2 y)</td>
<td>71% (2 y)</td>
</tr>
<tr>
<td>Temple</td>
<td>1989</td>
<td>25</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3000</td>
<td>0 (2 y)</td>
<td>NR</td>
</tr>
<tr>
<td>Eilber</td>
<td>1990</td>
<td>46</td>
<td>Doxorubicin, cisplatin</td>
<td>IV</td>
<td>2800</td>
<td>12% (NR)</td>
<td>71% (NR)</td>
</tr>
<tr>
<td>Levine</td>
<td>1993</td>
<td>55</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>2500</td>
<td>19% (5 y)</td>
<td>69% (5 y)</td>
</tr>
<tr>
<td>Eilber</td>
<td>1993</td>
<td>35</td>
<td>Doxorubicin, cisplatin, ifosfamide</td>
<td>IV</td>
<td>2800</td>
<td>2% (NR)</td>
<td>85% (NR)</td>
</tr>
<tr>
<td>Wanebo</td>
<td>1995</td>
<td>66</td>
<td>Doxorubicin</td>
<td>IA</td>
<td>3000-4600</td>
<td>2% (5 y)</td>
<td>59% (5 y)</td>
</tr>
<tr>
<td>Sauer</td>
<td>1999</td>
<td>23</td>
<td>Doxorubicin, ifosfamide</td>
<td>IV</td>
<td>6000-6400</td>
<td>NR</td>
<td>83% (3 y)</td>
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<tr>
<td>Edmonson</td>
<td>2002</td>
<td>39</td>
<td>Doxorubicin, cisplatin, ifosfamide, mitomycin</td>
<td>IV</td>
<td>4500</td>
<td>10% (5 y)</td>
<td>80% (5 y)</td>
</tr>
<tr>
<td>DeLaney</td>
<td>2003</td>
<td>48</td>
<td>Doxorubicin, ifosfamide, dacarbazine</td>
<td>IV</td>
<td>4400</td>
<td>8% (5 y)</td>
<td>87% (5 y)</td>
</tr>
<tr>
<td>Ruka</td>
<td>2004</td>
<td>100</td>
<td>Ifosfamide, doxorubicin, cisplatin</td>
<td>IV</td>
<td>2000</td>
<td>7% (NR)</td>
<td>76% (5 y)</td>
</tr>
<tr>
<td>Pisters</td>
<td>2004</td>
<td>27</td>
<td>Doxorubicin</td>
<td>Continuous IV</td>
<td>5000</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mack</td>
<td>2005</td>
<td>75</td>
<td>Doxorubicin</td>
<td>IA or IV</td>
<td>3000</td>
<td>3% (5 y)</td>
<td>63% (5 y)</td>
</tr>
<tr>
<td>Kraybill</td>
<td>2006</td>
<td>66</td>
<td>Doxorubicin, ifosfamide, dacarbazine</td>
<td>IV</td>
<td>4400</td>
<td>22% (5 y)</td>
<td>71% (5 y)</td>
</tr>
<tr>
<td>Ryan</td>
<td>2008</td>
<td>25</td>
<td>Epirubicin, ifosfamide</td>
<td>IV</td>
<td>2800</td>
<td>13% (2 y)</td>
<td>84% (2 y)</td>
</tr>
<tr>
<td>MacDermed</td>
<td>2010</td>
<td>34</td>
<td>Ifosfamide, various others</td>
<td>IV</td>
<td>2800</td>
<td>11% (5 y)</td>
<td>42% (5 y)</td>
</tr>
</tbody>
</table>

DeLaney et al reported a 48 patient study from the Massachusetts General Hospital using neoadjuvant chemotherapy and “interdigitated” radiotherapy for 8 cm or larger, high-grade extremity soft tissue sarcomas. Pre-operative treatment consisted of 3 pre-operative cycles of the MAID regimen (mesna, doxorubicin, ifosfamide, and dacarbazine) with 2 radiotherapy courses sandwiched between cycles to a total of 44Gy. Three additional cycles of MAID chemotherapy were given post-operatively. Toxicities of this treatment regimen included febrile neutropenia (25%), moist desquamation of skin (29%), grade 3 nausea (17%), grade 3 vomiting (10%), wound healing complications (29%), and myelodysplasia as a late complication in 1
patient. Five-year outcomes compared with historical controls included improved freedom for distant metastasis 75% vs. 44% (p=0.0016), disease-free survival 70% vs. 42% (p=0.0002), and overall survival 87% vs. 58% (p=0.0003), respectively. While such retrospective comparisons must be interpreted cautiously, these data were encouraging and prompted the initiation of a confirmatory Radiation Therapy Oncology Group (RTOG) multi-institutional trial.33 The 66 patient RTOG 9514 trial reported significant toxicity including 3 treatment-related deaths and an 83% incidence of grade 4 toxicity. The 5-year disease-free survival of 56% and overall survival of 71% were less robust than the single institution experience, suggesting that while a complicated neoadjuvant chemoradiotherapy regimen could be delivered in a multi-institutional setting, its general applicability outside of a dedicated center remained questionable.

Potential Advantages of Neoadjuvant Chemoradiotherapy

- Early treatment of micro-metastases
- Lower radiation doses
- Shrinking the tumor for surgery
- Prognostic information gained from the surgical specimen.

Potential Disadvantages of Neoadjuvant Chemoradiotherapy

- Increased wound complications
- Delay of surgery

Ryan et al investigated the use of an intensive chemotherapy regimen with ifosfamide and epirubicin in combination with pre-operative hypofractionated radiation in patients with high-risk soft tissue sarcomas of the extremity or body wall.28 Three pre- and 3 post-operative cycles of epirubicin and ifosfamide were administered at relatively high doses similar to those used in a randomized adjuvant trial.10 During the second pre-operative cycle, epirubicin was omitted and radiotherapy to 28Gy administered in 8 fractions, similar to the regimens reported by Eilber et al.15 The primary endpoint was rate of ≥95% pathologic necrosis at time of surgical resection which was reported at 40% (95% CI, 21-59%). Two-year disease-free and overall survival were 62% (95% CI, 37-86%) and 84% (95% CI, 66-100%), respectively. Toxicity was significant with 84% of patients experiencing grade 4 toxicities. Grade 3/4 anemia (64%), ifosfamide-induced encephalopathy (24%), and neutropenic fever (40%) were the most notable toxicities. A 20% post-operative wound complication rate was also seen. This study demonstrated that an intensive neoadjuvant chemoradiotherapy strategy could yield a significant pathological necrosis rate but with substantial toxicity.

The trials of neoadjuvant chemoradiotherapy to date have enrolled a heterogenous population of soft tissue sarcoma subtypes due to the inability of single institutions to effectively conduct histology-specific studies. As certain soft tissue sarcoma subtypes are generally considered to be more chemotherapy-sensitive (e.g. synovial sarcoma, myxoid round cell liposarcoma), outcomes of neoadjuvant approaches in such histologies are of interest and some retrospective attempts have been made to discern benefit. Data from 245 patients with high-risk liposarcoma of the extremities treated at UCLA and Memorial Sloan Kettering were analyzed based on whether they had received neoadjuvant or adjuvant ifosfamide-based, doxorubicin-based, or no chemotherapy.34 On multivariate analysis, treatment with ifosfamide was independently-associated with improved disease-specific survival (HR = 0.3 compared with no chemotherapy, P = 0.01). A similar analysis of 101 patients with high-risk synovial sarcomas also suggested a disease-specific survival benefit with ifosfamide over no chemotherapy (HR = 0.3, P = 0.007).35 However, a retrospective report of 100 patients with synovial sarcoma treated with pre-operative ifosfamide and radiation followed by post-operative ifosfamide, doxorubicin and
cisplatin reported an estimated 5-year disease-free survival rate of 50%, which is not suggestive of improved outcome compared with the overall soft tissue sarcoma population. While there are no definitive data supporting the neoadjuvant chemoradiotherapy approach in any particular soft tissue sarcoma subtype, its use especially in chemotherapy-sensitive subtypes is a strategy employed by some centers.

Combined preoperative chemotherapy and radiation strategies should be primarily considered for patients with high-risk sarcomas (> 5 cm, high-grade, deep tumors). The relative effectiveness in individual sarcoma subtypes has not been defined, but special consideration may be given to sarcomas thought to be more responsive to chemotherapy, such as synovial sarcoma or myxoid round cell liposarcoma.

**HISTOPATHOLOGIC RESPONSE TO NEOADJUVANT THERAPY**

One potential benefit to the use of pre-operative therapy is the information gained from examination of the surgical specimen after resection (Figure 1). While pathologic necrosis to pre-operative chemotherapy has been established as a prognostic factor in osteosarcoma and Ewing’s sarcoma, relatively little has been published regarding its value in soft tissue sarcomas. The UCLA group reported on treatment-induced pathologic necrosis as a predictor of local recurrence and survival in a retrospective analysis of 496 soft tissue sarcoma patients treated with neoadjuvant therapy at their institution. Ten-year local recurrence rates were lower in patients with ≥95% necrosis (11% vs. 23%, respectively) and 10-year overall survival was likewise higher in patients with ≥95% necrosis (71% vs. 55%, respectively).

MacDermed et al demonstrated a positive correlation between treatment-induced pathologic necrosis and freedom from distant metastasis in a retrospective study of neoadjuvant rapid fractionation radiation with ifosfamide-based chemotherapy. Fifty percent of tumors demonstrated ≥90% treatment-induced necrosis. Freedom from distant metastasis was superior in the patients who had ≥90% treatment-induced necrosis (84.6% vs. 19.9%, p=0.02). However, for the overall population the 5-year overall survival rate of 42.3% was less than reported in the other series.
The trial by Ryan et al was unique in its use of histopathologic response as the study’s primary endpoint.\textsuperscript{28} Validation of pathologic necrosis as a surrogate endpoint should be considered in future prospective trials of pre-operative therapy for soft tissue sarcomas. Early detection of response to neoadjuvant therapy with imaging modalities such as PET or DCE-MRI may likewise provide important predictive information and are actively being studied in this setting.\textsuperscript{39-41}

**FUTURE DIRECTIONS**

Collectively, phase II trials have shown high rates of local control and histologic response with neoadjuvant chemoradiotherapy for extremity soft tissue sarcomas. While overall survival rates are favorable, benefit cannot be proven in the absence of randomized trials and a significant proportion of high-risk patients still succumb to the disease. New approaches are needed to advance treatment options and to provide alternatives to current neoadjuvant chemotherapy regimens with their associated significant toxicity.

Refinement of the radiation component of pre-operative therapy is one current area of investigation. RTOG 0630 is a phase II study of image-guided pre-operative radiotherapy for primary extremity soft tissue sarcomas aimed at reducing late radiation morbidity.\textsuperscript{42} This study consists of 2 cohorts. Subjects in cohort A will receive neoadjuvant and/or adjuvant chemotherapy plus 50Gy of radiation in 25 daily fractions, or concurrent or interdigitated chemotherapy plus 44Gy of radiation in 22 daily fractions. Subjects in cohort B are those not receiving chemotherapy who will receive 50Gy of radiation in 25 daily fractions. All subjects will then receive surgery followed by a post-operative radiotherapy boost in those subjects with positive margins. Cohort A closed in January 2010 and results are pending.

A promising adjunct to neoadjuvant therapy is regional hyperthermia, a process in which tumor tissue is heated to improve the effects of chemotherapy or radiation. In a recently published phase III trial, 341 patients with large, high-grade sarcomas (both extremity and non-extremity) were randomized to neoadjuvant chemotherapy (etoposide, ifosfamide, and doxorubicin) with or without concurrent hyperthermia.\textsuperscript{43} Local progression-free survival (LPFS) was improved in the hyperthermia group (HR 0.58, 95% CI 0.41–0.83; p=0.003), with 2-year LPFS of 76% in the chemotherapy plus regional hyperthermia group vs. 61% in the chemotherapy-alone group. While hyperthermia in conjunction with pre-operative chemoradiotherapy has not yet been reported, an ongoing phase II study is investigating such an approach using ifosfamide, radiation, and hyperthermia and employing magnetic resonance imaging for non-invasive hyperthermia monitoring.\textsuperscript{44}

Another unique neoadjuvant modality is isolated limb perfusion, a technique in which the blood supply to the limb is isolated from the rest of the body through extracorporeal circulation, allowing the infusion of high doses of biochemotherapy into the affected limb. Tumor necrosis factor-alpha (TNF-α, available only in Europe) is infused together with chemotherapy agents such as melphalan, often under mild hyperthermic conditions.\textsuperscript{45,46} While this treatment is not used in combination with radiation and full discussion is out of the scope of this review, its high response rates and potential utility in large, unresectable sarcomas is worthy of mention.

Integration of novel systemic agents with neoadjuvant chemoradiotherapy is another strategy that is being explored. Okuno et al reported on the use of aerosolized GM-CSF in attempt to decrease the development of pulmonary metastatic disease when given with a pre-operative regimen of ifosfamide, mitomycin, doxorubicin, cisplatin and radiation.\textsuperscript{47} This was considered a negative study by the authors as the 2-year pulmonary-metastasis free rate of 75% (95% CI 62-91%) was no better than their historical experience with chemoradiotherapy alone.

Anti-angiogenic agents have held promise in the treatment of sarcoma.\textsuperscript{48,49} The RTOG investigated the addition of thalidomide to pre-operative MAID chemotherapy with interdigitated radiation followed post-operatively by 12-months of adjuvant thalidomide.\textsuperscript{50} Unfortunately 40% of
subjects had grade 3/4 vascular adverse events leading to early closure of the study. Our group at Oregon Health & Science University is investigating the addition of the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor, sorafenib, to our previously reported regimen of pre-operative epirubicin/ifosfamide and hypofractionated radiation. We are also studying whether DCE-MRI can detect early changes in tumor perfusion during treatment with anti-angiogenic therapy.

As the field of oncology continues to elucidate the molecular pathways that regulate tumor growth and progression, it will become increasingly important to match individual tumors with appropriate targeted therapeutic agents. The pre-operative treatment period provides an invaluable setting in which to test agents based on analysis of biopsy specimens. Comparison of the post-therapy surgical specimen with baseline biopsy material may reveal important clues as to mechanisms of drug resistance, and such approaches should be incorporated in future studies of neoadjuvant therapy.

CONCLUSIONS

Multi-disciplinary treatment of soft tissue sarcomas is paramount for optimal outcome. Wide surgical excision with the addition of radiotherapy remains the mainstay of treatment of locally advanced soft tissue sarcomas. Neoadjuvant chemoradiotherapy has thus far been studied in relatively small, non-randomized trials. Therefore the impact of these approaches on patient outcomes remains speculative. While centers with dedicated treatment teams have reported good outcomes with neoadjuvant chemoradiotherapy, the overall benefit and general applicability of such regimens remains unknown in the absence of multi-center, randomized trials. Further progress will be dependent upon the discovery of new and active treatments for soft tissue sarcomas that can be tested in the high-risk setting.

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