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Original Research

The role of perioperative chemotherapy in primary high-grade extremity soft tissue sarcoma: a risk-stratified analysis using PERSARC



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Abstract Objective: The aim of the study is to assess the effect of perioperative chemotherapy (CTX) in patients with grade II-III extremity soft tissue sarcoma (eSTS) on overall survival (OS) and evaluate whether the PERSARC prediction tool could identify patients with eSTS more likely to benefit from CTX.

Methods: Patients (18–70 years) with primary high-grade eSTS surgically treated with curative intent were included in the retrospective cohort study. The effect of any perioperative CTX and anthracycline + ifosfamide (AI)-based CTX on OS was investigated in three PERSARC-risk groups (high/intermediate/low). The PERSARC-risk groups were defined by the 33% and 66% quantile of the predicted 5-year OS of the study population equal to a 5-year OS of 65.8% and 79.8%, respectively. The effect of CTX on OS was investigated with

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weighted Kaplan–Meier curves and multivariable Cox models with an interaction between risk group and CTX.

Results: This study included 5683 patients. The weighted Kaplan–Meier curves did not demonstrate a beneficial effect of any CTX and AI-based CTX on OS in the overall population. However, in the high PERSARC-risk group the 5-year OS of AI-based CTX was significantly better than no CTX (69.8% vs 59.0%, respectively, $p = 0.004$) (HR 0.66, 95% CI 0.53–0.83).

Conclusions: This study demonstrated a beneficial effect of AI-based CTX on OS in a selected group of high-risk patients with an absolute survival benefit of 11% as stratified by the PERSARC prediction tool. However, no beneficial effect of CTX on OS was found in the overall population of patients with primary high-grade eSTS younger than 70 years. © 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Soft tissue sarcomas (STSs) are rare tumours of mesenchymal origin with various histologic and clinical features, with an estimated incidence of 4.7 per 100,000 persons in Northern Europe [1]. The mainstay of treatment for patients with primary extremity STS (eSTS) is surgery, often accompanied by radiotherapy (RTX) [2]. However, approximately 30% of the patients with eSTS will eventually develop distant metastasis within 5 years [3]. Therefore, perioperative chemotherapy (CTX) is increasingly considered in patients with high-risk eSTS worldwide in order to prevent future metastatic disease and improve survival rates.

The rarity and heterogeneity of eSTS, however, poses significant difficulties in demonstrating the beneficial effect of perioperative CTX in eSTS patients, and especially to identify patients that are more likely to benefit from CTX. Despite the efforts of several studies, the level of evidence for perioperative CTX remains debated. Post-hoc analyses within recent trials showed a beneficial effect of adjuvant CTX with anthracycline and ifosfamide (AI) in patients with a low predicted overall survival (OS) suggesting that beneficial outcomes of perioperative CTX are particularly limited to a selected group of patients with high-risk [4–7]. Patients with high-risk are defined as patients with a higher grade and worse predicted survival. Consequently, greater improvement in survival and thus potentially a higher efficacy of CTX is to be expected in the high-risk group, when compared to patients with a more favourable risk profile [4,8]. Therefore, we hypothesised that the effect of perioperative CTX differs within different subgroups of baseline risk.

The primary aim of this study was to assess the effect of all CTX regimens in general and of AI-based CTX specifically on OS compared to local treatment alone, in a large cohort of patients with primary high-grade eSTS (FNCLCC grade II and III), who were surgically treated

with curative intent. The secondary aim was to identify whether the potential benefit of perioperative CTX varies between patients with low-, intermediate- and high-risk, as defined by the PERSARC prediction tool, an externally validated prediction tool for primary high-grade eSTS [9–11].

2. Methods

2.1. Study design

The effect of CTX was investigated in a retrospective cohort of patients with high-grade eSTS, in accordance with the PATH-statement [12]. The PATH-statement outlines a set of principles and criteria for predictive approaches to heterogeneity of treatment effect analyses. The study cohort contained data from multiple specialised sarcoma centres (Appendix A1).

Data were collected between 1st January 2000 and 31st December 2016, except for the data from the EORTC trial 62931 which were collected between February 1995 and December 2003 [13]. Ethical approval was obtained by the institutional review board prior to the study (G20.006).

The primary outcome was OS defined as the time from surgery until death of any cause or last recorded follow-up.

2.2. Participants

Adults (18–70 years) with primary high-grade (FNCLCC grade II and III [14]) eSTS surgically treated with curative intent with correctly registered time-to-events were included in this study. Patients were excluded if they had a Kaposi's sarcoma or alveolar rhabdomyosarcoma or received isolated limb perfusion as perioperative treatment. Patients with spindle cell sarcoma were excluded in our analyses as they were underrepresented in the perioperative AI-based CTX-group (1 out of 92 patients). In addition, patients older

than 70 years were excluded in this analysis, as older age is often a contra-indication for perioperative chemotherapy [15].

2.3. Variables

The primary variable of interest was CTX (yes/no). Neoadjuvant and adjuvant CTX were grouped together as one category. All CTX regimens were included, independent of specific drugs, the number of cycles or dose. The other variables considered in this analysis were age at definitive surgery (years), size (cm), depth (deep/superficial), surgical margins (R0/R1-R2), RTX (neoadjuvant/adjuvant/no RTX) and histological subtype. A detailed description of the definitions of each variable could be found in [Appendix A1](#).

Another variable considered was the 5-year predicted OS which was predicted using the PERSARC prediction tool [9]. The 33% and 66% quantiles of the predicted probabilities were used to create three PERSARC-risk groups; the 5-year predicted OS <33% quantile was high PERSARC-risk, 33–66% quantile was intermediate PERSARC-risk and $\geq 66\%$ quantile was low PERSARC-risk. PERSARC includes the variables: age, size, depth, histology, surgical margin and RTX.

2.4. Statistical analysis

Baseline characteristics were described with proportions for categorical variables and means with standard deviations or medians with interquartile ranges for normally distributed and non-normally distributed continuous variables, respectively. Differences in categorical variables were tested with the Chi-square test or Fisher's exact test. Differences in continuous variables were tested with the Student's t-test.

The effect of any CTX and AI-based CTX was investigated in the overall population and in the three risk groups (high/intermediate/low), based on the PERSARC prediction tool.

Median follow-up was assessed with the reverse Kaplan–Meier method [16]. The effect of CTX in the PERSARC-risk groups was investigated with crude Kaplan–Meier curves (cKMs), weighted Kaplan–Meier curves (wKMs) and a multivariable Cox proportional hazards model.

wKMs for OS were used to compare patients who received CTX and those who did not [17]. Weights were computed using the Inverse Probability of Treatment Weighting approach. Within each PERSARC-risk group, the distribution of covariates was modelled with a logistic regression model with CTX (yes/no) as the outcome variable ([Appendix A3 table 1](#), [A5 table 1](#)). The included variables in this model were age, tumour

size, depth, histology, grade, surgical margin and RTX. Based on this model, weights were computed for each patient to create a weighted data set ([Appendix A3 Fig. 1](#), [A5 Fig. 1](#)). Differences in OS were evaluated with the log-rank test.

Multivariable Cox proportional hazards models were used to estimate the effect of CTX on OS adjusted for age, tumour size, depth, histology, grade, surgical margin and RTX. An interaction term between CTX (yes/no) and PERSARC-risk group (high/intermediate/low) was included in the model to investigate the effect of CTX per risk group.

Multiple imputation for missing covariates was applied using the 'mice' package in R (version 4.0.3) with 20 imputations. The results were pooled using Rubin's rule [18].

All analyses were performed in the R-software environment and a p-value of less than 0.05 was considered significant [19].

3. Results

This study included 5683 patients with primary high-grade eSTS. The median follow-up was 5.21 years (95% CI 5.11–5.31). The mean age was 52 years. The PERSARC prediction tool was used to predict the 5-year OS probability from baseline for each patient. The predicted 5-year OS ranged between 11.8% and 96.4% with a median of 73.4%. The PERSARC-risk groups were defined by the 33% and 66% quantile of these predicted 5-year OS probabilities equal to a 5-year OS of 65.8% and 79.8%, respectively ([Appendix A2](#), [Fig. 1](#)). Twenty-nine percent of the overall population ($n = 1635$) received perioperative CTX. In the high, intermediate and low PERSARC-risk group, 38.7% ($n = 735$ out of 1897), 31.1% ($n = 590$ out of 1897) and 16.4% ($n = 310$ out of 1889) received perioperative CTX, respectively. [Table 1](#) provides an overview of the patient characteristics in the no CTX and CTX group. [Appendix A2 table 1](#) provides an overview of the patient characteristics in the overall population and per PERSARC-risk group. Patients who received perioperative CTX were younger, had larger and more grade III tumours ([Table 1](#), [appendix A3 table 1](#)).

3.1. All chemotherapy regimens

3.1.1. Overall survival

[Figs. 1 and 2](#) display the cKM and wKM stratified by CTX for the overall population and for the PERSARC-risk groups, respectively. There was no significant difference in the survival curve between patients who received CTX and who did not receive CTX in the overall population ($p = 0.663$). However, a significant difference in OS in favour of CTX was found in the high PERSARC-risk group with a p-value of 0.018 ([Fig. 2](#)).

Table 1
Baseline characteristics in patients with and without (AI-based) CTX.

	Overall (N = 5683)	No CTX (N = 4047)	CTX (all regimens) (N = 1635)	AI-based CTX (N = 1036)	No versus all CTX P ^b	No versus AI-based CTX P ^b
Baseline predicted 5-year OS (%)					<0.001	<0.001
Mean (SD)	70.7 (15.3)	72.4 (15.2)	66.3 (14.4)	67.5 (13.9)		
Median (IQR)	73.4 (61.2–82.9)	76.0 (63.7–84.1)	67.9 (57.0–77.4)	68.9 (58.7–78.2)		
Age at surgery (years)					<0.001	<0.001
Mean (SD)	51.7 (13.6)	52.9 (13.3)	48.6 (13.9)	47.9 (13.7)		
Median (IQR)	54 (42–63)	56 (44–64)	50 (38–61)	49 (38–60)		
Size (cm)					<0.001	<0.001
Mean (SD)	8.60 (5.60)	8.14 (5.63)	9.74 (5.36)	9.47 (5.41)		
Median (IQR)	7.0 (4.5–11.0)	6.7 (4.0–10.5)	9.0 (6.0–12.0)	8.0 (5.7–12.0)		
Missing	298 (5.2%)	229 (5.7%)	69 (4.2%)	48 (4.6%)		
Depth					<0.001	<0.001
Deep	3902 (68.7%)	2605 (64.4%)	1297 (79.3%)	899 (86.8%)		
Superficial	1476 (26.0%)	1245 (30.8%)	230 (14.1%)	135 (13.0%)		
Missing	305 (5.4%)	197 (4.9%)	108 (6.6%)	2 (0.2%)		
Histological subtype					<0.001	<0.001
LMS	589 (10.4%)	426 (10.5%)	163 (10.0%)	115 (11.1%)		
LPS	1180 (20.8%)	850 (21.0%)	330 (20.2%)	243 (23.5%)		
MFS	786 (13.8%)	646 (16.0%)	140 (8.6%)	52 (5.0%)		
UPS and NOS	1515 (26.7%)	1073 (26.5%)	441 (27.0%)	265 (25.6%)		
MPNST	368 (6.5%)	275 (6.8%)	93 (5.7%)	49 (4.7%)		
SS	731 (12.9%)	393 (9.7%)	338 (20.7%)	237 (22.9%)		
Other	512 (9.0%)	383 (9.5%)	129 (7.9%)	75 (7.2%)		
Missing	2 (0.0%)	1 (0.0%)	1 (0.1%)	0 (0%)		
Grade					<0.001 ^a	<0.001 ^a
2	847 (14.9%)	771 (19.1%)	75 (4.6%)	49 (4.7%)		
3	2033 (35.8%)	1618 (40.0%)	415 (25.4%)	78 (7.5%)		
High-grade not further specified	2803 (49.3%)	1658 (41.0%)	1145 (70.0%)	909 (87.7%)		
Margin					<0.001	<0.001
R0	5066 (89.1%)	3545 (87.6%)	1520 (93.0%)	999 (96.4%)		
R1-R2	457 (8.0%)	382 (9.4%)	75 (4.6%)	29 (2.8%)		
Missing	160 (2.8%)	120 (3.0%)	40 (2.4%)	8 (0.8%)		
Radiotherapy					<0.001	<0.001
No radiotherapy	3026 (53.2%)	2024 (50.0%)	1002 (61.3%)	709 (68.4%)		
adjuvant	1674 (29.5%)	1214 (30.0%)	460 (28.1%)	234 (22.6%)		
neoadjuvant	923 (16.2%)	772 (19.1%)	151 (9.2%)	91 (8.8%)		
Neo- and adjuvant	21 (0.4%)	17 (0.4%)	4 (0.2%)	2 (0.2%)		
Missing	39 (0.7%)	20 (0.5%)	18 (1.1%)	0 (0%)		

OS: overall survival, SD: standard deviation, IQR: interquartile range, LMS: leiomyosarcoma, LPS: liposarcoma, MFS: myxofibrosarcoma, UPS: undifferentiated pleomorphic sarcoma, NOS: (pleomorphic) soft tissue sarcomas not-otherwise-specified, MPNST: malignant peripheral nerve sheath tumour, SS: synovial sarcoma, CTX: chemotherapy.

^a Based on the multiply imputed dataset.

^b Global P value for difference in distribution between CTX and no CTX-group.

The 5-year OS for the CTX-group was 75.8% versus 77.3% for the no CTX-group ($p = 0.405$). In the low PERSARC-risk group, the 5-year OS for the CTX-group and no CTX-group was 88.0% and 95.0% ($p = 0.055$); in the intermediate PERSARC-risk group, the 5-year OS was 81.9% and 78.2% ($p = 0.138$), and in the high PERSARC-risk group, the 5-year OS was 61.0% and 58.4% ($p = 0.375$), respectively (Table 2).

After adjustment for age, size, depth, histology, grade, margin and RTX, no difference in CTX effect on OS in the low and intermediate PERSARC-risk groups could be found in the multivariable cox model (HR 1.27

(95% CI 0.878–1.84) and 0.803 (95%CI 0.631–1.02), respectively). The HR in the high-risk group was 0.822 (95%CI 0.697–0.969).

3.2. AI-based chemotherapy regimen only

Of the 1635 patients who received perioperative CTX in this series, details about CTX regimen were available for 1259 patients of which 82.3% ($n = 1036$) received AI-based CTX (Table 1). Appendix A4 table 1 provide an overview of the patient characteristics per PERSARC-risk group.

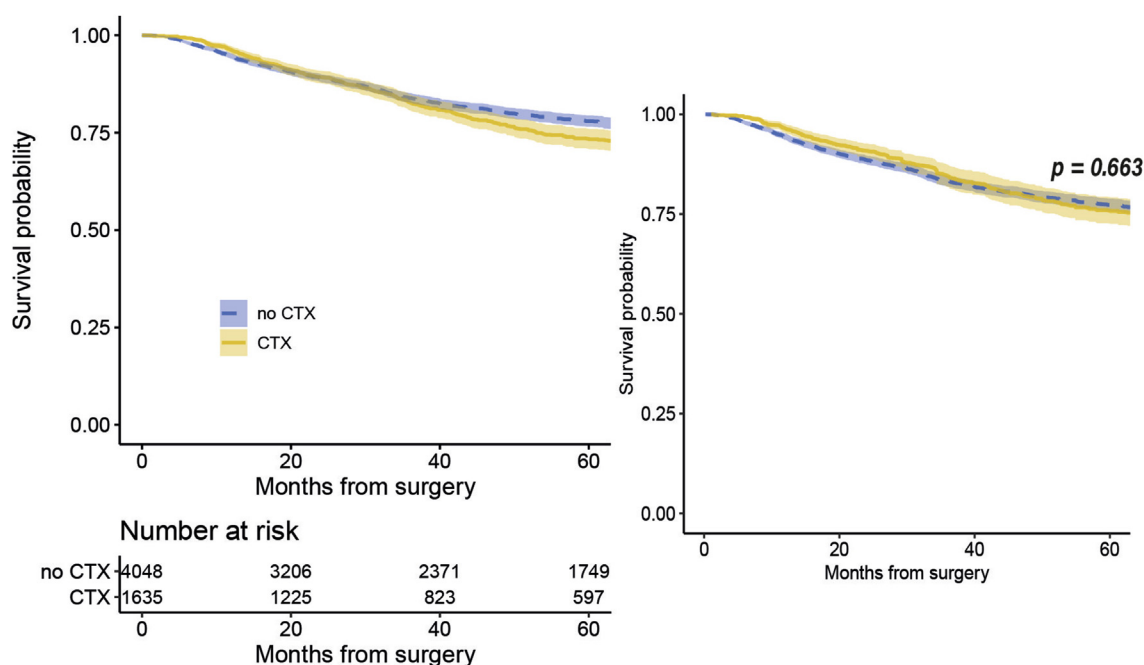


Fig. 1. Crude (left) and weighted (right) Kaplan–Meier of OS stratified by CTX in the overall population. CTX, perioperative chemotherapy; OS, overall survival.

3.2.1. OS in patients who received AI-based CTX

Figs. 3 and 4 display the cKM and wKM stratified by AI-based CTX for the overall population and for the PERSARC-risk groups, respectively. Patients who received AI-based CTX seemed to have a better OS than patients who did not receive CTX but this was not statistically significant ($p = 0.060$) (Fig. 3). A significant difference in OS in favour of AI-based CTX in the high PERSARC-risk group was found with a p -value of <0.001 . No difference in OS was found in the low and intermediate PERSARC-risk groups ($p = 0.422$ and $p = 0.181$, respectively) (Fig. 4).

The 5-year OS for the AI-based CTX-group was 82.2% versus 77.6% for the no CTX-group ($p = 0.014$). In the high PERSARC-risk group, the absolute risk difference in 5-year OS between the AI-based CTX-group and no CTX-group was 10.7 percentage points in favour of AI-based CTX ($p = 0.004$). There was no significant difference in 5-year OS in the low and intermediate PERSARC-risk group (Table 2).

After adjustment for the baseline characteristics, the HR of AI-based CTX on OS was 0.661 (95%CI 0.527–0.828) in the high PERSARC-risk group, 0.813 (95%CI 0.608–1.09) in the intermediate PERSARC-risk group, and 1.00 (95%CI 0.616–1.62) in the low PERSARC-risk group.

4. Discussion

The present study exploring the role of perioperative CTX in primary high-grade eSTS did not demonstrate a

beneficial effect of any CTX on OS in the overall population. However, perioperative AI-based CTX led to improved OS for patients with a high PERSARC-risk profile, with a 5-year absolute risk reduction in mortality of 11%.

To our knowledge, this is the largest multicentre cohort study to date examining the effect of perioperative CTX in patients with primary high-grade eSTS. The strength of this study is that we only included high-grade eSTS and used a validated multivariable risk-based model to assess heterogeneity of treatment effect instead of conventional ‘one-variable-at-the-time’-subgroup analyses. This allows us to reduce the risk of false-positives due to multiple comparisons and to better inform individual treatment decisions since it accounts for the fact that patients have multiple characteristics that vary simultaneously [12].

Despite several published randomised and non-randomised studies, the role of perioperative CTX for eSTS is still subject of discussion [4,13,20–29]. In 2008, a meta-analysis of 18 doxorubicin-based trials showed an absolute risk reduction of 6% on OS in patients with STS (at what time point was not reported) [27]. To date, five randomised trials compared the effect of perioperative AI-based CTX versus no CTX in patients with STS [13, 20–23]. The 5-year OS in these studies ranged between 65 and 72% for the CTX arm, and between 47 and 69% for the no CTX arm. Furthermore, other more recent trials including an AI-based CTX arm, showed 5-year survival rates between 61 and 76% for the CTX group [5, 30–32]. In our cohort, the 5-year OS was 82% in the AI-based

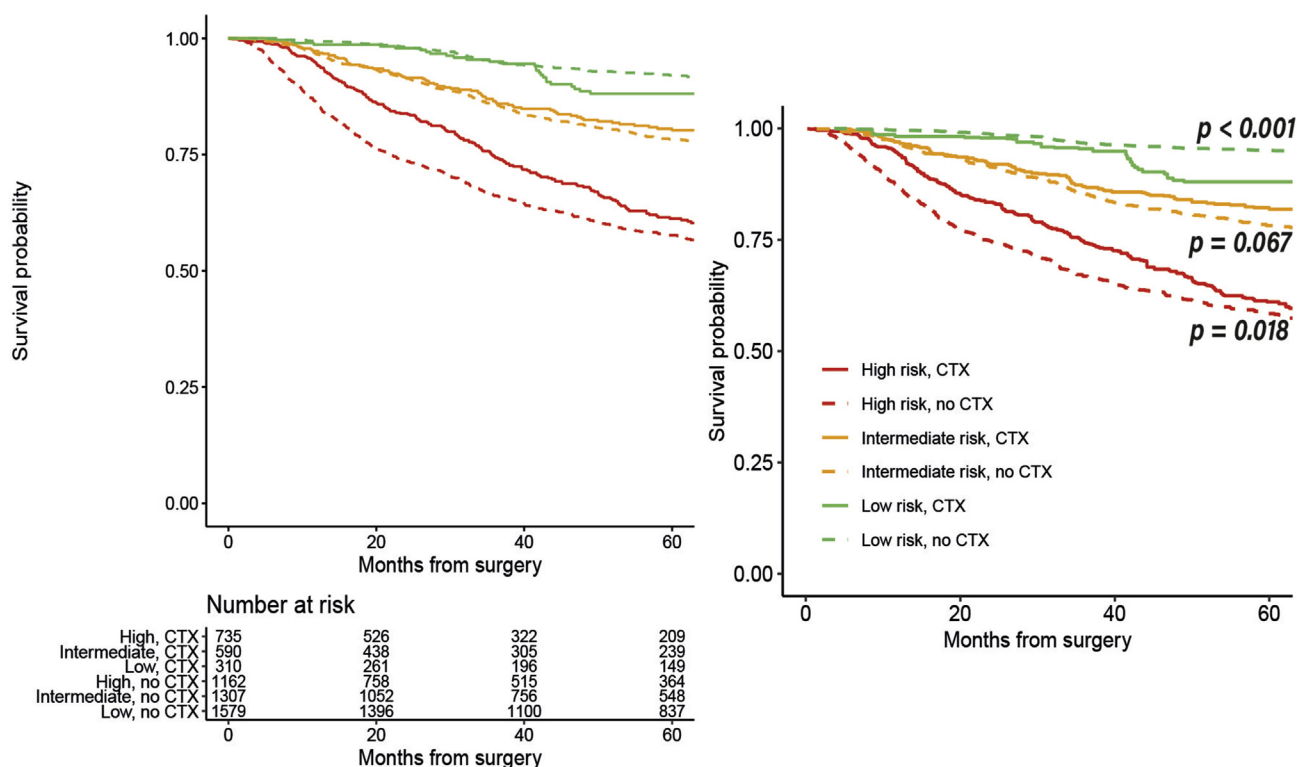


Fig. 2. Crude (left) and weighted (right) Kaplan–Meier of OS for patients with high, intermediate and low PERSARC-risk stratified by CTX administration. OS, overall survival.

CTX group and 78% in the no CTX group. The higher 5-year OS in our cohort might be explained by an on average smaller tumour size compared with the abovementioned studies, as most studies included selection criteria for size [5, 30, 31]. Furthermore, most trials are relatively old and started patient accrual before 2000 [13, 20–23, 31]. These patients might have had an in general lower life expectancy than in our cohort.

The largest trial to date comparing perioperative AI-based CTX with local treatment did not find an additional value of CTX in patients with STS [13]. However, in this trial, 6% of the patients had a low grade tumour and 24% had a tumour smaller than 5 cm [13], which in general are

considered to be low-risk tumours [2, 33]. A recent post-hoc subgroup analysis of this trial showed a beneficial effect (HR 0.50) of AI-based CTX in a small subgroup of patients with a predicted 10-year OS of $\leq 60\%$ based on the prognostic nomogram Sarculator [4]. In addition, another study found a 5-year OS of 66% in a subgroup of patients who received AI-based CTX with a predicted 10-year OS of $\leq 60\%$ based on the Sarculator [6]. These findings are comparable with our results, in which we found a HR of 0.66 for AI-based CTX with a 5-year OS of 70% in the AI-based CTX group and 59% in the no CTX group in the high PERSARC-risk population with a predicted 5-year OS of $\leq 66\%$.

Table 2

5-year OS for the overall population stratified by the PERSARC-risk group and CTX.

	5-year OS (95% CI)		Absolute risk difference (95% CI)	P
	All CTX	No CTX ^a		
Overall population	75.8 (72.5–79.2)	77.3 (75.8–78.9)	–1.52 (–5.10–2.06)	0.405
High risk	61.0 (56.3–66.2)	58.4 (55.1–62.0)	2.63 (–3.18–8.44)	0.375
Intermediate risk	81.9 (77.8–86.1)	78.2 (75.5–81.0)	3.65 (–1.17–8.46)	0.138
Low risk	88.0 (82.0–94.4)	95.0 (91.1–99.2)	–7.03 (–14.2–0.144)	0.055
	AI-based CTX	No CTX ^b		P
Overall population	82.2 (78.9–85.8)	77.6 (76.1–79.1)	4.65 (0.935–8.37)	0.014
High risk	69.8 (63.3–76.9)	59.0 (55.7–62.5)	10.7 (3.48–18.0)	0.004
Intermediate risk	82.7 (77.9–87.8)	78.6 (76.0–81.2)	4.12 (–1.33–9.58)	0.139
Low risk	94.0 (89.7–98.6)	92.1 (90.6–93.7)	1.88 (–2.70–6.46)	0.421

^a Based on the wKM of all CTX regimens.

^b Based on the wKM of AI-based CTX regimens only.

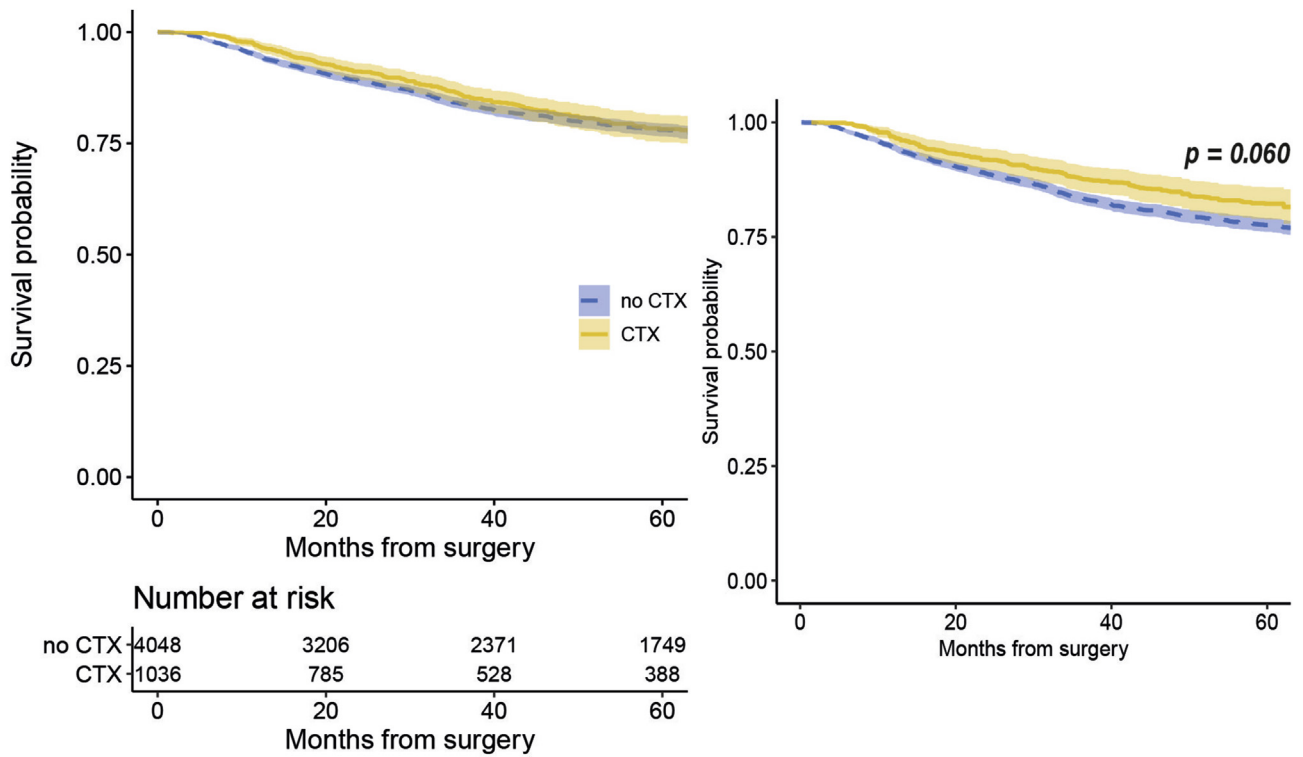


Fig. 3. Crude (left) and weighted (right) Kaplan–Meier of OS stratified by AI-based CTX in the overall population. AI, anthracycline + ifosfamide; CTX, perioperative chemotherapy; OS, overall survival.

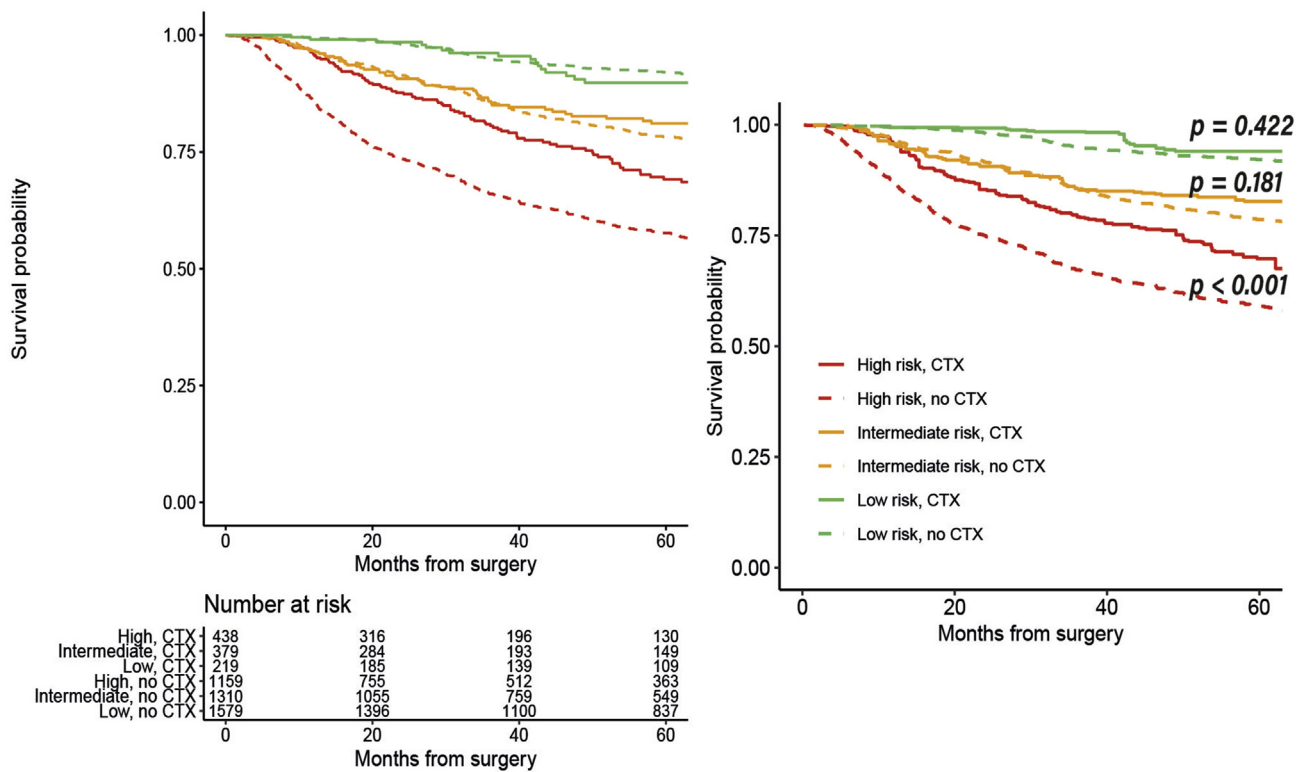


Fig. 4. Crude (left) and weighted (right) Kaplan–Meier of OS stratified by AI-based CTX administration and PERSARC-risk group. AI, anthracycline + ifosfamide; CTX, perioperative chemotherapy; OS, overall survival.

This study did not find a beneficial effect of (AI-based) CTX on OS in patients with low PERSARC-risk eSTS. These results are in line with previous studies that suggest that perioperative CTX should only be offered in a selected group of patients with high-risk, as well as clinical guidelines that state that CTX is not standard of care but could be considered in patients with high-risk [2, 4, 24, 26, 33–35]. However, accurate identification of this high-risk subgroup remains unclear. Some studies suggested that patients with high-grade, large eSTS (≥ 8 or 10 cm) should receive CTX [24, 26, 34, 35], while other studies suggested that patients with a 10-year predicted OS $< 60\%$ should be selected [4, 6]. Our study showed that patients with a predicted 5-year OS of $< 66\%$ benefit of perioperative AI-based CTX. Although, this study showed that the risk stratification with PERSARC might be useful for the identification of patients who benefit from perioperative AI-based CTX; with this study design, we were unable to identify the optimal threshold when AI-based CTX is beneficial. In addition, this threshold could be varying across histological subtypes as some subtypes are more chemo sensitive than others. However, due to limited power, we were unable to stratify our analyses for histological subtype.

In this study, we identified a subgroup of patients with high PERSARC-risk who benefit from AI-based CTX based on the PERSARC prediction tool. This prediction tool includes clinical parameters only and has an overall good discriminative ability (C-index: 0.68) [9]. However, it might be that the identification of patients with high-risk based on clinical parameters only is less adequate and that the prediction of CTX response might be improved by biological factors [36, 37]. A promising biomarker is the gene expression signature CINSARC, which showed to be a strong predictor for metastatic disease [36, 38]. The potential of this gene expression signature to identify patients with high-risk who may benefit from CTX will be evaluated in future trials [39].

This study has some weaknesses inherent to its retrospective and observational design. We acknowledge that there is a confounding by indication bias in all cohort studies in which the effectiveness of a treatment is assessed. Despite our effort to account for the most important confounders using weights (Inverse Probability of Treatment Weighting), the difference in OS between AI-based CTX and no CTX might also (partially) be explained by residual confounding due to unmeasured or not-fully-modelled explanatory covariates such as performance score. In addition, this study lacked the ability to capture additional relevant information about CTX dose, number of cycles, motivation for chemotherapy administration and toxicity. Details about CTX regimen were available for 1259 out of 1635 patients of which 82% received AI-based CTX. Although these results imply that the standard practice of AI-based CTX was mainly used, we were unable to

account for differences in CTX administration. Therefore, we performed a subgroup analysis including AI-based CTX only, excluding a considerable part of the patients of whom the CTX regimen was unknown. Furthermore, this study included EORTC data in which patients received 50 mg/m² doxorubicin and 5 g/m² ifosfamide, which are both relatively low doses compared with the current most commonly used dose of 75 mg/m² doxorubicin and 9–10 g/m² ifosfamide [40]. Furthermore, in this study, patients older than 70 years were excluded, as these patients rarely receive CTX. Therefore, the conclusions of this study may not be extrapolated to this age group.

Moreover, this study only included patients who were surgically treated. The starting point of this study was the date of surgery rather than date of first treatment. This means that patients who received neoadjuvant CTX but did not receive surgery because of disease progression or death were excluded. The consequent exclusion of patients failing to neoadjuvant CTX might have biased the results in favour of CTX. On the other hand, in patients who received neoadjuvant CTX (14.7% in this series), surgery is usually delayed with ± 3 months because of the neoadjuvant chemotherapy. Therefore, patients who received neoadjuvant CTX with surgery had a delay of ± 3 months before they received surgery compared to patients who received surgery alone. This might have resulted in an underestimation of the survival within the CTX group compared to the no CTX group.

To conclude, in a selected group of patients with a high-risk eSTS profile (predicted 5-year OS $\leq 66\%$) based on the PERSARC prediction tool, perioperative AI-based CTX has a beneficial effect on OS with an absolute 5-year survival benefit of 11%. In concordance with the literature, we did not find a beneficial effect of all type CTX in the overall population of primary high-grade eSTS. Therefore, perioperative AI-based CTX should only be considered in patients predicted with high-risk eSTS. Given the retrospective nature of this study, the findings should be independently, preferably prospectively, validated in a harm-benefit analysis.

Author contributions

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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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.2022.01.013>.

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