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REVIEW ARTICLE

Perioperative Management of Extremity Soft Tissue Sarcomas

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A B S T R A C T

Surgery is potentially curative for primary nonmetastatic extremity soft tissue sarcomas. After surgery alone, patients may remain at risk for local recurrences and/or metastatic disease. To reduce the likelihood of a local relapse, the addition of radiotherapy (RT) to limb-sparing surgery may result in higher local control rates of at least 85%. Generally, it can be stated that local control after both preoperative and postoperative RT is comparable, but that preoperative RT comes with a more favorable toxicity profile after prolonged follow-up, albeit at the cost of a higher wound complication rate. Furthermore, recent data suggest that preoperative RT is more cost effective. To reduce the risk of subsequent metastatic disease, systemic chemotherapy can be introduced early during the primary management of these patients. These systemic chemotherapy regimens can also be applied both preoperatively and postoperatively. Finally, with the aim of increasing the antitumor response of perioperative RT, these agents may even be combined with RT, concurrently and sequentially. While designing new preoperative combination regimens, responses should be carefully monitored by both sophisticated radiologic and pathologic evaluations. This article reviews all these aspects, in addition to limb-sparing surgery.

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INTRODUCTION

The role of surgery aiming to cure primary nonmetastatic extremity soft tissue sarcomas (ESTS), is undebated. However, the addition of radiotherapy (RT) to limb-sparing surgery may result in higher local control rates of at least 85%, especially when resection margins are negative, compared with surgery alone.[1-4] This combined modality approach, as indicated by both National Comprehensive Cancer Network[5] and European Society for Medical Oncology guidelines,[6] has widely replaced the need for amputations.[7]

Predominantly dependent on age, histologic subtype, grade, and size, a substantial proportion of patients may develop subsequent metastatic disease.[8] Attempts have been made to reduce this risk by the introduction of systemic chemotherapy early during the primary management of these patients. With the aim of increasing the antitumor response of perioperative RT, these agents may even be combined with RT, concurrently and sequentially. These aspects should be thoroughly discussed before management by experienced multidisciplinary teams in referral hospitals. Careful investigations on radiologic and pathologic response evaluation are mandatory, especially when new preoperative combination regimens are designed.

Timing of Perioperative RT

On the basis of the results of the Canadian SR-2 trial[1] and other nonrandomized comparisons,[9,10] it can be stated that local control after both preoperative and postoperative RT is comparable. Recent data suggest that preoperative RT is more cost effective.[11] The following sections discuss the main differences between both approaches.

Postoperative RT

Conventionally, the postoperative RT regimen consists of two phases. First, the entire operative bed (with a margin) is irradiated to 50 Gy in 1.8-2 Gy fractions followed by a boost of 10-16 Gy to the tumor site before surgery. Details on this regimen have been described previously.[2] Because postoperative RT combines both large volumes and high doses, the long-term results include higher rates of permanent and progressive morbidities, such as fibrosis, joint stiffness, and edema[12] compared with patients treated with preoperative RT. Albeit, the incidence of early wound complications is lower.[1] Studies from both Scandinavia[13] and France[14] have questioned the

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gain in local control by the 10-16 Gy boost after R0 resections. Currently, the question of timing is being investigated by the NCT02565498 study, which is a randomized trial comparing 50 Gy preoperative RT with 50 Gy postoperative RT after an R0 resection.

Preoperative RT

For preoperative RT, the volume of tissue irradiated is smaller, and the dose delivered is lower than during postoperative RT. Specifically, the tumor (plus a margin) is irradiated to 50 Gy in 1.8-2 Gy fractions. Although this regimen has been shown to result in an increased incidence of (sometimes severe) wound healing problems,[1] these complications are of a temporary nature. Conversely, the permanent long-term complications of fibrosis, joint stiffness, and edema are reduced with preoperative RT compared with postoperative RT.[12] Moreover, with the sarcoma in situ during preoperative RT, the opportunity arises to investigate individual and histotype-specific regimens with respect to fraction size, total dose, and combination with radiosensitizers.

In the past, several preoperative RT regimens with unconventional fraction sizes and/or total doses other than 50 Gy have been investigated, each with their own wound complication and local control profiles. Temple et al[15] observed a relatively low wound complication rate of 15%, while maintaining local control at 97% at 5 years of follow-up after 10 × 3 Gy. Between 1974 and 1987, Eilber et al[16] performed three consecutive phase II studies, all applying 3.5 Gy fraction sizes. They eventually concluded the 8 × 3.5 Gy schedule provided the most favorable balance of local control and wound healing rates.[16,17] In all these schedules, intra-arterial or intravenous doxorubicin was delivered during RT. The most extreme hypofractionation schedule to date is the Polish 5 × 5 Gy preoperative schedule, which enrolled 272 patients and reported a local control rate of 81% at 3 years.[18]

The histologic subtype myxoid liposarcoma is known for its exceptional radiation sensitivity, demonstrated by high local control rates after 50 Gy preoperatively.[19] On the basis of this finding, an international prospective phase II clinical trial (NCT02106312) is investigating the efficacy of a reduced dose of 18 × 2 Gy for this subtype.

Experience with carcinomas has demonstrated that, compared with RT alone, concurrent regimens of preoperative (or definitive) RT in combination with systemic agents may result in improved local control and, sometimes, survival (albeit at the risk of an increased acute toxicity profile). Similar concurrent regimens have been explored for sarcomas aiming to increase antitumor efficacy and/or to use concurrent systemic agents as a means to lower the concurrent RT dose. Examples of tested combinations are ifosfamide 2,500 mg/m^2 per day for 5 days (+ 8 × 3.5 Gy[20]), epirubicin 30 mg/m^2 per day, and ifosfamide 2,500 mg/m^2 per day, both on days 1 to 4 (+ 8 × 3.5 Gy[21]). Biologically more interesting are studies with targeted agents, such as bevacizumab in combination with 28 × 1.8 Gy,[22] sorafenib either in combination with 8 × 3.5 Gy[23] or with 25 × 2 Gy,[24] pazopanib with 25 × 2 Gy,[25] and sunitinib in combination with 50 to 50.4 Gy.[26,27] Except for concurrent single-agent ifosfamide, all these schedules seem to be associated with pathologic (near) complete response rates significantly higher than the 8% to 10% rates historically observed after RT alone, as listed in Table 1.[28,29] However, it is important to point out that for soft tissue sarcoma (STS), pathologic response is not yet a valid surrogate end point.[31] Of more clinical relevance are parameters such as local control and overall survival (OS), but they take years to mature. For now, outside the setting of well-designed prospective clinical trials, the 1.8-2 Gy fraction regimens should be considered the standard of care.

Preoperative RT: Balancing Local Control and Surgical Complications

The use of preoperative RT has offered new possibilities in limb salvage. After neoadjuvant therapy, narrow margins against critical structures can be allowed, while maintaining local control and functional outcome after resection[3,32,33] because local control after both preoperative and postoperative RT seems comparable.[1,9,10] An increased local control rate has been observed delivering preoperative RT when such an expected positive margin against critical structures is planned and expected. This has also been observed in

Table 1. Preoperative RT Series With Respect to Concurrent Systemic Therapy: Local Control and Histologic Response Rates Compared With RT Only

Setting	First Author	No.	RT Regimen	Chemotherapy Regimen	% Local Control at NN Years	(near) pCR, %
RT only	O'Sullivan[1]	94*	25 × 2 Gy	—	92 at 6.9 †	—
	Canter[28]	25	25 × 2 Gy	—	100 at 3	8
	Shah[29]	30	25 × 2 Gy	—	100 at 5	10
RT plus conventional chemotherapy	MacDermed[20]	34	8 × 3.5 Gy	Ifosfamide	89 at 5	11.8
	Ryan[21]	25	8 × 3.5 Gy	Epirubicin plus /ifosfamide	88 at 2	40
	Gronchi[30]	135	25 × 2 Gy	Epirubicin plus ifosfamide	95.2 at 10	—
RT plus targeted agents	Yoon[22]	20	28 × 1.8 Gy	Bevacizumab	95 at 2	20
	Meyer[23]	16	8 × 3.5 Gy	Sorafenib	100 at 2	44
	Canter[24]	8	25 × 2 Gy	Sorafenib	100 at 3	38
	Haas[25]	11	25 × 2 Gy	Pazopanib	91 at 2	40
	Jakob[26]	9	28 × 1.8 Gy	Sunitinib	88 at 3	33
	Lewin[27]	9	28 × 1.8 Gy	Sunitinib	‡	§

Abbreviations: (near) pCR, defined as more than 95% necrosis; NN, specified number of years follow-up; pCR, pathologic complete response; RT, radiotherapy.
*Preoperative RT arm only.
†Update at ASCO and Connective Tissue Oncology Society presentations in 2004.
‡At 3.7 years median follow-up, five of nine had local relapses.
§Median percentage of necrosis was 75%; range, 1% to 95%, suggestive of a (near) pCR rate of 0%.

a recent trial combining preoperative chemotherapy and RT in high-risk STS after prolonged follow-up.[30,34] Early wound healing difficulties are the disadvantage of this multimodality treatment strategy.[1,35,36] Comparing results of prospective and retrospective studies, it must be noted that wound complications may occur in up to 42% of patients treated without (neo)adjuvant RT.[3,37-40] The Canadian SR-2 trial reported a significantly higher wound complication rate after neoadjuvant RT (17% *v* 35%), especially in the lower extremity (20% *v* 43%).[1] Comparable rates were observed in a study of patients > 70 years old (40% *v* 19%), with a particular emphasis to the adductor compartment and the groin.[41]

In the modern era, the incidence of wound complications within a phase III study combining RT with anthracycline plus ifosfamide neoadjuvant chemotherapy in localized extremity or trunk wall STS was less than 20%, whereas that of neoadjuvant chemotherapy followed by adjuvant external beam RT was 10%.[42] Commonly, wound healing problems in low-risk patients are delayed and can be expected on average 3 weeks after surgery.[35] When present, they are often successfully treated with modern wound healing strategies, such as vacuum treatment, and can therefore be regarded as temporary. Significant wound healing problems necessitating additional surgical intervention are uncommon.[43,44]

Although fully acknowledging the acute toxicity profile of preoperative RT as described above, two merits should be highlighted. First, long-term toxicity results are in support of neoadjuvant RT because less edema and fibrosis, fewer fractures, and superior limb function are reported.[12,45] Second, preoperative RT may compensate for (anticipated) R1 resections.[46-49] Furthermore, the acute toxicity profile inherent in preoperative RT can be mitigated by experienced surgeons in tertiary referral centers, using techniques such as free and pedicle flaps for high-risk locations (recurrences, large tumors, and lower extremity locations, especially in the adductor compartment and the groin).[43,44,50,51]

The patient's age and comorbidities should also influence decision making, because older age, obesity, vascular insufficiency, smoking, and diabetes have a negative effect on wound healing. Finally, some histologic subtypes are more sensitive than others (ie, myxoid liposarcoma, solitary fibrous tumor, extraskeletal myxoid chondrosarcoma, etc.), whereas some others have a higher local recurrence risk (ie, myxofibrosarcoma and malignant peripheral nerve sheath tumors).[52,53]

When a decision for RT is made, timing should be influenced by tumor characteristics, such as presentation (need to preserve function or not), site of origin, histologic subtype, and malignancy grade and size, as well as the patient's characteristics, as mentioned above. The balance of pros and cons might increasingly favor the use of preoperative RT, where its toxicities should be manageable in experienced centers.

Timing of Perioperative Systemic Therapy: Adjuvant Chemotherapy

For many bone tumors, perioperative chemotherapy is the standard of care. However, adjuvant chemotherapy has failed to prove an unequivocal clinical benefit in the heterogeneous group of STS. Nevertheless, the high rate of local or distant relapse and ultimate mortality (approximately 50% for high-grade tumors), even after adequate local treatment of STS,[54] has inevitably sustained the clinical interest of using adjuvant chemotherapy toward improving recurrence-free survival (RFS) and overall survival (OS).

An attempt to systematically analyze data on adjuvant chemotherapy, overcoming the problem of inadequately powered small trials and minimizing potential biases, was the 1997 Sarcoma Meta-Analysis Collaboration (SMAC).[55] This landmark examination is the only STS meta-analysis to date on the basis of individual patient data. SMAC suggested adjuvant chemotherapy to significantly improve local and distant recurrence-free intervals (4% at 10 years), especially for men and ESTS (7% at 10 years; HR, 0.80; $P = .029$). Pervaiz et al[56] updated this meta-analysis in 2008, adding another four trials, confirming the marginal efficacy of doxorubicin-based adjuvant chemotherapy.

After SMAC, the Italian Randomized Cooperative Trial,[57] involving 104 high-grade patients with ESTS, studied an intensified adjuvant epirubicin/ifosfamide treatment arm (total cycle dose of ifosfamide, 9 g/m^2). After a median follow-up of 59 months, the study showed a significant improvement in median RFS and OS; however, it was not sustained at longer follow-up.

The most recent adjuvant chemotherapy trial, coordinated by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), is the largest conducted to date. This study, involving 351 patients, failed to demonstrate any impact of adjuvant chemotherapy (five cycles of doxorubicin/ifosfamide) on either RFS or OS, especially after R0 resections.[58,59]

These trials should be included in new meta-analyses. Until then, adjuvant chemotherapy has not reproducibly improved RFS or OS in an unselected patient population, as listed in Table 2. Whether adjuvant chemotherapy can be proposed to high-risk individual patients in still-to-be-determined subtypes is a matter of shared decision making.[6] New drugs, including novel molecularly driven agents, have been introduced in the treatment arena of STS. Future adjuvant chemotherapy trials with the same regimen for all STS subtypes are undeniably over. They should be driven by yet-to-be-identified and validated prognostic biomarkers. Options are (1) randomized trials in selected groups of histologic subtypes with specific systemic agents, (2) conventional chemotherapy in several STSs but with a specific molecular signature,[61] and (3) selected regimens according to pathway signatures (eg, adjuvant imatinib in GI stromal tumors[62]).

Induction (Neoadjuvant) Chemotherapy: Is It Better Than Adjuvant?

For locally advanced STS, options to be discussed include neoadjuvant chemotherapy (NACT) with adequately dosed anthracyclines plus ifosfamide,[63] isolated limb perfusion, or regional hyperthermia combined with chemotherapy.[64,65]

Several phase II trials have evaluated NACT combined with RT in series of up to 70 to 80 patients.[66] However, lacking randomization, the exact benefit of these strategies in terms of progression-free survival and the percentage of patients achieving limb-sparing resections has not been prospectively addressed. The only randomized trial comparing NACT followed by surgery with surgery only, reported by the EORTC-STBSG, failed to demonstrate a significant tumor control rate or survival advantage.[67]

Finally, a large prospective trial compared three cycles of a conventional, full-dosed, anthracycline-ifosfamide (EI) regimen

Table 2. End Point Parameters in Adjuvant Chemotherapy Studies

Parameter	SMAC55	Italian Cooperative Study57	EORTC-STBSG 6293158	Pooled Data EORTC-STBSG 62931 and 6277159	Italian, Spanish, French, Polish Intergroup Study (ISG-STS 1001)60
No.	1,568	104*	351	819	287
Median follow-up	9.4 years	59 months (minimum observation period 36 months)	7.99 years	8.2 years	12.3 months
Drugs	Doxorubicin based†	Per course: epirubicin 120 mg/m^2 + ifosfamide 9 g/m^2; total 5 courses	Per course: doxorubicin 75 mg/m^2 + ifosfamide 5 g/m^2; total 5 courses.	For 62931: doxorubicin 75 mg/m^2 + ifosfamide 5 g/m^2, total 5 courses .58 For 62771: CYVADIC	Histo-type based v standard epirubicin 120 mg/m^2 + ifosfamide 9 g/m^2
Local RFI	HR, 0.73 (0.56 to 0.94); P = .016	—	—	—	85% *v* 86% at 46 months
Absolute local relapse-free benefit at NN years (CI)	6% at 10 years (1% to 10%)	0% *v* 10% at 2 years (P = .02), 6% *v* 17% at 4 years (P = .09)	18.9% *v* 23.7% at 5 years	—	
Distant RFI	HR, 0.70 (0.57 to 0.85); P = .0003	—	—	—	HR, 2.147 (1.172 to 3.930); P = .011
Absolute distant relapse-free benefit at NN years (CI)	10% at 10 years (5% to 15%)	28% *v* 45% at 2 years (P = .08), 44% *v* 45% at 4 years (P = 0.94)	—	—	45% *v* 74% at 46 months
Overall RFI	HR, 0.75 (0.64 to 0.87); P < .001	HR, 0.59 (0.36 to 0.99); P = .04	HR, 0.91 (0.67 to 1.22); P = .51	—	—
Absolute overall relapse-free benefit at NN years (CI)	10% at 10 years (5% to 15%)	27% at 2 years, 13% at 4 years		—	—
Overall survival	HR, 0.89 (0.76 to 1.03); P = .12	HR, 0.52 (0.29 to 0.93); P = .03	HR, 0.94 (0.68 to 1.31), P = .72	—	HR, 2.687 (1.104 to 6.940); P = .034
Absolute overall survival benefit at NN years (CI)	4% at 10 years (1% to 9%)	13% at 2 years, 19% at 4 years; P = .04		After marginal resection: 27.6% *v* 44.7% at 10 years, P = .048; after optimal resection: approximately 60% with or without chemotherapy regardless of sex or age	64% *v* 89% at 46 months
Subgroup analyses	Men benefit more than women; extremities benefit more than other locations	No significant differences for age, sex, center of surgery, histology, grading, site of primary tumor, presentation, diameter, local treatment, and stratification	Trends toward more benefit from chemotherapy for larger, high-grade, and extremity tumors were not significant	Men benefit more than women; chemotherapy detrimental in younger women?; patients age > 40 years benefit more than younger patients; marginal *v* radical resection negatively influenced overall survival; adjuvant CYVADIC reduced local recurrence rate without any impact on survival	Difference in disease-free survival favoring standard chemotherapy was consistently seen in all strata except for high-grade myxoid liposarcoma
DI		Average median relative DI: 83.3%, 63% of cycles at DI ≥ 80%, 48% of cycles at DI ≥ 90%	80% completed full 5 cycles, 68% received full dose on time; 22% delays, 6% dose reductions, and 4% both		10% *v* 18% dose reductions

Abbreviations: CYVADIC, doxorubicin 50 mg/m² day 1, dacarbazine 400 mg/m² days 1-3, cyclophosphamide 500 mg/m² day 1, and vincristine 1.5 mg/m² day 1; DI, dose intensity; EORTC-STBSG, European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group; HR, hazard ratio; NN, specified number of years follow-up; RFI, recurrence-free interval; SMAC, Sarcoma Meta-analysis Collaboration.
*Preplanned interim analysis revealed benefit for chemotherapy, P = .001.
†Doxorubicin dose per study predominantly 50-70 mg/m² and cumulative 400-550 mg.

with histotype-tailored chemotherapy (HT-CT) in localized, high-grade, > 5-cm, adult ESTS,[60] aiming to reduce the relapse risk with the HT-CT regimen by 30%. The HT-CT regimen in the experimental arm was based on results observed in the advanced setting during the last decade.[42] After a median follow-up of more than 1 year, unexpectedly, patients receiving EI experienced a better prognosis. The projected RFS at 4 years was 62% with the EI regimen versus 38% in the experimental arm. After 70 events, at the third preplanned interim analysis, the study was closed. The results observed in the experimental arm are surprising. Whatever the hypotheses, EI compared with HT-CT is still superior in most common subtypes of localized STS.

Referral to specialized centers of all patients with (suspected) STS will help to develop precision medicine programs to identify new actionable targets and new ambitious programs, even in the context of localized diseases.[68-71] The collection of fresh/frozen tissue and tumor imprints is encouraged because new molecular pathology assessments could be made at a later stage in the patient's interest.

Pathologic Response Evaluation After Preoperative Therapy

Whereas several clinical trials have demonstrated the relevance of histopathologic appearance in bone sarcomas, mainly in osteosarcomas and Ewing sarcomas, it is still under debate whether there should be a comparable response evaluation scheme for STS. Generally accepted rules on how the tumor specimen should be worked up after preoperative treatment and how the results should be reported are lacking. However, the EORTC-STBSG has proposed a standardized protocol for neoadjuvant therapy response assessment on the basis of a consensus of their STS experienced reference pathologists. They proposed a five-tier histologic response score on the basis of the percentage of remaining stainable tumor cells ranging from zero to > 50%.[72] Subsequently, this proposed response score was assessed for its prognostic value by another group at Harvard Medical School in Boston.[31] In this retrospective study of 100 patients with STS treated with preoperative RT, The EORTC-STBSG response score was not found to be prognostic, but the extent of hyalinization and fibrosis was associated with a favorable outcome. These results can only be viewed as hypothesis generating, and a prospective trial with well-defined criteria for specimen analysis is necessary.

Furthermore, after neoadjuvant treatment, it is difficult if not impossible to evaluate whether areas of necrosis are the result of the treatment or have been a consequence of insufficient blood supply due to insufficient neovascularization. Therefore, it seems to be more effective to estimate the percentage of remaining tumor cells, although their tumorigenic capability cannot be seen under the microscope. In summary, a prospective clinical trial including high-grade sarcomas in defined locations that are evaluated by a consensus protocol developed by a group of pathologists will be the only way to clarify the relevance of preoperative neoadjuvant treatment.

Radiologic Response Evaluation After Preoperative Therapy

Magnetic resonance imaging (MRI) is standard imaging before and after RT. However, histopathologic changes that occur after RT confound dimension-based assessments of response. Except for myxoid liposarcoma,[73] significant dimensional radiologic responses after preoperative RT are rare events and have been reported to be as low as 0%.[28] Consequently, dimension-based assessments have been shown to have no correlation with outcome or histopathologic response,[74,75] and alternative response assessments are needed. Tumor characteristics on computed tomography scans (such as the Choi criteria) or tumor contrast enhancement at MRI may complement tumor size as a criterion to better predict pathologic response. In a study of neoadjuvant chemotherapy or chemoradiotherapy response to chemotherapy with or without RT was associated with a better outcome in patients with high-risk STS, and Choi criteria were better predictors than conventional Response Evaluation Criteria In Solid Tumors.[76,77] Although in standard clinical practice, post-RT imaging of the primary sarcoma is unlikely to alter the decision regarding operability,[78] evolving therapeutic options do require a robust assessment of response and clinical trials necessitate quantitative measurements.

Current consensus from the EORTC-STBSG suggests that the addition of functional diffusion-weighted MRI (DW-MRI) to standard anatomic and postcontrast MRI greatly facilitates interpretation because the combination of reduced enhancement and increasing apparent diffusion coefficient (ADC) may increase confidence for response.[79] After RT, new enhancement alone should be interpreted with caution because this may be a result of vascular disruption rather than histologic response. Moving forward into clinical trials, DW-MRI is also promising as a quick, noninvasive tool showing excellent reproducibility for ADC measurements, which reflect tumor cellularity and microarchitecture in STS (coefficient of variation [CoV], 1.7%).[80] Preclinical data suggest that DW-MRI may also be valuable in assessments as early as 2 days after RT.[81] ADC can be supplemented with quantitative measures of perfusion, such as enhancing fraction (CoV, 8.6%), or model-based measures, such as K^{trans} (CoV, 13.9%).[82] Dual baseline quantitative MRI allows individual patient response assessments rather than cohort measures, which may not reflect response in heterogeneous patient groups. However, the relationship of these MRI parameter changes with clinical outcomes has not yet been validated; therefore, their use as clinical trial end points must be carefully considered and used in conjunction with proven end points (such as local control and survival). Alternative methods of assessment are also poorly understood; however, a small study of [^{18}F]fluorodeoxyglucose positron-emission tomography/computed tomography in high-grade sarcomas did show some promise for fluorodeoxyglucose uptake measurements of standardized uptake value.[83]

In conclusion, nonmetastatic sarcomas should be surgically removed whenever possible. Perioperatively, the addition of RT and/or chemotherapy should be considered, on the basis of both tumor and patient characteristics. With respect to radiation, applying RT preoperatively should be considered. These discussions should take place between patients and experienced teams in tertiary referral centers. Treatment-related early end points, such as radiologic and histologic response, are appealing and should be included in future prospective trials to assess for correlations with clinical outcomes, such as local control and survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Perioperative Management of Extremity Soft Tissue Sarcomas

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