original article

Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group

A. Gronchi[1]*, S. Stacchiotti[2], P. Verderio[3], S. Ferrari[4], J. Martin Broto[5], A. Lopez-Pousa[6], A. Llombart-Bosch[7], A.P. Dei Tos[8], P. Collini[9], J. Cruz Jurado[10], A. De Paoli[11], D.M. Donati[12], A. Poveda[13], V. Quagliuolo[14], A. Comandone[15], G. Grignani[16], C. Morosi[17], A. Messina[17], R. De Sanctis[18], S. Bottelli[3], E. Palassini[2], P.G. Casali[2] & Piero Picci[19]

Departments of [1]Surgery; [2]Cancer Medicine; [3]Unit of Medical Statistics, Biometry and Bioinformatics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [4]Department of Cancer Medicine, Istituto Ortopedico Rizzoli, Bologna, Italy; [5]Department of Cancer Medicine, Hospital Universitario Virgen del Rocio, Sevilla; [6]Department of Cancer Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona; [7]Department of Pathology, Medical School University of Valencia, Valencia, Spain; [8]Department of Pathology, Treviso General Hospital, Treviso; [9]Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [10]Department of Cancer Medicine, University of Canarias Hospital, La Laguna, Spain; [11]Department of Radiation Oncology, Centro di Riferimento Oncologico, Aviano; [12]Department of Orthopedic Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy; [13]Department of Cancer Medicine, Valencian Oncologic Institute, Valencia, Spain; [14]Department of Surgery, Humanitas Cancer Center, Rozzano; [15]Department of Cancer Medicine, Presidio Sanitario Gradenigo, Torino; [16]Department of Cancer Medicine, IRCC Fondazione Piemontese per la Ricerca sul Cancro, Candiolo; [17]Department of Radiology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [18]Department of Cancer Medicine, Humanitas Cancer Center, Rozzano; [19]Laboratory of Oncologic Research, Istituto Ortopedico Rizzoli, Bologna, Italy

Background: To report on long-term results of a phase 3 trial comparing three versus five cycles of adjuvant chemotherapy (CT) with full-dose epirubicin+ifosfamide in high-risk soft tissue sarcomas (STS).

Methods: Patients (pts) were randomized to receive three preoperative cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 (Arm A) or to receive the same three preoperative cycles plus two postoperative cycles (Arm B). Radiotherapy could be either delivered in the preoperative or in the postoperative setting. Non-inferiority of the primary end point, OS, was assessed by the confidence interval of the hazard ratio (HR; Arm A/Arm B) derived from Cox model.

Results: Between January 2002 and April 2007, 164 pts were assigned to arm A and 164 to arm B. At a median follow-up (FU) of 117 months (IQ range 103–135 months), 123 deaths were recorded: 58 in Arm A and 65 in Arm B. Ten-year OS was 61% for the entire group of patients: 64% in Arm A and 59% in Arm B. The intention-to-treat analysis confirmed that three cycles were not inferior to five cycles (one-sided 95% upper confidence limit was 1.24). A per protocol analysis was consistent with these results. Pts with leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS) had the lowest, and the highest response rates, respectively. Consistently, Leiomyosarcoma and UPS had the worse and the best prognosis, respectively.

Conclusions: At a longer FU, the non-inferiority of three cycles of a full-dose conventional CT in comparison to five is confirmed. Response to therapy is also confirmed to be associated with better survival. This regimen is currently tested within an ongoing international trial against three cycles of a neoadjuvant histology-tailored CT (ClinicalTrials.gov Identifier: NCT01710176).

Key words: sarcoma, soft tissue sarcoma, adjuvant chemotherapy, response, quality of surgery, survival

introduction

Standard treatment of localized high-risk soft tissue sarcoma (STS) of the extremities and trunk wall consists of surgery and radiation therapy (RT) [1, 2]. Adjuvant chemotherapy (CT) is not standard treatment, but clinical practice guidelines encompass it as an option in high-risk patients.

An Italian Sarcoma Group (ISG) randomized study had demonstrated a survival benefit with five cycles of adjuvant CT with full-dose epirubicin+ifosfamide in high-risk STS of the extremities versus nil [3]. The limited number of enrolled patients was the main cause for the loss of statistical significance on a

Correspondence to: Dr Alessandro Gronchi, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy. Tel: +39-0223903234; Fax: +39-0223902404; E-mail: alessandro.gronchi@istitutotumori.mi.it

longer follow-up (FU) [4] and a trend in favor of the adjuvant CT arm remained evident.

An observation of the previous ISG trial was that the dose-intensity of the last two cycles of CT had dropped [3]. Based on the hypothesis that the first three cycles were the most significant ones to the final outcome, we carried out a trial comparing three versus five cycles of the same adjuvant full-dose anthracycline plus ifosfamide regimen and found no difference at a 5-year median FU [5]. This led to the conclusion that—when adjuvant CT is considered—an improvement in cost–benefit ratio may be obtained by limiting the number of cycles to 3.

We report herein the results of this study at a 10-year median FU.

patients and methods

Between January 2002 and March 2007, 328 patients with high-risk (grade 3 [6], deep site, size ≥5 cm) localized adult-type STS arising from extremities or trunk wall were recruited in a randomized, phase III, Italian and Spanish clinical trial comparing the effect on overall survival (OS) and relapse free survival (RFS) of a full-dose CT regimen with epirubicin and ifosfamide for five versus three cycles. The intention-to-treat (ITT) population comprised all randomized patients, although seven were retrospectively found to be ineligible for major violations (four major histological inconsistencies and three consent withdrawals).

The trial was approved by Institutional Review Boards and/or Independent Ethics Committee at each Center participating in the study and registered at European Union Drug Regulating Authorities Clinical Trials with No. 2004-003979-36. Written informed consent was obtained by all patients.

Neoadjuvant CT was given for three cycles both in patients belonging to the experimental arm (A) and in patients belonging to the control arm (B). Two additional adjuvant cycles were administered in patients belonging to the control arm (B). One hundred and sixty-one patients were randomly assigned to the control arm and 160 patients were attributed to the experimental arm.

Each cycle was delivered every 3 weeks on an inpatient basis and was as already reported [5]: epirubicin 60 mg/sqm/day on days 1 and 2; ifosfamide 3000 mg/sqm/day on days 1, 2, and 3; MESNA 1000 mg/sqm × 3/day on days 1, 2, and 3. Granulocyte stimulating factor 300 μg/day was used in all patients starting on day 7 to day 14 or until white blood cells complete recovery.

At the discretion of the local investigator, radiation therapy could be delivered either in the neoadjuvant setting in combination to CT or in the adjuvant one. A total dose of 44–50 Gy (2 Gy/day 5 days in a week) was given in the neoadjuvant phase, starting after the first CT cycle and concurrent to the second and third. A total dose of 60–66 Gy (2 Gy/day 5 days a week) was foreseen in the adjuvant phase.

Surgery was planned 3–4 weeks after the last administration of the third CT cycle and 4 weeks after the end of radiation therapy.

Surgical excisions were considered as macroscopically complete in the absence of gross residual disease. All macroscopically complete resections were classified according to the closest surgical margin, which was microscopically categorized as positive (tumor within 1 mm. from the inked surface) or negative (absence of tumor within 1 mm. from the inked surface).

Radiological response was evaluated according to RECIST (version 1.1) [7] and Choi criteria [8, 9] and centrally reviewed.

The results of this study [5], the toxicity of this regimen and the feasibility of the concurrent administration of CT-RT in the preoperative setting [10], the correlations between response and outcome [9, 11], and quality of surgery and outcome [12] were published previously with a median FU of 5 years. Here we focus on the long-term outcome of the study as well as the correlations between response and outcome and quality of surgery and outcome at a median FU of 10 years.

statistical analysis

The study design and the sample size calculation of the trial were reported elsewhere [5]. The considered end points were OS from randomization (OSr) and from surgery (OSs) as well as the freedom from progression (FFP) and RFS. Osr and OSs were defined as the time elapsed from randomization and from surgery to death, respectively; FFP and RFS were defined as the time elapsed from randomization and from surgery to the first evidence of recurrence, respectively. As concerns the survival pattern, it was estimated by means of the Kaplan–Meier method [13]. When the risk of local and distant relapses after surgery was assessed, data were processed according to the competing risks approach [14]. The primary study outcome was evaluated according to the ITT principle by including all patients who underwent random assignment and signed the informed consent form. We investigated the prognostic role on the defined end points of conventional variables (age, histological subtype, microscopic margins status, and tumor size), treatment arm and also the response criteria (RECIST [7] and Choi [8, 9]) using a Cox regression model in both univariate and multivariate fashion [15]. In this model, each regression coefficient represents the logarithm of the HR, which is assumed to be constant over time. The hypothesis of HR=1.00 was tested using the Wald statistic. Age and tumor size were analyzed as continuous variables and the relationship between them and the outcome was investigated by resorting to a regression model based on restricted cubic splines [16]. These results are reported as supplementary material. All statistical analyses were carried out with the SAS software (version 9.2; SAS Institute, Cary, NC).

results

primary end-points

Clinical characteristics of the 328 patients considered for the primary end points are reported elsewhere [5].

Median FU from randomization of the ITT population was 117 months (IQR, 103–135) and from surgery was 114 months (IQR, 100–133).

When compared with the original publication [5], 24 more patients died after randomization, 10 in arm A and 14 in arm B; 23 of them died after surgery, 10 in arm A and 13 in arm B. All events are described in Figure 1.

By considering the ITT series, the probability of OSr and FFP for the entire study population were 0.61 (95% confidence interval, CI: 0.56–0.67) and 0.57 (95% CI: 0.51–0.62) at 10 years; 0.64 (95% CI: 0.56–0.71) and 0.56 (95% CI: 0.47–0.63) in arm A and 0.59 (95% CI: 0.51–0.66) and 0.58 (95%CI: 0.50–0.66) in arm B, respectively (Figure 2A and B). The hazard ratio (HR) of OSr and FFP of arm A versus arm B was 0.92 (one-sided 95% CI: 0.68–1.23) and 1.04 (one-sided 95% CI: 0.78–1.38), respectively. Similar figures were obtained for OSs and RFS for the entire study population, which were 0.61 (95% CI: 0.56–0.67) and 0.58 (95% CI: 0.52–0.63) at 10 years; 0.64 (95% CI: 0.56–0.71) and 0.57 (95% CI: 0.48–0.64) in arm A and 0.59 (95% CI: 0.50–0.66) and 0.60 (95% CI: 0.51–0.67) in arm B, respectively. The HR for OSs and RFS of arm A versus arm B was 0.91 (one-sided 95% CI: 0.67–1.23) and 1.02 (one-sided 95% CI: 0.76–1.37) respectively. A per-protocol analysis confirmed these results.

In total, eight more events were observed when compared with the original publication [5]. Of them two were local recurrences, all in arm A, and six were distant metastases, three in arm A and three in Arm B.

Overall, 10 years crude cumulative incidence (CCI) of local recurrence was 0.076 (SE: 0.016), 0.092 (SE: 0.025) in arm A and 0.059 (SE: 0.019) in arm B, respectively (Figure 2**C**).
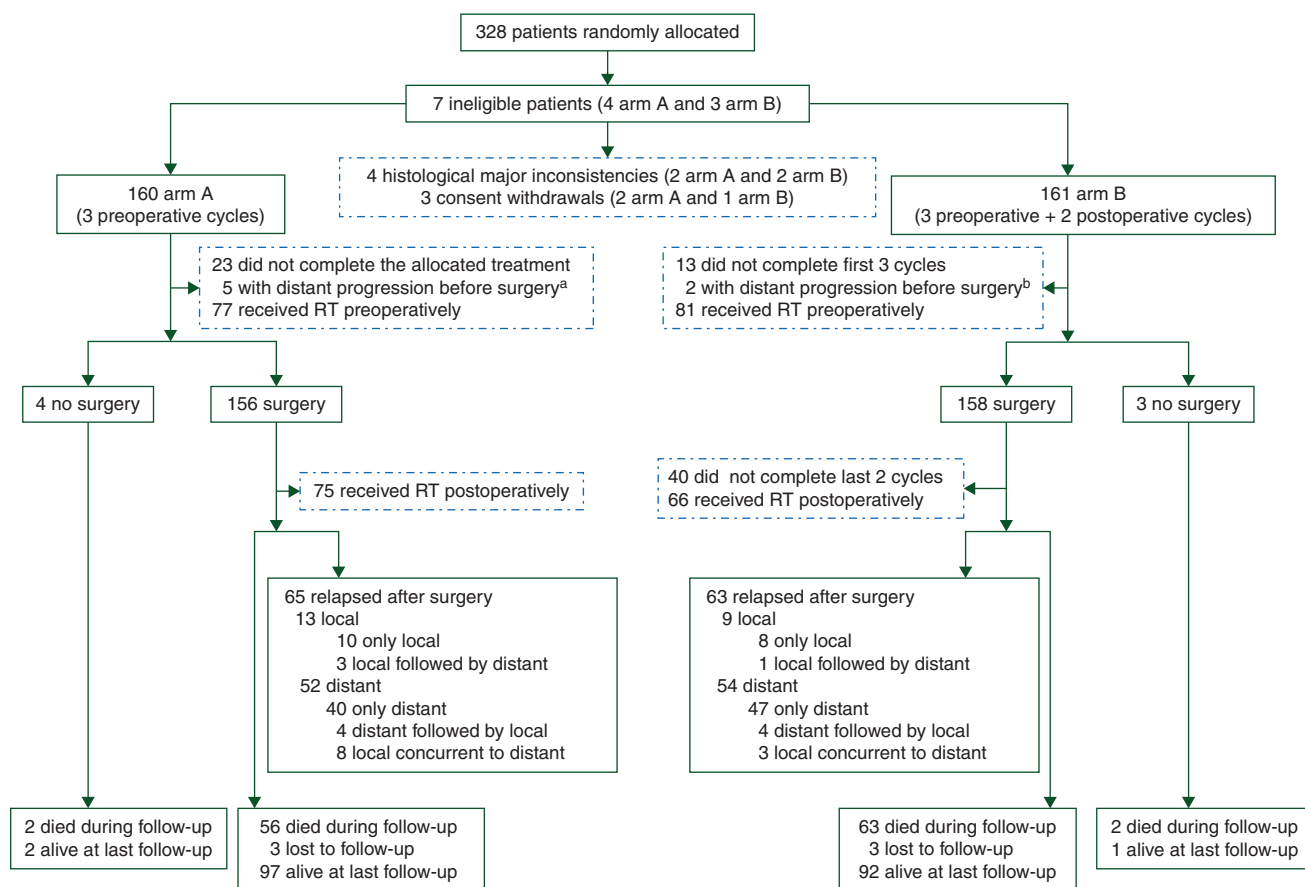
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                        ┌──────────────────────────────────┐
                        │  328 patients randomly allocated  │
                        └──────────────────────────────────┘
                        ┌──────────────────────────────────┐
                        │ 7 ineligible patients (4 arm A and 3 arm B) │
                        └──────────────────────────────────┘
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4 histological major inconsistencies (2 arm A and 2 arm B)
3 consent withdrawals (2 arm A and 1 arm B)

160 arm A
(3 preoperative cycles)

161 arm B
(3 preoperative + 2 postoperative cycles)

23 did not complete the allocated treatment
5 with distant progression before surgery[a]
77 received RT preoperatively

13 did not complete first 3 cycles
2 with distant progression before surgery[b]
81 received RT preoperatively

4 no surgery   156 surgery   158 surgery   3 no surgery

75 received RT postoperatively

40 did not complete last 2 cycles
66 received RT postoperatively

65 relapsed after surgery
  13 local
    10 only local
    3 local followed by distant
  52 distant
    40 only distant
    4 distant followed by local
    8 local concurrent to distant

63 relapsed after surgery
  9 local
    8 only local
    1 local followed by distant
  54 distant
    47 only distant
    4 distant followed by local
    3 local concurrent to distant

2 died during follow-up
2 alive at last follow-up

56 died during follow-up
3 lost to follow-up
97 alive at last follow-up

63 died during follow-up
3 lost to follow-up
92 alive at last follow-up

2 died during follow-up
1 alive at last follow-up

[a]2 patients with distant progression before surgery did not also complete the allocated treatment (arm A);
[b]1 patient with distant progression before surgery did not also complete the first 3 cycles (arm B);

Figure 1. CONSORT diagram.

The overall 10 years CCI of distant metastases were 0.343 (SE: 0.028), 0.340 (SE: 0.039) in arm A, and 0.346 (SE: 0.039) in arm B, respectively (Figure 2**D**).

By considering the continuous variables (age and size) used in the Cox regression models, a linear relationship between the logarithm of hazard and their values was found to be appropriate. Univariate and multivariate analyses showed that histological subtype and size were significantly associated with OSs (Table 1).

response and outcome and quality of surgery and outcome

Updated results of the two above-mentioned subgroup analyses already published at a median FU of 5 years [11, 12] are reported in supplementary (see also supplementary Table S1, available at *Annals of Oncology* online) and shown in supplementary Figures S1 and S2, available at *Annals of Oncology* online.

discussion

At a median FU of 10 years in this randomized clinical trial, 328 patients with localized high-risk STS of the extremities and trunk wall had a 10 years OSs and RFS of 61% and 58%, respectively, confirming no difference between a regimen of three

versus five cycles of full-dose CT with anthracyclines+ifosfamide. Of note, while OSs declined by 10% from the 5th to the 10th year, RFS remained stable (60% → 58%) with a very limited number of new events observed in either arm during that period. Tumor response to preoperative CT± RT remained predictive of a better outcome, even with longer FU. Choi criteria, extended to MRI, were also confirmed to be better predictors than RECIST. Leiomyosarcoma was the histology with the worse and UPS the one with the best outcome and this was consistent with the response to the chemo-radiation therapy. The microscopic status of surgical margins retained its early negative prognostic impact on local outcome, but did not show any meaningful later impact on distant relapse and OSs. Finally, when RT was administered pre-operatively with CT, the negative prognostic impact of positive surgical margins on local outcome was steadily lost, with a high probability of achieving cure in patients who remained disease free at 10 years.

This trial was not aimed to address the contentious issue of the benefit of adjuvant CT in STS, but rather to investigate the efficacy of three versus five cycles of full-dose anthracycline-ifosfamide to maximize the benefits of CT while minimizing toxicity. Designed as a non-inferiority trial, it was powered to detect a clinically acceptable difference, the level of which was defined by an upper limit of the 90% CI >1.5. In fact, the trial
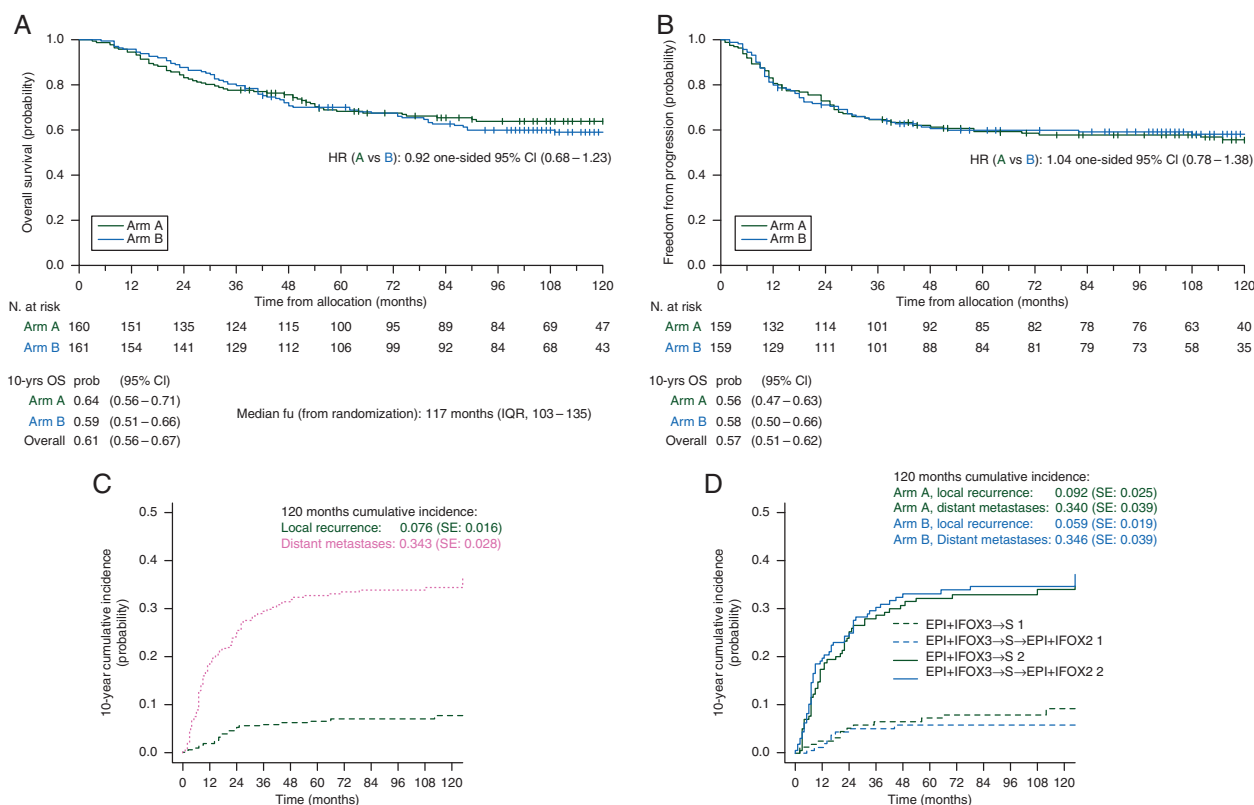
Figure 2. Ten-year probability of OS from random assignment (A) and freedom from progression (B) according to study arm. Ten-year cumulative incidence of local recurrence and distant metastases overall (C) and according to study arm (D).

Variables	HR (95% CI)	Wald P-value	LRT P-value
Table 1 Overall survival from surgery: multivariate Cox analysis — Final model			
Histological subtype			
Leiomyosarcoma versus mfh/ups+spin. cell sar. Nos[a]	2.510 (1.507–4.180)	<0.001	
Synovial sarcoma versus mfh/ups+spin. cell sar. Nos[a]	1.677 (1.013–2.777)	0.044	0.005
Others versus mfh/ups +spin. cell sar. Nos[a]	1.183 (0.723–1.937)	0.504	
Size (continous)	1.064 (1.033–1.095)	<0.001	<0.001

[a]Reference category.
HR, hazard ratio estimated by multivariate Cox regression model; 95% CI, 95% confidence interval; Wald P-value, P-value associated to the Wald χ^2 statistic; LRT P-value, P-value associated to the LRT χ^2 statistic.

resulted in two curves that were superimposable even at 10 years, and the upper 90% CI interval on their difference at 10 years was 1.23 when compared with 1.39 at 5 years. Notwithstanding the width of the accepted CI, these results suggest that the two treatments appear to be equal. This is re-assuring in light of the subsequent international Italian, Spanish, French, and Polish study (ClinicalTrials.gov Identifier: NCT01710176) comparing the use of three cycles of

anthracycline-ifosfamide as the standard arm against a hist-ology-tailored regimen. The results of this study are anticipated soon.

In spite of a median FU period twice that of the original report, only six new distant recurrences were observed—three in both arms—confirming that disease recurrence tends to occur early in this population of high-risk patients. Patients who survive without evidence of disease for 5 years or longer are very likely to be cured. This seems not to be influenced by the use of CT, in contrast to what has been suggested in previous studies. While it has been hypothesized that the benefit of adjuvant CT consists of a delay of distant recurrence and possibly death, we demonstrate here that events after 5 years of FU are rare and therefore any potential benefit of adjuvant CT is maintained over a long period of time, and may in fact represent cure.

Patients who responded to CT had better early oncologic out-comes than those who did not, and this effect was sustained over a longer FU period. This association between response to CT and outcome was better assessed by the use of Choi criteria compared with RECIST, as Choi criteria more accurately predict pathologic response, as already shown in a subgroup of patients who entered this trial [9]. This association cannot contribute to the debate about the long-lasting issue of the efficacy of adjuvant CT in STS. Nevertheless, one may well speculate that if there were no effect, there should not be any correlation between tumor response and outcome. However, detecting some associ-ation, as we did, does not necessarily indicate that adjuvant CT is effective (due to the potential selection bias which could

theoretically lead to both a tumor response and a better outcome independently), but it may well suggest it. Notably, histology was shown to be a significant prognostic factor for OSr, with UPS having the most favorable outcome, and leiomyosarcoma portending the worst. This trend was observed, although not statistically significant, also for FFP. UPS consistently demonstrated a higher response rate by both RECIST and Choi criteria than leiomyosarcoma, again suggesting a possible benefit of adjuvant CT in some histologies. This is currently being investigated prospectively in the international study mentioned above.

Finally, the concurrent administration of preoperative CT and RT, the feasibility of which has been recently reported in detail [10], seems to be of particular value when the tumor is of borderline resectability or when preservation of function is a goal. Other series of preoperative RT alone have demonstrated that a 'planned positive' margin after preoperative RT entails LR rates in the same range as is observed after resection with negative margins [17–19]. Indeed, the goal of preoperative RT should be to decrease the risk of viable tumor cells at the resection margin when a wide margin cannot be achieved. Interestingly, the administration of an intra- or postoperative boost after preoperative RT does not appear to change the local outcome after a positive margin. Similarly in our series, local control in the context of microscopically positive surgical margins did not appear to be impacted by postoperative RT to the same extent as with preoperative CT-RT. Thus, our data support the hypothesis that preoperative CT-RT may have a role when surgical excision is expected to be marginal along a close anatomic structure, or when preservation of function is a goal. This strategy proved to be of value even over a long FU period.

In conclusion, the long-term FU of this study confirms the findings reported earlier concerning the equivalence of a short full-dose regimen of neoadjuvant CT compared with standard dosing, the association of response to neoadjuvant CT with better OS, especially if assessed by Choi criteria, and the importance of the concurrent preoperative administration of RT when preservation of function is the goal. These findings may be useful in guiding decision-making by both patients and providers while we await the results of the trial comparing three cycles of EI with the use of a histology-tailored regimen in selected histotypes.

funding

disclosures

All authors have declared no conflicts of interest.

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