Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall


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Background: To explore correlation between the quality of surgery and outcome in high-risk soft tissue sarcoma (STS) patients treated within a phase III randomized trial.

Patients and Methods: In the trial, all patients received three cycles of preoperative chemotherapy (CT) with epirubicin 120 mg/m² and ifosfamide 9 g/m² and were randomly assigned to receive two further postoperative cycles. Radiotherapy (RT) could be delivered in the preoperative or postoperative setting. The association between surgical margins and overall survival (OS) was studied in a univariate and multivariate fashion.

Results: Two hundred and fifty-two patients completed the whole treatment and were operated conservatively. At a median follow-up of 60 months (IQR, 45–74 months), the 5-year OS was 0.73, even in patients with positive and negative margins. The 5-year cumulative incidence (CI) of local recurrence (LR) in patients with positive and negative microscopic margins was 0.17 (standard error, SE, 0.08) and 0.03 (SE, 0.01), respectively. In the subgroup of patients receiving combined preoperative CT–RT and with positive surgical margins, the CI of LR was 0.

Conclusions: In this setting of high-risk STS treated by preoperative CT or CT–RT, the negative impact of positive margins on the outcome was limited. When close margins can be anticipated preoperative CT–RT may be a reasonable option to maximize the chance of cure.

Key words: chemotherapy, local recurrence, radiation therapy, sarcoma, surgical margins, survival

Introduction

The quality of surgical margins is critical in soft tissue sarcoma (STS) management. Several reports have consistently shown this to be one of the strongest prognosticators of local outcome [1–7]. Moreover, there is an association between local failure and distant spread, though the causative role of the former is still debated [8, 9].

Adjuvant therapies [chemotherapy (CT) and/or radiotherapy (RT)] have been shown in few prospective [10–13] and several retrospective series [1–7, 14, 15] to partially offset the negative impact of positive surgical margins on the outcome. In most series, they were delivered postoperatively.

High-risk STS may be challenging surgically, and optimal margins may be hardly achievable in a number of cases, while paying attention to function sparing as well.

We recently reported the results of a prospective trial on neoadjuvant CT in the extremity and trunk wall high-risk STS [16]. All patients received three cycles of preoperative full-dose CT, being randomly assigned between receiving only these three courses and also two additional ones postoperatively. One half of the patients also received concurrent preoperative RT, according to local investigator’s decision. The trial showed that the addition of two postoperative cycles of the same preoperative CT did not influence the outcome.
We then analyzed the impact of quality of surgery in the overall population and in the two subgroups, i.e. patients undergoing preoperative CT alone and those receiving preoperative concurrent CT–RT. This is the object of this paper.

patients and methods

From January 2002 to March 2007, a prospective randomized study on preoperative CT in localized high-risk (high-grade, deep, size ≥5 cm) STS of the extremities and trunk wall enrolled 321 eligible patients in Italy and Spain. We included in this analysis all patients who received both CT and RT and underwent conservative resection; these patients were evaluated before and following treatment by magnetic resonance imaging (MRI) or computed tomography (CT) scan. The present study was therefore conducted on a total of 252 patients, of whom 135 patients received preoperative concurrent CT–RT, while 117 preoperative CT and postoperative RT.

Institutional Review Boards approved the trial; signed informed consent was obtained for all patients. All patients received three cycles of epirubicin 120 mg/m² plus ifosfamide 9000 mg/m² in the preoperative setting, while 98 patients (53 treated with preoperative CT and 45 with preoperative CT–RT) completed two further cycles of the same CT in the postoperative one as the control arm.

Radiotherapy was given concurrent to CT to a median dose of 50 Gy (range 24–60) in the preoperative setting and 60 Gy (range 30–70) in the postoperative one.

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) [17] and Choi criteria [18] and centrally reviewed. Follow-up was carried out every 3 months for the first 3 years after the end of treatment, by contrast enhanced chest CT and MRI or CT of the affected site. Then six monthly for the fourth and fifth year after the end of treatment and yearly after from the 6th year onwards.

statistical analysis

The association of microscopic margin status (categorized as positive versus negative) with histological subtype and with treatment modality (categorized CT–RT versus only CT) was studied by means of univariate logistic regression analysis [19]. The distribution of the continuous variables such as age and tumor size within the modalities of microscopic margin status was compared using the Kolmogorov–Smirnov test (KST) [20]. Overall survival (OS) was defined as the time from surgery to death for any cause. The pattern of OS was estimated by means of the Kaplan–Meier method [21]. The cumulative incidence (CI) of local recurrence (LR) and distant metastasis (DM) after surgery was assessed by processing data according to the competing risks approach [22]. The role of the variables such as age, tumor size, microscopic margin status, preoperative RT and histological subtype in OS was assessed in the whole case series by means of Cox regression analysis [23] in both univariate and multivariate fashion. The age and tumor size were used in the Cox regression model as a continuous variable. The relationship between them and the outcome was investigated by resorting to a regression model based on restricted cubic splines [24]. In order to account for the two different modalities of the involved treatment (CT–RT and CT) and thus to appropriately assess the possible effects of preoperative RT as well as to compare the microscopic margin status within patients receiving only CT, we also considered the new variable ‘treatment/microscopic margin status’ obtained by combining the modalities of treatment and of the microscopic margin status in the following categories: (i) CT only/positive margin, (ii) CT only/negative margin and (iii) preoperative RT and CT (RT and CT). In the initial model of the Cox multivariate regression analysis, we included the variables such as age, tumor size, microscopic margin status, histological subtype and treatment modality. The only interaction term retained as clinically relevant was microscopic margin status × preoperative RT. This interaction was first investigated in a bivariate fashion resorting to a Cox model including the main effects and the first-order interaction term. A final more parsimonious model was then obtained using a backward selection procedure that retained only the variables reaching the conventional significance level of 5% (final model). In this model, the variable microscopic margin status was retained, regardless of statistical significance. The impact of each variable on OS in addition to that of the remaining variables was assessed by means of the likelihood ratio test (LRT). We evaluated the predictive capacity of the final model and the contribution of each variable to the predictive capacity itself by means of Harrell’s c statistics [25].

All statistical analyses were carried out with the SAS software (version 9.2, SAS Institute Inc., Cary, NC).

results

microscopic margin status and its association with other features

The distribution of the considered variables is reported in Table 1. In the logistic analysis, no statistically significant association was seen between the microscopic margin status and any of the other considered categorical variables (data not shown). The difference between the distribution of age and tumor size within the modalities of microscopic margin status was not statistically significant, as indicated using the Kolmogorov–Smirnov test (age: KST = 0.58, P = 0.89; tumor size: KST = 0.99, P = 0.28).

overall survival

At a median follow-up time of 60 months (IQR, 45–74 months), 67 patients died after surgery (59 of 218 operated with negative margins, 6 of 24 with positive ones and 2 of 10 with unknown surgical margins). The probability of OS for the whole series of patients was 0.73 (95% confidence interval, CI 0.67–0.79), 0.73 (95% CI 0.66–0.79) in patients operated with negative margins and 0.73 (95% CI 0.49–0.87) in patients operated with positive ones (Figure 1A).

A linear relationship between the logarithms of hazard was found to be appropriate for both the continuous variables (age and tumor size) used in the Cox regression models. As reported in Table 2 in univariate Cox regression analysis carried out on the whole series of patients, only histological subtype was significantly associated with OS, but not microscopic margin status. When considering the subset of patients treated with CT–RT, 41 patients died after surgery (37 of 116 operated with negative margins, 2 of 10 with positive ones and 2 of 9 with unknown surgical margins). The corresponding probabilities of OS in patients operated with negative and positive margins were 0.67 (95% CI 0.57–0.75)
and 0.80 (95% CI 0.41–0.95), respectively (Figure 1B). When considering the three classes of the variable ‘treatment/microscopic margin status’, 4 of 14 patients treated by CT and with positive surgical margins, 22 of 102 patients treated by CT and with negative surgical margins and 41 of 135 patients treated by CT–RT died after surgery. The corresponding probabilities of OS were 0.70 (95% CI 0.38–0.88) in patients treated by CT and with positive surgical margins, 0.80 (95% CI 0.70–0.87) in patients treated by CT and with negative surgical margins and 0.68 (95% CI 0.59–0.76) in patients treated by CT–RT (Figure 1C).

**local recurrence and distant metastases**

Recurrent disease was seen in 89 patients. Among these, 14 developed LR, whereas 75 had distant metastases (DM, in seven patients concurrent to LR) as the primary event. Moreover, one patient developed DM after LR and seven patients developed LR after DM.

The overall CI of LR at 5 years was 0.05 [standard error (SE), 0.01], 0.07 (SE, 0.02) in patients treated with CT and 0.04 (SE, 0.02) in those treated with CT–RT. Overall CI of DM at 5 years was 0.31 (SE, 0.03), 0.25 (SE, 0.04) in patients treated with CT and 0.36 (SE, 0.04) in those treated with CT–RT (Figure 2A–C).

Among the 24 patients with positive microscopic margin status, 4 out of 14 treated with CT and zero of 10 treated with CT–RT developed LR, while 4 out of 14 treated with CT and 2 out of 10 treated with CT–RT developed DM. Among the 218 patients with negative microscopic margin status, 4 out of 102 treated with CT and 42 out of 116 treated with CT–RT developed LR, while 26 out of 102 treated with CT and 42 out of 116 treated with CT–RT developed DM.

Overall, the 5-year CI of LR and DM was 0.17 (SE, 0.08) and 0.27 (SE, 0.09), respectively, in patients with positive microscopic margin status, 0.03 (SE, 0.01) and 0.31 (SE, 0.03) in those with negative microscopic margin status (Figure 3A).

When considering the subset of patients treated with CT–RT, zero and 2 out of 10 patients operated with positive margins and 4 and 42 out of 116 patients operated with negative margins developed LR and DM, respectively. The corresponding CI figures for LR and DM were 0 and 0.20 (SE, 0.13) in patients with positive margins, 0.03 (SE, 0.02) and 0.38 (SE, 0.05) in those with negative ones (Figure 3B).

When considering the combination of treatment and surgical margins, 4 of 14 patients treated by CT and with positive surgical margins, 4 of 102 patients treated by CT and with negative surgical margins and 6 of 135 patients treated by CT–RT developed LR. The corresponding figures of CI of LR at 5 years were 0.29 (SE, 0.12), 0.04 (SE, 0.02) and 0.04 (SE,
Four of 14 patients treated by CT and with positive surgical margins, 26 of 102 patients treated by CT and with negative surgical margins and 45 of 135 patients treated by CT–RT developed DM. The corresponding figures of CI of DM at 5 years were 0.30 (SE, 0.13), 0.24 (SE, 0.04) and 0.36 (SE, 0.04), respectively (Figure 3C).

In Table 3, an explorative analysis of the relation between the microscopic margin status and the risk of LR and DM in the subset of patients treated with preoperative CT only according to the response to the therapy is also reported. The responses were both classified according to RECIST and/or Choi criteria [26]. The results reported in this table are clearly meant to be explorative and hypothesis-generating.

A multivariate Cox analysis was carried out in the whole series of patients in terms of OS. The first-order interaction in terms of microscopic margin status and treatment modality was not statistically significant. In the initial model, the following variables were included: age, tumor size, microscopic margin status, histological subtype and treatment modality. In the final multivariate regression model, the microscopic margin status confirmed its lack of prognostic value for OS. The only statistically significant prognostic indicators were tumor size and histological subtype (supplementary Table S1, available at Annals of Oncology online). The overall capability of the variables in the final regression model to predict OS was weak (c = 0.63). The highest predictive capability was given by the histological subtype followed by tumor size. The contribution of the microscopic margin status was less relevant (supplementary Table S2, available at Annals of Oncology online).
In this series of 252 patients with high-risk STS of extremities and trunk wall, treated by neoadjuvant full-dose CT with anthracyclines and ifosfamide within a phase III randomized trial, the microscopic status of surgical margins was a prognostic marker of local outcome, but not of distant relapse and OS. Indeed, even this behavior was offset when RT was preoperatively administered with CT: in this subgroup, we found no association between positive surgical margins and local outcome.

Interestingly, this did not apply to patients responsive to CT who did not receive concurrent RT.

The prognostic meaning of the quality of surgery in STS has long been debated in the sarcoma literature [1–7]. In fact,
positive surgical margins have been consistently reported to adversely correlate with the outcome. This has mainly to do with local control, whilst the correlation is weaker with distant spread and cause-specific mortality, although it seems to exist on a long follow-up for patients who ‘escape’ early DM. In other words, local inadequacy apparently correlates with locale relapse and late metastases [7–9]. Indeed, it is difficult to prove the causative role of local failure for distant relapse, because the same prognostic factors may well be influencing both local and distant control: in the end, both may be the sign of higher tumor aggressiveness. As a matter of fact, however, there is a correlation, whether causative or not, between local adequacy and both local and distant outcome [1–9]. At variance with this, in this series of patients treated preoperatively, positive surgical margins were not associated with an increased risk of distant spread and even with local failure when preoperative combined CT–RT was used. This may reflect some protection on distant spread provided by CT and on both local and distant spread by CT–RT.

A pooled analysis of two prospective studies on adjuvant CT made by EORTC would be consistent with this speculation. In the EORTC series, patients who were more likely to have a survival benefit from adjuvant CT were those who had been operated with positive microscopic margins [27]. This effect may be mediated by a reduction of either LR, which in critical sites may eventually become a direct cause of death [7], and/or by a reduction of subsequent DM, as directly or indirectly brought about by inadequacy of surgery [28]. Further studies are needed to better clarify this potential impact of adjuvant CT, since, if confirmed, local surgical aspects could well be factored in the currently problematic clinical decision-making about adjuvant CT.

As far as the addition of preoperative RT to CT is concerned, ‘planned positive’ margins were shown to carry LR rates in the same range as observed after resections with negative margins in other series of preoperative RT alone [29, 30]. Indeed, the goal of preoperative RT is to ‘sterilize’ the periphery of the tumor, thereby eradicating or functionally disabling tumor cells, which are potentially left behind in the wound. In other words, RT should help to decrease the risk that the surgeon resects close to viable tumor cells. It is intriguing that, vice versa, the administration of intraoperative/postoperative boost after preoperative RT would not seem to change the local outcome in positive margin resections [31]. Also in our series, local control in the presence of positive microscopic surgical margins was not apparently 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, or when function preservation of a close anatomical structure is a goal. The only caveat might then be that the administration of RT in the preoperative setting substantially increases the wound complications risk [12–14], but we believe that this may well be accommodated in the discussion with the single patient and factored in the final decision.

We acknowledge that these observations can just generate hypotheses, inasmuch as this is a retrospective unplanned analysis of patient subgroups within a prospective randomized trial. In addition, numbers are limited. Resections with negative margins should remain the gold standard of surgical adequacy. On the other side, it is hard to foresee prospective studies specifically focusing on whether preoperative CT–RT has an impact on surgically problematic STS. Currently, the proportion of positive margin excisions is in the 15% range. Furthermore, all positive margins are not created equal, and we should always pay attention to the fact that STS are a variegated family of tumors. We already showed how margins impact differently across the commonest five sarcoma subtypes [7]. In this study, the population was rather homogeneous and marked by a uniform local risk. It is left to be investigated whether these findings could apply to low-grade STS, not included in the present analysis.

In conclusion, we observed that the administration of preoperative therapies in high-risk STS of the extremities and trunk wall minimized the local risk of relapse and the prognostic impact of close margins on the local and distant outcome. This gives rise to interesting hypotheses, and may well help in the multidisciplinary decision-making especially on the proportion of STS patients in whom problematic margins are foreseeable. Referral of these patients to specialized centers is highly recommended.

disclosure

All authors have declared no conflicts of interest.

references


Table 3. Five-year cumulative incidence of microscopic margin status in only CT patients classified as PR according to RECIST and/or Choi

<table>
<thead>
<tr>
<th>Margin</th>
<th>PR according to RECIST</th>
<th>PR according to Choi</th>
<th>PR according to RECIST and Choi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR/n</td>
<td>LR-CI (SE)</td>
<td>DM/n</td>
</tr>
<tr>
<td>Negative</td>
<td>0/20</td>
<td>–</td>
<td>7/20</td>
</tr>
<tr>
<td>Positive</td>
<td>1/2</td>
<td>0.50 (0.35)</td>
<td>0/2</td>
</tr>
<tr>
<td>Overall</td>
<td>1/22</td>
<td>0.05 (0.04)</td>
<td>7/22</td>
</tr>
</tbody>
</table>

LR = local recurrence; DM = distant metastasis; n = total number of patients; CI = cumulative incidence; SE = standard error; PR = partial response


