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·专家述评·

躯干和肢体软组织肉瘤的围手术期化疗与放疗

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[摘要] 虽然手术是肢体和躯干原发软组织肉瘤的根治性治疗手段,但对于高危患者单纯手术常难以获得疾病的长期控制。治疗失败的主要原因为远处转移,其次为局部复发。一些局部进展期的患者可能面临无法手术切除,或仅边缘可切除,因此预后很差。围手术期的系统治疗和放疗可提高手术疗效。如何确立围手术期系统治疗的价值颇具挑战。系统治疗可以缩小肿瘤。但要证明其对局部控制的价值从而促进实施更为保守的外科手术的证据仍不充分。对于那些原发肿瘤被认定为难以或不可能切除的患者,新辅助化疗可能为疾病的局部控制提供一种选择。围手术期的系统治疗也可以避免远处转移的发生。近期的研究表明,以蒽环类药物/异环磷酰胺为基础的辅助治疗能够使患者获益,虽然证据来自于对一项大型研究的再次分析。一项新辅助化疗的随机研究提示,对某些经过选择的肉瘤组织学亚型,以蒽环类药物/异环磷酰胺为基础的系统化疗可能改善患者无病生存和总生存期。其疗效的获得主要是通过改善远处无转移生存而不是局控率的提高。这两项研究所采用的方法均存在一定的局限性,因此需要进一步探索。尽管如此,我们相信这些结果支持在局部进展期、肢体和躯干原发的软组织肉瘤患者中进行新辅助化疗。放疗与手术结合在软组织肉瘤的治疗中有确切的疗效。虽然预后并不因放疗和手术的先后顺序而异,但不良反应却存在差异。辅助放疗较新辅助放疗有更低的围手术期伤口并发症,但相对于新辅助放疗而言,辅助放疗需要更高的放射剂量,对长期功能的预后差于新辅助放疗。因此,我们相信围手术期放疗与化疗一样,在可能的情况下,应尽可能在术前进行。

[关键词] 软组织肉瘤;躯干;肢体;化疗;放疗

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Peri-operative chemotherapy and radiation therapy in management of soft tissue sarcomas of the trunk and extremities: review of the evidence

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[Abstract] Surgery is the definitive treatment for soft tissue sarcomas of the extremities and trunk, but is often unable to achieve long-term disease control in high-risk patients. The dominant mode of treatment failure is distant metastasis, with local relapse being secondary. Some patients with advanced local disease may be unresectable, or marginally so, and consequently face a poor prognosis. Peri-operative systemic therapy and radiotherapy may be able to enhance outcomes of surgical treatment. Peri-operative systemic therapy has been challenging to validate. Systemic therapy can lead to decreased tumor sizes. Validation of local control benefits in facilitating more conservative surgical procedures remains incomplete. For those with primary tumors judged difficult or impossible to resect, neoadjuvant chemotherapy may provide a route to local disease control. Peri-operative systemic therapy may also prevent development of metastatic disease. A recent study suggested benefit from adjuvant therapy with anthracycline/ifosfamide-based therapy, albeit in a post hoc reanalysis of a large trial. A randomized trial of neoadjuvant systemic therapy suggested that anthracycline/ifosfamide-based therapy may improve disease-free and overall survival in selected histologic sarcoma subtypes. This effect appeared mediated by improved distant metastasis-free survival, rather than improved local control. Methodological limitations in both trials necessitate further investigation. Nevertheless, we believe the results support the use of neoadjuvant systemic therapy in management of locally advanced soft tissue sarcomas of the extremities and trunk. Radiotherapy has a well-established position in conjunction with surgery for sarcomas treatment. While outcomes do not seem to vary depending on sequencing of radiotherapy administration versus surgery, adverse effects do so. Adjuvant radiotherapy is associated with lower peri-operative wound complication rates than

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neoadjuvant therapy, but the higher radiation doses required for adjuvant treatment yield long-term functional outcomes inferior to neoadjuvant radiotherapy. For this reason, we believe that peri-operative radiotherapy, like systemic therapy, should be administered neoadjuvantly, when possible.

[**Key Words**] soft tissue sarcomas; trunk; extremities; chemotherapy; radiation therapy

Sarcomas comprise about 1% of all cancers[1]. The relatively young age of the population affected and the frequently life-altering surgeries required for their control amplify the magnitude of their impact, beyond what simple numbers would indicate. The National Cancer Institute of the United States (NCI) has recognized sarcomas as an area of unmet need from the biomedical research community[2].

The mainstay of treatment is surgical excision, often combined with radiotherapy[3]. Clinico-pathologic factors associated with disease-free survival (DFS) include tumor grade, tumor size, resection margin status, type of clinical presentation (prior local recurrence or not), tumor location, patient age and histiotype[4]. All except clinical presentation have also been associated with disease-specific survival (DSS). In one large series of patients treated with surgery and radiation therapy at a single center, 15-yr local, distant and overall DFS were 79%, 66%, and 55%, respectively. Outcomes in individual patients are strongly dependent on stage at presentation[5].

A large prospective database of 10 000 patients treated at a single institution from 1982-2013 reported local recurrence and DSS rates of 25% and 60% at 10 years after diagnosis[6]. At another center, among 1 225 patients, 55% experienced long-term disease control[4]. Distant recurrence was the dominant mode of treatment failure, present in about 70% of recurrences. Local recurrences at the site of primary treatment were observed in about one-half of recurrences. A proportion of patients experiencing recurrence are eligible for salvage treatment, including surgical metastectomy[7]. Some of these patients will achieve long-term control through these salvage measures, but the majority will ultimately die of their conditions.

Several nomograms have been developed to assess local recurrence risk and overall survival (OS) of those patients with soft tissue sarcomas (STS) of the extremities and trunk[8-11]. Adjunctive therapies can then be focused on those at highest risk. In sarcomas, presently available adjunctive therapies include systemic chemotherapy and radiation therapy. In primary sarcoma therapy, these treatments may be employed either after completion of surgical treatment (adjuvant) or prior to surgical therapy (neoadjuvant). Here, we review the relative merits of each temporal mode of therapy. We contend that presently available data support the use of neoadjuvant treatment, when possible.

1 Adjunctive therapy of sarcomas with systemic chemotherapy

Adjunctive systemic therapy offers two potential benefits to sarcoma patients: (1) regression of the existing disease, rendering local therapies (surgery and/or radiotherapy) more effective, and (2) early treatment of micro-metastatic disease, preventing its later emergence. Improvement of local control can include circumstances in which tumors are initially unresectable or marginally so. Positive margins at the time of definitive surgery are associated with increased local recurrence rates, and decreased distant relapse-free and DSS rates[12]. Potential benefit in the form of decreased positive margins rates can only accrue if systemic therapy is administered neoadjuvantly.

Experiences from the metastatic setting give some idea of the responsiveness of STS to systemic therapy, as assessed by objective response rate (ORR). The combination of doxorubicin and ifosfamide is probably the best studied regimen from a response standpoint. The clinical trial of Judson and co-workers compared doxorubicin monotherapy with doxorubicin and ifosfamide[13]. This clinical trial, enrolling patients with advanced disease, demonstrated ORR of 26%,

with 2% complete responses, among the 227 patients receiving doxorubicin and ifosfamide. This contrasted with 14% for those receiving doxorubicin monotherapy (P=0.000 6). The increased ORR of the combination agrees with the results of an earlier meta-analysis[14].

2 Local control effects of neoadjuvant systemic therapy

Assessing local control benefit from neoadjuvant chemotherapy is difficult. Multiple retrospective[4,15-18] and prospective[19-21] studies demonstrate that the combination of surgery and radiation therapy, whether adjuvant or neoadjuvant, achieves high rates of local disease control in sarcomas of the trunk and extremities. These rates range from about 80%-100% local DFS at 5-15 years after initial treatment.

Most studies examine the role of neoadjuvant combination chemotherapy and radiotherapy protocols. Even the type and timing of the neoadjuvant treatments varies substantially. Such high rates of local control and variation in treatment protocols make difficult any attempt to parse out local control benefit specifically attributable to the neoadjuvant chemotherapy component of treatment.

Further, different approaches to assess the local control benefit have varying strengths and weaknesses. ORR is attractive because it can be applied objectively (for example, through blinded imaging review using standardized assessment criteria) and yields numerical outcomes allowing simple comparisons between groups. The clinical significance of ORR however is unclear, except perhaps for the unusual circumstance of a complete response (CR) to systemic treatment.

More relevant would be some measure of change in surgical management after neoadjuvant therapy. Such measures require more subjective assessments of surgical resectability and categorization. Both factors decrease precision of effect estimates, necessitating larger subject numbers in any assessment. Inadequate sample sizes have not been easy to surmount in sarcoma clinical trials.

Local effects of neoadjuvant therapy were assessed in a single-institution, retrospective study of 112 patients with STS of the extremities[22]. Prior to surgery, patients received combined neoadjuvant radiation therapy and chemotherapy (n=39), neoadjuvant radiation therapy (n=37) or surgery alone (n=36). All patients had intermediate- or high-grade tumors. Patients with larger tumors were more likely to receive chemotherapy and/or radiation therapy, while those with relapsed disease were more likely to be treated with surgery alone. Only 12 of 39 chemotherapy-treated patients received combination therapy including doxorubicin and ifosfamide. Notably, 20 of 39 patients received cisplatin concurrently with radiation, a regimen that we believe would not presently qualify as standard neoadjuvant systemic therapy for STS.

For patients treated with limb preservation, there was no difference in the quality of resection (negative resection margins/R0 versus microscopically positive margins/R1) among the three treatment groups. Rate of limb amputation was identical for patients receiving neoadjuvant chemoradiotherapy or neoadjuvant radiation therapy alone. No difference was evident in local or distant relapse-free survival (RFS) or OS among the groups. For those with tumors greater than 5 cm, chemoradiotherapy and radiotherapy were associated with superior survival. Wound complications were more frequent among those receiving neoadjuvant therapy than among those treated with surgery alone (50% for neoadjuvant chemoradiotherapy and 42% for neoadjuvant radiation therapy *vs* 11% for those treated with surgery alone, P=0.003 and P=0.02, respectively). However, in multivariable logistic regression, receipt of neoadjuvant therapy was not associated with wound complications.

The limited study size, heterogeneity of the study populations and great variation in systemic treatment plans make it difficult to draw definitive conclusions from this study. The additional time required to administer neoadjuvant therapies did not worsen resection quality. Administration of neoadjuvant therapy did not appear to be harmful, beyond anticipated increased rates of wound

complication, a known and anticipated consequence of neoadjuvant radiation therapy.

DeLaney and co-workers conducted a prospective single-arm study in patients with large (≥8 cm), intermediate- or high-grade extremity STS[23]. Subjects received three cycles of neoadjuvant doxorubicin, ifosfamide and dacarbazine and three cycles of adjuvant systemic therapy. Neoadjuvant radiotherapy was interdigitated with chemotherapy, and a post-operative radiation boost was administered for those with positive margins at surgery. Outcomes were compared to historical controls matched for tumor size, tumor grade, age and era of treatment. Of the 48 control patients, 39 received neoadjuvant radiotherapy and 9 received only adjuvant radiotherapy. Two of the control patients received some forms of neoadjuvant systemic therapy and 12/48 received adjuvant systemic therapy.

Among 47 evaluable patients, ORR after neoadjuvant chemoradiotherapy was 11% (5/47). Six patients demonstrated evidence of disease-progression on imaging. However, 70%-100% pathologic necrosis was present on subsequent surgery, indicating discordance between radiologic and pathologic outcomes. Local RFS at 5 years was not different when comparing the test group to the historical controls (92% *vs* 86%, $P=0.12$). Neither extent of pathologic necrosis, change in tumor size, nor tumor location were associated with distant-metastasis free survival (DMFS), DFS or OS. Survival outcomes favored the test group receiving systemic chemotherapy, when compared to the historical control group. At 5 years, these outcomes included DMFS (75% *vs* 44%, $P=0.002$), DFS (70% *vs* 42%, $P=0.000\ 3$) and OS (87% *vs* 58%, $P=0.000\ 3$).

Local skin reactions associated with radiation therapy were noted in 29% (14/48) patients. Wound healing complications, defined as secondary wound surgery, hospital admission for wound care or deep packing/prolonged dressing within 120 days after tumor resection, were also evident in 29% (14/48). Whether these were more frequent than in the control population was not reported.

Treatment-related toxicities were as expected from multi-agent chemotherapy. Febrile neutropenia occurred in 12 patients (25%). Granulocyte-colony stimulating factor was given to 39 patients (81%), although it appears to have been administered reactively after severe neutropenia or febrile neutropenia, rather than prophylactically. One patient developed therapy-associated myelodysplasia 38 months after completion of chemotherapy, dying from pancytopenia.

This study provides evidence for potential benefit in controlling distant disease emergence for this regimen. From a local control standpoint, radiologic responses are documented, although cases with "progression" based on imaging criteria did not necessarily have such evidence when assessed pathologically. Given administration of both neoadjuvant chemotherapy and radiation, local effects attributable specifically to chemotherapy, whether beneficial or harmful, cannot be assessed.

A cooperative group study attempted to confirm the results of DeLaney and co-workers in a multi-institutional setting[24-25]. This study used a slightly higher dose of ifosfamide (7.5 g/m^2 per cycle *vs* 6 g/m^2 per cycle) and a lower dose of dacarbazine (675 mg/m^2 per cycle *vs* 1 000 mg/m^2 per cycle)[23]. Sixty-six patients were enrolled from 31 institutions. Two patients were deemed ineligible, leaving 64 assessable. All patients had primary tumors at least 8 cm in maximal dimension and intermediate- or high-grade (80% grade 3). Radiotherapy treatment was identical to that described in the single-institution study[23].

After neoadjuvant therapy, ORR was 22% (13/59 assessable patients). Fourteen percent (8/59) experienced disease progression on neoadjuvant treatment. Out of 51 assessable patients, 14 (27%) had a pathologic CR at surgery. R0

resections were attained in 91% (58/61) of patients, including five patients with amputations. Three patients had microscopically positive margins (R1), and three did not undergo surgery (two due to disease progression and one due to patient refusal).

With a median follow-up time of 7.7 years, 5-yr loco-regional freedom-from-failure, DFS, DMFS and OS were 78%, 56%, 64%, and 71%, respectively. These outcomes were significantly improved versus historical controls[26]. This is especially notable given the enrollment of patients with large (median 15 cm, range 8.2-55 cm) and high-grade (80% grade 3/3) tumors.

Three patients (5%) died of treatment-attributable effects. Two patients developed treatment-related acute myelogenous leukemia 28 and 29 months after chemotherapy. Another patient developed sepsis during neoadjuvant chemotherapy, possibly associated with a biopsy site as portal of entry. Five of 53 (9%) patients required amputation, of which two were necessitated by leukopenia-associated sepsis at biopsy sites. At the time of definitive surgery, 7/61 (11%) had serious or severe wound complications delaying planned adjuvant chemotherapy or potentially being associated with severe tissue loss or amputation.

From a local control standpoint, the authors felt that the rate of loco-regional failure and rate of amputation were higher than expected. This could perhaps be accounted for by the large number of participating sites, leading to significant variation in selection of patients for the study and planned surgical procedures. Interpretation of the significance of these observations is again hindered by lack of a control group. The contribution of systemic therapy to both local control and toxicity could not be determined due to use of combination neoadjuvant chemoradiotherapy.

Gortzak and co-workers conducted a randomized phase Ⅱ study in which patients with high-risk STS received three cycles of pre-operative chemotherapy with doxorubicin and ifosfamide (50 mg/m^2 and 5 g/m^2 per cycle, respectively), or proceeded directly to definitive local surgery[27]. Radiotherapy was indicated in about half of the patients enrolled, but was given post-operatively. High-risk tumors were defined as (1) any tumors greater than 8 cm in maximal dimension, (2) intermediate- or high-grade tumors of any size, or (3) intermediate- or high-grade tumors which were locally recurrent or which underwent inadequate surgery in the preceding 6 weeks. Seventy-five patients were randomized to each arm of the study, of which a relatively large proportion (8/75 in each arm, 11%) were deemed ineligible.

Here, any effect of chemotherapy on local control and surgical outcomes could be assessed. Among those receiving neoadjuvant chemotherapy, ORR was 29% (14/49) among those assessable for response prior to surgery. Lack of measurable disease at the start of the study in 15/18 was the dominant reason that patients were not assessable for response. Among 9/49 (18%), disease progressed radiologically in the face of chemotherapy. Radiological progression was not associated with inadequate subsequent surgery. The extent of histopathologic treatment effect in these patients was not reported.

While some patients had different surgical procedures than initially planned, no gross differences were evident in comparing the actual versus initially planned surgical procedures. No unplanned amputations occurred. Negative surgical margins were obtained in 89% of those treated. Chemotherapy was not associated with delayed wound-healing or increased post-operative complications.

The study was reported with a median follow-up time of 7.3 years. The 5-yr RFS and OS estimates did not differ between the treatment arms (64% chemotherapy *vs* 65% surgery alone [$P=0.22$], and 55% *vs* 52% [$P=0.35$], respectively). The study had initially planned to transition to a phase Ⅲ study, but was discontinued early due to slow accrual. As

conducted, the study was underpowered to detect a survival benefit of preoperative chemotherapy: this would have required at least 269 patients to detect a 15% improvement in 5-yr survival.

The conclusions were hampered by the limited number of evaluable patients enrolled (67 per arm), broad range of patient profiles (tumor size, grade, treatment-naïve versus recurrent), multiple possible surgical outcomes and low doses of chemotherapy versus present practice. Despite its shortcomings, this study indicates that interval of time required to administer neoadjuvant chemotherapy, 9-12 weeks, does not compromise surgical therapy. A better picture of the surgical impact of neoadjuvant chemotherapy might have been revealed if the full study had been completed as planned. Marked improvements in local control attributable to systemic therapy were not demonstrated.

3 Distant disease control effects of systemic therapy

Systemic therapy may treat existing micrometastatic disease, preventing its later emergence. This strategy has revolutionized the treatment of sarcomas of childhood (osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma), in which micrometastatic disease is present at diagnosis in the majority of patients[28]. For other STS, the benefits are less clear.

Two meta-analyses evaluated randomized clinical trials of adjuvant systemic therapy for STS up to 2007[29-30]. The most recent of these favored chemotherapy administration in regards to local relapse, distant relapse, overall recurrence and OS[30]. No improvement in OS was evident for doxorubicin-based therapies, but there was such a statistical improvement for doxorubicin/ifosfamide-based combinations. Absolute risk reductions for local and distant recurrence and for OS were 4% (95%CI 0%-7%), 9% (95%CI 5%-14%) and 6% (95%CI 2%-11%), respectively. Improvement in OS was driven by the doxorubicin/ifosfamide combinations, as doxorubicin-based therapy (absent ifosfamide) was not associated with improved OS. Notably, the included randomized studies were relatively small in size, with 12-67 patients per treatment arm.

More recent randomized trials have been unable to confirm these findings. One trial enrolled patients with large (≥5 cm or recurrent) high-grade tumors to receive adjuvant epirubicin and ifosfamide (n=53) or observation[31]. Improvement in DFS and OS were reported, with an absolute estimated OS benefit favoring chemotherapy of 13% at 2 years and 19% at 4 years. Updated results failed to confirm these observations[32-33]. Another study of ifosfamide/doxorubicin/dacarbazine adjuvant chemotherapy enrolled 58 patients (31 chemotherapy, 27 observation) with intermediate-grade tumors ≥5 cm or high-grade tumor of any size[34-35]. No improvements in local or distant relapse, overall relapse or OS were observed. Possible benefit in high-grade tumors was hypothesized. Both studies suffered from their modest size, making them essentially phase Ⅱ assessments of adjuvant therapy.

A significantly larger phase Ⅲ study was conducted by the European Organization for Research and Treatment of Cancer (EORTC; study designated EORTC-STBSG 62931)[32]. This study enrolled patients with intermediate- or high-grade sarcomas, randomizing them to receive 5-21 day cycles of adjuvant doxorubicin (75 mg/m^2) and ifosfamide (5 g/m^2) (n=175) or observation after initial therapy (n=176). On central review, only 46% of the enrolled patients had high-grade tumors, with 48% intermediate grade and 6% low-grade. Although the median tumor sizes were large at 7.5-8.6 cm, there was also a broad range (0.3-38 cm).

Treatment did not impact RFS or OS, whether analyzed by intent-to-treat (ITT) or per protocol analyses. Subgroup analyses, including tumor grade and size, failed to indicate improved RFS or OS for those receiving chemotherapy. A reanalysis of the trial's results used a prognostic estimation algorithm to classify anticipated survival

of patients enrolled[11-36]. In this reanalysis, adjuvant treatment improved DFS and OS in the subgroup with a predicted 10-yr survival of<60%. The high-risk group consisted of only 80 of the 351 patients enrolled in the trial. If true, the presence of low/intermediate risk patients, in whom no beneficial DFS or OS effect for adjuvant chemotherapy could be discerned, substantially diluted the ability of the study to detect a benefit. It is curious that the subgroup analyses of the primary study assessed such factors as tumor size and grade, but did not identify benefit from adjuvant chemotherapy. This may be explained by the power derived from the multi-variable predictive algorithm, allowing simultaneous consideration of multiple prognostic factors, rather than the univariable analysis approach of subgroup analyses.

Despite this positive reanalysis, the EORTC-STBSG 62931 trial was negative in its primary analysis. The reanalysis results are hypothesis-generating and must be formally confirmed.

A meta-analysis that included these data and also data from several more recent studies demonstrated a statistical improvement in OS favoring adjuvant, doxorubicin-based chemotherapy (OR 0.86, 95% CI 0.75-0.97)[29,31-32,37]. A pooled analysis of this and an earlier EORTC adjuvant therapy trial suggested that biological factors (tumor size/grade/male patients greater than 40 years) and quality of surgical resection impacted OS[38]. Adjuvant chemotherapy improved RFS without altering OS.

Several reasons may explain failure of adjuvant chemotherapy trials to show consistent results[33]. These include, but are not limited to:

Heterogeneity of patient populations enrolled. Benefit of adjuvant chemotherapy may be limited to subgroups, such as those with large and/or high-grade tumors[39]. Even the large, randomized clinical trials of Woll and colleagues included a majority of patients with low- and intermediate-grade tumors, as well as some patients with small tumors[32]. If benefit is limited to the groups at highest risk, as suggested by the reanalysis of Pasquali and co-workers, those with lower risk disease may substantially dilute the planned power of a clinical trial, even for relatively large trials[36].

Inadequate subject numbers. Randomized trials assessing adjuvant chemotherapy in STS are reported with as few as 26 patients, and a median size of only 77 patients among 19 trials subject to meta-analyses[29-30,32]. In illustration, a randomized study of 77 patients to test the proposition that adjuvant chemotherapy improves the 5-yr survival rate from 50% to 65% with 95% confidence (as assessed by Woll and co-workers[32]) has a statistical power to detect such a difference of only 26%. While meta-analyses may attempt to overcome these limitations, the failure of larger trials to demonstrate benefit argues for a modest benefit, perhaps limited to high-risk subsets.

Quality of local therapy may have improved over time. Complete surgical resection is strongly associated with both RFS and OS[38]. Studies included in meta-analyses of adjuvant systemic therapy go back as far as the early 1970's. Disease status assessment and local therapy technologies (surgery and radiotherapy) have clearly evolved substantially in the ensuing 40 years.

Different tumor histologies may have markedly different sensitivities to cytotoxic agents. Exclusion of histologies displaying high inherent resistance to these therapies and inclusion of sensitive histologies seek to enroll patients most likely to respond[40]. Such focusing of the enrolled study populations on those most likely to benefit will maximize the statistical power of clinical trials.

Chemotherapy regimens under assessment are not necessarily identical over time, even when similar or identical agents are used. Dose-intensity has increased, especially with the addition of growth factors. Treatments have largely focused on anthracyclines (doxorubicin and epirubicin) combined with ifosfamide. It appears that the doxorubicin/ifosfamide combinations are driving improvements in OS noted in meta-analyses, rather than non-ifosfamide-containing regimens[30,32].

4 Control of distant recurrence with neoadjuvant chemotherapy

In the administration of peri-operative chemotherapy, early treatment of micrometastatic disease is a prime objective. Several trials of neoadjuvant therapy have yielded favorable long-term outcomes, versus historical controls[23-25]. The one randomized trial in which only chemotherapy was administered pre-operatively, versus no pre-operative therapy, failed to demonstrate improved 5-yr RFS or OS.

A recently presented study may signal a change in the series of negative results, albeit with some methodological limitations[40]. This study was intended to assess the value of systemic neoadjuvant therapy tailored to specific histologic sarcoma subtypes occurring in the extremities or the wall of the trunk. Patients were eligible if they had one of five subtypes: myxoid liposarcoma (ML), leiomyosarcoma, synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST), or undifferentiated pleomorphic sarcoma (UPS). In addition, patients had tumors that were high-grade (grade 3) according to Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) criteria, or FNCLCC grade 2 with at least 50% necrosis on pre-treatment imaging. Tumors were deep to the investing fascia and were at least 5 cm in maximal dimension. Thus, the patients to be enrolled were at high risk of recurrence and metastasis.

Patients were randomly assigned to either standard chemotherapy with epirubicin and ifosfamide ($n = 145$) or to "histiotype-tailored" therapy (HTT; $n = 142$) (Table 1). Patients received three cycles of the assigned therapy. Patients with MPNST or SS could receive neoadjuvant or adjuvant radiotherapy, while those with leiomyosarcoma, ML or UPS received post-operative radiotherapy, if indicated. Patients receive surgery 3-4 weeks after completion of neoadjuvant chemotherapy and at least 4 weeks after pre-operative radiotherapy.

Table 1 Treatment regimens in Gronchi et al., 2017[40]

Treatment arm	*n*	Regimen	Cycle length (days)	Notes
Control/standard	145	Epirubicin 60 mg/m^2 days 1-2		
		Ifosfamide 3 g/m^2 days 1-3	21	
Myxoid liposarcoma	28	Trabectedin 1.3 mg/m^2	21	3 patients received doxorubicin 75 mg/m^2 instead of trabectedin
Leiomyosarcoma	16	Gemcitabine 1 800 mg/m^2 days 1 and 15		
		Dacarbazine 500 mg/m^2 days 1 and 15	28	
Synovial sarcoma	34	Ifosfamide 14 g/m^2 by continuous infusion days 1-14	28	
MPNST	12	Etoposide 150 mg/m^2 days 1-3		
		Ifosfamide 3 g/m^2 days 1-3	21	
UPS	52	Gemcitabine 900 mg/m^2 days 1 and 8		
		Docetaxel 75 mg/m^2	21	

MPNST: malignant peripheral nerve sheath tumor; UPS: undifferentiated pleomorphic sarcoma

The primary study endpoint was DFS. The trial was designed to assess for a one-third reduction in relapse risk (HR=0.667), with 80% power at the 5% one-sided level of significance (italicized for emphasis). This design was selected due to the primary objective of assessing whether HTT was better than standard anthracycline/ifosfamide therapy, and to limit the needed sample size to a realistic accrual period.

Among the 287 patients enrolled, all but one, assigned to standard epirubicin/ifosfamide, were included in the ITT analysis. The excluded patient appears to have entered the study as it was being closed

as part of a futility analysis (see below). A relatively large number of patients were deemed ineligible after registration and randomization or did not receive their assigned treatment. In the standard treatment arm, 5/145 (3.4%) were ineligible and 16/145 (11%) did not complete assigned therapy. For HTT, the corresponding numbers were 6/142 (4.2%) and 17/142 (12%). These protocol deviations would have tended to minimize differences between the treatment arms.

This study was intended to demonstrate superiority, over standard therapy, of HTT. It did not meet this endpoint. The study was halted for futility at the time of a third, planned futility analysis.

Instead, HTT was inferior to standard therapy with epirubicin/ifosfamide (Table 2). DFS, OS and DMFS were all inferior in the HTT group. Local failure-free survival (LFFS) was not statistically different between the treatment arms, although the HR favored standard therapy. This is a negative study with respect to its pre-planned primary endpoint: HTT is not superior to standard therapy with epirubicin and ifosfamide.

Table 2 Outcomes reported in Gronchi et al., 2017[40]

Outcome	Control/standard (95% CI)	HTT (95% CI)
DFS*	62% (48%-77%)	38% (22%-55%)
DFS HR	-	2.00 (1.22-3.26, $P=0.006$)
OS*	89% (78%-99%)	64% (27%-100%)
OS HR	-	2.687 (1.104-6.940, $P=0.034$)
LFFS*	86% (74%-97%)	85% (77%-92%)
LFFS HR	-	1.990 (0.833-4.575, $P=0.11$)
DMFS*	74% (59%-88%)	45% (26%-65%)
DMFS HR	-	2.147 (1.172-3.930, $P=0.011$)

* Outcomes all reported at 46 months. CI: confidence interval; DFS: disease-free survival; DMFS: distant metastasis-free survival; HR: hazard ratio; HTT: histiotype-tailored therapy; LFFS: local failure-free survival; OS: overall survival

It would be hard to argue that treatment in the HTT group led to outcomes inferior to those that might be expected for observation or placebo treatment (if a placebo treatment could actually be administered). If one argues that the HTT were ineffective, essentially delaying provision of definitive surgery, one is still left with the conclusion that the standard therapy is superior to HTT, and probably superior to placebo. The only alternative explanation is that the HTT regimens were actually harmful versus observation or a placebo. Yet all HTT regimens have demonstrated activity in the advanced disease setting.This seems an unlikely scenario.

This study has some substantial limitations that must be recognized. First, it is based on a median follow-up time of only 12.3 months. This is quite short. Other studies addressing neoadjuvant therapy report results after over 7 years of follow-up[24,41]. Longer follow-up could change the conclusions, as has been seen in at least one other study[32-33].

Second, the patients represent a broad range of STS subtypes, representing 80% of those STS at high risk of metastasis. The distribution of these subtypes into the standard and HTT arms of the trial is not significantly different ($P=0.66$ by Pearson's χ^2 test). The subtypes were also selected due to the availability of recognized treatment regimens. In this regard, selection of MPNST and UPS is counter-intuitive.These subtypes, representing 43% of enrolled patients, received regimens of HTT "…based on weaker data than the other three regimens because… [the authors] found little available evidence on other histology-driven regimens for [them] …." [p. 813] [40] Selecting all included histologic subtypes based on similar evidence for treatment activity would have decreased variability in the HTT. Analysis of the outcomes based on subtype showed no statistically significant differences favoring standard or HTT therapy, though the collective data favored epirubicin/ifosfamide.

The 14%-16% rate of ineligibility/non-receipt of assigned in the two treatment arms is relatively high. It

is however balanced between the arms. These cases would have tended to minimize differences between the treatment arms, leading to a false negative result.

This remains a study which is technically negative with regard to its primary endpoint. Planned accrual was 350 patients, but the study was stopped prior to accrual completion at a planned futility analysis. This post hoc analysis of the study is hypothesis-generating. These intriguing results must be confirmed.

5 The role of peri-operative radiation therapy in STS of the extremities and trunk

Radiotherapy has a critical role in facilitating local control, and thereby limb preservation, in extremity STS. As noted above, modern surgical and radiotherapy techniques, local control rates of 80%-100% are reported, with a minority of patients requiring amputation for curative treatment[4,15-21].

Prior to the 1980s, amputation was the surgical treatment of choice for STS. In 1975, the NCI organized a randomized trial comparing amputation versus limb-preserving surgery with post-operative radiotherapy[19]. This study included 43 patients treated with resection and doxorubicin-based chemotherapy. Sixteen underwent amputation, while twenty-seven received limb-preserving surgeries, followed by 60-70 Gy external beam radiotherapy. While surgical margins were found to be the most important predictor of local recurrence, local control rates were excellent in the group receiving both surgery and radiotherapy. There were no statistically significant differences in 5-yr DFS or OS rates. As a result, limb-preserving surgery combined with radiotherapy became the primary management approach for extremity STS.

Two large subsequent trials evaluated the necessity of radiotherapy after limb-preserving surgical resection. Yang and colleagues randomized 141 patients with extremity STS to receive limb-preserving surgery with or without postoperative radiotherapy[20]. With more than 9 years of follow up, there was no difference in OS. There was however a statistically significant difference in local control rates, showing improved results with radiotherapy (99% *vs* 78% local control for patients with high-grade sarcomas).

Similarly, Pisters and colleagues randomized 164 patients to receive surgery with or without radiotherapy delivered as brachytherapy[42]. This study also showed that radiotherapy improved local control rates in high grade patients (5-yr local control rates 89% *vs* 66%, $P=0.002\ 5$). There was no difference in DSS. These two trials showed a clear local control benefit for the addition of radiotherapy to limb-preserving surgical resection for extremity sarcoma[20,42].

Several questions remained, including the ideal selection of patients for combined modality therapy and the ideal sequencing of radiotherapy and surgery. While high-grade and deep-seated tumors demonstrated a clear local control benefit with radiotherapy, the benefit was less pronounced for low-grade lesions. Retrospective data from Baldini and colleagues reported that radiotherapy could be omitted for small (<5 cm), low-grade lesions excised with wide margins, with a local recurrence risk of about 10%[43]. Similarly, another prospective study from Pisters and colleagues reported that highly selected patients with small (< 5 cm) sarcomas receiving margin-negative surgical resection could forgo radiotherapy with a local failure risk, again about 10%[44]. Thus, small low-grade tumors could be treated safely with surgery alone, if negative margins could be obtained. Notably, patients in these series were carefully evaluated in a multidisciplinary sarcoma specialty setting. Whether similar results would hold in a general oncologic setting is unclear.

6 Neoadjuvant radiotherapy in STS of the extremities and trunk

The earliest trials of combined modality therapy delivered radiation post-operatively. However, there are several advantages to delivery of radiation prior to surgery. Pre-operative radiotherapy allows treatment to a more-clearly defined target with a smaller overall target volume. This also allows treatment with a lower dose of radiation to a well-vascularized target.

This is critical, as the presence of oxygen in a well-perfused tumor will enhance the efficacy of radiotherapy by increasing free radical generation in tumor cells.

O'Sullivan and colleagues compared pre-operative and post-operative delivery of radiation in 190 patients in a randomized prospective Canadian trial[21]. Patients received either 50 Gy prior to surgery or 66 Gy after surgery. Local control results were equivalent (93% in both arms). There was a higher risk of wound complications with pre-operative radiotherapy, particularly for patients with lower extremity sarcomas (35% *vs* 17%). However, a later analysis of morbidity and functional scores in this study reported that those treated with larger fields and higher radiation doses in the post-operative radiotherapy arm tended to have a greater risk of permanent fibrosis and joint stiffness, features predictive of lower function scores[45].

Both pre- and post-operative radiotherapy yield excellent local control results. Pre-operative therapy carries an increased risk of acute wound-healing complications (particularly for large lower extremity tumors). Post-operative radiotherapy carries an increased risk of chronic limb toxicities, such as fibrosis, joint stiffness, and edema. Radiotherapy sequencing with respect to surgery has to carefully balance these issues.

The therapeutic benefit of pre-operative radiotherapy may be improved in the future by the use of technologies such as intensity modulated radiotherapy (IMRT). In a retrospective analysis of 319 extremity STS, IMRT was associated with lower risk of dermatitis, edema, and local recurrence than three-dimensional conformal radiotherapy (the technique used in previous noted trials)[46]. O'Sullivan and colleagues also examined the use of IMRT to spare skin flaps overlying a tumor during preoperative radiation to decrease the risk of wound complications[47].

In summary, the combination of radiotherapy and surgery yields excellent local control results, allowing limb preservation in the majority of extremity STS patients. Pre-operative delivery of radiation allows treatment of a clearly defined and well-vascularized target with smaller fields and a lower overall dose of radiation than with post-operative radiotherapy. While this is accomplished at the cost of an increased risk of acute wound healing complications, the larger field sizes and radiation doses associated with post-operative radiation carry an increased risk of permanent fibrosis, joint stiffness, and edema. Going forward, advanced techniques such as IMRT and image guided radiation therapy may further improve the risk profile of pre-operative radiotherapy by reducing the risk of wound healing complications.

7 Opportunities for progress

There is much room for improvement in the use of peri-operative therapy for STS. The existing data leave uncertainty regarding potential benefits, even after decades of investigation. Several avenues exist for progress.

Systemic peri-operative therapy offers the possibility of improving both local and distant disease control. However, activity of current regimens is modest. New regimens to be considered in the peri-operative setting typically derive from treatment of advanced unresectable or metastatic disease. For peri-operative therapy, treatments that yield increased ORR or increased survival might be predicted to impact local resectability and long-term disease control rates, respectively. In STS, much effort has been devoted to identifying companions for doxorubicin with increased activity.

Several derivatives of ifosfamide have recently been assessed in STS trials combined with doxorubicin. These have been investigated in large, well-conducted phase Ⅲ clinical trials, using essentially the same design as that of Judson and co-workers, described earlier[13]. Palifosfamide is a derivative of the active

metabolite of ifosfamide, with more favorable pharmacokinetics, less complex administration protocols and a more favorable safety profile[48]. In a phase Ⅲ study in STS combined with DOX, no improvement in PFS or OS were observed over DOX monotherapy. The phase Ⅲ study was stopped for futility before completion.

Evofosfamide is a prodrug related to ifosfamide which is activated by hypoxic tumoral environments. Hypoxia activates the drug, yielding a nitrogen mustard "warhead"[49]. This was also explored in combination with doxorubicin. In a large, phase Ⅲ trial, the combination did not show improved OS versus doxorubicin monotherapy. The doxorubicin control arm of this trial, enrolling 323 patients, demonstrated mOS of 19.0 months (95%CI 16.2-22.4 months). This is markedly prolonged versus the prior experience. As most patients were treated at sarcoma specialty centers, this may reflect improved outcomes or better subject selection at such centers.

A most recent development in doxorubicin-based combination therapy is the trial of olaratumab in combination with doxorubicin[50]. Olaratumab is a humanized monoclonal antibody against platelet-derived growth factor-alpha. Pre-clinical studies indicated that this antibody possessed significant anti-neoplastic activity in sarcoma xenografts. Combined therapy with doxorubicin was additive.

Olaratumab was initially assessed in a phase Ⅰb study to establish the tolerability of the combination and a subsequent randomized phase Ⅱ study for preliminary efficacy assessment. The primary efficacy endpoint was PFS; OS was a secondary endpoint. PFS was not improved in the combination (mPFS 6.6 months, 95%CI 4.1-8.3 months *vs* 4.1 months, 95% CI 2.8-5.4 months for DOX; HR=0.67, 95% CI 0.44-1.02, P=0.061 5). However, OS was markedly improved with the combination (mOS 26.5 months, 95%CI 20.9-31.7 months *vs* 14.7 months, 95%CI 9.2-17.1 months for DOX; HR=0.46, 95%CI 0.30-0.71, P=0.000 3). ORR for the combination was numerically higher than DOX (18% *vs* 12%, P=0.34), but not statically significant.

These data led the United States Food and Drug Administration to grant conditional approval to olaratumab for use in the combination treatment of advanced STS[51]. A confirmatory phase Ⅲ study (see *clinicaltrials.gov* NCT02451943) was conducted. Unfortunately, the study did not have its primary endpoint of improved OS[52]. Detailed results are to be presented at the 2019 meeting of the American Society of Clinical Oncology.

Phase Ⅲ studies of all three agents were predicated on positive Phase Ⅱ studies[48,20,53]. This included randomized phase Ⅱ studies of the palifosfamide and olaratumab combinations[48,50]. All three phase Ⅲ studies were adequately powered studies with pertinent endpoints. A common finding of the two published phase Ⅲ studies was much better outcomes for doxorubicin monotherapy treatment than might be otherwise predicted.

Design of phase Ⅲ trials based on antecedent phase Ⅱ data is not trivial[54]. Changes in any of a variety of factors, including primary endpoint, study population, and site of study conduct, can alter outcome in a confirmatory trial. Perhaps the most compelling lesson of these failures to confirm phase Ⅱ results is that regimens for STS intended to have broad activity against a wide range of STS subtypes are unlikely to be successful.

Gastrointestinal stromal tumors (GIST) perhaps provide a successful model for peri-operative systemic therapy of sarcomas[55]. Here, randomized trials have supported the use of imatinib as peri-operative therapy. These successes however rely on an understanding of the underlying biology of the disease under treatment and availability of active agents exploiting the disease biology. Notably, imatinib was first validated in advanced GIST, prior to its exploitation as a peri-operative therapy. Thus, studies to segment the STS population into those with common biology, and hopefully common therapies, will

likely yield new peri-operative systemic approaches. These could include treatments with activity in specific sarcoma subtypes (for example, the tyrosine kinase inhibitor in alveolar soft part sarcomas) or even histology agnostic therapies such as larotrectinib in tropomyosin receptor kinase-fusion positive malignances and pembrolizumab in mismatch-repair deficient tumors)[56-58].

Another opportunity for improved peri-operative therapy lies in the realm of response evaluation. As we note earlier, discordance between size-based response criteria and pathologic response has been reported previously in neoadjuvant STS therapy[23]. Better approaches to response evaluation may allow earlier assessment of response. This could then dictate continuation or abandonment of systemic therapy, focusing continued treatment on those with favorable biological changes.

Changes in PET tracer uptake in response to neoadjuvant systemic therapy might be one marker of benefit. Among a study of high-grade sarcomas treated with neoadjuvant chemotherapy, decrease in mean standard uptake value (SUV) predicted histologic response more strongly than change in size by Response Evaluation Criteria In Solid Tumors[59]. Indeed a 35% reduction in SUV after a single cycle of neoadjuvant systemic therapy identified with 100% sensitivity and 67% specificity those with at least 95% histopathologic necrosis at the time of subsequent surgery[60].

A study at different institutions examined the value of pre-treatment maximum SUV and the change in SUV after two cycles of neoadjuvant systemic therapy on outcomes[61]. In multi-variable analyses, change in SUV was significantly associated with OS, PFS and local PFS. Pre-therapy maximum SUV was significantly associated with OS and local PFS, but not PFS. Thus, PET imaging, in conjunction with neoadjuvant therapy, provides information not only regarding the potential pathologic outcomes, but also regarding near- and long-term outcomes.

PET imaging remains a relatively expensive technology for response assessment. Use of more commonly used imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), would be desirable. A recent study compared responses after two cycles of neoadjuvant chemotherapy for STS[62]. MRI was found to be markedly inferior in distinguishing those with or without at least a 35% reduction in maximum SUV after two cycles of neoadjuvant systemic therapy. Sensitivity and specificity of MRI were 50% and 63%, respectively.

Thus, employment of PET imaging appears to be the standard for STS neoadjuvant response assessment at present. Evaluation to define potential benefit from neoadjuvant chemotherapy prior to any treatment and with more economical modalities would be desirable. Radiomics, the "…quantitative computerized algorithm-based feature extraction from imaging data…[,]" may provide a tool to achieve this[63]. A recent study of STS patients, all of whom received neoadjuvant radiation therapy, developed models combining clinical and radiomic indices. These were able to predict OS and local PFS in a validation cohort of patients. Critically, these models were developed using pre-therapy CT imaging. Thus, such technology might be applied to neoadjuvant systemic or radiation therapy to identify features predicting benefit from such therapy, or lack thereof. For peri-operative radiotherapy, imaging modalities could be applied to select those more or less likely to benefit from radiotherapeutic treatment, a subject of the previously noted radiomic study[64]. Some have even suggested that treatment at an experienced center may allow omission of peri-operative radiotherapy in high-risk STS patients for whom such treatment would conventionally be standard[65]. Avoidance of radiation therapy would have the benefit of avoiding both early and late radiation therapy toxicities. Nonetheless, the authors concede that "[f]uture studies on a selective approach to…[radiotherapy] administration are awaited"[65].

The therapeutic index of peri-operative radiotherapy could be improved by increasing its efficacy or by decreasing its toxicities. With 80%-100% rates of local control fur the surgery/radiotherapy combination at 15 year, noted above, further improvements in this measure of efficacy will be challenging. New treatment technologies allowing more conservative treatments volumes may however decrease toxicity without compromising efficacy.

Image-guided, intensity-modulated radiation therapy (IMRT) is one such technology allowing more precise radiation dose placement. A prospective, phase Ⅱ evaluation of neoadjuvant IMRT was conducted in those with high-risk STS of the lower extremities. [47] Primary endpoint of the study enrolling 70 patients (59 evaluable) was the rate of development of acute wound complications at subsequent surgery. Compared to historical controls, there was no significant difference in the rate of wound complications (30% among 59 evaluable, versus 43% based on historical data). That authors note some improvement in indices of radiation toxicity, including rate of primary closure and secondary operations. The study probably suffered from the limited sample size for its somewhat subjective endpoint.

The effect of IMRT on fracture risk was also studied in this population[46]. Here, patients with primary STS of the lower extremities were enrolled. Their fracture risk was calculated using a predictive nomogram. Thirteen patients received neoadjuvant RT and 79 received adjuvant RT. The cumulative risk of fracture was 6.7% at 5 years, versus predicted risk of 26%. While not a randomized comparison, this study uses a systemic method to establish the anticipated outcomes in an identical control population. IMRT appears favorable in this regard as a peri-operative modality.

Another non-randomized study compared IMRT to brachytherapy in the management of high-grade sarcomas of the extremities[66]. This study examined patients enrolled in a prospectively collected database, although the analysis was retrospective. Patients between 1995 and 2006 identified 134 patients with high-grade STS of the extremities receiving either adjuvant radiotherapy or IMRT. Adjuvant radiotherapy was given to 71 patients. Among patients receiving IMRT, 10 received preoperative neoadjuvant treatment and 53 received postoperative adjuvant treatment. Patients receiving IMRT were more likely to have indices of less favorable local control, including close margins, large tumors and requirement for bone or nerve stripping/resection. Nevertheless, local control was improved with IMRT, with five-year local control of 92% (95% CI 85%-100%) versus 81% (95% CI 71%-90%; $P=0.04$) for brachytherapy. Image-guided radiation therapy is another modality that can improve the delivery of peri-operative therapy to sarcoma patients. Here, imaging is used to maintain pre-specified targeting at different radiation treatment session, thereby decreasing the margins required for variables (such as patient placement) that very between sessions[67]. It may also be combined with the more precise targeting offered by IMRT. An analysis at a single center suggested that this combined modality therapy offered oncologic outcomes comparable to IMRT alone, with lower target volumes and comparable or better complication rates.

A prospective phase Ⅱ study of IGRT as neoadjuvant therapy in sarcomas of the extremities was also conducted. A total of 86 patients were enrolled. Radiation techniques included either three-dimensional conformal radiotherapy or IMRT. The primary endpoint of the study was the rate of grade 2 or greater radiation morbidity 2 years after treatment. The rate of such toxicities was 10.5%, decreased from the anticipated rate of 37% noted in a prior randomized trial of neoadjuvant therapy. This therapy did not appear to lead to a decrement in oncologic outcomes.

8 Recommendations and conclusions

Treatment of STS of the extremities and trunk with surgery alone is inadequate for locally advanced tumors. Local disease control of a primary tumor is generally excellent when considered in aggregate. Even so, some patients still require amputation, with its attendant lifelong functional limitations. Others have disease that is unresectable, even if non-metastatic at presentation. Current high rates of local control generally rely on the combination of definitive surgery with peri-operative radiotherapy. Efforts to improve adjunctive treatment, whether through improved use of radiotherapy or systemic therapy, are needed.

Optimally, such changes in practice would be driven by the availability of high-quality data from prospective clinical trials. As described herein, the existing data set has significant limitations. Additional results to build on the existing knowledge base may take years to develop. While those efforts must be pursued, patients must receive treatment now, using information that exists presently.

Treatment for each patient must be personalized, based on simultaneous consideration of numerous factors (Fig. 1). The benefits of peri-operative radiotherapy are clear; decision-making regarding its omission is limited to identifying the subset of patients who lack any features of elevated risk (i. e. small, low-grade tumors amenable to complete surgical excision with widely negative margins). Otherwise, consideration of adjunctive therapy is part of the treatment process.

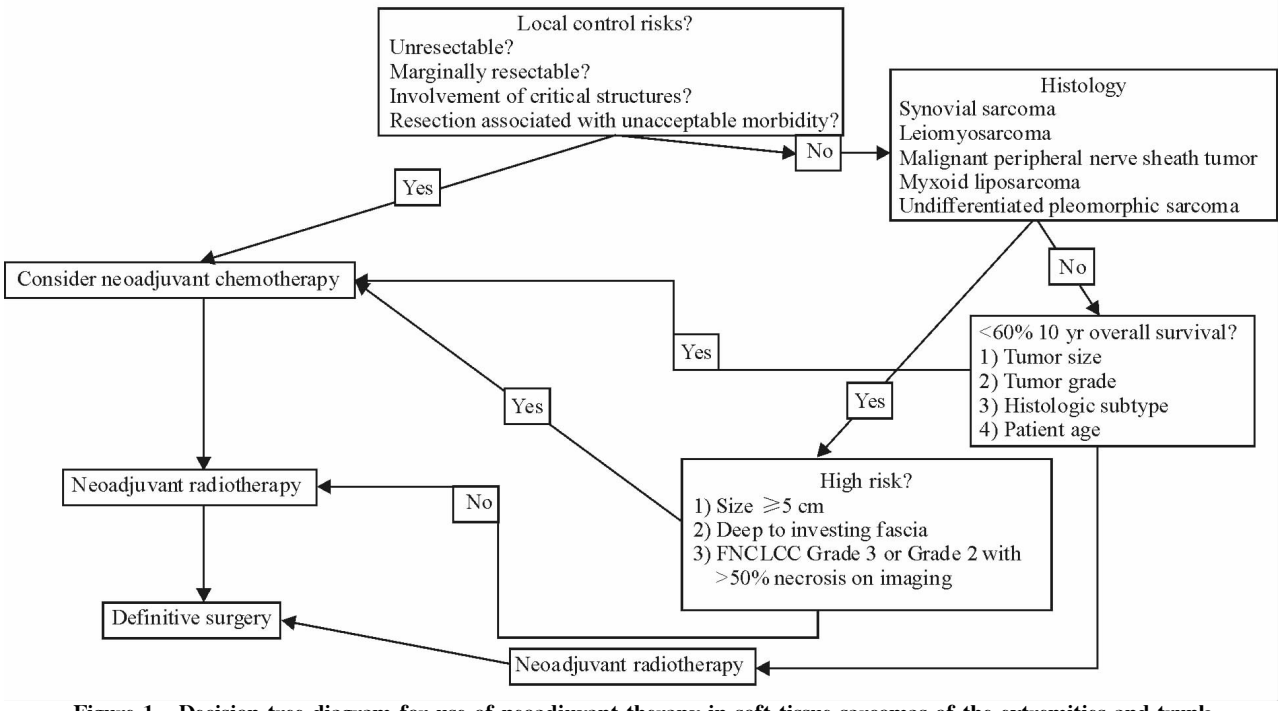

Figure 1 Decision tree diagram for use of neoadjuvant therapy in soft tissue sarcomas of the extremities and trunk

Histologies potentially eligible for neoadjuvant treatment and risk estimate based on Gronchi and co-workers[40]. Estimate of 10 yr overall survival according to Callegaro and co-workers[11,32]

On balance, we believe that the existing data support use of a neoadjuvant treatment with chemotherapy and radiotherapy, versus an adjuvant strategy. For radiotherapy, both modes of treatment appear effective in local control when combined with definitive surgery. However, as the ultimate objective of treatment among the patients under discussion herein is cure, we believe an increased rate of near-term surgical wound complications are outweighed by the longer term benefits in decreased functional impairment consequent

to the smaller fields and lower doses of neoadjuvant radiation. Of course, each case is unique, and it is the close collaboration between surgeon and radiation oncologist that is able to consider all available information and come to a decision regarding treatment sequencing for a given patient.

Decisions regarding peri-operative chemotherapy are more complicated. This is both due to its less well defined benefits and different modes of activity (treatment of existing local disease versus effects on distant micrometastases).Chemotherapy can clearly yield decreases in tumor size, as measured by ORR. Its ability to change the local treatment context for a given patient has not been clearly established. This is not surprising: surgical evaluation is a particularly subjective affair. While some cases obviously are either resectable or unresectable, there are many cases that fall between these extremes. For cases with marginally resectable or unresectable primary tumors, it is appropriate to administer chemotherapy with the objective of achieving tumor shrinkage sufficient to allow definitive surgery/radiotherapy to be administered. This provides one rationale for use of neoadjuvant chemotherapy.

The other rationale relates to treatment of micrometastatic disease. Interestingly, features that define poorer local control (high-grade, large tumor size, deep tumors) also are associated with increased propensity for emergence of metastatic disease. Thus, patients with tumors that are unresectable or marginally so are generally also be at elevated risk of metastasis.

Neither surgery nor radiotherapy offer improved distant disease control. As we note earlier, distant failure is the major mode of failure in sarcoma patients [Italicized for emphasis]. Only systemic therapy can hope to alter this.

As evidenced by the many trials of adjuvant and neoadjuvant therapy, this fact has not escaped the attention of those working to improve sarcoma therapy. Multiple factors have hindered the conduct of clinical trials to address these issues. Even the most recent reports, which offer the hope of explaining past negative results and hinting at clinical success, have faced methodological problems.

Two reports provide guidance at present. The reanalysis of the EORTC-STBSG 62931 adjuvant therapy study by Pasquali and co-workers indicated that patients at especially high risk of metastatic disease benefitted from adjuvant chemotherapy in terms of DFS and OS[32,36]. High-risk was defined as <60% OS at 10 yr after initial treatment. In the reanalysis, risk was defined using a prognostic algorithm, accounting for tumor size, grade, patient age, and histologic subtype[11]. Again, this is a reanalysis of existing data, and thus hypothesis-generating, rather than a definitive determination. This does provide evidence that peri-operative chemotherapy has potential benefit in those at high-risk of recurrence. Five cycles of adjuvant therapy with doxorubicin and ifosfamide were administered. Notably, all STS except Ewing's and embryonal rhabdomyosarcoma were eligible.

Bearing in mind its limitations, the report of Gronchi and co-workers provides evidence of a DFS and OS benefit after administration of only three cycles of neoadjuvant therapy with epirubicin/ifosfamide[40]. Improvements in DFS and OS appear driven by improved DMFS. The included histologies are more restricted than in the Woll trial, limiting its generalizability. In addition, the design limitations of the Gronchi trial imply that the results are again hypothesis-generating, requiring confirmation.

We have incorporated these results into our clinical practice (Fig. 1). We first consider obstacles to local control. If these are applicable, we consider neoadjuvant chemotherapy. If not, risks associated with metastatic disease development are considered. If patients meet either histologic and risk criteria specified by Gronchi, or high-risk classification as in Callegaro, we consider neoadjuvant chemotherapy[11,32,40].

In patients not meeting any of these three sets of criteria for neoadjuvant chemotherapy, we consider whether peri-operative radiotherapy might be omitted. Based on the rationale described above, neoadjuvant radiotherapy is the preferred mode of peri-operative radiotherapy administration at our institution. Definitive surgery is undertaken after completion of any neoadjuvant therapy. Patient factors or local treatment

patterns may lead to definitive surgery prior to adjuvant radiotherapy.

In patients selected for neoadjuvant systemic therapy, we typically administer three-21-day cycles of neoadjuvant doxorubicin (75 mg/m^2, one cycle) and ifosfamide (10 g/m^2, one cycle), with mesna uroprotectant and growth factor[13]. Imaging assessment is repeated after three cycles. If a significant local treatment response is observed, up to three additional cycle (for a total of six cycles) are administered. If disease is stable radiologically, then systemic treatment is discontinued after three cycles, and further peri-operative radiotherapy and definitive surgery are undertaken[40].

In summary, we believe that the outcomes of patients with STS of the extremities and trunk can be improved through use of neoadjuvant therapies. Neoadjuvant systemic therapy may facilitate local control in challenging cases and improve long-term outcomes in patients at high risk of distant metastasis and death. For radiotherapy, we believe that long-term benefits of neoadjuvant treatment outweigh the short-term increase in wound complications. These recommendations are based on the presently available data, which have significant limitations. Further investigations will yield new insights allowing progressive refinement in the peri-operative STS treatment.

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·消 息·

复旦大学附属中山医院医学科技领域捷报频传

近日，我院医学科技领域捷报频传，多个集体与个人在上海科技类奖项上斩获佳绩。

5月15日，2018年度上海市科学技术奖励大会召开，隆重表彰为上海科技创新事业和经济社会发展作出突出贡献的科技工作者，共授予青年科技杰出贡献奖10项，国际科技合作奖1项，自然科学奖28项，技术发明奖30项，科技进步奖231项。我院颜志平教授团队的“介入治疗门脉高压技术体系的创建与推广”科研项目与亓发芝教授团队的“复杂创面组织修复关键治疗技术与临床应用”科研项目荣获了上海市科技进步奖三等奖。

5月16日，第十七届上海医学科技奖颁奖仪式顺利落幕。上海医学科技奖经上海市政府科技主管部门批准，由上海市医学会设立，旨在表彰奖励在医学领域科技进步中做出贡献的优秀个人和集体，促进上海医学科技事业的发展。我院心实验室孙爱军研究员团队的“线粒体代谢异常致心力衰竭的机理及防治策略”项目荣获上海医学科技奖一等奖。神经内科汪昕教授团队的“难治性癫痫的发病机制与干预研究”项目、泌尿外科郭剑明教授团队的“肾癌精准微创诊疗体系的建立”项目、心内科宿燕岗教授团队的“心脏再同步疗法治疗慢性心力衰竭的应用与推广”项目荣获上海医学科技奖二等奖。中医科蔡定芳教授团队的“祛风通络及其演变方药提高急性缺血性卒中临床疗效的机制与应用”项目荣获上海医学科技奖三等奖。

5月18日，第十六届上海市科技精英颁奖大会在上海科学会堂隆重举行，我院骨科主任董健教授获评“上海市科技精英”，肾内科主任丁小强教授获“上海市科技精英”提名奖。

医学创新旨在最大程度解除患者的痛苦。中山人秉持“以病人为中心”的精神，不惧挑战，勇于创新，再接再厉攀登科技高峰。