A phase III randomized trial on neo-adjuvant chemotherapy in high-risk soft tissue sarcomas (ISG-STS 1001): feasibility and activity of concurrent chemotherapy and radiation therapy

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Abstract

Background

The ISG-STS 1001 was an international, randomized, phase III, clinical trial for localized, high-risk, soft tissue sarcoma comparing neoadjuvant chemotherapy (ChT) with a standard regimen of epirubicin plus ifosfamide (EI) versus an histology-tailored regimen (HT) in five histological types, within the context of an integrated multimodality strategy. In addition, in this study, a parallel group of patients (pts) was not randomized but just registered and treated with EI. Radiation-therapy (RT) could be delivered either pre-operatively (concurrent to ChT) or post-operatively, according to clinical judgement. Final results of ISG-STS 1001, published in 2020, showed a benefit in favor of EI, in terms of overall survival, in comparison to HT. Herein, we analyzed tolerability and activity of ChT with EI either in the standard arm of the trial or in the parallel group, whether alone and concurrent to RT.

Methods

The EI regimen was made up of epirubicin 120 mg/m² plus ifosfamide 9 g/m² per cycle, and was administered during 3 cycles every 3 weeks. RT was delivered at a dose of 44-50 Gy pre-operatively or 60-66 Gy post-operatively. In the current analysis, ChT dose-intensity (DI) and grade ≥3 ChT-related haematological toxicities were analyzed separately in the group receiving concurrent pre-operative ChT and RT and in the group treated with pre-operative ChT alone and receiving RT post-operatively. Acute RT-related toxicities, post-operative local complications, and radiological response according to RECIST were analyzed in the above mentioned two groups.

Results

Among the 548 pts (323 randomized and 225 registered) included in the ISG-STS 1001, 287 pts were considered for the current analysis (111 pts randomized in the EI arm and 176 pts just registered). 146 pts were treated with pre-operative RT and 141 with post-operative RT. Median ChT DI was >90% in both groups for both drugs. Concerning haematological toxicities, no statistically significant differences were found between pts treated with pre-operative concurrent ChT and RT and pts treated with pre-operative ChT alone. When post-operative complications were considered, a higher number of wound dehiscence (9% vs 3.6%, respectively, p = 0.057) and seroma (10.4% vs

2.8%, respectively, p = 0.010) were observed in pts treated with pre-operative concurrent ChT and RT compared to pts treated with pre-operative ChT alone. Finally, a statistically significant association between RECIST response and pre-operative RT was found (p = 0.023), RECIST partial responses (PR) being 20.3% and 9.8% in pts receiving concurrent pre-operative ChT plus RT and in pts treated with pre-operative ChT alone, respectively.

Conclusions: The concurrent administration of EI and RT was confirmed to be feasible and safe, resulting in an increased number of PR. Also given the final results of this randomized trial, favoring the EI arm, this combination may help when tumors are of borderline resectability or function preservation is a goal.

Introduction

The management of adult-type localized soft tissue sarcoma (STS) is based on surgery. En-bloc excision with R0 margins is the standard surgical treatment [*Gronchi 2021*]. Radiation-therapy (RT) is generally added to surgery in case of high grade lesions [*Beane 2014, Pisters 1996*], being adjuvant and neoadjuvant settings superimposable in terms of local control [*O'Sullivan 2002*].

The use of adjuvant or neoadjuvant chemotherapy (ChT) is still formally considered as not part of the standard treatment, although there is consensus amongst sarcoma experts that it can be proposed to patients at high-risk of death [*Gronchi 2021*]. In fact, despite the conflicting results of the several randomized clinical trials performed in the last decades on the role of adjuvant or neoadjuvant ChT in STS [*Pervaiz 2008, Woll 2012*], at least in the most common histological types of extremities and superficial trunk, there is some evidence that a ChT with anthracycline and ifosfamide may increase relapse-free-survival (RFS) and overall survival (OS) in the STS population at higher risk [*Frustaci 2001, Gronchi 2016, Gronchi 2020, Pasquali 2018, Pasquali 2019, Pasquali 2022*].

More particularly, the last Italian Sarcoma Group (ISG) trial on neoadjuvant chemotherapy in STS (namely the ISG-STS 1001 study), in collaboration with the Spanish, the French and the Polish sarcoma groups, compared a ChT with epirubicin plus ifosfamide (EI) with and an histology-tailored (HT) regimen in five high-risk STS histologies, in the context of an integrated approach in which RT could be delivered either in the pre-operative setting or in the post-operative setting. Final results were published in 2020, showing a statistically significant benefit in terms of OS in favor of EI and a statistically non-significant benefit in terms of RFS. Additionally, when a risk-predicting tool was applied, the benefit of ChT resulted higher in patients with a predicted-OS probability at ten years lower than 60% [*Pasquali 2022*].

Herein we report on the tolerability and activity of ChT with EI, whether alone and concurrent to RT, in the context of the ISG-STS 1001 study.

Methods

The ISG-STS 1001 study (ClinicalTrials.gov, ID number NCT01710176, and with the European Union Drug Regulating Authorities Clinical Trials, number EUDRACT 2010-023484-17) was a phase III, academic trial (funding source: European Union grant, Eurosarc FP7 278472), in patients with localized, high-risk (deep location, tumor size >5 cm, grade 3 according to FNCLCC grading system [*Trojani 1984*], or grade 2 and >50% necrosis at baseline radiological assessment), primary, resectable STS of extremities and trunk wall, conducted in 32 centres in Italy, Spain, France and Poland [*Gronchi 2017, Gronchi 2020*]. The study included a randomized part and a non-randomized part.

In the randomized part of the ISG-STS 1001 study, patients were randomly assigned to receive in the pre-operative setting either a ChT with EI (standard arm) or a HT regimen (experimental arm). This part of the study enrolled patients with one of the following five histological types: high-grade myxoid liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST), and undifferentiated pleomorphic sarcoma (UPS). Radiation-therapy could be delivered either pre-operatively (concurrent to ChT) or post-operatively, according to clinical judgement. In 2016, the randomized part of the ISG-STS 1001 study closed, and it was re-opened in 2017 only for the subgroup of patients with myxoid liposarcoma.

In the non-randomized part of the ISG-STS 1001 study, patients were just registered and treated with EI, in the pre-operative setting. This part of the study initially included only patients with additional histological types (myxofibrosarcoma, unclassified spindle cell sarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma) and patients with myxoid liposarcoma, leiomyosarcoma, or UPS, in whom a pre-operative RT was needed, in the lack of safety data on the administration of the HT regimen and concurrent RT. Starting from 2017, all patients with leiomyosarcoma, synovial sarcoma, MPNST, or UPS were included in the non-randomized part of the study.

In the ISG-STS 1001 study, three cycles of ChT were planned. The ChT schedule of EI was as follows: epirubicin 120 mg/m² (60 mg/ m²/d, day 1, 2), ifosfamide 9 g/m² (3 g/ m²/d, day 1, 2, 3), every 21 days. The prophylactic use of G-CSF (filgrastim or peg-filgrastim) was recommended. Histology-tailored regimens were reported in detail elsewhere [*Gronchi 2017, Gronchi 2020*]. With regard to RT, in the pre-operative setting, it was administered starting after the first ChT cycle and concurrent

to the second and the third, with a planned dose of 44-50 Gy and a conventional fractioning of 2 Gy/day for 5 days a week; in the post-operative setting, RT was administered with a planned dose of 60-66 Gy and a conventional fractioning of 2 Gy/day for 5 days a week.

Adverse events were recorded and graded according to the Common Toxicity Criteria for Adverse Events, NCI CTCAE, v4.03 [available at https://evs.nci.nih.gov/ftp1/CTCAE/]. At least three serial complete blood counts were performed after each cycle, beginning on day 9 or later and occuring on alternate days until the time of hematological recovery. Doses were modified on the basis of the toxicities according to the scheme listed in **Table 1 available as supplementary material**.

Acute RT-related toxicities and post-operative local complications were prospectively recorded and graded for each patient during the ISG-STS 1001 study according to NCI CTCAE, v4.03 and Canadian SR.2 Trial Criteria [*O'Sullivan 2002*], respectively.

A radiological assessment with local MRI and thorax plus abdomen CT scan were foreseen at baseline, after the first cycle of ChT and before surgery. The maximum diameter of the lesion was reported and radiological response according to RECIST was assessed [*Eisenhauer 2009*].

As mentioned above, outcomes of patients enrolled in the randomized part of the ISG-STS 1001 study over the period from 2011-2016 were already published, toghether with the main toxicities observed in the standard arm and in the experimental arm [*Gronchi 2020*]. More recently, outcomes of the subgroup of patients with myxoid liposarcoma enrolled in the randomized part from 2011-2020 have been reported [*Gronchi 2024*].

In the current analysis within the ISG-STS 1001 study, we considered patients treated with EI in the standard arm of the randomized part and in the non-randomized part, enrolled over the period from 2011 to 2020, focusing on toxicities and activity in the group of patients who received concurrent ChT and RT pre-operatively and in the group of patients who received ChT alone pre-operatively and RT postoperatively. Patients who did not receive RT neither in the pre-operative setting or in the post-operative setting were excluded. Patients treated with an HT regimens were excluded, as well.

The following data were considered: patient and tumor characteristics at baseline; details on treatment received including type of surgery, type of margins, median dose of RT, RT completation, reason for RT discontinuation, ChT reductions, ChT completation, reason for ChT discontinuation; RECIST best responses during pre-operative ChT and changes in the maximum diameter.

Chemotherapy dose intensity (DI) was calculated for each patient by dividing the total milligrams administered by the product of their body surface area and the total duration of treatment. The latter was computed by assuming the time interval necessary for surgery as an additional cycle of 21 days. The DI was then normalized for the planned DI to obtain relative DI. Finally, to summarize the course of treatment of an individual patient, we computed the average relative DI (ARDI) for all of the drugs in the regimen.

Grade ≥3 haematological toxicities were analyzed. Specifically, for every haematological adverse event, the worse toxicity per patient over the three cycles of ChT was taken into account. Acute RT-related toxicities and post-operative local complications were considered, as well.

Statistical analysis

The association between continuous variables and categorical variables was evaluated by Wilcoxon rank sum test or Kruskal-Wallis test. The association between two categorical variables was assessed by Chi-square or Fisher's exact tests. All statistical analysis were carried out with the SAS software (version 9.4, SAS Institute Inc., Cary, NC) and the R software (URL: http://www.r-project.org). Statistical tests were considered significant by adopting a significance level of alpha=0.05.

Results

Patients and treatments

A total of 548 patients were enrolled in the ISG-STS 1001 study over the period from May 2011 and June 2020. Specifically, 323 patients were included in the randomized part of the study (287 from 2011 to 2016 and 36 from 2017 to 2020) and 225 in the non-randomized part (148 from 2011 to 2016 and 77 from 2017 to 2020). Overall, 261 patients were excluded from the current analysis (211 patients in the randomized part and 49 patients in the non-randomized part) and 287 (111 patients in the randomized part and 176 patients in the non-randomized part) were included, of whom 146 treated with concurrent pre-operative ChT and RT (group CT/RT) and 141 treated with pre-operative ChT alone and post-operative RT (group ChT). More details on the population of the current analysis and reasons of exclusion were reported in the consortium diagram (**Figure 1**).

Patient and tumor characteristics in the entire population of the current analysis and in the two groups (ChT/RT and ChT group) are detailed in **Table 1**. Median age at the time of diagnosis was 51 years (IQR range, 42-62 years) in the ChT/RT group and 53 years (IQR range, 42-60 years) in the ChT group. Most of the patients were males: 99/146 (67.8%) in the ChT/RT group and 86/141 (61.0%) in the ChT group. Performance status was 0 in most patients (details are reported in **Table 1**). Median tumor size was 120 mm (IQR 83-164 mm) in the ChT/RT group and 102 mm (IQR 80-130 mm) in the ChT group. The most common site was lower limb, with 107/146 patients (73.3%) in the ChT/RT group and 98/141 (69.5%) in the ChT group. Distribution of histological types were reported in **Table 1**.

Treatments received in the entire population of the current analysis and in the two groups are reported in **Table 2**. All patients but one (because of progression with distant relapse during pre-operative ChT) received surgery in the ChT/RT group (144/146, 98.6%), with one patient lost to follow-up; all patients were treated with surgery in the ChT group. Surgery was conservative in the vast majority of patients (in 140/146 patients, 95.9%, in the ChT/RT group, in 138/141, 97.9%, in the ChT group). Surgical margins were microscopically free in 119/146 patients (81.5%) in the ChT/RT group and in 116/141 (82.3%) in the ChT group. R1 and R2 margins were achieved in 24/146 patients (16.4%) and 0 patients in the ChT/RT group and in 23/141 (16.3%) and 2/141 (1.4 %) in the ChT group, respectively.

RT was completed in most patients (in 141/146 patients, 96.6%, in the ChT/RT group, in 138/141, 97.9%, in the ChT group) with a median dose of 50 Gy (IQR 50-50 Gy) and 60 Gy (IQR 54-64.8 Gy) in in the ChT/RT group and in the ChT group, respectively.

ChT was completed as per protocol with three pre-operative cycles in 127/146 patients (87.0%) in the ChT/RT group and in 133/141 (94.3%) in the ChT group, with few patients who have received more than three cycles (7/146, 4.8%, in the ChT/RT group and 1/141, 0.7%, in the ChT group). A limited number of patients (12/146, 8.2%, in the ChT/RT group and 7/141, 5%, in the ChT group) discontinued ChT, mainly for toxicities (8/146, 5.5%, in the ChT/RT group, and 5/141, 3.5%, in the ChT group). Other reasons for discontinuation are detailed in **Table 2**. Overall, ChT reductions higher than 25% were observed in 30/146 patients (22.4%) in the ChT/RT group and in 18/141 (13.5%) in the ChT group.

With regard to ChT DI, the median average relative ChT DI was 90.0% (IQR 81.1%-94.3%) in the ChT/RT group and 93.9% (IQR 84.2%-96.9%) in the ChT group (p=0.0004), being the epirubicin DI 90.0% (IQR 80.8%-95.2%) and 93.8% (IQR 85.7%-96.9%) in the ChT/RT group and in the ChT group, respectively (p=0.0007), and the ifosfamide DI 90.2% (IQR 81.6%-95.1%) and 94.0% (IQR 84.5%-96.9%) in the ChT/RT group and in the ChT group, respectively (p=0.0014) (**Figure 2**).

Grade ≥3 haematological toxicities, acute RT-related toxicities and post-op complications

When looking to grade 3/4 anemia, grade 3/4 WBC decreased, grade 3/4 neutrophil count decreased, platelet count decreased and grade 3/4 febrile neutropenia, no statistical differences were observed between the ChT/RT group and the ChT group, as reported in details in **Table 3A**. No grade 5 haematological toxicities were observed.

With regard to acute RT-related toxicities, ChT/RT group was associated with a reduced number of any type of toxicities, including skin, neurological and vascular toxicities. Overall, a limited number of grade 3/4 toxicities were seen in both groups (**Table 3B**). Data on skin, neurological and vascular toxicities were missing in 106, 79 and 79 patients, respectively. No grade 5 toxicities were found.

A significant increase of local complications was seen in the ChT/RT group, with a rate of wound dehiscence of 9% (13/144 patients) and 3.6% (5/141) in the in the ChT/RT group and in the ChT group, respectively (borderline significance p=0.0572) and a rate of seroma (with drain tube >15

days) of 10.4% (15/144 patients) and 2.8% (4/141 patients) in the ChT/RT group and in the ChT group, respectively (p=0.0103) (**Table 3C).**

Activity

According to RECIST criteria, the large majority of the patients achieved a stable disease, as best response: 92/133 patients (69.2%) in the ChT/RT group and 110/132 (83.3%) in the ChT group. Partial responses were seen in 27/133 patients (20.3%) in the ChT/RT group and in 13/132 (9.8%) in the ChT group (p=0.023). Few patients experienced progression disease, with 14/133 patients (10.5%) in the ChT/RT group (of which two for distant progression) and 9/132 (6.8%) in the ChT group. Overall, 20 patients were excluded from the current analysis (8 because not evaluable for response and 12 in the lack of the radiological assessment before surgery). When dimensional changes on maximum diameter was considered as continuous variable (waterfall plot, **Figure 3**), tumor shrinkage <30% was seen in most cases formally defined as stable disease by RECIST criteria.

In the most common histological types of the current analysis, best responses according to RECIST criteria were as follows: in patients with myxoid liposarcoma, 11/43 (25.6%) and 1/27 (3.7%) had partial response in the ChT/RT group and in the ChT group, respectively (p=0.025), with 31/43 (72.1%) and 24/27 (88.9%) stable disease in the ChT/RT group and in the ChT group, respectively, and 1/43 (2.3%) and 2/27 (7.4%) progression disease in the ChT/RT group and in the ChT group, respectively; in patients with UPS, 7/34 (20.6%) and 4/33 (12.1%) had partial response in the ChT/RT group and in the ChT group, respectively (p=0.461), with 21/34 (61.8%) and 25/33 (75.8%) stable disease in the ChT/RT group and in the ChT group, respectively, and 6/34 (17.6%) and 4/33 (12.1%) progression disease in the ChT/RT group and in the ChT group, respectively.

Discussion

Among the 548 patients enrolled in the ISG-STS 1001 study over the period 2011-2020, 287 patients treated with pre-operative EI were included in the current analysis, of whom 146 have received concurrently pre-operative ChT/RT and 141 pre-operative ChT alone and post-operative RT. All patients but two received surgery, with a completion rate around 90% either for ChT and RT, in both groups. Chemotherapy dose reductions >25% were observed in 22.6% of patients in the ChT/RT group and in 13.5% of patients in the ChT group, resulting in a limited, statistically significant, reduction of DI in the ChT/RT group. However, median ChT DI was >90% in both groups for both drugs. In regard to grade 3/4 haematological toxicities, no statistical differences were found between the two groups. When acute RT-related toxicities were considered, few events of grade 3/4 were seen in both groups and pre-operative RT resulted associated to a reduced rate of any grade of skin, neurological and vascular toxicities. Conversely, a higher number of wound dehiscence (9%) and seroma (10.4%) were seen in patients treated in the ChT/RT group. Finally, a statistically significant increase of partial responses by RECIST criteria was observed in patients treated with pre-operative ChT and RT.

In 2015, we published the results of an analysis including 152 patients treated with concurrent pre-operative EI and RT in the context of the previous ISG trial on neoadjuvant ChT (ISG-STS 0101), in which the same EI regimen was used in the same population of patients [*Palassini 2015*]. With the current analysis, in which ChT and RT completion rate was around 90% and ChT DI was higher than 90%, the feasibility of concurrent ChT/RT in localized STS of extremities and superficial trunk is confirmed. Of notice, haematological toxicities were as frequent and severe as expected with this regimen, but they were not increased with the addition of pre-operative RT. Again, as in the previous analysis, a higher number of post-operative local complications was seen in the ChT/RT group in comparison to the ChT group. This finding confirmed what seen also by others, since several randomized trials have demonstrated that pre-operative RT increases the risk of wound complications compared with post-operative RT [*O' Sullivan 2002, O' Sullivan 2013, Davis 2002, Moore 2014, Baldini 2013*]. However, probably thanks to the improvement of RT techniques, the rate of post-operative local complications reported in the current analysis was lower than in historical series. Moreover, wound complications may impact quality of life of patients in the short term, but they are generally manageable and reversible, without causing permanent disability.

One limitation of this analysis is that late RT-related toxicities were not reported. In fact, the collection of these data was not initially foreseen and we decided not to provide them retrospectively. However, there is robust evidence from previous studies that a lower number of late, typically irreversible, RT-related toxicities (lymphedema, fibrosis, decreased range of motion and bone fracture) is associated with pre-operative RT, in comparison to post-operative RT, probably as a result of the lower dose used [*O'Sullivan 2002, Davis AM 2005, Cannon CP 2006*]. For this reason, even if the risk of acute wound complications is increased, pre-operative RT is generally preferred. On the other side, the addition of a systemic treatment to pre-operative RT is unlikely to increase the risk of late RT-related toxicities.

In terms of activity, in the current analysis, concurrent pre-operative ChT/RT was associated overall with a statistically significant increase of RECIST responses in comparison to ChT alone. The number of progression disease was limited (10.5%) and did not have impact on surgery, since surgery was performed in all patients but one who progressed with distant disease. Of course, a close monitoring of the response with MRI is crucial during pre-operative treatments, in order to possibly anticipate surgery whenever is needed. So, these data support the use of the combination of pre-operative ChT and RT when tumor shrinkage is needed and/or critical structures are proximal or involved, in the aim to possibly preserve function. Addionally, as we previously have demonstrated, pre-operative ChT and RT is able to minimize the negative prognostic impact of R1 margins much more than post-operative RT [*Gronchi 2013*], so that, when a surgery with close margins is planned, the use of pre-operative RT is favoured.

Histological type should be factored when the combination of ChT and RT is offered, since the sensitivity to RT and ChT varies across histological types. Unfortunately, in the current analysis some histological types were poorly represented and data of activity could be detailed only for the most numerous histological types. In particular, in myxoid liposarcoma, a clinically and statistically significant difference of activity was seen between patients treated with pre-operative ChT/RT and patients receiving pre-operative ChT alone (25.6% and 3.7% partial responses, respectively). On the other hand, considering that in this subgroup of patients, in the ISG-STS 1001 study, trabectedin has shown non-inferior efficacy and a better tolerability profile in comparison to EI [*Gronchi 2024*] and that data on feasibility of concurrent trabectedin and RT have been provided [*Sanfilippo 2023*], the combination of pre-operative trabectedin and RT could be an alternative option for patients with localized high-risk myxoid liposarcoma.

Recently, the use of an immunotherapeutic agent (pembrolizumab), both in pre-operative setting (in addition to RT) and in post-operative setting, in grade 2 and 3 localized UPS and dedifferentiated or pleomorphic liposarcoma of the extremities resulted in a promising improvement of RFS in comparison to pre-operative RT alone and surgery [*Mowery 2024*]. In this scenario, it is reasonable to imagine that future trials on localized high-risk STS should investigate a strategy including either ChT and an immunotherapeutic approach. At the same time, as in other field of oncology, several trials have tested hypofractionated RT in STS in localized disease, providing data of acceptable local control and toxicity, besides the attractive advantage related to the shorter treatment duration [Guadagnolo 2022; Kao 2023; Cury 2024]. How to integrate hypofractionated RT and chemotherapy or immune check point inhibitors is left to be properly investigated.

In conclusion, concurrent pre-operative ChT with EI and RT was confirmed to be feasible in STS of extremities and trunk wall, achieving an increased number of partial responses. Considering that pre-operative RT is generally favoured over post-operative RT, we can affirm that whenever pre-operative RT would be selected in a high-risk population of STS patients, ChT can be added safely, with a view to preservation of function, quality of margins and surgical ease.

Figure and table legend

Table 1 Patient and tumor characteristics of the entire population of the current analysis, of the ChT/RT group and of the ChT group.

Table 2 Treatment received by the entire population of the current analysis, the ChT/RT group and the ChT group.

Table 3 Grade 3/4 haematological toxicities (3A), acute RT-related toxicities (3B), local post-operative complications (3C) of the entire population of the current analysis, of the ChT/RT group and of the ChT group.

Figure 1 Consort diagram of the population of the analysis.

Figure 2 Epirubicin dose-intensity (a), ifosfamide dose-intensity (b) and average relative dose intensity (c) in in ChT/RT group and in ChT group. ChT dose-intensity was calculated on the 285 patients who received surgery, excluding the 2 patients who were not treated with surgery or with no data about surgery.

Figure 3 Waterfall plot of dimensional changes during pre-operative treatment in the ChT/RT group (A) and in the ChT group (B).

Table 1

	All patients (N=287)		ChT/RT group (N=146)		ChT group (N=141)	
Age, yrs						
mean (SD)	50.9 (12.3)		50.6 (12.2)		51.2 (12.3)	
median (IQR)	52 (42 - 61)		51 (42 - 62)		53 (42 - 60)	
Sex						
female	102	35.5%	47	32.2%	55	39.0%
male	185	64.5%	99	67.8%	86	61.0%
PS						
0	211	73.5%	102	69.9%	109	77.3%
1	65	22.7%	33	22.6%	32	22.7%
missing	11	3.8%	11	7.5%	0	0
Tumor size, mm						
mean (SD)	118.8 (54)		128.2 (62.0)		109.0 (42.2)	
median (IQR)	110 (80 - 148)		120 (83 -164)		102 (80 - 130)	
Site						
thoracic wall	5	1.7%	2	1.4%	3	2.1%
abdominal wall	4	1.4%	2	1.4%	2	1.4%
paravertebral	5	1.7%	2	1.4%	3	2.1%
shoulder girdle	18	6.3%	11	7.5%	7	5.0%
upper limb	27	9.4%	11	7.5%	16	11.4%
pelvic girdle	23	8.0%	11	7.5%	12	8.5%
lower limb	205	71.5%	107	73.3%	98	69.5%
Histological Type						
high grade myxoid liposarcoma	74	25.8%	45	30.8%	29	20.6%
synovial sarcoma	38	13.2%	12	8.2%	26	18.4%
malignant peripheral nerve sheath tumor	10	3.5%	4	2.7%	6	4.3%
leiomyosarcoma	20	7.0%	9	6.2%	11	7.8%
undifferentiated pleomorphic sarcoma	72	25.1%	35	24.0%	37	26.2%
myxofibrosarcoma	41	14.3%	24	16.4%	17	12.1%
unclassified spindle cell	8	2.8%	3	2.1%	5	3.6%
pleomorphic liposarcoma	16	5.6%	8	5.5%	8	5.7%
pleomorphic rhabdomyosarcoma	7	2.4%	5	3.4%	2	1.4%
other	1	0.4%	1	0.7%	0	0.0%

Table 2

	All patients (N=287)		ChT/RT group (N=146)		ChT group (N=141)	
Surgery						
yes	285	99.3%	144	98.6%	141	100%
no	1*	0.3%	1	0.7%	0	0.0%
NA	1**	0.3%	1	0.7%	0	0.0%
Type of surgery						
conservative	278	96.9%	140	95.9%	138	97.9%
demolitive	7	2.4%	4	2.7%	3	2.1%
NA	2	0.7%	2	1.4%	0	0.0%
Margins						
R0	235	81.9%	119	81.5%	116	82.3%
R1	47	16.4%	24	16.4%	23	16.3%
R2	2	0.7%	0	0.0%	2	1.4%
missing or NA	3	1.0%	3	2.1%	0	0.0%
RT completation						
yes	275	95.8%	141	96.6%	134	95.0%
no	12	4.2%	5	3.4%	7	5.0%
RT dose						
median, Gy (IQR, Gy)	50 (50-50)		50 (50-50)		60 (54-64.8)	
ChT completation						
compl. per protocol	260	90.6%	127	87%	133	94.3%
compl. with >3 cycles	8	2.8%	7	4.8%	1	0.7%
ChT discontinued	19	6.6%	12	8.2%	7	5%
Reason for discontinuation						
toxicity	13	4.5%	8	5.5%	5	3.5%
consent withdrawn	2	0.7%	1	0.7%	1	0.7%
progression	4	1.4%	3	2%	1	0.7%
ChT reduction (>25%)***						
no	220	82.1%	104	77.6%	116	86.6%
yes	48	17.9%	30	22.4%	18	13.4%

* Patient progressed with distant relapse during pre-op ChT

** Patient lost to follow-up

*** The 19 patients who discontinued ChT were excluded

Table 3A

	All patients (N=287)		ChT/RT group (N=146)		ChT group (N=141)		p
Anemia							
G3/G4	54	18.8%	27	18.5%	27	19.1%	0.88
WBC decreased							
G3/G4	162	56.5%	84	57.5%	78	55.3%	0.65
Neutrophil count decreased							
G3/G4	188	65.5%	100	68.5%	88	62.4%	0.24
Neutrophil count decreased							
G3/G4	72	25.1%	40	27.4%	32	22.9%	0.38
Febril neutropenia							
G3/G4	76	26.5%	40	27.4%	36	25.5%	0.72

Table 3B

	All patients		ChT/RT group		ChT group		p
Skin toxicity (erythroderma, skin induration and ulceration)*							
any grade	158	87.3%	67	75.2%	91	98.9%	<.0001
G3/G4	10	5.5%	2	2.2%	8	8.7%	
Neurological toxicity (disesthesia, paresthesia, peripheral motor neuropathy)**							
any grade	25	12.1%	8	7.3%	17	17.2%	0.0294
G3/G4	0		0		0		
Vascular toxicity (lymphedema, phlebitis, thromboembolic event) **							
any grade	19	9.2%	6	9.2%	13	13.1%	0.0566
G3/G4	0		0		0		

* 106 patients with no data about skin toxicity were excluded

** 79 patients with no data about neurological and vascular toxicity were excluded

Table 3C

	All patients (N=285*)		ChT/RT group (N=144)		ChT group (N=141)		p
Wound dehiscence							
yes	18	6.3%	13	9.0%	5	3.6%	0.0572
Seroma, drain tube >15 days							
yes	19	6.7%	15	10.4%	4	2.8%	0.0103
Second intervention							
yes	12	4.2%	7	4.9%	5	3.6%	0.5805
Hospitalization >20 days							
yes	10	3.5%	6	4.2%	4	2.8%	0.7496

* 285 patients who received surgery

Figure 1

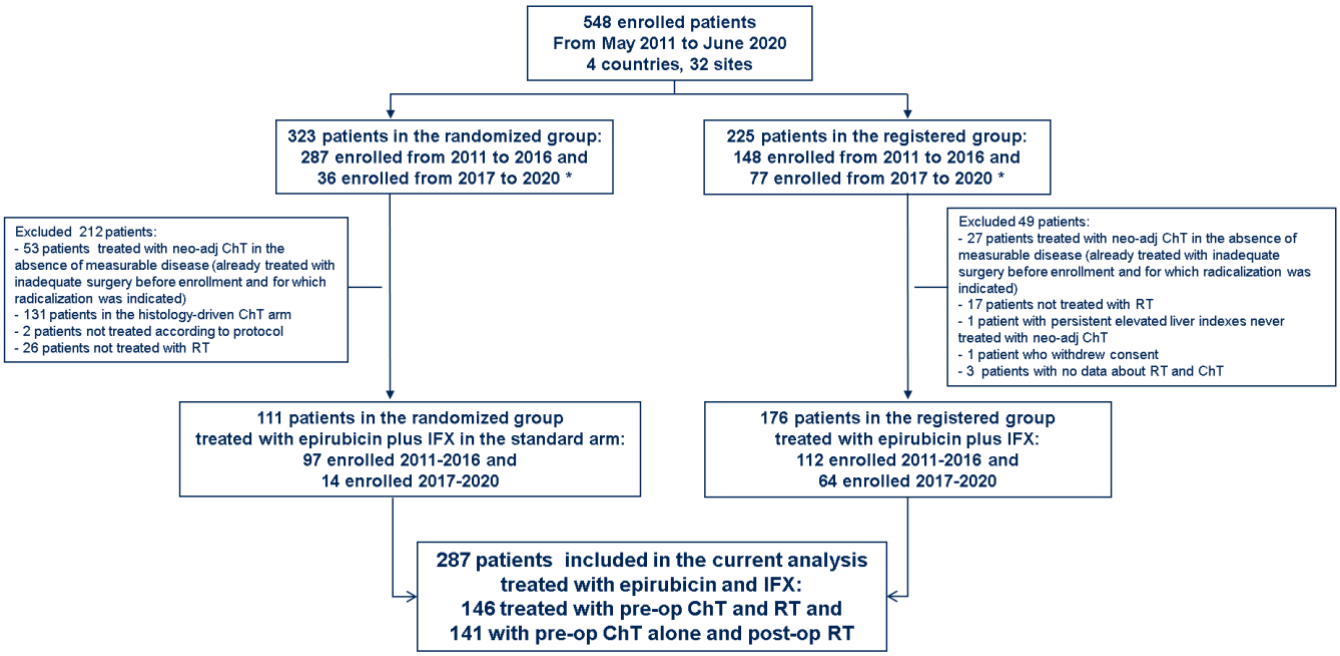

548 enrolled patients
From May 2011 to June 2020
4 countries, 32 sites
323 patients in the randomized group:
287 enrolled from 2011 to 2016 and
36 enrolled from 2017 to 2020 *
225 patients in the registered group:
148 enrolled from 2011 to 2016 and
77 enrolled from 2017 to 2020 *
Excluded 212 patients:
- 53 patients treated with neo-adj ChT in the absence of measurable disease (already treated with inadequate surgery before enrollment and for which radicalization was indicated)
- 131 patients in the histology-driven ChT arm
- 2 patients not treated according to protocol
- 26 patients not treated with RT
Excluded 49 patients:
- 27 patients treated with neo-adj ChT in the absence of measurable disease (already treated with inadequate surgery before enrollment and for which radicalization was indicated)
- 17 patients not treated with RT
- 1 patient with persistent elevated liver indexes never treated with neo-adj ChT
- 1 patient who withdrew consent
- 3 patients with no data about RT and ChT
111 patients in the randomized group
treated with epirubicin plus IFX in the standard arm:
97 enrolled 2011-2016 and
14 enrolled 2017-2020
176 patients in the registered group
treated with epirubicin plus IFX:
112 enrolled 2011-2016 and
64 enrolled 2017-2020
287 patients included in the current analysis
treated with epirubicin and IFX:
146 treated with pre-op ChT and RT and
141 with pre-op ChT alone and post-op RT

Figure 2

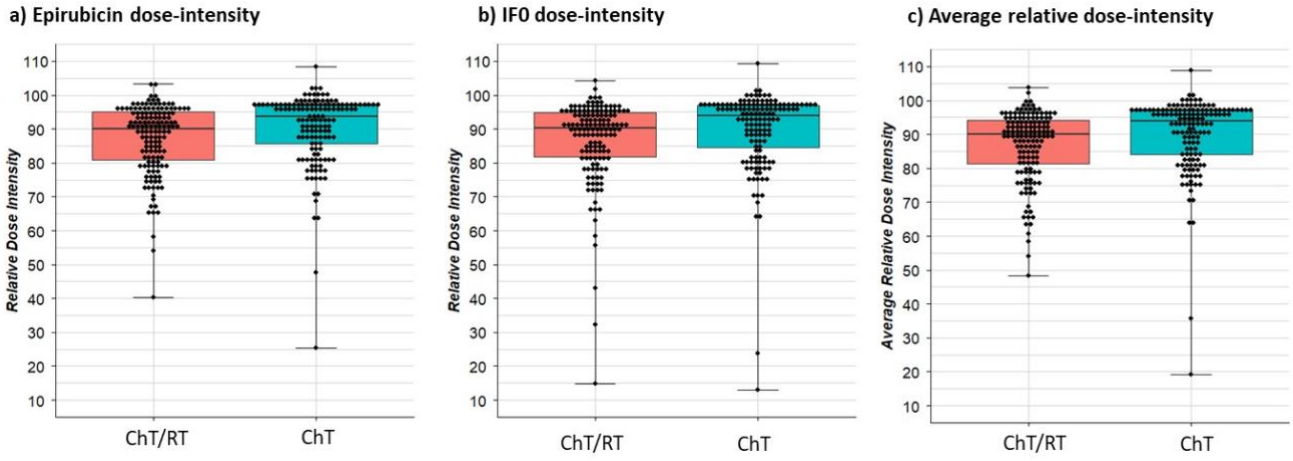
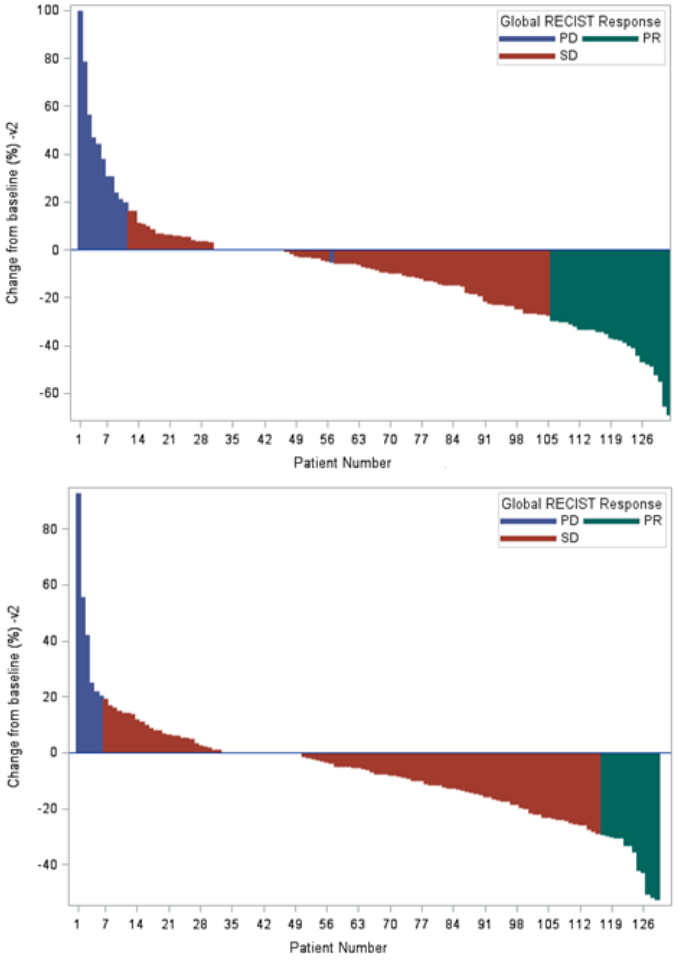

a) Epirubicin dose-intensity
b) IF0 dose-intensity
c) Average relative dose-intensity
Relative Dose Intensity
Average Relative Dose Intensity
110
100
90
80
70
60
50
40
30
20
10
ChT/RT
ChT

Figure 3.


Global RECIST Response
PD
PR
SD
Change from baseline (%) -v2
100
80
60
40
20
0
-20
-40
-60
1 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112 119 126
Patient Number
Global RECIST Response
PD
PR
SD
Change from baseline (%) -v2
80
60
40
20
0
-20
-40
1 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112 119 126
Patient Number

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