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Annals of Oncology 25: 2425–2432, 2014
doi:10.1093/annonc/mdu460
Published online 6 October 2014

Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials

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Received 15 April 2014; revised 19 September 2014; accepted 23 September 2014

Background: The EORTC-STBSG coordinated two large trials of adjuvant chemotherapy (CT) in localized high-grade soft tissue sarcoma (STS). Both studies failed to demonstrate any benefit on overall survival (OS). The aim of the analysis of these two trials was to identify subgroups of patients who may benefit from adjuvant CT.

Patients and methods: Individual patient data from two EORTC trials comparing doxorubicin-based CT to observation only in completely resected STS (large resection, R0/marginal resection, R1) were pooled. Prognostic factors were assessed by univariate and multivariate analyses. Patient outcomes were subsequently compared between the two groups of patients according to each analyzed factor.

Results: A total of 819 patients had been enrolled with a median follow-up of 8.2 years. Tumor size, high histological grade and R1 resection emerged as independent adverse prognostic factors for relapse-free survival (RFS) and OS. Adjuvant CT is an independent favorable prognostic factor for RFS but not for OS. A significant interaction between benefit of adjuvant CT and age, gender and R1 resection was observed for RFS and OS. Males and patients >40 years had a significantly better RFS in the treatment arms, while adjuvant CT was associated with a marginally worse OS in females and patients <40years. Patients with R1 resection had a significantly better RFS and OS favoring adjuvant CT arms.

Conclusion: Adjuvant CT is not associated with a better OS in young patients or in any pathology subgroup. Poor quality of initial surgery is the most important prognostic and predictive factor for utility of adjuvant CT in STS. Based on these data, we conclude that adjuvant CT for STS remains an investigational procedure and is not a routine standard of care.

Key words: soft tissue sarcoma, adjuvant chemotherapy, predictive factors, treatment outcome

introduction

Surgery remains the cornerstone of treatment and the only curative locoregional approach for localized resectable soft tissue sarcoma (STS). The worldwide most commonly accepted first-line treatment is a wide local excision followed by postoperative radiation therapy (RT), especially in case of narrow margins or a microscopically non-radical resection [1]. An optimal initial resection is one of the most reproducible and reliable prognostic factors of absence of relapse in resectable STS [2–4]. Nevertheless, despite improved local control rates over time, around half of the

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patients still develop and die of unresectable, locally advanced relapsing disease and/or metastatic disease [5, 6], sustaining the clinical interest of using adjuvant systemic treatments to improve relapse-free (RFS) and overall survival (OS).

Adjuvant chemotherapy has however failed to prove unequivocal clinical benefit in the heterogeneous group of STS, with the notable exceptions of the chemosensitive Ewing's sarcoma family of tumors (ESFTs) and alveolar/embryonal rhabdomyosarcomas where chemotherapy is a standard [2].

Nineteen randomized phase III trials in high-grade STS patients with localized disease have evaluated the potential of postoperative adjuvant chemotherapy to reduce local and/or distant relapse when compared with observation only. Most trials have involved a relatively small number of patients, with heterogeneous groups of histological/molecular sarcomas subtypes, initial sites of the disease and patient's characteristics. A single meta-analysis based on individual data from these studies has confirmed a significant impact of adjuvant chemotherapy on either local relapse or distant metastasis, but without any significant benefit on OS [7]. However, three meta-analyses carried out on published data only have suggested opposite conclusions [8–10].

Short-term follow-up of more recent trials suggested a possible benefit of chemotherapy only in the first few years following adjuvant treatment [11–14], but this could not be confirmed in longer term follow-up in a large adjuvant trial coordinated by the EORTC-STBSG, which failed to demonstrate any impact of chemotherapy on both RFS and OS [15]. The inclusion of the latter trial in the previous meta-analysis [8–10] did not affect on its conclusion with a small, although still significant, benefit in OS and RFS [16]. Actually, an obvious conclusion is that adjuvant chemotherapy still remains of debatable benefit in an unselected population of patients and cannot be considered as a standard option for patients with STS [1].

In this context, it is important to assess and prospectively identify whether or not there are small subpopulations of patients benefiting more than others from adjuvant chemotherapy.

For this purpose, we have pooled individual patient data from two consecutive EORTC trials comparing adjuvant chemotherapy (Cyclophosphamide/Vincristine/Doxorubicin/Dacarbazine or CYVADIC in trial 62771 [17] and Doxorubicin/Ifosfamide or AI in the more recent trial 62931 [15] to a no further treatment arm in completely resected STS (R0 or R1): (i) to identify prognostic factors, by univariate and multivariate analyses, influencing patient's RFS and OS, independently of the adjuvant chemotherapy regimen; (ii) to identify predictive factors or to select subgroups of patients who benefit more than others from adjuvant therapy. The outcome of patients was subsequently compared between the two groups of patients according to each investigated prognostic factor.

patients and methods

patient population

Patients eligible for this analysis were included in two large randomized phase III trials comparing adjuvant chemotherapy to observation in completely resected high-grade STS (R0 or R1). The first study (EORTC 62771) included 468 patients and chemotherapy consisted of doxorubicin 50 mg/m² 1 day, dacarbazine 400 mg/m², 1–3 days, cyclophosphamide 500 mg/m² 1 day and vincristine 1.5 mg/m² 1 day (CYVADIC) every 4 weeks for eight cycles [17]. The second study (EORTC 62931) included 351 patients and chemotherapy involved doxorubicin 75 mg/m² day 1, ifosfamide 5 g/m² day 1 plus granulocyte colony-stimulating factor 3–5 μg/kg, day 3–12 (AI) for five cycles given every 3 weeks [15].

The rate of radical (R0) versus marginal (R1) resections in both trials was not significantly different across genders and was similar in all subgroups of patients according to age: 21.4% of marginal resection in patients aged 30–40 years, 19.4% in those 40–50 years, 22.0% in those 50–60 years and 20.7% in those over 60 years.

In addition, adjuvant RT was equally delivered within both study arms (50.8% in the control group of patients, 49.2% in the group of patients receiving adjuvant chemotherapy, but use of RT was more frequent in the recent trial (55.7% of patients) than in the previous one (44.3% of patients).

Characteristics of the total of 819 patients included per protocol are listed in Table 1.

results of the clinical trials

Results of both trials were independently published elsewhere [15, 17]. Briefly, adjuvant CYVADIC reduced the local recurrence rate without any impact on survival [15] and adjuvant AI failed to demonstrate any advantage on both RFS and OS [17]. Increased use of postoperative RT and development of the concept of referral centers for rare tumors could possibly account for the better survival in both arms in the more recent trial.

Since these two consecutive prospective EORTC trials have been designed for and carried out in similar cohorts of patients, asking similar questions and obtaining similar conclusions (at least for OS), it was scientifically attractive to pool these two trials and to retrospectively analyze prognostic and predictive factors influencing outcome of included patients.

prognostic factors. Prognostic factors analysis aims to identify subgroups of patients who have a favorable RFS or OS, independently of adjuvant therapy. The potential prognostic value of all factors was first investigated by univariate analysis, using a univariate Cox model stratified by the trial (Table 1). Factors with a significant prognostic value were subsequently analyzed in a multivariate step-down Cox model. RFS and OS curves are presented for significant prognostic factors. The predictive ability of models is quantified by calculating the concordance index of Harrell (C-index). A C-index of 0.5 indicates that outcomes are completely random, whereas a C-index of 1 indicates that the model is a perfect predictor. The assessment of model stability is verified by a bootstrap re-sampling method based on 500 samples.

predictive factors analysis. The aim of this analysis is to identify subgroups of patients who benefit more from adjuvant therapy than others. Patients are divided in two groups according to each investigated factor. Outcome of patients in terms of RFS or OS, is subsequently compared between patients treated with adjuvant chemotherapy and control patients within both subgroups; results of the comparison are expressed by hazard ratio (HR < 1 indicates a favorable impact of adjuvant treatment).

HR is subsequently compared between the two subgroups using an interaction test. If this test is significant, one may conclude that patients from one subgroup benefit more from adjuvant chemotherapy than patients from the other subgroup. Results of this analysis are illustrated by showing the overall or progression free survivals in both subgroups by treatment arm stratified by 'study'.

results

prognostic factors analysis

Table 2 summarizes the significant prognostic factors influencing RFS and OS. Tumor size, grade, quality of resection and adjuvant

Table 1. Characteristics of patients included in both adjuvant trials

Variables	Study 62771 ($N = 468$) *n* (%)	Study 62931 ($N = 351$) *n* (%)	Total ($N = 819$) *n* (%)
Gender			
Male	242 (51.7)	192 (54.7)	434 (53.0)
Female	197 (42.1)	155 (44.2)	352 (43.0)
Local recurrence			
Primary	353 (75.4)	311 (88.6)	664 (81.1)
Recurrent	86 (18.4)	36 (10.3)	122 (14.9)
Resection level			
Marginal	53 (11.3)	100 (28.5)	153 (18.7)
Radical	384 (82.1)	234 (66.7)	618 (75.5)
Grade			
I	51 (10.9)	17 (4.8)	68 (8.3)
II	92 (19.7)	150 (42.7)	242 (29.5)?
III	230 (49.1)	184 (52.4)	414 (50.5)
Histological cell type			
Leiomyosarcoma	73 (15.6)	55(15.7)	128 (15.6)
Liposarcoma	59 (12.6)	45 (12.8)	104 (12.7)
Synovial sarcoma	68 (14.5)	40 (11.4)	108 (13.2)
Other cell type	242 (51.7)	211 (60.1)	453 (55.3)
Tumor site			
Limb	284 (60.7)	237 (67.5)	521 (63.6)
Trunk-HN	100 (21.4)	52 (14.8)	152 (18.6)
Central	28 (6.0)	50 (14.2)	78 (9.5)
Uterus	27 (5.8)	9 (2.6)	36 (4.4)
Age (years)			
Median	43.0	49.1	45.6
Range	3.3–70.3	17.3–70.4	3.3–70.4
N obs	443	351	794
Tumor size (cm)			
Median	7.0	8.0	7.0
Range	1.0–51.0	0.3–35.0	0.3–51.0
N obs	369	346	715

N obs correspond to the number of patients in each arm where the tumor size were available.

Table 2. Prognostics factors for overall survival and relapse-free survival

Multivariate analysis				
Variable	Overall survival		Relapse-free survival	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Treatment				
Control			1.00	0.0056
Adjuvant			0.74 (0.60–0.92)	
Tumor size (cm)	1.06 (1.04–1.08)	<0.0001	1.05 (1.04 –1.07)	<0.0001
Histological grade (continuous)	1.71 (1.38 –2.11)	<0.0001	1.53 (1.28 –1.82)	<0.0001
Resection level				
Marginal	1.00	<0.0001	1.00	<0.0001
Radical	0.51 (0.38 –0.67)		0.55 (0.42 –0.71)	

chemotherapy were the four independently significant prognostic factors of RFS. Tumor size, grade and quality of resection were the three independently significant prognostic factors of OS. Age and tumor site lost their significance in the multivariate model. All other parameters tested (gender, study, local recurrence versus primary, histological subtype of sarcoma) were not significant in the univariate analysis. Marginal versus radical resection negatively influenced the OS (Figure 1).

The significant prognostic factors remained stable with predictivity (C-index 0.65 for OS and 0.63 for RFS) and

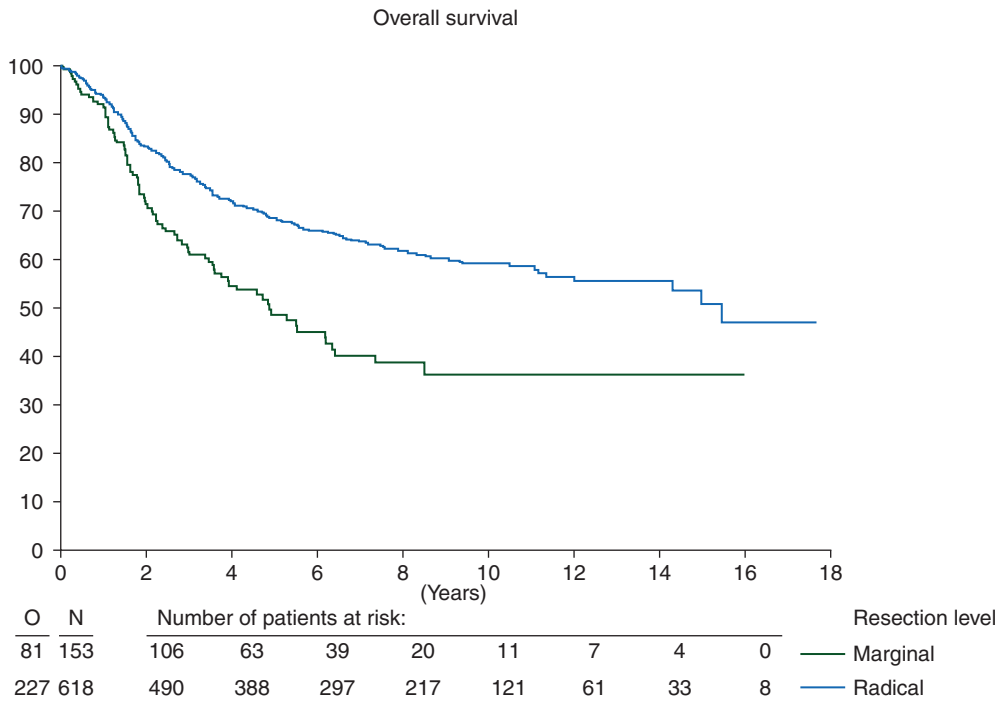


Figure 1. Overall survival of patients included in the two trials according to the quality of initial resection.

bootstrap methods (data not shown) for the RFS and OS analysis. Thus, the final models included the quality of resection, tumor size and grade for OS and the three previous factors plus the adjuvant treatment of PFS.

predictive factor analysis

Table 3 summarizes the results of the interaction tests for OS and RFS, and for all investigated factors. For continuous factors, the cutoff value used for building the binary factor is indicated between brackets. As this study is a meta-analysis, the model is stratified by 'study'. The 'study' factor does not have any predictive value, which means that the overall results are homogeneous between the two studies (supplementary Figure S1A and B, available at *Annals of Oncology* online).

Significant predictive values were observed for gender and age for both end points: males benefitted more from adjuvant therapy than females, and patients over 40 years benefitted more than younger patients (Figure 2A and B). Because of the predictive value of gender, we also investigated the subgroup of patients with uterine sarcoma: patients with uterine sarcoma did not seem to benefit from adjuvant chemotherapy (HR is >1 both for RFS and OS) (data not shown), but the sample size is very small (36 patients in total). Finally, we have looked at the predictive value of synovial sarcoma histology versus others histological subtypes, and this was also not significant.

A predictive value was also observed for the level of resection, but only for OS: patients with marginal resection benefitted more from adjuvant therapy than patients with radical resection (Figure 2B). Impact of the quality of resection on OS is highlighted in Figure 3. Patients who underwent a marginal resection (after one or two consecutive surgeries) and who did not receive adjuvant chemotherapy had a 10-year OS of 27.6%; this rate increased significantly ($P = 0.048$) up to 44.7% with systemic treatment. This benefit was more frequently observed in males (regardless of age) than in females. Adjuvant chemotherapy actually may even be detrimental in younger female patients, albeit that the small number of patients per subgroup precludes any formal conclusion (data not shown).

Table 3. Predictive factors analysis: results of the interaction tests for overall and relapse-free survival, between treatment (control versus adjuvant CT) and for all investigated factors

	Interaction test	
	Overall survival	Relapse-free survival
Study (62771 versus 62931)	0.9179	0.3119
Gender (Males versus Female)	**0.0351**	**0.0357**
Age (40 years)	**0.0412**	0.0561
Tumor size (7 cm)	0.6401	0.7746
Local recurrence (primary versus recurrent)	0.2513	0.6853
Radical resection (marginal versus radical)	**0.0391**	0.1595
Grade (I–II versus III)	0.0860	0.7155
Leiomyosarcoma (no versus yes)	0.5056	0.4055
Liposarcoma (no versus yes)	0.4907	0.9203
Synovial (no versus yes)	0.8574	0.7670
Limb (no versus yes)	0.4953	0.5336
Trunk—head and neck (no versus yes)	0.5034	0.5933
Central (no versus yes)	0.4732	0.4707
Uterus (no versus yes)	0.2041	0.1438

Patients are divided in two groups of patients according to each investigated factor.
The significant *p* value of the interaction test is in bold.

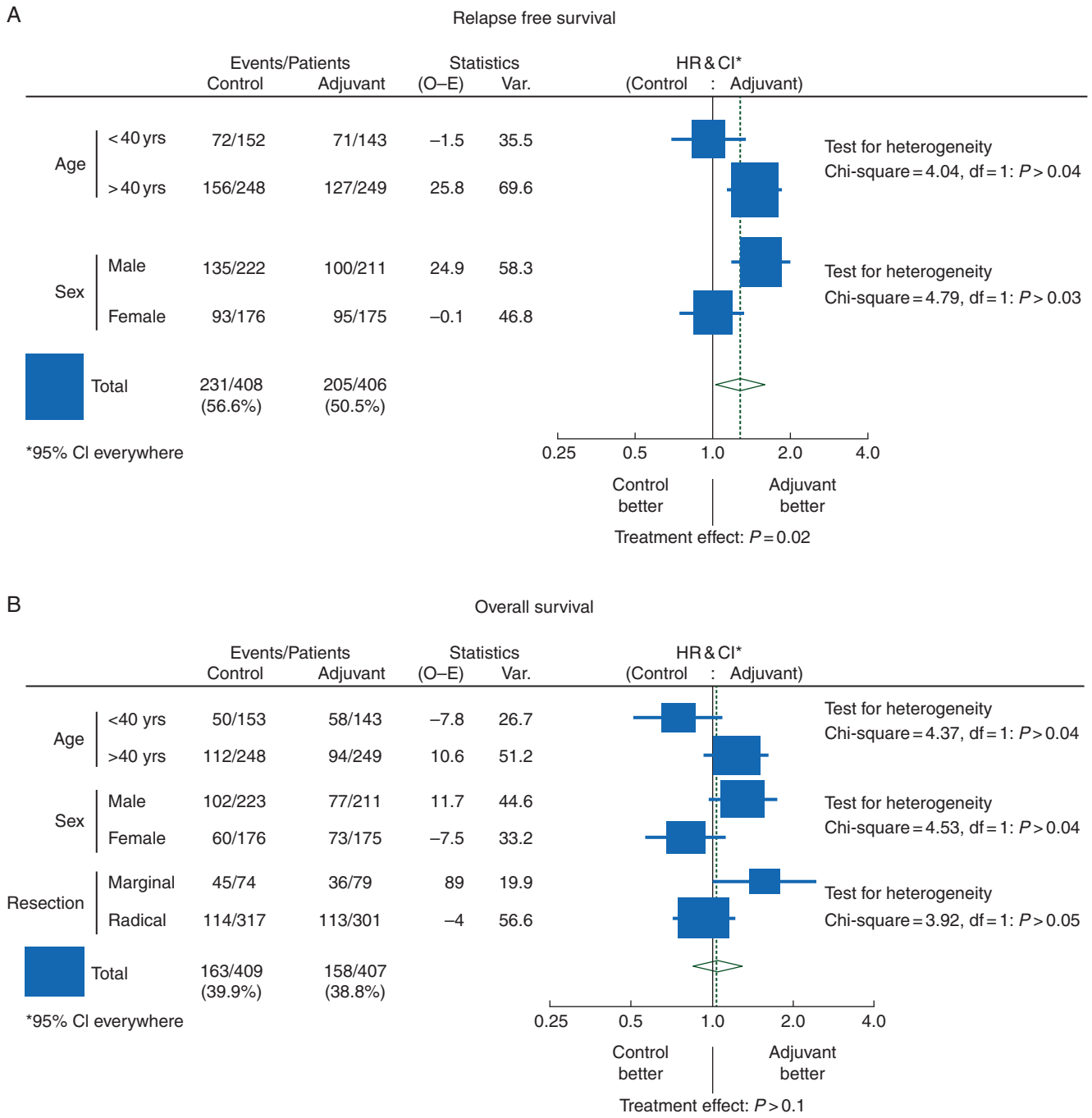


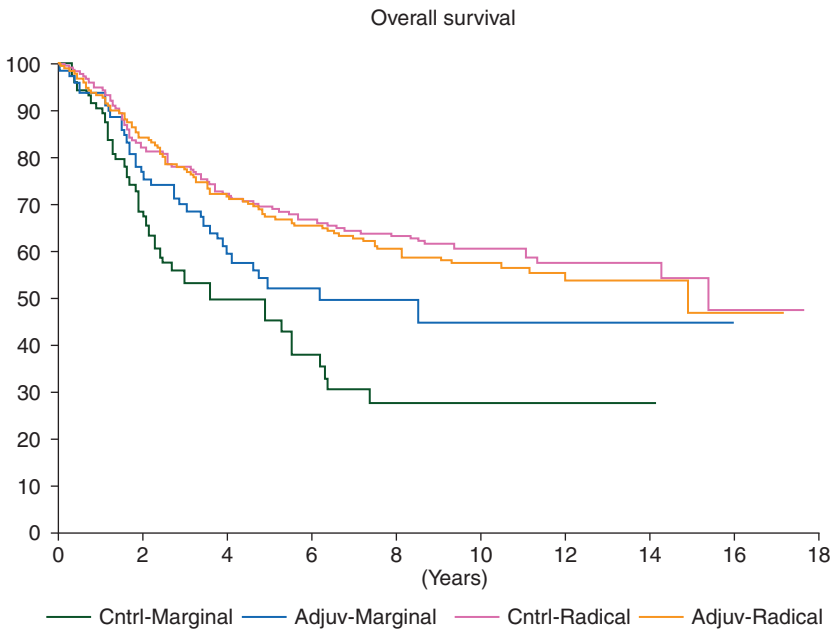
Figure 2. (A) Relative risk of relapse in relation per sex and age. (B) Relative risk of death in relation per type of resection, gender and age.

In contrast, patients with optimally resected disease (R0) had a 10-year OS close to 60%, with or without systemic treatment. In case of radical resection neither gender nor age influenced OS of patients independently by site and grade. Similarly, in grade 3 limb STS, the quality of initial surgery seems to be a predictive factor for a favorable outcome, not influenced by adjuvant chemotherapy (supplementary Figure S2, available at *Annals of Oncology* online).

RT improves the outcome (RFS and OS) of patients undergoing a R1 resection but only 15% of these patients have not received any adjuvant RT. Similarly, the 51% of patients who had received adjuvant RT after a R0 resection had a better outcome than those who did not, both on PFS and OS. Since the indication of RT remains physician related to the characteristics of the resected sarcoma (size, site, grade, center's policy, …), the design of both studies do not allow to establish the true impact of RT on patient's outcome.

discussion

The value of adjuvant chemotherapy after resection of a high-grade STS remains controversial due to the lack of a reproducible



Resection	Treatment	Patients (N)	Events (O)	Median (95% CI) (Years)	% at 10 Year(s) (95% CI)	Hazard ratio (95% CI)	*P*-value
Marginal	Control	74	45	4.87 (2.38, 6.20)	27.60 (15.84, 40.68)	1.00	0.0488
	Adjuvant	79	36	6.22 (3.93, N)	44.69 (30.01, 58.34)	0.64 (0.42, 1.00)	
Radical	Control	317	114	15.44 (9.38, N)	60.63 (54.36, 66.31)	1.00	0.5951
	Adjuvant	301	113	14.96 (8.13, N)	57.74 (51.13, 63.79)	1.07 (0.82, 1.39)	

Figure 3. Predictive factor of resection on overall survival by treatment.

impact on survival in an unselected population of patients [7]. These two consecutive EORTC trials comparing adjuvant chemotherapy to a control in completely resected STS are the two largest trials ever carried out in this field and may be the last addressing this critical issue in unselected sarcoma with a conventional doxorubicin-containing chemotherapy regimen [15, 17]. Both studies failed to demonstrate any advantage of adjuvant chemotherapy on OS and at the moment, this therapeutic approach can be proposed only as an option to the high-risk individual patient for shared decision making in conditions of uncertainty [1]. There is therefore an urgent need to determine whether or not there are subpopulations of patients potentially benefiting from adjuvant chemotherapy.

Improvement of surgical procedures over the years [18, 19], optimization of initial patient management and the more frequent use of RT in the recent trial could partly explain the absolute 10% increase in 5-year OS of patients included in the control arms (patients treated with local treatments only i.e. surgery ± RT) in a period of 10 years [59% in the sarcoma meta-analysis collaboration (SMAC) report including the 62771 EORTC trial [7] and 69% in the latest 62931 EORTC trial].

Large tumor size, high histological grade and marginal resection were independent significant adverse prognostic factors for both OS and RFS, while adjuvant CT had an independent favorable prognostic value only for RFS. The current analysis confirms previously documented prognostic factors in completely resected STS [20, 21], and shows that patients with adverse prognostic factors (large tumor size and high histological grade) are not necessarily those who benefit from adjuvant chemotherapy.

Patients with grade 3 advanced/metastatic STS have been suggested to benefit from chemotherapy in terms of response or clinical benefit [22]. While the French Sarcoma Group has suggested that similar benefit could be found in the adjuvant setting for RFS and OS in grade 3 patients (absolute risk reductions of 9% and 13%, respectively), this observation may have been due to short follow-up since the benefit decreases over time and loses its significance after three years [23]. This is in line with previously published study reports [11] and data from meta-analyses on published data [8–10, 16]. Taken together, these results may suggest that adjuvant treatment actually only postpones relapses, but does not prevent them, whatever the duration of the adjuvant treatment is, as observed in high-risk GIST with imatinib [24, 25].

Our results confirm the importance to maintain a stringent follow-up for radically resected sarcoma patients over time, regardless of the applied therapeutics. Half of the recurrences (local and/or distant) occurred beyond the first 4 years of follow-up, even in the favorable group of patients (R0 resection).

Of interest, the quality of surgical resection, which is often poorly reported in terms of details, or not included as a stratification covariate in prospective trials seems to represent a crucial parameter for resectable STS. Despite the difficulty of

homogeneously assessing this quality of surgical resection retrospectively, it seems the most important prognostic and predictive factor for presence (marginal resection) or absence (radical resection) of benefit from adjuvant chemotherapy for RFS and OS. The average OS for R0 resection patients not receiving adjuvant chemotherapy largely exceeded the respective OS for R1 resection patients, even with the addition of systemic treatment. Therefore, adjuvant chemotherapy cannot fully rescue an inadequate initial surgery. And since persistence of microscopic residual disease is associated with a higher risk of relapse, a re-resection first needs to be systematically reconsidered before making any decision on adjuvant treatments.

Optimal surgery remains the cornerstone of treatment and the only curative locoregional approach of localized resectable STS. It has been reported that conformity of surgery to clinical practice guidelines (CGP) improves RFS and OS in patients with STS [26]. The rate of R0 resection increased from 24% to 55% when patients were operated outside or inside a national clinical network with a sarcoma tumor board judgment, before locoregional treatments were applied. Nevertheless, only one-third of newly diagnosed patients in France in 2011 were treated within this context [27]. This stresses the need to focus our energy on appropriate initial multidisciplinary management of patients and development of and adherence to CGP, rather than on prospective randomized adjuvant trials in heterogeneous populations. Future adjuvant studies should be designed only in selected homogeneous populations based on initial surgery (R2 re-excised, R1 not re-excised, R1 with tumor fragmentation, R1 after two consecutive surgeries …).

Age above 40 years and male gender may be associated with a benefit of adjuvant therapy, while there was no correlation between age and quality of resection. These observations require prospective validation, but do suggest that host-related factors, may still influence the risk of relapse. Recently for instance, metastasis development in synovial sarcomas was reported to be associated with chromosome complexity of the primary tumor, more frequently in adults than in younger patients [28].

Conventional cytotoxic chemotherapy is likely going to be used less in the future. New molecularly targeted drugs have been introduced for mesenchymal tumors and new treatment algorithms will be implemented with more intricated and individualized treatment implications. In view of these, the future randomized adjuvant treatment trials could either explore: (i) a specific drug (or combination) with demonstrated relevant activity in metastatic disease of a selected histotype of sarcoma [5, 29]; (ii) a conventional chemotherapy regimen in STS harboring a gene expression signature able to predict high risk of metastasis development, such as the CINSARC signature based on genome complexity and histological grade [30] or a signature based on expression of a particular protein such as Topoisomerase 2A selecting a more doxorubicin-chemosensitive subgroup of STS [31]; (iii) a selected agent adapted to a driver mutation involved in a transformation and progression process and where a proof of concept has been highlighted in advanced disease. Examples of the latter include imatinib in GIST [32] but also in dermatofibrosarcoma protuberans [33] or denosumab in giant-cell tumor of bone [34] and to a lesser extent, trabectedin in myxoid liposarcoma where its relevant activity suggests a targeted therapeutic approach in this specific histological subtype [35]; or (iv) use of agents targeting the tumor environment such as cediranib or pazopanib either in selected translocation-related STS where the VEGF/VEGFR pathway seems to play a key role such as alveolar soft part sarcomas [36] or a more broad range of histotypes possibly driven by VEGF [37].

In conclusion, we would like to stress that this retrospective analysis carried out on two prospective trials can only be used to generate hypotheses for future trials, and cannot be used for clinical practice recommendations. However, based on these data, take-home messages could be as follows: (i) adjuvant CT for STS remains an investigational procedure and cannot routinely be recommended for high-grade STS; (ii) adjuvant chemotherapy cannot rescue for inadequate initial surgery, albeit that the most extensive effect was seen in the poor surgery group; (iii) the era of adjuvant trials applying the same chemotherapy regimen to all histological subtypes of sarcoma has likely ended and (iv) prognosis of patients with a localized STS is depended on the very first steps in patient's management, i.e. proper diagnostic procedures and treatment applications by an expert physician, in the context of a multidisciplinary sarcoma board.

acknowledgements

We thank Olivier Mir for his helpful contribution as well as the Data Center of EORTC.

disclosure

The authors have declared no conflicts of interest.

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