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Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas
An exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)

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ABSTRACT

Background: Adult patients with advanced soft tissue sarcomas (STS) are generally treated similarly, regardless of great differences between STS subtypes, disease presentation and patients' characteristics. As ifosfamide is frequently applied in first line systemic therapy, we aimed to establish prognostic and predictive factors for outcome to ifosfamide-based therapy.

Methods: A retrospective, exploratory analysis was performed on data from 1337 advanced STS patients who received first-line ifosfamide-containing chemotherapy. For predictive factor analysis, 660 patients treated with doxorubicin monotherapy served as comparators.

Results: Independent favourable prognostic factors for overall survival (OS) were good performance status, female gender, low histological grade, extremity primary tumour site and locally advanced disease; for progression-free survival (PFS), the combination of doxorubicin and ifosfamide, locally advanced disease, and tumour entity with a lower risk to progress for synovial sarcoma patients compared to leiomyosarcoma. For response, independent favourable prognostic factors were doxorubicin combined with ifosfamide, higher histological grade, and histology with synovial sarcoma patients having the highest chance to respond. Predictive factor analysis showed that compared to doxorubicin monotherapy, patients who benefited less from ifosfamide-based therapies were leiomyosarcoma patients in terms of OS, and patients with liposarcoma for response. No predictive factors were found for PFS.

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Conclusion: In this study, we established an independent set of prognostic and predictive factors for outcome to ifosfamide-based chemotherapy in advanced STS patients. This study provides important information for the interpretation and design of clinical trials for specific STS entities and may contribute to further treatment individualisation of advanced STS patients.

1. Introduction

Soft tissue sarcomas (STS) form a rare group of tumours comprising over 40 histological entities differing in pathogenesis, clinical behaviour and sensitivity to systemic agents.[1–4] Despite this, together with differences in disease presentation and patients' characteristics, adult patients with advanced non-gastrointestinal stromal tumours (GIST) STS are in general treated similarly. Palliative chemotherapy can be considered for patients with advanced disease, but until now, only a few agents with consistent anti-tumour activity have been identified. Of these, doxorubicin is regarded first line standard therapy.[5]

Another drug with anti-tumour activity is ifosfamide. In phase II trials, ifosfamide produced outcomes comparable to those achieved by doxorubicin.[6] Moreover, a recent phase III trial comparing two different schedules of ifosfamide to doxorubicin was prematurely stopped as an interim analysis revealed that no statistical differences between the three arms would be shown.[7] Apart from its application as monotherapy, ifosfamide is frequently part of combination regimens, in particular with doxorubicin, although evidence is lacking that such combinations yield an overall survival benefit over monotherapy.[8]

Despite its frequent use in STS patients and in contrast to doxorubicin-containing regimens,[9] data on prognostic and predictive factors for outcome to ifosfamide-containing regimens are not available from large series. Identification of such factors is essential for patient management and clinical trial design, in particular for STS given its heterogeneity. In this study, an exploratory, retrospective analysis for prognostic and predictive factors for outcome to ifosfamide-containing treatment in first-line was performed on advanced STS patients treated in prospective trials of the European Organisation for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) aiming to establish independent prognostic and predictive factors for best overall response (RR), progression-free survival (PFS) and overall survival (OS).

2. Patients and methods

2.1. Patients

Patients were treated in one of ten prospective EORTC-STBSG trials that included a treatment arm with ifosfamide, doxorubicin, or the combination (Table 1).[7,10–18] Of 2112 patients captured in our data-set, 115 patients who received prior (neo)-adjuvant chemotherapy were excluded. Details on eligibility criteria, treatment regimens and outcomes have been published.[7,10–18]

2.2. End-points

The end-points of this analysis were RR, PFS and OS. Responses were defined according to the World Health Organisation (WHO) criteria. Patients with a complete or partial response were considered 'responders', with stable or progressive disease were 'non-responders'. PFS was the time elapsing from study registration to first progression or death, whichever occurred first. OS was the time between the study registration and reported date of death. Patients alive at the last follow-up were censored.

2.3. Study population

In the studies exploring ifosfamide-containing regimens, either ifosfamide as a single agent or combined with doxorubicin, several different doses of ifosfamide and doxorubicin were used. In order to obtain adequate power to detect clinically relevant associations, it was decided to aggregate all patients receiving ifosfamide-containing regimens and to analyse the type of ifosfamide-containing regimen (monotherapy versus the combination with doxorubicin) and ifosfamide dose ($<$ and $\geqslant 9$ g/m^2 per cycle) as co-variables.

For identification of prognostic factors, 1337 patients treated with ifosfamide-containing chemotherapy were studied. Data lacked on 169, 18 and 18 patients, for RR, PFS and OS, respectively.

For the predictive factor analysis, 660 who received doxorubicin monotherapy served as comparators of whom data on 76, 12 and 12 patients were not available for response, PFS and OS, respectively.

2.4. Explored covariates

Investigated variables were demographic factors at the start of chemotherapy, histological entity, histological grade, initial therapy at diagnosis, time between initial diagnosis and start of chemotherapy, disease sites at the start of chemotherapy and type of ifosfamide regimen.

Demographic factors included gender, age (by cohorts of 10 years) and performance status. The histological STS entities were aggregated in five commonly occurring groups: synovial sarcoma, leiomyosarcoma, liposarcoma, GIST and a group containing all remaining STS types. Further characterisation of tumour type within these five diverse tumour groups is not available. In the GIST group, patients with a GIST diagnosis as well as with a diagnosis of gastrointestinal tract leiomyosarcoma were included. This was done since many tumours diagnosed as gastrointestinal leiomyosarcomas in studies before 1998 are actually GIST. Analysis showed no differences in terms of RR, PFS and OS between tumours

Table 1 – Chemotherapy regimens from studies included in this analysis. All regimens were applied every three weeks.

Regimen	Dose	No. patients included	No. patients used	References
Doxorubicin	75 mg/m^2	660	648	7,10–13
Ifosfamide	5 g/m^2	52	52	14
Ifosfamide	3 × 3 g/m^2/d	160	160	7,14
Ifosfamide	9 g/m^2 continuously over 3 d	107	107	7
Ifosfamide	12 g/m^2 continuously over 3 d	95	95	15
Doxorubicin Ifosfamide	50 mg/m^2 5 g/m^2	655	637	11,16,17
Doxorubicin Ifosfamide	75 mg/m^2 5 g/m^2	268	268	17,18

Abbreviations: Ifosfamide 3 × 3 g/m^2; 3 g/m^2 ifosfamide was administered on three consecutive days.

diagnosed as GIST and those initially diagnosed as gastrointestinal leiomyosarcomas (data not shown).

Histological grade was determined according to the FNLCC grading system. Patients whose tumours were initially diagnosed as low grade, were only entered in case of rapid progression prior to first line systemic therapy as such clinical behaviour is consistent with a higher grade tumour rather than a low grade one. To determine whether diagnoses made by a local pathologist could be used in case no central review was available (39% of the cases), central and local diagnoses were estimated in a contingency table. The discrepancy between the two was around 12%. As there were no differences in outcomes between cases with only a local diagnosis versus those for which the diagnosis was centrally reviewed, with exception of PFS for synovial sarcoma (data not shown), we decided to use the local diagnosis in case no central review was performed.

Variables concerning treatment at first diagnosis were surgery and/or radiotherapy. Other covariates included the presence of locally advanced versus metastatic disease, the presence of local recurrence, and metastatic site (lung, liver, bone, or other sites). Treatment characteristics were ifosfamide monotherapy versus the combination with doxorubicin, and the ifosfamide dose (< and $\geqslant$9 g/m^2 per cycle).

2.5. *Statistical methods*

The categorical data were summarised by frequencies and percentages, the continuous covariates by median, range and numbers of observations. Survival data were estimated by the Kaplan–Meier method.

The prognostic factor analysis aims to identify subgroups of patients who have a favourable outcome, independently of the administered treatment. The predictive factor analysis is to reveal subgroups of patients who respond differently to ifosfamide-containing treatment compared to doxorubin monotherapy. Strictly, a predictive factor analysis should use data from randomised studies. But in order to obtain adequate power, we decided to add data from non-randomised studies from the EORTC-STBSG database.

For identification of prognostic factors, univariate analysis was performed among baseline covariates by logistic regression (Wald test) for RR and concerning PFS and OS, log-rank test for binary variables, and PHCox model (Wald test) for the categorical and continuous variables. The statistical significance was set at 0.05 based on a two-sided statistical test. Subsequently, multivariate regression models were built: a logistic model for response and Cox models for OS and PFS including all factors with a significant or borderline prognostic value in the univariate analyses. Non-significant factors were removed according to a backward selection procedure with the statistical significance set at 0.01 based on a two-sided test. The univariate analysis was the first step of the process aiming at rejecting the less significant variables from the multivariate regression models. We choose a *p*-value level of 0.05 for this step to avoid early rejection of variables with a possible interaction. For the second step generating the final models, we used a more conservative *p*-level at 0.01, consistent with the large sample size. Finally, the obtained models were validated by bootstrap resampling. Using the same sample size as the original data set, 1000 data sets were created by random sampling (with replacement) of cases from the original data-set.

To identify predictive factors for ifosfamide-containing therapies, patients treated with doxorubicin alone served as comparators. All covariates were recoded as binary variables. Continuous variables were classified according to their approximate median value to obtain variables with two modalities. For the performance status, the scores 1, 2 and 3 were aggregated. The histological subtypes and grades were recoded as multiple binary variables. We defined four variables for the histological type: leiomyosarcoma, synovial sarcoma, liposarcoma and GIST; and two for the histological grade: grade I and grade III. All these variables were coded Yes/No.

For revealing predictive factors for RR, logistic models were computed and Cox models for OS and PFS. These models were generated with the investigated factor, the treatment arm and the interaction of both. The statistical significance for the interaction term was set at 0.05 using a two-sided test. To verify the validity of the predictive factors revealed, these were applied to three different groups of the database; one group comprising the patients from a randomised trial comparing doxorubin versus ifosfamide,[7] another group with patients from a randomised trial comparing doxorubicin versus a combination of doxorubicin and ifosfamide,[11] and a group containing all cases in the database

Table 2 – Main patients' characteristics. Not all percentages presented make up to 100% because of missing data.

Variable	Dose			
	DOX (*N* = 660) *N* (%)	IFO (*N* = 414) *N* (%)	DOX + IFO (*N* = 923) *N* (%)	Total (*N* = 1997) *N* (%)
Demographic data				
Gender				
Male	318 (48.2)	222 (53.6)	431 (46.7)	971 (48.6)
Female	324 (49.1)	192 (46.4)	466 (50.5)	982 (49.2)
Missing	18 (2.7)	0 (0.0)	26 (2.8)	44 (2.2)
Performance status				
PS 0	249 (37.7)	172 (41.5)	420 (45.5)	841 (42.1)
PS 1	299 (45.3)	235 (56.8)	389 (42.1)	923 (46.2)
PS 2+	87 (13.2)	4 (1.0)	82 (8.9)	173 (8.7)
Missing	25 (3.8)	3 (0.7)	32 (3.5)	60 (3.0)
Median age at registration (years)	51.9	51.0	49.9	50.9
Prior surgery				
No	89 (13.5)	44 (10.6)	93 (10.1)	226 (11.3)
Yes	445 (66.4)	267 (64.5)	373 (40.4)	1085 (54.3)
Missing	126 (19.1)	103 (24.9)	457 (49.5)	686 (34.4)
Histological type				
Leiomyosarcoma	177 (26.8)	115 (27.8)	270 (29.3)	562 (28.1)
Synovial sarcoma	57 (8.6)	46 (11.1)	86 (9.3)	189 (9.5)
Liposarcoma	65 (9.8)	46 (11.1)	59 (6.4)	170 (8.5)
GIST	37 (5.6)	33 (8.0)	39 (4.2)	109 (5.5)
Other STS entity	259 (39.2)	159 (38.4)	367 (39.8)	785 (39.3)
Missing	65 (9.8)	15 (3.6)	102 (11.1)	182 (9.1)
Histological grade				
Grade I	49 (7.4)	44 (10.6)	80 (8.7)	173 (8.7)
Grade II	154 (23.3)	135 (32.6)	193 (20.9)	482 (24.1)
Grade III	186 (28.2)	89 (21.5)	272 (29.5)	547 (27.4)
Missing	271 (41.1)	146 (35.3)	378 (41.0)	795 (39.8)
Primary tumour site				
Extremity	151 (22.9)	130 (31.4)	184 (19.9)	465 (23.3)
Other	294 (44.5)	233 (56.3)	356 (38.6)	883 (44.2)
Missing	215 (32.6)	51 (12.3)	383 (41.5)	649 (32.5)
Extent disease				
Metastatic disease				
No	132 (20.0)	60 (14.5)	172 (18.6)	364 (18.2)
Yes	418 (63.3)	354 (85.5)	640 (69.3)	1412 (70.7)
Missing	110 (16.7)	0 (0.0)	111 (12.0)	221 (11.1)
Bone metastases				
No	383 (58.0)	194 (46.9)	411 (44.5)	988 (49.5)
Yes	81 (12.3)	29 (7.0)	69 (7.5)	179 (9.0)
Missing	196 (29.7)	191 (46.1)	443 (48.0)	830 (41.6)
Lung metastases				
No	280 (42.4)	147 (35.5)	385 (41.7)	812 (40.7)
Yes	325 (49.2)	240 (58.0)	497 (53.8)	1062 (53.2)
Missing	55 (8.3)	27 (6.5)	41 (4.4)	123 (6.2)
Liver metastases				
No	415 (62.9)	263 (63.5)	663 (71.8)	1341 (67.2)
Yes	118 (17.9)	72 (17.4)	156 (16.9)	346 (17.3)
Missing	127 (19.2)	79 (19.1)	104 (11.3)	310 (15.5)
Other metastases				
No	215 (32.6)	257 (62.1)	461 (49.9)	933 (46.7)
Yes	186 (28.2)	157 (37.9)	307 (33.3)	650 (32.5)
Missing	259 (39.2)	0 (0.0)	155 (16.8)	414 (20.7)

Abbreviation: PS, performance score.

from the other, non-randomised studies with ifosfamide-containing regimens.[14–18]

Outcomes are reported as odd ratio (RR) or hazard ratios (PFS and OS) with confidence intervals (CI) for prognostic factors, and as significance level (interaction) for predictive factors.

Statistical Analysis Software version 9.1.3 (SAS Institute, Cary, NC) was used for statistical analyses.

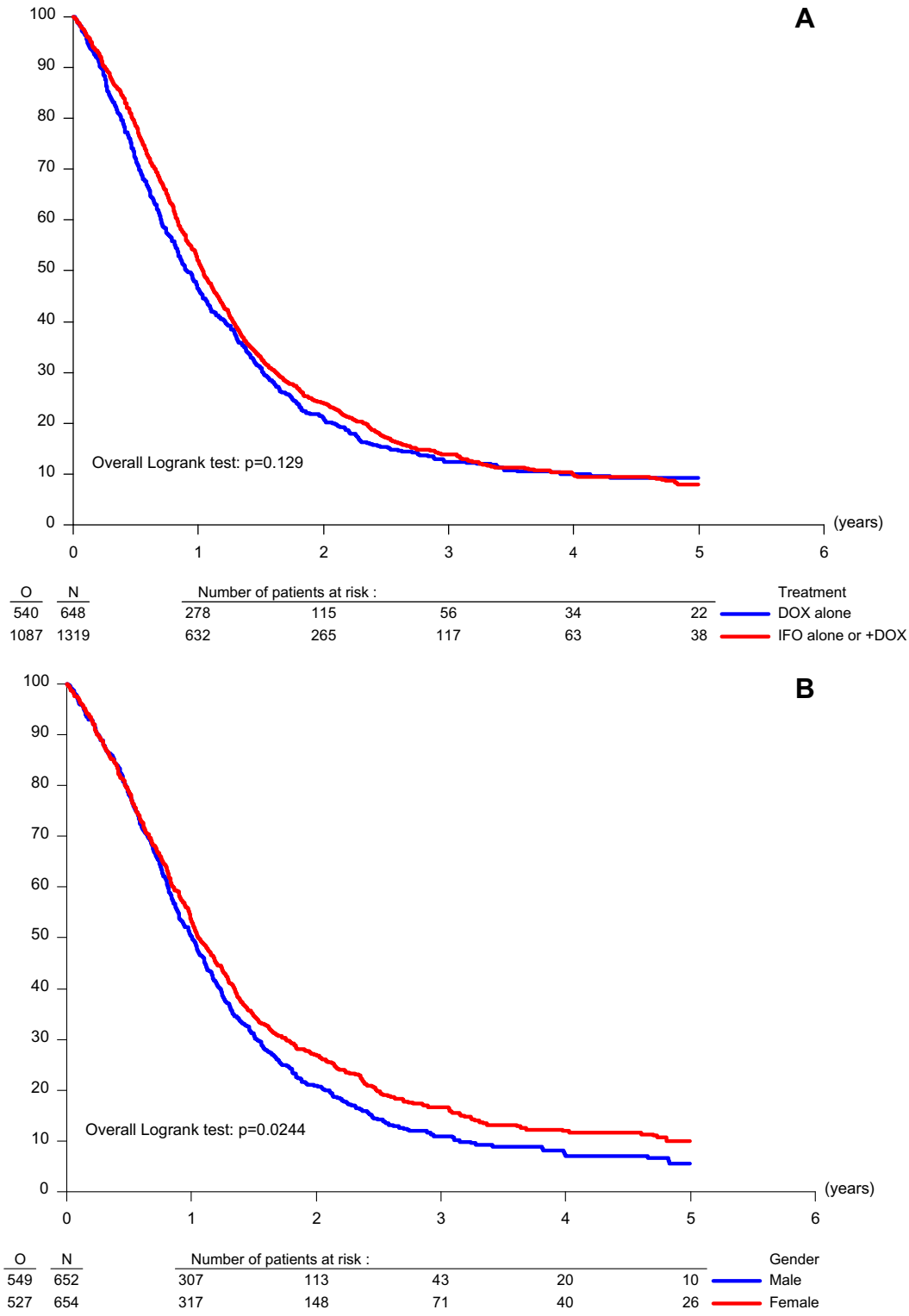


Fig. 1 – (A) Overall survival of all patients; (B) overall survival by gender, (C) performance and (D) by histological grade. O, observed failures; N, total number of cases.

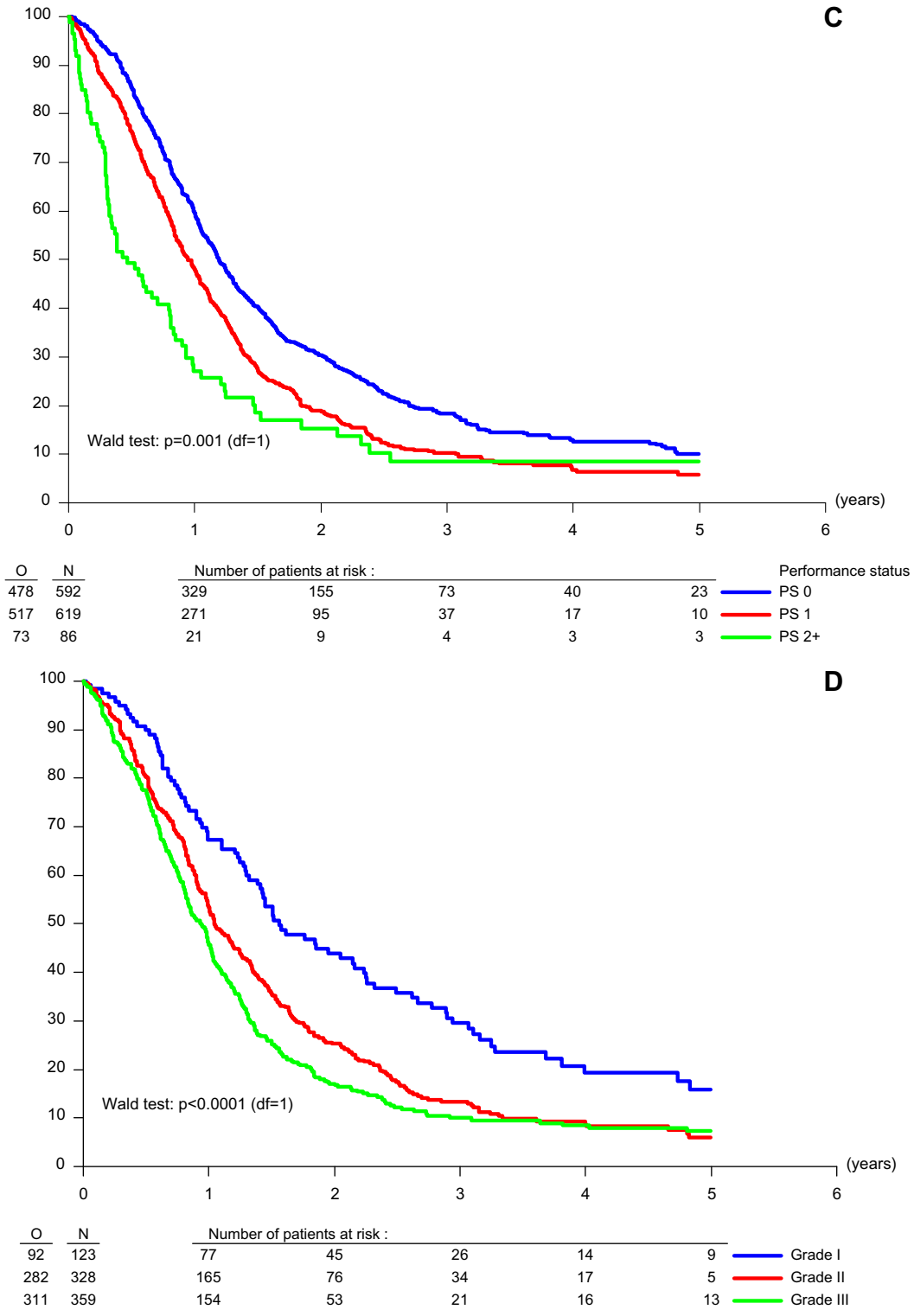


Fig. 1 *(continued)*

3. Results

Collectively, 660 patients received doxorubicin alone, 414 ifosfamide alone and 923 a combination of doxorubicin and ifosfamide (Table 1). Table 2 depicts patients' characteristics.

3.1. *Prognostic factors for overall survival*

Ifosfamide-based therapy yielded a median OS of 54 weeks (Fig. 1A). In univariate analysis, performance status, gender, age, grade, primary tumour site, metastatic disease,

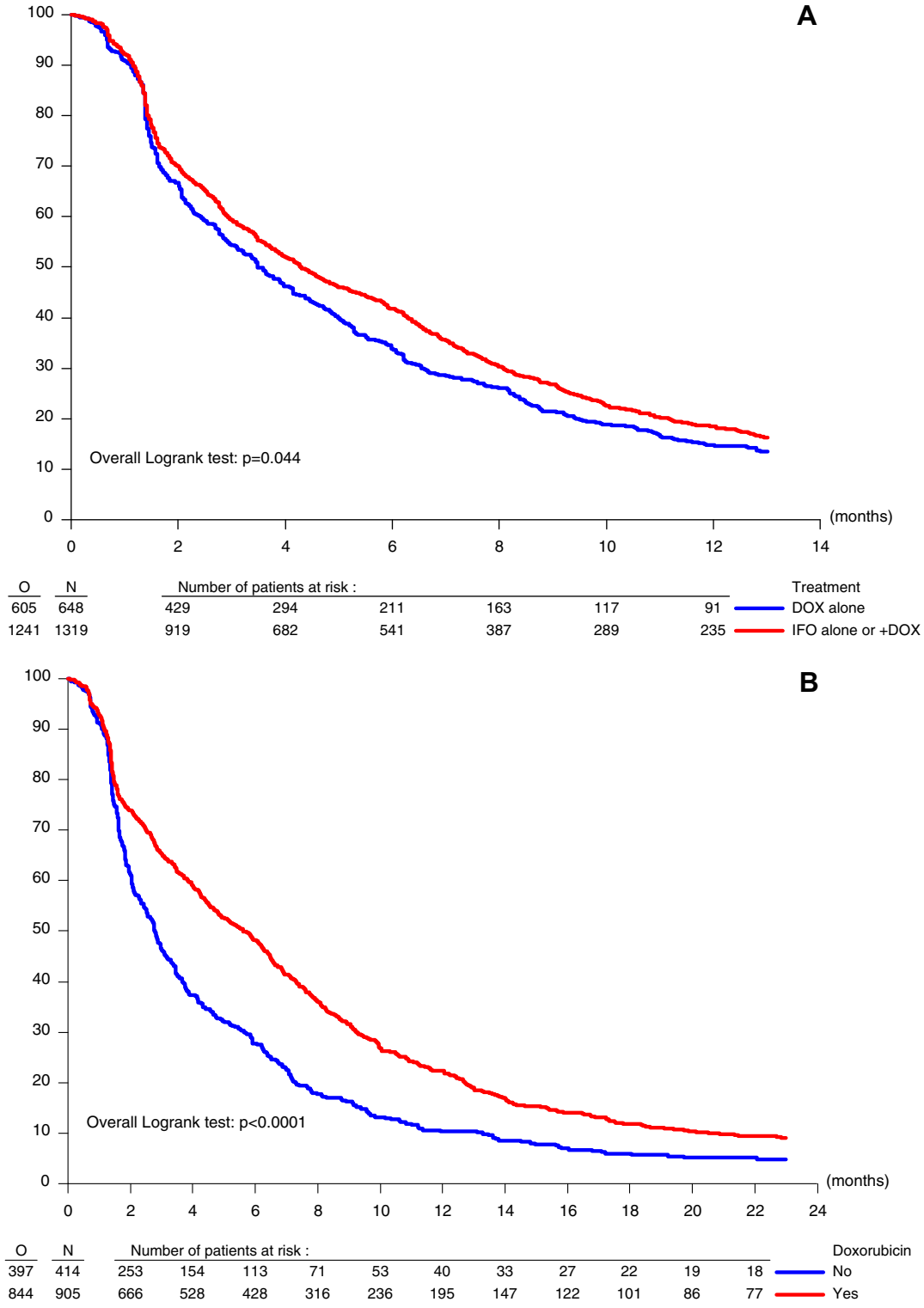


Fig. 2 – (A) Progression-free survival of all patients; (B) progression-free survival by combination with doxorubicin and (C) by histological entity. O, observed failures; N, total number of cases.

metastases at sites other than liver, bones, and lungs, time between initial diagnosis and registration, and the histological entity are all significant. For the histological entities, leiomyosarcoma served as comparator. Patients with synovial sarcoma or liposarcoma are less at risk of death. Risk of death for GIST did not differ from that for leiomyosarcoma patients (Appendix Table A1).

In the multivariate analysis, favourable prognostic factors for OS were good performance status (HR = 0.732; 99% CI, 0.602–0.890), low grade (HR = 0.716; 99% CI, 0.606–0.846),

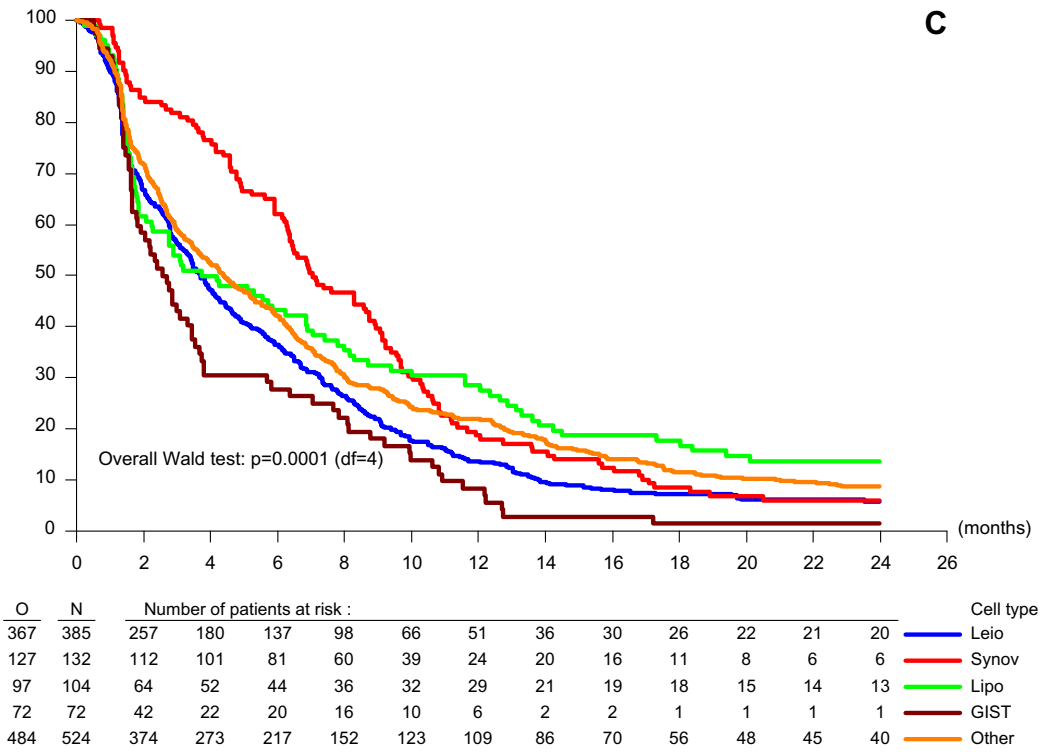


Fig. 2 *(continued)*

non-metastatic disease (HR = 0.676; 99% CI, 0.494–0.926), female gender (HR = 0.729; 99% CI, 0.573–0.928), and extremity primary site (HR = 0.663; 99% CI 0.511–0.859) (Fig. 1B, C and D). As performance status and histological grade are continuous variables, risk of death increases with each higher score by 37% and 40%, respectively. The bootstrap procedure showed that this final model was the most stable one.

3.2. *Prognostic factors for progression-free survival*

In the 1319 patients, the median PFS was 19 weeks (Fig. 2A). In univariate analysis, combination regimens with doxorubicin, good performance status, low age, an extremity primary tumour, non-metastatic disease, no liver or bone metastases, no metastatic sites other than lungs and histological entity were significantly associated with longer PFS. Concerning histology, patients with synovial sarcoma, liposarcoma, and tumours belonging to the group of remaining STS types, are less at risk to progress than leiomyosarcoma patients (Table A2).

In multivariate analysis, combination with doxorubicin (HR = 0.676; 99% CI, 0.584–0.904), non-metastatic disease (HR = 0.727; 99% CI, 0.585–0.904), and STS entities were revealed as favourable prognostic factors for PFS. Compared to leiomyosarcoma, synovial sarcomas had a lower risk to progress (HR = 0.683; 99% CI, 0.518–0.899), while there was a trend to a lower risk for STS from the remaining entities group (HR = 0.842; 99% CI, 0.698–1.016) (Fig. 2B and C).

3.3. *Prognostic factors for response*

RR to ifosfamide-based therapy was 25%. Combination with doxorubicin, low ifosfamide dose, prior surgery, higher grade, lower age, an extremity primary site, no liver metastases, presence of lung metastases, presence of other metastases than bone or liver metastases, longer time between initial diagnosis and registration, and synovial sarcomas and other sarcomas compared to leiomyosarcomas were favourable factors for response in univariate analysis (Table A3).

In the multivariate analysis, independent favourable prognostic factors for response are the combination with doxorubicin (OR = 3.041; 99% CI, 1.701–5.437), high grade (OR = 1.645; 99% CI, 1.157–2.339) and histology. Compared to leiomyosarcomas, synovial sarcomas had a higher chance to respond (OR 3.116; 99% CI, 1.435–6.765). As grade is a continuous variable, the chance to respond increases by 65% with each higher grade.

4. Predictive factor analysis

Compared to doxorubicin monotherapy, PFS ($p = 0.044$, log-rank test) (Fig. 2) and RR (20.4% versus 24.7% ($p = 0.0415$, χ^2 test)) were better for ifosfamide-based therapies. OS did not differ (Fig. 1). Predictive factor analyses revealed that compared to doxorubicin monotherapy, patients who benefited less from ifosfamide-based therapies in terms of OS were patients with leiomyosarcomas ($p = 0.0247$, interaction test) (Fig. 3). There was a trend that patients with liver metastases did better after ifosfamide-based therapy than with doxorubicin monotherapy ($p = 0.0712$, interaction test). For PFS, no predictive factors were found. In terms of responses, patients with liposarcoma ($p = 0.0324$, interaction test) benefited less from ifosfamide-containing therapy compared to doxorubicin (Fig. 4). For leiomyosarcoma patients, there was a trend for lower RR after ifosfamide-based therapy ($p = 0.0589$,

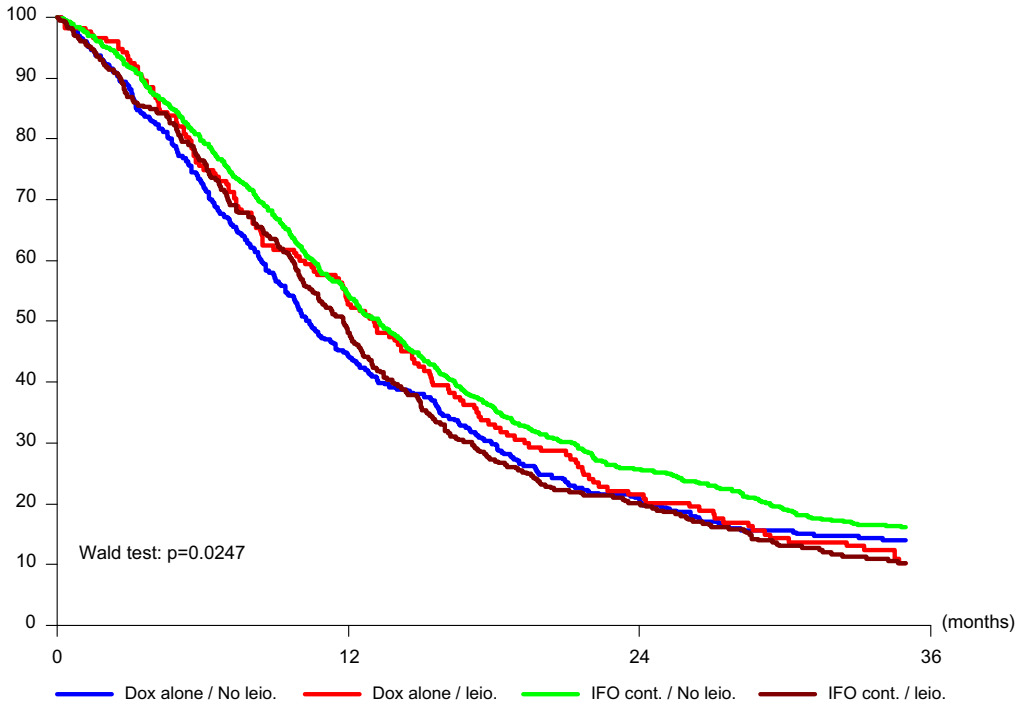
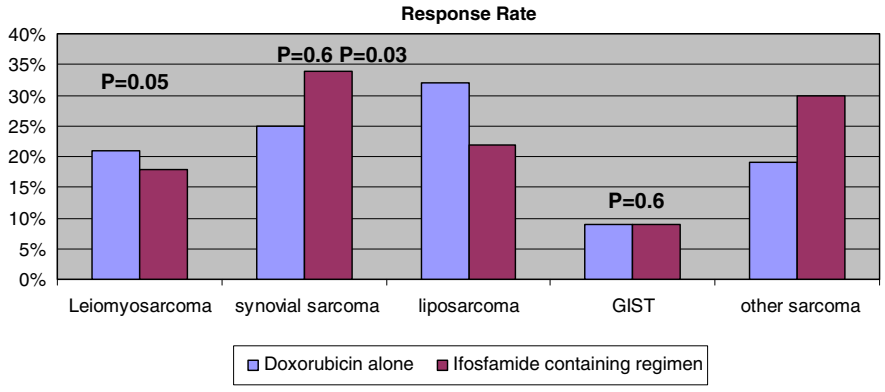


Fig. 3 – Leiomyosarcoma as a predictive factor for overall survival to ifosfamide-based therapy compared to doxorubicin monotherapy. Doxo alone, doxorubicin alone; no leio, patients with a STS other than leiomyosarcoma; leio, patients with leiomyosarcoma; IFO, ifosfamide-based.



Abbreviations p: the p-value for the interaction test

Fig. 4 – Responses to doxorubicin alone and ifosfamide-based therapies by histological entity.

interaction test) while RR for synovial sarcoma patients was higher compared to doxorubicin, but not significant.

The validity of these predictive factors was underscored by applying them to the data from the two randomised studies included in the database. In these two studies, one comparing doxorubicin to ifosfamide[7] and the other doxorubicin versus the combination of doxorubicin and ifosfamide,[11] the predictive effects were constantly in the same direction, though their significance was not always the same in the two studies (data not shown).

5. Discussion

Doxorubicin and ifosfamide, alone or in combination, are the most widely used first line agents for the treatment of advanced STS patients. Previously, we have determined prognostic factors for outcome to doxorubicin-based regimens.[9] As such factors are currently missing for ifosfamide-based, we established a set of independent prognostic and predictive factors for outcome to ifosfamide-based therapy in terms of OS, PFS and RR.

Good performance status, female gender, non-metastatic disease, extremity primary tumour and low grade were independent favourable prognostic factors for OS. Also in other tumour types, performance score and female gender were independently associated with OS.[19] The mechanisms underlying the generally more favourable outcome for women are uncertain, but slower clearance of cytotoxic drugs, and thereby increased exposure, has been suggested.[19] However, consistent with this suggestion, it would have been likely that female gender was also associated with RR or PFS in our analysis, which was not the case. Furthermore, gender was not related to OS in other reports on prognostic factors in advanced STS.[9,20] Regarding the findings that extremity primary tumour and non-metastatic disease are associated with an improved OS, it is likely that subsequent local therapies, reaching local control and thereby improving OS, contributed to the apparent better outcome.

Although initially developed to estimate relapse risk for localised disease, histological grade of the primary tumour was related to OS in our series of advanced patients. Its impact was considerable; risk of death increased by 39% for each higher grade. By contrast, high grade was a favourable factor for response, which may be explained by a higher proportion of proliferating tumour cells that generally display more sensitivity to cytotoxic drugs than non-proliferating cells. However, these responses are short-lived and followed by rapid deterioration and a short OS. This inverse relationship of grade with OS on one hand, and with RR on the other was also observed in other series[20,21] including a previous EORTC-STBSG analysis on prognostic factors for outcome to anthracycline-based chemotherapy.[9] It must be noted that 905 patients treated with the combination of doxorubicin and ifosfamide in that analysis[9] were also included in the current analysis.

There was some overlap in favourable prognostic factors for PFS and RR. The combination of doxorubicin and ifosfamide, histological entity and non-metastatic disease were independent prognostic factors for PFS; the combination of doxorubicin and ifosfamide, histological entity, and grade for RR.

Concerning the combination with doxorubicin being a favourable factor for both RR and PFS compared to ifosfamide alone, there are no randomised studies directly comparing these two approaches. Doxorubicin served as comparator in two randomised trials exploring doxorubicin combined with ifosfamide.[11,22] In one study, the combination improved RR; PFS was not provided.[22] In the other, included in our dataset, no differences in terms of RR or PFS were observed.[11] In another study, RR and PFS were increased by the triplet of doxorubicin, dacarbazine and ifosfamide compared to doxorubicin combined with dacarbazine.[21] In our analysis, the combination of doxorubicin and ifosfamide was not a prognostic factor for OS, and likewise, none of these three randomised studies demonstrated an OS benefit for the ifosfamide-containing combinations.[11,21,22] However, many combinations evaluated in the past, including the ones in our analysis, have been criticised for the relatively low doses used. There are indications that doxorubicin and ifosfamide should be given at doses of at least 70 mg/m^2 and 9 g/m^2 per cycle, respectively.[5,6] Given these uncertainties, it remains to be established whether, and if so in which end-points, combination chemotherapy yields a benefit compared to monotherapy. The current EORTC 62012 study exploring doxorubicin at 75 mg/m^2 versus the combination of doxorubicin at 75 mg/m^2 and ifosfamide at 10 g/m^2 per cycle will hopefully answer this question definitely.

The different sensitivity to systemic agents amongst the diverse histological STS entities was further underscored in our analysis. Patients with synovial sarcomas had a lower risk to progress and a higher chance to respond compared to leiomyosarcoma patients. Previously, synovial sarcoma has been suggested to exhibit great sensitivity to chemotherapy,[22,23] in particular to ifosfamide.[6] The latter was not confirmed, as OS, PFS and RR in synovial sarcoma patients were equivalent for doxorubicin compared to ifosfamide-based therapies. Furthermore, there were trends for worse PFS and RR for GIST, consistent with its known chemo-resistant phenotype,[2] and for better PFS and RR for other STS entities compared to leiomyosarcomas. It appeared that in terms of OS, patients with leiomyosarcomas benefited less from ifosfamide-based therapy compared to doxorubicin alone. It is questionable however, whether this bears clinical relevance as the difference was small, though statistically significant. Concerning RR, patients with liposarcoma benefited less from receiving ifosfamide-based therapies compared to doxorubicin monotherapy. If confirmed, this might have clinical implications when achieving a radiological response is a major treatment aim.

Besides histology and a trend that patients with liver metastases did better after ifosfamide-based therapy, the predictive factor analysis did not elucidate other factors that may help to identify patients who respond differently to ifosfamide-based chemotherapy compared to doxorubicin.

There are several important caveats when considering this retrospective, exploratory analysis. The prognostic and predictive factors found in this study, should be prospectively validated. The previously mentioned ongoing study of the EORTC and the National Cancer Institute of Canada (NCI-C) exploring doxorubicin versus the combination of doxorubicin will be used for this validation. Furthermore, numerous associations were examined, which may give rise to false-positive results. Another potential bias might be the large number of years over which the studies included in this report were conducted. During this time frame of 25 years, supportive measures have been improved and pathology classification systems have changed. To check for the consistency of the data obtained over the years, we have explored the PFS and OS of the patients treated in the different studies with doxorubicin at 75 mg/m^2. As no statistical differences in OS and PFS for these patients exist between the diverse studies (data not shown), we feel that this is not a major bias, if existing at all. Non-randomised studies were included in our database which might have affected the predictive factors analysis. Strictly speaking, a predictive factor analysis should only be done using data from randomised studies as data from non-randomised studies may induce selection bias. Using only data from randomised studies however, would have resulted in numbers too low for such an analysis. We have retrospectively checked for all identified predictive values that the predictive effect was in the same direction in data from

randomised as well as from non-randomised studies, though not always significant given the smaller numbers of patients in these separate studies (data not shown). Importantly, it is nowadays increasingly recognised that the different tumour entities should be classified further given different characteristics. For instance, myxoid liposaromas are suggested to exhibit greater sensitivity to chemotherapy than other liposarcomas.[24] And also the group of leiomyosarcomas and other STS entities is characterised by great heterogeneity among the diverse tumour types. However, further classification of the different categories would have resulted in groups too small to draw conclusions. Another potential criticism is that the doses chemotherapy used in the studies captured in our analysis are nowadays considered low. As mentioned, it is generally assumed that doxorubicin and ifosfamide should be administered in doses of at least 70 mg/m^2 and 9–11 g/m^2 per cycle, respectively.[5,6] However, although ifosfamide doses $\geqslant$9 g/m^2 per cycle were a favourable prognostic factor for RR in univariate analysis, no impact of ifosfamide dose was revealed in multivariate analyses. This lack of association might be due to the fact that the majority of patients treated with ifosfamide at doses lower than 9 g/m^2 per cycle received it in combination with doxorubicin.

Nevertheless, despite these caveats, this analysis provides important insights into factors associated with outcome to ifosfamide-based regimens in advanced STS. For example, if confirmed, the finding that in terms of response liposarcoma patients benefited less from ifosfamide-based therapies compared to doxorubicin monotherapy, may guide patient management. Furthermore, this information can be used for study design and to interpret trials as it clearly underlines how selection of patients can largely determine the outcomes of early clinical trials. None of the factors favourably associated with a single endpoint was a favourable factor for all three end-points. For example, by including a large proportion of patients with high-grade, synovial sarcomas into a phase II study on a cytotoxic agent with RR as primary endpoint, a high RR is likely while this does not imply that this will be translated into an OS benefit. Therefore, this largest series on prognostic and predictive factors for outcome to ifosfamide-based chemotherapy in first-line therapy for advanced STS provides important information for the design and interpretation of studies and may contribute further to a more individualised approach of STS patients.

Authors' contribution

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.09.022.

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