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Original Research

The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial

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KEYWORDS
Soft tissue sarcoma;
Adjuvant;
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Abstract ***Background:*** This study was aimed at determining whether patients with high-risk soft tissue sarcoma (STS), as identified using the nomogram Sarculator, benefitted from adjuvant chemotherapy in the EORTC-STBSG 62931 randomised controlled trial (RCT), which failed to detect an impact for adjuvant doxorubicin plus ifosfamide (Adj) over observation

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High risk;
Overall survival;
Randomised controlled trial

(Obs).
Methods: Patients with extremity and trunk wall STS in the EORTC-STBSG 62931 RCT were analysed (N = 290/351). Ten-year predicted probability of overall survival (pr-OS) was calculated using the prognostic nomogram Sarculator. Patients were grouped into three categories of predicted pr-OS: high (pr-OS>66%), intermediate (51<pr-OS≤66) and low (pr-OS≤51%). OS and disease-free survival (DFS) were calculated.
Results: Nomogram pr-OS was dispersed (median 72%, interquartile range 57–83%) and had prognostic value for OS and DFS (log-rank test: $P < 0.001$). One hundred seventy, 68 and 52 patients had high (58.6%, 90 Obs/80 Adj), intermediate (23.5%, 34 Obs/34 Adj) and low pr-OS (17.9%, 24 Obs/28 Adj), respectively. Adjuvant chemotherapy halved the risk of recurrence (hazard ratio [HR] = 0.46, 95% confidence interval [CI] 0.24–0.89) and death (HR = 0.46, 95% CI 0.23–0.94) in the low pr-OS category, while no effect was detected in intermediate and high pr-OS categories. To strengthen these findings, study participants with pr-OS<60% were combined (N = 80, 27.6%, 39 Obs/41 Adj), and a significant DFS (HR = 0.49, 95% CI 0.28–0.85) and OS (HR = 0.50, 95% CI 0.30–0.90) benefit was detected.
Conclusion: Patients of the EORTC-STBSG 62931 RCT with extremity and trunk wall STS and a low predicted pr-OS (high-risk patients) had better outcomes when treated with adjuvant chemotherapy. This may help reconcile the disparate results of clinical studies on adjuvant/neoadjuvant chemotherapy in STS.

1. Introduction

Surgery and radiation therapy are the standard treatment options for high-risk soft tissue sarcoma (STS) of extremity and trunk wall with adverse prognostic features, such as the large size and high tumour grade [1,2]. Neoadjuvant and adjuvant systemic chemotherapies have been tested to reduce risk of metastatic spread, leading to a 5–10% long-term overall survival (OS) benefit in meta-analyses [3–5], which has been considered inconclusive mainly because of the conflicting results of individual trials [2,6–9]. It has been suggested that several of the trials included patients of intermediate or low risk, which may have less benefit from adjuvant treatment. This lack of conclusive evidence has generated variations in treatment strategies [10–13]. In particular, a large randomised controlled trial (RCT), the EORTC-STBSG 62931, which compared doxorubicin plus ifosfamide with observation after surgery for STS, failed to identify a survival benefit for adjuvant chemotherapy [14,15]. However, an updated meta-analysis of 2145 patients including those in EORTC 62931 showed an OS benefit for adjuvant chemotherapy (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75–0.97) [14]. International guidelines suggest to discuss the option of chemotherapy with patients affected by a primary high-risk STS of extremity and trunk wall within a shared decision in the context of challenging evidence [16,17].

A recent RCT investigating a relatively homogenous group of adult high-risk patients affected by the five most common STS histologies of extremity and trunk wall (i.e., high-grade myxoid liposarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumours and synovial sarcoma) showed an improvement in 4-year disease-free survival (DFS) and OS of approximately 20% for anthracycline-based chemotherapy compared with an histology-tailored schedule not including anthracycline [18].

The prognostic nomogram Sarculator [19,20], which was developed using predictive information of the tumour histology, patient age and AJCC TNM prognostic features such as the tumour grade and size [21,22], was tested and validated on large patient series [19]. This tool was used to stratify prognosis of patients with high-risk STS enrolled in a randomised trial from Italian and Spanish Sarcoma Groups (ISG and GEIS) testing different perioperative anthracycline–ifosfamide chemotherapy durations [23,24] and identified a wide range of predicted 10-year OS of enrolled patients ranging between 9 and 92% [25].

We hypothesised that these variations in survival of patients with STS of extremity and trunk in studies conducted to date may have diluted a potential survival benefit for chemotherapy in higher risk patients, thus offering an explanation for conflicting results between different RCTs, such as the EORTC-STBSG 62931 [14] and the ISG-1001 [18]. In this study, we fitted the Sarculator [20] to the individual patient data of the negative EORTC-STBSG 62931 RCT [14] to identify whether there were patients who had a survival benefit after adjuvant chemotherapy.

2. Methods

2.1. Patients

This study analysed data from patients enrolled in the EORTC-STBSG 62931, an unblinded RCT conducted

by the EORTC in 36 sarcoma centres in Europe and Canada (ClinicalTrials.gov, ID number NCT00002641) [14]. Briefly, this study randomised 351 adult patients (allocation ratio 1:1) affected by histologically proven localised adult-type STS located at any site with an intermediate and high histologic malignancy grade (Trojani grade II and III). Patients were assigned to receive either five adjuvant chemotherapy cycles (treatment arm, N = 175) or observation (control arm, N = 176). The chemotherapy regimen was doxorubicin (75 mg/m^2) plus ifosfamide (5 g/m^2) with mesna and lenograstim (3 μg/kg) given every 21 days. Radiotherapy was delivered postoperatively at a total dose of 60–66 Gy when surgical excision was marginal or in case of previous incomplete surgery. In this RCT, five postoperative chemotherapy cycles (treatment arm) were expected to increase 5-year survival from 50% to 65% with 95% significance and 80% power ($\alpha = 0.05$, $\beta = 0.2$). The protocol of the EORTC-STBSG 62931 study was approved by the EORTC Protocol Review Committee and institutional review boards. The patients gave informed consent according to applicable laws in all participating countries. The present study was approved by EORTC through the 'Request for data platform' (http://www.eortc.org/request-for-data/).

2.2. Nomogram predictions

The prognostic nomogram for extremity STS included in the Sarculator (http://www.sarculator.com) was fitted to individual participant data from the EORTC-STBSG 62931 trial. This nomogram considers patient age (continuous variable: 18–100 years), tumour size (continuous variable: 0.1–35 cm), tumour grade (categorical variable: I, II and III) and tumour histology (categorical variable: leiomyosarcoma, dedifferentiated or pleomorphic liposarcoma, myxoid liposarcoma, malignant peripheral nerve sheath tumour, myxofibrosarcoma, synovial sarcoma, sarcoma of vascular origin, undifferentiated pleomorphic sarcoma and other) of a single patient to estimate probability of OS (pr-OS) at 5 and 10 years after surgery. The Sarculator was previously retrospectively tested and validated on 1452 and 2300 patients, respectively [19] and further validated in a prospective randomised trial investigating perioperative anthracycline-based chemotherapy for high-risk STS of extremities and trunk wall [23–25].

Ten-year pr-OS was predicted with Sarculator for each study participant and reported as a percentage. Participants were stratified according to three pr-OS categories as follow: high (pr-OS > 66%), intermediate (51< pr-OS ≤ 66) and low (pr-OS ≤ 51%). These survival groups were identified in a previous analysis that fitted Sarculator to data of patients with high-risk primary STS of extremities and trunk wall enrolled in an RCT comparing three and five cycles of perioperative chemotherapy [25]. The median pr-OS of this previous study [25], which was estimated 60%, was also used to generate two groups of patients to strengthen findings of the previous analysis.

2.3. Statistical analysis

Participants of the EORTC-STBSG 62931 were included in this analysis if their STS was located in an extremity or trunk wall. Patients with tumours located in other sites, including head and neck, abdominal wall, abdomen, retroperitoneum and uterus, were excluded. Also, patients were excluded when data needed for computing pr-OS with Sarculator were unavailable.

Statistical analysis has been conducted considering pr-OS as the variable of interest. OS and DFS were the outcome variables. OS was defined as the time from randomisation to the last follow up or death for any cause. OS was estimated by means of the Kaplan–Meier method [26]. A Cox regression model was fitted to assess the association between the variable pr-OS (categorical variable) and OS [27]. Additionally, a multivariate Cox regression model including the main effects and the first-order interaction was used to study the interaction between pr-OS and the treatment arm (i.e. chemotherapy vs observation). The same analyses were conducted considering DFS, calculated as the time between randomisation to the first recurrence or the last follow-up for non-recurring participants. Relative risk reduction and the number needed to treat (NNT) were calculated for both OS and DFS [28].

All statistical analyses were carried out with the SAS software (version 9.4, SAS Institute Inc., Cary, NC).

2.4. Role of the funding source

This was an academic non-funded study. The EORTC-STBSG 62931 trial was funded by European Organisation for Research and Treatment of Cancer (EORTC) and Rhone-Poulenc Rorer.

3. Results

Participants randomised in the EORTC-STBSG 62931 trial were followed up for a median time of 96 months (interquartile range [IQR] 70–118 months). The 8-year OS and DFS was 0.58 (95% CI: 0.52–0.63) and 0.51 (95% CI: 0.46–0.57), respectively.

The EORTC-STBSG 62931 trial randomised 351 participants who underwent surgery for STS either to adjuvant chemotherapy (N = 175) or to observation (N = 176). For the purpose of this analysis, 61 participants were excluded for having their STS located in the head and neck (N = 7), abdominal wall (N = 7), gastrointestinal tract (N = 6), retroperitoneum (N = 15), uterus (N = 11) and other sites (N = 13). One patient did not have all the data variables recorded

that are needed to calculate Sarculator predictions, and one patient had a tumour other than an STS.

The clinical and pathologic data of the remaining 290 patients who were deemed eligible for this analysis are reported in Table 1 and the CONSORT diagram is given in Supplementary Fig. 1. There were 142 participants in the chemotherapy arm and 148 in the observation arm of the study.

3.1. Overall survival

In the group of patients with extremity and trunk wall STS enrolled in this study, administration of adjuvant chemotherapy was not associated with an OS benefit (HR = 0.91, 95% CI 0.63–1.31), a finding that is consistent with the lack of survival benefit for chemotherapy observed in all patients enrolled in the EORTC-STBSG 62931 trial.

Data from each patient were fitted to the prognostic nomogram Sarculator. Predicted pr-OS in this study ranged between 5% and 96%, with a median value of 72% (IQR 57–83%, Supplementary Fig. 2), showing wide variation across trial participants and highlighting the prognostic heterogeneity of patients enrolled in this trial. Participants were then stratified into the three previously defined categories [25]. Most study participants (N = 170 [58.6%], 90 Obs/80 Adj) were included in the high pr-OS group (pr-OS > 66). The remaining 68 (23.5%, 34 Obs/34 Adj) and 52 (17.9%, 24 Obs/28 Adj) fell into the intermediate (51 < pr-OS ≤ 66) and low (pr-OS ≤ 51) pr-OS category, respectively. Distribution of patient and tumour characteristics used for calculating

Table 1
Clinicopathological characteristics of 290 patients enrolled in EORTC-STBSG 62931 RCT and eligible for this analysis.

Variables	ALL, N = 290		Observation, N = 148		Adjuvant chemotherapy, N = 142	
	N	%	N	%	N	%
Age, median (range) in years	49	(18–71)	49	(18–71)	49	(18–69)
Sex						
Male	167	57.6	85	57.4	82	57.8
Female	123	42.4	63	42.6	60	42.3
Tumour size, median cm (range)	12	(0.3–35)	8.25	(0.3–35)	7.2	(1.2–30)
Tumour grade						
Grade I	12	4.1	6	4.1	6	4.2
Grade II	115	39.7	59	39.9	56	39.4
Grade III	163	56.2	83	56.1	80	56.4
Primary tumour site						
Lower limb	183	63.1	91	61.5	92	64.8
Upper limb	51	17.6	27	18.2	24	16.9
Pelvic girdle	24	8.3	13	8.8	11	7.8
Scapular girdle	18	6.2	10	6.8	8	5.6
Thoracic wall	10	3.5	5	3.4	5	3.5
Paraspinal muscles	4	1.4	2	1.4	2	1.4
Tumour histology						
MFH/UPS	81	28.0	49	33.2	32	22.5
Fibrosarcoma	12	4.1	4	2.7	8	5.6
Liposarcoma	50	17.2	30	20.3	20	14.1
Leiomyosarcoma	35	12.1	11	7.4	24	16.9
Rhabdomyosarcoma	6	2.1	3	2.0	3	2.1
Angiosarcoma	3	1.0	3	2.0	0	0.0
Synovial sarcoma	48	16.6	21	14.2	27	19.0
MPNST	14	4.8	7	4.7	7	4.9
Unclassified sarcoma	31	10.7	16	10.8	15	10.6
Other	10	3.4	4	2.7	6	4.2
Type of surgery						
Exarticulation	13	4.5	5	3.4	8	5.6
Compartimental	48	16.6	21	14.2	27	19.0
Wide	137	47.2	73	49.3	64	45.1
Marginal	79	27.2	41	27.7	38	26.8
Intralesional	1	0.3	1	0.7	0	0.0
Missing	12	4.1	7	4.7	5	3.5
Protocol radiotherapy						
Not performed	42	14.5	24	16.2	18	12.7
Performed	225	77.6	114	77.0	111	78.2
Not delivered	23	7.9	10	6.8	13	9.2

RCT, randomised controlled trial; MFH, malignant fibrous histiocytoma; UPS, undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour.

pr-OS (i.e. patient age, tumour grade, size, histology) did not differ between study treatment arm within each of the three pr-OS categories (Table 2).

The estimated pr-OS at the median follow-up time corresponding to the low (pr-OS $\leq$ 51), intermediate (51 $<$ pr-OS $\leq$ 66) and high (pr-OS $>$ 66) pr-OS were 0.33 (95% CI 0.18–0.48), 0.43 (95% CI 0.30–0.55) and 0.71 (95% CI 0.63–0.78), respectively. Cox regression analysis showed that patients belonging to the low (HR 2.90, 95% CI 1.84–4.57, P $<$ 0.001) and intermediate (HR 2.69, 95% CI 1.75–4.12, P $<$ 0.001) pr-OS category were at statistically significant higher risk of death compared with the patients classified in the high pr-OS category.

The study treatment arm was then factored in the analysis. Fig. 1 reports the pattern of OS by jointly considering the variables pr-OS and treatment arm of this RCT. Adjuvant chemotherapy halved the risk of death in patients with low Pr-OS (HR = 0.46, 95% CI 0.23–0.94). This effect was not detected in the intermediate (HR = 1.00, 95% CI 0.53–1.88) and high Pr-OS categories (HR = 1.08, 95% CI 0.61–1.90). The estimated 8-year in the low pr-OS group resulted in a 21.3% 8-year absolute risk reduction of death (8-year OS: 42.1% and 20.8% for Adj and Obs, respectively) and in an NNT of 4.69.

To strengthen findings achieved investigating the three pr-OS groups and identify patients who might benefit from adjuvant chemotherapy, a further analysis was conducted, categorising patients in two groups, low (pr-OS $<$ 60%) and high (pr-OS $\geq$ 60%) predicted survival (Table 3). The value 60% represents the median predicted 10-year OS of the previously mentioned study [25]. As expected, patients with a low predicted OS (N = 80) were at greater risk of death compared with patients with higher predicted OS (N = 210, HR = 2.13, 95% CI 1.47–3.09). Consistently with the analysis conducted using the three categories, there was a statistically significant reduction of the risk of death when adjuvant chemotherapy was used in the group at low predicted survival (HR = 0.50, 95% CI 0.30–0.90), while this difference was not detected in patients with high OS (HR = 1.20, 95% CI 0.75–1.91, Fig. 2).

3.2. Disease-free survival

The association between risk stratification according to Sarculator, effectiveness of chemotherapy and DFS of study participants was also examined to determine the value of chemotherapy for patients with lower predicted survival. This analysis confirmed a DFS benefit for chemotherapy in the low pr-OS group (HR = 0.46, 95% CI 0.24–0.89) but not in the intermediate (HR = 0.74, 95% CI 0.41–1.34) and high pr-OS (HR = 0.90, 95% CI 0.54–1.50) groups, leading to a 21.0% 8-year absolute risk reduction for adjuvant chemotherapy (8-year DFS: 33.5% and 12.5% for Adj and Obs, respectively) and an NNT of 4.76 (Fig. 3). Consistently with the OS analysis, when patients were grouped according to the cut-off of 60%, there was again a statistically significant reduction of risk of recurrence when adjuvant chemotherapy was used in the group at low predicted survival, i.e. $<$60% (HR = 0.49, 95% CI 0.28–0.85), while this difference was not detected in patients with high pr-OS (HR = 0.95, 95% CI 0.62–1.44).

4. Discussion

This was an unplanned analysis conducted on individual data in a high-risk subgroup of patients enrolled into the EORTC-STBSG 62931 RCT [14]. That study had failed to detect any benefit for adjuvant chemotherapy over observation in the overall study population with primary localised STS. Within the high-risk subgroup, in contrast to the overall study conclusions, adjuvant chemotherapy was associated with a longer OS and DFS in comparison to the control arm. The subgroup was selected to overlap high-risk patients benefiting the most from a tumour response within the ISG-GEIS RCT on three vs five cycles of neoadjuvant chemotherapy with epirubicin plus ifosfamide in STS [23–25].

The gain in the long-term survival rate averaged 20%, a figure that is within the same range as that associated with epirubicin plus ifosfamide at the interim analysis of the last ISG-GEIS-FSG-1001 RCT [18] and non-randomised studies [29]. The ISG-GEIS-FSG-1001, which compared three cycles of epirubicin plus ifosfamide and three cycles of a histology-tailored regimen in the neoadjuvant setting, recruited 287 patients and was discontinued at a median follow-up of 12 months as the third futility analysis showed that patients treated with epirubicin plus ifosfamide had better prognosis (4-year DFS 62% vs 38%; 4-year OS 89% vs 64%). Indeed, such a difference contrasts with the negative results of the EORTC-STBSG 62931 RCT [14], although two main discrepancies were that in one trial, chemotherapy was administered preoperatively [18], while it was given as postoperative adjuvant in the other [14], and that the two studies implemented different chemotherapy schedules. However, it is intriguing that when a high-risk subgroup of patients is singled out in this EORTC-SBTBSG trial, the results may look much less discordant. A major difference between the two studies lies in the eligibility criteria. The ISG-GEIS-FSG-1001 RCT [18], following the previous ISG-GEIS study [23–25], selected a higher risk group of patients compared with the EORTC-STBSG 62931 trial [14], who were affected by undifferentiated pleomorphic sarcoma, high-grade myxoid liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumours and leiomyosarcoma of the extremities and trunk wall. The importance of enrolling patients at high risk of death in a clinical trial for perioperative chemotherapy is also

Table 2
Clinicopathological characteristics of 290 patients enrolled in EORTC-STBSG 62931 RCT and eligible for this analysis according to the study treatment arm and the three following Sarculator categories of probability of overall survival (pr-OS): high (pr-OS > 66%), intermediate (51< pr-OS ≤ 66) and low (pr-OS ≤ 51%).

Variables	High pr-OS (>66%)				Intermediate pr-OS (51–66%)				Low pr-OS (<51%)			
	Observation		Adjuvant chemotherapy		Observation		Adjuvant chemotherapy		Observation		Adjuvant chemotherapy	
	N	%	N	%	N	%	N	%	N	%	N	%
Age, median (range) in years	44 (37–57)		46 (34–54)		52 (39–58)		50 (40–58)		53 (46–60)		55 (43–63)	
Tumour size, median (range) in cm	6 (4–9)		5 (4–7)		11 (8–15)		10 (7–12)		14 (12–16)		14 (10–18)	
Sex												
Female	44	48.9	35	43.7	14	41.2	11	32.4	5	20.8	14	50.0
Male	46	51.1	45	56.3	20	58.8	23	67.6	19	79.2	14	50.0
Tumour grade												
Grade I	6	6.7	6	7.5	0	0.0	0	0.0	0	0.0	0	0.0
Grade II	46	51.1	46	56.3	7	20.6	8	23.5	6	25.0	3	10.7
Grade III	38	42.2	29	36.2	27	79.4	26	76.5	18	75.0	25	89.3
Tumour histology												
MFH/UPS	32	35.6	15	19.7	8	23.5	4	11.8	1	4.2	3	10.7
Fibrosarcoma	0	0.0	2	2.6	0	0.0	2	5.9	1	4.2	0	0.0
Liposarcoma	21	23.3	12	15.8	6	17.6	6	17.6	1	4.2	1	3.6
Leiomyosarcoma	6	6.7	14	18.4	4	11.8	5	14.7	6	25.0	13	46.4
Rhabdomyosarcoma	1	1.1	2	2.6	0	0.0	0	0.0	1	4.2	1	3.6
Angiosarcoma	1	1.1	0	0.0	1	2.9	0	0.0	1	4.2	0	0.0
Synovial sarcoma	14	15.6	13	17.1	5	14.7	6	17.6	4	16.7	6	21.4
MPNST	2	2.2	7	9.2	4	11.8	2	5.9	1	4.2	3	10.7
Unclassified sarcoma	3	3.3	9	11.8	4	11.8	7	20.6	5	20.8	1	3.6
Other	10	11.1	2	2.6	2	5.9	2	5.9	3	12.5	0	0.0

RCT, randomised controlled trial; MFH, malignant fibrous histiocytoma; UPS, undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour.

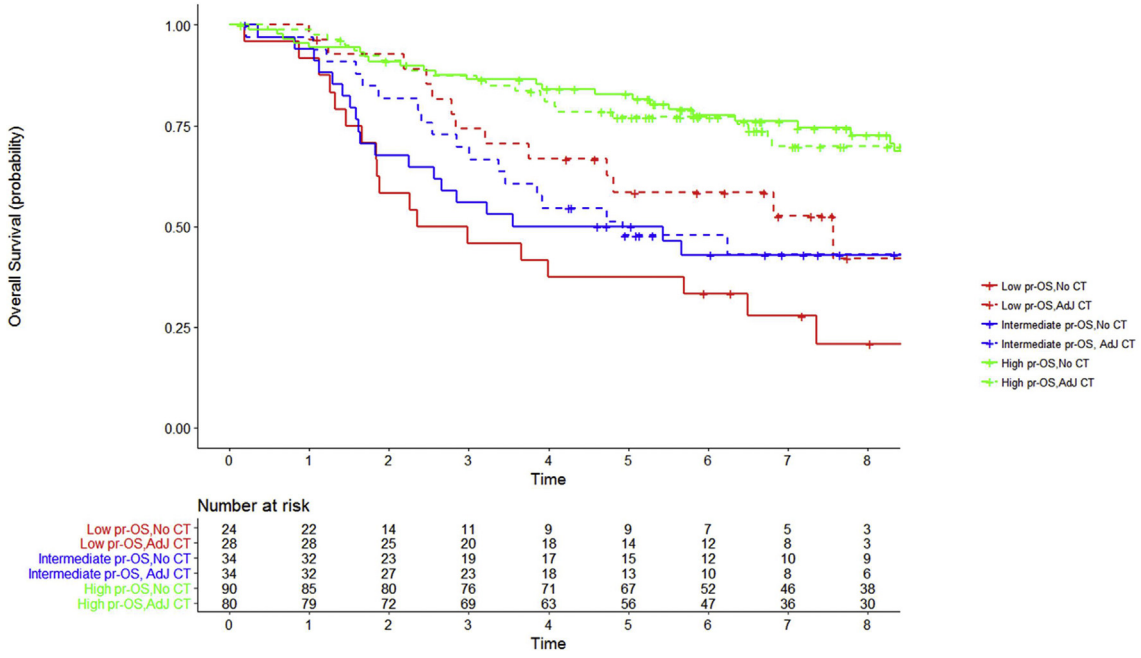

Fig. 1. Overall survival (OS) according to three probability of OS (pr-OS) categories established in a previous study [24] and the EORTC-STBSG 62931 study treatment arms.

underlined by the increased magnitude of a possible survival benefit for patients with low compared with intermediate pr-OS when chemotherapy is administered (Fig. 1). The dose of ifosfamide is another difference among the two studies (9 g/m2 in the ISG-GEIS-FSG 1001 trial and 5 g/m2 in the EORTC 62931 trial). However, its effect may have been limited, especially in the light of what on the contrary was a major similarity of the two trials, i.e. the full dose of anthracycline.

Perioperative chemotherapy was investigated also in the EORTC 62961, a randomised trial that assigned 341 patients to either neoadjuvant chemotherapy with

Table 3
Clinicopathological characteristics of 290 patients enrolled in EORTC-STBSG 62931 RCT and eligible for this analysis according to the study treatment arm and the two following Sarculator categories of probability of overall survival (pr-OS): pr-OS > 60% and pr-OS ≤ 60%.

Variables	pr-OS > 60%				pr-OS < 60%			
	Observation		Adjuvant chemotherapy		Observation		Adjuvant chemotherapy	
	N	%	N	%	N	%	N	%
Age, median (range) in years	45 (37–57)		46 (34–54)		52 (43–59)		55 (44–63)	
Tumour size, median (range) in cm	7 (4–10)		6 (4–9)		14 (10–16)		12 (9–17)	
Sex								
Female	51	46.8	41	40.6	12	30.8	19	46.4
Male	58	53.2	60	59.4	27	69.2	22	53.6
Tumour grade								
Grade I	6	5.5	6	5.9	0	0.0	0	0.0
Grade II	51	46.8	50	49.5	8	20.5	6	14.6
Grade III	52	47.7	45	44.6	31	79.5	35	85.4
Tumour histology								
MFH/UPS	38	34.8	18	17.9	3	7.7	4	9.8
Fibrosarcoma	0	0.0	4	4.0	1	2.6	0	0.0
Liposarcoma	25	22.9	16	15.8	3	7.7	3	7.3
Leiomyosarcoma	9	8.4	16	15.8	7	17.9	16	39.0
Rhabdomyosarcoma	1	0.9	2	2.0	1	2.6	1	2.4
Angiosarcoma	1	0.9	0	0.0	2	5.1	0	0.0
Synovial sarcoma	17	15.6	15	14.8	6	15.4	10	24.4
MPNST	4	3.7	9	8.9	3	7.7	3	7.3
Unclassified sarcoma	3	2.8	15	14.8	9	23.1	2	4.9
Other	11	10.0	6	6.0	4	10.3	2	4.9

RCT, randomised controlled trial; MFH, malignant fibrous histiocytoma; UPS, undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour.

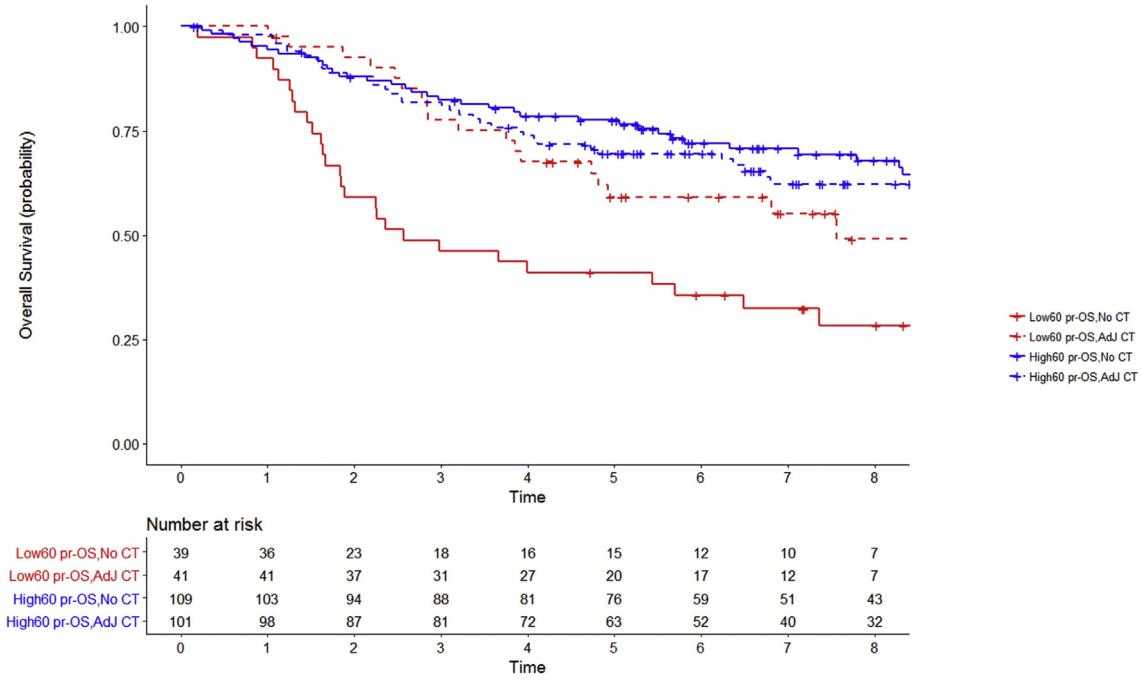

Fig. 2. Overall survival according to two categories according to the median survival value (10-year predicted OS: 60%) of a previous study [24] and the EORTC-STBSG 62931 study treatment arms. OS, overall survival.

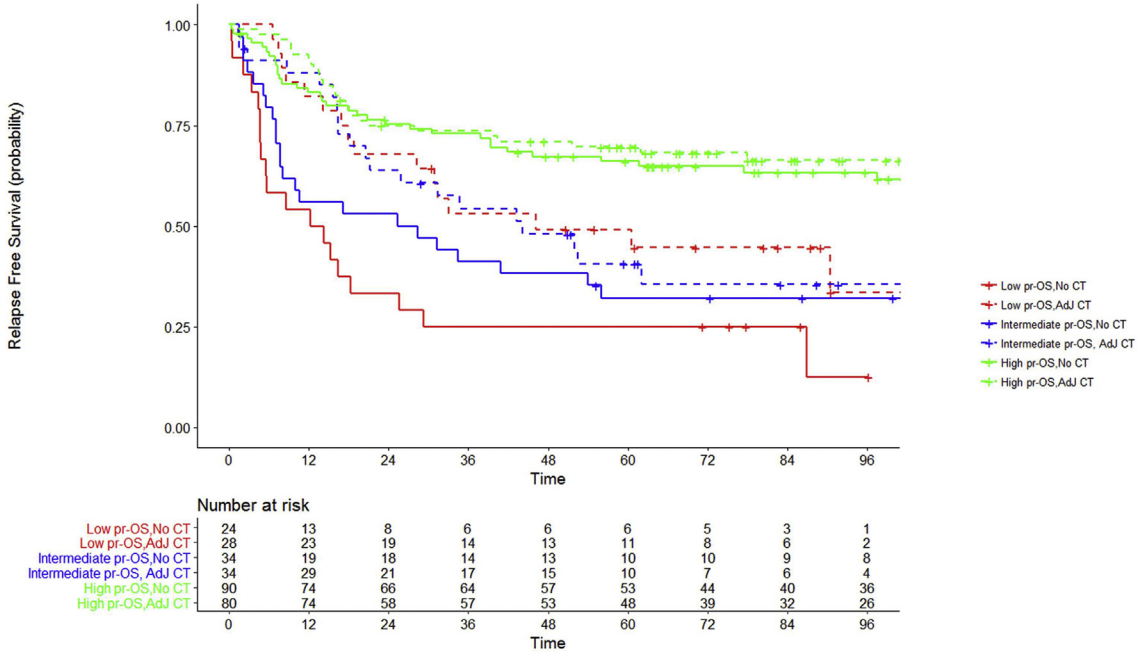

Fig. 3. Disease-free survival according to three probability of OS (pr-OS) categories established in a previous study [24] and the EORTC-STBSG 62931 study treatment arms.

anthracycline, ifosfamide and etoposide plus hyperthermia or neoadjuvant chemotherapy alone showing a DFS and OS benefit for hyperthermia after a median follow-up of 11 years [30,31]. Patients with extremity sarcoma (N = 143, 42%) also did better when treated with hyperthermia (10-year OS: 68% vs 59%). The control group of this trial had lower survival than the EORTC 62931 trial, probably reflecting the larger number of abdominal and retroperitoneal sarcomas [32] and making comparison of these studies challenging. Also, doxorubicin dose was 50 mg/m2, lower than that used in the EORTC 62931 trial.

This subgroup analysis exploits the value of prognostic risk stratification using the nomogram Sarculator.

Nomograms have been recently included in the 8th edition of the AJCC staging manual for several tumours, and they are expected to improve prognostic risk assessment compared with the AJCC TNM stage [22]. Sarculator, although created and validated on retrospective data [19], identifies patient risk effectively, in a way that is likely to work for patient selection for adjuvant treatments, although this nomogram was not available when studies on adjuvant and neoadjuvant chemotherapy were designed. The inclusion criteria of these studies were predominantly based on the malignancy grade, while Sarculator also includes the tumour size as a continuous variable and histological sarcoma subtype as well as patient age. They should be incorporated in future studies for selecting homogenous populations of patients, such as patients with predicted OS $< 60\%$. In addition, recent data showed how the inclusion of biological signatures, such as CIN-SARC [33,34] or genomic index [35], in sarcomas may improve further the prognostic accuracy of these tools. An effort to validate prospectively these biological signatures both as prognostic and predictive biomarkers is presently underway. If their value is proven, they will be added to available nomograms, to refine them further.

Results from this subgroup analysis have some limitations. First, the selected subgroup of patients is relatively small (N = 52); however, by using a different cut-off, the number of patients was increased (N = 80), and a difference was still observed. Second, this was an unplanned analysis of an RCT, although it used a validated prognostic tool, the Sarculator. These findings should be viewed as exploratory and hypothesis generating. However, they may help reconcile the results of different randomised trials conducted in STS. Indeed, available meta-analyses on all published RCTs favoured adjuvant chemotherapy [19,20]. This may be viewed as suggesting that a subgroup of patients may benefit from chemotherapy and that this subgroup is defined by a high risk of relapse. Clearly, a high risk entails a higher absolute benefit for chemotherapy, under the assumption of the same proportional risk reduction. Probably, however, high-risk STSs are also more sensitive to anthracycline-based chemotherapy, as long as their malignancy grade is higher on average. As a matter of fact, the same proportional reduction did not fully apply to patients with an intermediate or low predicted risk of recurrence.

5. Conclusions

In conclusion, this unplanned subgroup analysis of the EORTC-STBSG 62931 RCT may help explaining conflict results on adjuvant chemotherapy for STS, especially if the final analysis of the ISG-GEIS-FSG-1001 RCT confirms the survival benefit for anthracycline-based chemotherapy detected at the interim analysis. They may also help to view results provided on neoadjuvant chemotherapy as less necessarily because of the placement of chemotherapy before surgery. These data emphasise that results of RCTs should always be interpreted and viewed in the light of all the available evidence.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.009.

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