Prognostic relevance of distant metastases versus locally advanced disease in soft tissue sarcomas: an EORTC-STBSG database study

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Introduction

In patients with advanced soft tissue sarcoma treated with chemotherapy, WHO performance status, histologic subtype and histologic grade are known prognostic factors. Although the difference between the subgroups: locally advanced disease only, metastatic disease only and both local and metastatic disease is easily made, its prognostic relevance is thus far unknown. The aim of this EORTC database study was to study the difference in prognosis between these subgroups in patients receiving first line chemotherapy for advanced soft tissue sarcoma.

Methods

A retrospective database analysis was performed on 2473 patients receiving first line chemotherapy for advanced soft tissue sarcoma from 12 EORTC sarcoma trials in order to establish the difference in prognosis for the three subgroups. Endpoints were overall survival, progression-free survival and overall response rate. Factors studied were age, sex, histologic subtype, histologic grade, WHO performance status, treatment and time since initial diagnosis.

Results

Overall survival differed significantly between patients with locally advanced disease only, with metastatic disease only and with both locally advanced and metastatic disease with a median overall survival of 15.4, 12.9 and 10.6 months respectively. Similar differences were seen for progression-free survival (5.8, 4.3 and 3.2 months respectively).

Conclusion

This large retrospective database study shows that patients with advanced soft tissue sarcomas treated with first line chemotherapy with locally advanced disease, metastatic disease and both local and metastatic disease have different outcomes. This should be accounted for in future study design, interpretation and comparison of study results and daily practice.

Highlights

- Overall survival differs between locally advanced and metastatic disease in STS
- Prognostic factors are also different between these groups
- Future trials should account for these differences

Key words

Soft tissue sarcoma

Survival

Chemotherapy

Prognostic factors

Retrospective study

Manuscript

Introduction

Soft tissue sarcomas (STS) are a rare group of tumours consisting of more than 70 histological different subtypes.(1) For the treatment of most subtypes, doxorubicin alone or in combination remains first line treatment with e.g. pazopanib and trabectedin as second line options.(2-5) For anthracycline and ifosfamide based treatments, prognostic and predictive factors were established.(6-9) These studies identified response to chemotherapy, WHO performance score, histological subtype and time since initial diagnosis to be prognostic for overall survival (OS) in STS.(6-9) One of these studies also identified a difference in OS between patients with locally advanced disease (LAD) and patients with distant metastases (DM), favouring the first subgroup when treated with first-line ifosfamide therapy.(6)

Although the difference between LAD and DM is easily made, no study investigated whether differences in outcome and response exist between these two subgroups, which could make them factors of prognostic relevance. The identification of prognostic factors is necessary for patient care and design of clinical trials. The aim of this study is to investigate whether important differences exist in OS, progression free survival (PFS) and response rate (ORR) between the different disease subgroups and is an exploratory analysis of the prognostic factors for OS, PFS and ORR in patients with STS and either LAD or DM at the moment of inclusion in a first line chemotherapy study of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG).

Methods

Patients

The EORTC-STBSG database contains data of 3708 patients from 15 EORTC advanced STS trials considering first line treatment.(4, 5, 10-22) Supplementary table 1 and 2 describe the different studies and the number of patients included in this study. From this database patients were excluded who had no documentation of lesions at trial entry, who had no survival data available, who were treated with a CYVADIC (cyclophosphamide/vincristine/doxorubicin/dacarbazine) regimen (EORTC-study 62761)(10) or docetaxel (1 arm of 62941)(17), who had prior (adjuvant or palliative) chemotherapy, for whom not enough information was available to distinguish primary from metastatic disease (62883 and 62901)(14, 15), or who were diagnosed with gastrointestinal stromal tumour (GIST) or an ineligible tumour, being not STS.

Patients were grouped in a group with local disease only (LAD), a group with metastatic disease only (DM) and both locally advanced and metastatic disease. LAD was defined either as locally advanced disease not amenable to surgery or locally recurrent disease. DM only was defined as distant metastatic disease without evidence for local disease. Patients in the group with both had local disease and distant metastatic disease at study inclusion.

Endpoints

Study endpoints were OS, PFS and ORR to therapy. OS was computed from the date of randomization or the date of prospective registration (nonrandomized trials) to date of death. Patients alive at last follow up were censored. PFS was defined as time interval between date of randomization or prospective registration and date of first documented progression or death, whichever comes first. ORR to chemotherapy was evaluated according to WHO or RECIST criteria depending on the study.(23-25) In this study it was analysed as binary variable, i.e. complete response and partial response are considered response and stable disease, progression or non-evaluable assessment were considered failures.

Statistical methods

Covariates

Demographic data included were age, sex and performance status before the start of chemotherapy. Performance status was measured on the WHO scale. Variables related to the history of the sarcoma were the site of the primary tumour, the use of prior radiotherapy and/or prior surgery, and time since first diagnosis of sarcoma. Because information on prior radiotherapy or prior surgery was not collected in the more recent trials it has not been included in the univariate and multivariate prognostic factor analysis to reduce the loss of data due to missing information. In most of the included studies patients had to have progression in the six months before study inclusion or have had to a histological grade of at least 2 or intermediate. Treatment was aggregated in 4 categories: anthracyclines alone (doxorubicin, epirubicin), ifosfamide alone, combination of anthracyclines and ifosfamide and other (brostallicin and trabectedin).

The way histological grade and histological subtype were used was earlier described in a study by our group.(6) Histological subtype was aggregated into the 4 most common groups: synovial sarcoma, leiomyosarcoma, liposarcoma and others. If both a local and central histological subtype were available, the central diagnosis was used. Twenty-five percent of patients had a discrepancy between the central and local diagnosis. If only a local diagnosis was available this diagnosis was used.

Statistics

Categorical data were summarized by frequencies and percentages, continuous covariates were summarized by median, interquartile range and overall range and were presented according to the three different groups. The characteristics were compared with a χ^2-test for categorical variables and a (non-parametric) Kruskal Wallis test for the continuous variables.

The potential prognostic value of all factors was investigated by univariate analysis, using univariate Cox or logistic regression models according to outcome. The prognostic value of the factors was subsequently assessed in a multivariate model, using stepwise selection. All models were stratified by treatment for heterogeneity that may be introduced by merging data from several clinical trials. Statistical significance was set at 0.05 for all analyses.

To reduce the loss of a considerable amount of information for the multivariate analysis due to a substantial amount of missing data for grade and site of primary tumour, the value “missing” was a

separate category in all these models. Sensitivity analyses were performed to study the impact of this approach on the final interpretation of the models.

In addition, the analyses were repeated for only those patients included in studies after 1999 to account for the diagnosis of GIST, improved radiology techniques and improved treatment regimens, which is included in the supplementary materials.

Results

Patients

In total, 2473 patients from 12 trials were included in this study, which were separated in 3 subgroups: LAD (329 patients), DM (1202 patients) and patients with both LAD and DM (942 patients). (Supplementary figure 1) Table 1 shows the characteristics of the three subgroups.

Median follow-up in years, as determined by the reverse Kaplan-Meier estimates, was 3.6 years (interquartile range 2.2-6.4) for LAD, 3.2 years (2.1-4.9) for DM, and 3.6 years (2.1-6.4) for patients with both.

Differences in survival and ORR

Compared to LAD, patients with DM had a worse prognosis (hazard ratio (HR) 1.25 (95% CI 1.08-1.45)) and patients with both LAD and DM had the worst (HR 1.59 (1.37-1.84)) (P<0.001). (Figure 1A) Median OS was 15.4 (95% CI 13.0-16.9), 12.9 (12.4-13.9) and 10.6 months (9.8-11.3) respectively. Of all patients 94.5% showed disease progression during follow-up. For PFS the same differences in survival were seen, with HR of 1.40 (1.23-1.59) for DM and 1.58 (1.38-1.81) for both LAD and DM (P<0.001). (Figure 1B) Median PFS was 5.8 (95% CI 4.4-6.5), 4.3 (3.9-4.7) and 3.2 months (2.9-3.5) respectively.

ORR differed among the three groups with the lowest ORR in patients with both LAD and DM (p=0.003). (Table 2)

Prognostic factors for OS

Table 3 shows the results of the univariate analysis. Multivariate analyses for LAD identified good performance status, histological subtype (synovial and liposarcoma), time since initial diagnosis (being not 6-12 months) and extremity site of tumour as favourable prognostic factors (table 4). For DM, the favourable prognostic factors were good performance status, histological subtype (synovial and liposarcoma) and long interval since initial diagnosis (table 4). Favourable prognostic factors for OS for patients with both LAD and DM were good performance status, female gender, younger age, lower grade, extremity site of primary tumour and long interval since initial diagnosis (table 4).Prognostic factors for PFS

Table 5 shows the results of the univariate analysis. Multivariate analyses for LAD identified good performance status and time since initial diagnosis (being not 6-12 months) as favourable prognostic factors (table 6). For DM, the favourable prognostic factors were good performance status, histological subtype (synovial and liposarcoma) and long time since initial diagnosis (table 6). Favourable prognostic factors for PFS for patients with both LAD and DM were good performance status, histological subtype (synovial and liposarcoma) and lower grade (table 6).

Prognostic factors for overall response

Results of the univariate analysis and multivariate analysis for prognostic factors for ORR are shown in table 7 and 8.

Discussion

This study is the first showing that for all frontline treatments in locally advanced and/or metastatic soft tissue sarcomas OS, PFS and ORR outcomes differ according to disease subgroup. This difference should be accounted for in daily practice and when designing and interpreting clinical trials. We also established prognostic factors for OS, PFS and ORR in these different disease subgroups and important differences in prognostic factors between these disease subgroups were identified, which underlines the importance of accounting for the different disease subgroups. Patients with LAD had a better prognosis compared to both other groups. This difference may be explained by additional treatment with either surgery or radiotherapy in the locally advanced setting. No data on post-chemotherapy treatment was available in the study database used for this project and so we cannot provide evidence for this statement. The difference in survival between the different disease subgroups stresses the importance of stratification for disease subgroup in future trials.

In line with this observation, locally advanced tumours of the extremity had a better OS than other tumour sites, because these are more accessible to surgery and radiotherapy with relatively low morbidity. This was also found recently in an Indian study which showed that patients with extremity tumours and patients with multimodality treatment had a favourable prognosis, suggesting that the possibility of aggressive treatment of the primary tumour localization may result in a better survival.(26) Tumour site is also a known prognostic factor in surgically treated non-metastatic sarcoma patients.(27) Time since initial diagnosis behaves differently as prognostic factor between patients with LAD (both a very short time and a very long time from initial diagnosis were associated with a favourable prognosis) and both the other groups (only a long time interval from initial diagnosis having a favourable diagnosis). This could be because aggressive tumours tend to respond fast to chemotherapy and so become amenable to surgical therapy as a local treatment, which could prolong the OS. This was already shown in a previous database study of our group.(7) In the metastatic setting surgery usually is not an option and aggressive tumours will progress early. The fact that high histological grade is a favourable prognostic factor for ORR in patients with both LAD and DM supports this hypothesis. On the other hand, very early relapse, i.e. recurrence within 6 months after resection, could be caused by incomplete surgery, which would result in a group with mixed biology, and early relapse, i.e. recurrence between 6 and 12 months after resection, is caused mainly by bad

biology. Because bad biology will lead to more rapidly progression compared to the mixed biology of the very early relapse group. This could also explain the difference in prognosis.

As in earlier studies for STS and other tumours performance status, histologic subtype and time since initial diagnosis were prognostic factors for OS.(8, 9, 28-30) Remarkably, in the multivariate analyses histologic subtype was no longer prognostic for patients with both LAD and DM. As was already mentioned in the methods section, histopathologic diagnosis was in approximately 25% of the patients different between local and central review. This difficulty with correctly classifying sarcomas could result in the differences in outcome between the various studies when studying histological subtype as prognostic factor. Histologic grade, also a known prognostic factor, was not identified as prognostic factor for OS in patients with LAD and dropped out in the multivariate model of metastatic disease, however this could be due to an underpowered comparison due to the lower number of patients in this group.(8) In general, synovial and liposarcoma are known to be sarcomas with a relatively good prognosis.(31) For both patients with LAD and patients with both LAD and DM, age and gender were both prognostic factors for patients with both local and metastatic disease compared to the two other groups. The difference in prognosis between sexes was found previously in other studies and it was hypothesized that it was caused by differences in pharmacokinetics of cytostatic drugs of amongst other cyclophosphamide and doxorubicin, with a decreased metabolism in women and so a higher drug exposure.(32) On the other hand the difference could be explained by the high grade undifferentiated uterine sarcomas, which of course only occur in women and have a very poor prognosis.(33) However, whether these two explanations are the full explanation is questionable because it was not a prognostic factor for OS in patients with LAD or DM and it was not a prognostic factor for PFS and ORR. For PFS the known risk factors performance status, histological subtype, time since initial diagnosis and grade were identified as prognostic factors. No new prognostic factors were identified. The same difference for time since initial diagnosis was found as for OS. Grade was only prognostic for patients with both LAD and DM and such that a higher grade was associated with a worse PFS.(8) For LAD no prognostic factors for ORR were identified in contrast to patients with DM and patients with both LAD and DM. For patients with DM histology and site of primary tumour were identified. The role of primary tumour site may relate to later diagnosis and bulkier disease at presentation for non-extremity disease. As earlier mentioned low grade and high grade had a favourable prognosis compared to intermediate grade tumours for ORR in patients with both LAD and

DM. High histologic grade was previously found to be prognostic, but the finding that low histologic grade was associated with a better overall response rate is surprising.(7) As grading of sarcomas is difficult and it was an inclusion criterion for the studies to be progressive within 6 months before study inclusion, it could be that the included grade I sarcomas had a more aggressive behaviour like grade III tumours.

The results of this retrospective study should be interpreted with care. First, the database contains studies over 32 years. In this time, treatment has changed and supportive measurements have improved. These could influence the prognostic factors. Also, the histologic subtypes of STS have changed over the years. High incident subtypes like malignant fibrous histiocytoma no longer exist in the current WHO classification.(1) Also new subtypes were identified during these years, like GIST often diagnosed as leiomyosarcoma before 2000.(34-36) An additional subgroup analysis with only those patients included in studies after 1999 was done to account for these changes. Although this subgroup analysis was hampered by the reduced number of patients, it resulted in comparable outcomes. (Supplementary data: additional subgroup analysis)

In the future, treatment will be more and more histological subtype and molecular driver specific. Furthermore, some studies included regimens which are currently no longer in use, such as ifosfamide 5 g/m2 as a 24-hour infusion and doxorubicin/ifosfamide combinations with lower doses than currently used. Ideally the results of this study should be validated in a prospective observational study, comparing the overall survival in these three subgroups under the current treatments available.

The results of this study are important for daily practice, because current treatment regimens are based on phase III studies currently not accounting for these differences and thereby introducing bias, as these studies suggest that included LAD patients are comparable to patients with both locally advanced and distant metastatic disease. Second, the prognosis is essential information for patients when considering palliative treatment and the differences in prognosis between patients with LAD, DM and both should be used in this decision.

In conclusion, this study shows a difference in prognosis between patients with LAD, DM and patients with both LAD and DM. This study does indicate that there are a number of differences in prognostic factors between patients with LAD, DM and with both LAD and DM. Thus, in future trials the randomization should be stratified for disease stage.

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Figure and table legends

Table 1 Patient's characteristics

Table 2 Overall response rate

Table 3 Univariate analysis for prognostic factors for overall survival

Table 4 Multivariate analysis for prognostic factors for overall survival

Table 5 Univariate analysis for prognostic factors for progression free survival

Table 6 Multivariate analysis for prognostic factors for progression free survival

Table 7 Univariate analysis for prognostic factors for overall response rate (a lower odds ratio indicates a higher change for good response)

Table 8a Multivariate analysis for overall response rate for metastatic disease only (a lower odds ratio indicates a higher change for good response)

Table 8b Multivariate analysis for overall response rate for patients with both locally advanced and metastatic disease (a lower odds ratio indicates a higher change for good response)

Figure 1 Overall survival (A) and progression free survival (B) according to disease stage

1 **Article tables and figures**

2 **Table 1 Patient's characteristics**

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
Gender					0.002
Male	143 (43.5)	565 (47.0)	500 (53.1)	1208 (48.8)	
Female	186 (56.5)	637 (53.0)	442 (46.9)	1265 (51.2)	
Performance status					<0.001
PS 0	132 (40.1)	635 (52.8)	390 (41.4)	1157 (46.8)	
PS 1	155 (47.1)	515 (42.8)	476 (50.5)	1146 (46.3)	
PS 2+	38 (11.6)	50 (4.2)	74 (7.9)	162 (6.6)	
Unknown	4 (1.2)	2 (0.2)	2 (0.2)	8 (0.3)	
Age (years)					0.387
< 40 yrs	78 (23.7)	257 (21.4)	216 (22.9)	551 (22.3)	
40-50 yrs	66 (20.1)	278 (23.1)	210 (22.3)	554 (22.4)	
50-60 yrs	85 (25.8)	360 (30.0)	274 (29.1)	719 (29.1)	
>=60 yrs	95 (28.9)	285 (23.7)	230 (24.4)	610 (24.7)	
Median	52	51	51	51	0.949[a]
Range	16 - 79	17 - 84	10 - 88	10 - 88	
Q1-Q3	40 - 61	42 – 60	41 - 60	41 - 60	
Unknown	5 (1.5)	22 (1.8)	12 (1.3)	39 (1.6)	
Prior radiotherapy					<0.001
No	274 (83.3)	590 (49.1)	690 (73.2)	1554 (62.8)	
Yes	33 (10.0)	464 (38.6)	170 (18.0)	667 (27.0)	
Unknown	22 (6.7)	148 (12.3)	82 (8.7)	252 (10.2)	
Prior Surgery					<0.001
No surgery	53 (16.1)	16 (1.3)	161 (17.1)	230 (9.3)	
Non-optimal surgery	91 (27.7)	106 (8.8)	184 (19.5)	381 (15.4)	
Complete surgery	68 (20.7)	487 (40.5)	178 (18.9)	733 (29.6)	
Unknown	117 (35.6)	593 (49.3)	419 (44.5)	1129 (45.7)	
histology					<0.001
Leiomyosarcoma	85 (25.8)	412 (34.3)	281 (29.8)	778 (31.5)	
Synovial sarcoma	23 (7.0)	160 (13.3)	77 (8.2)	260 (10.5)	
Liposarcoma	48 (14.6)	114 (9.5)	87 (9.2)	249 (10.1)	
Other	173 (52.6)	516 (42.9)	497 (52.8)	1186 (48.0)	
Histopathological grade					0.259

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
GRADE I	36 (10.9)	97 (8.1)	68 (7.2)	201 (8.1)	
GRADE II	86 (26.1)	345 (28.7)	261 (27.7)	692 (28.0)	
GRADE III	104 (31.6)	436 (36.3)	315 (33.4)	855 (34.6)	
Unknown	103 (31.3)	324 (27.0)	298 (31.6)	725 (29.3)	
Site of primary tumour					<0.001
Other	222 (67.5)	501 (41.7)	540 (57.3)	1263 (51.1)	
Extr	37 (11.2)	457 (38.0)	233 (24.7)	727 (29.4)	
Unknown	70 (21.3)	244 (20.3)	169 (17.9)	483 (19.5)	
Time between the initial diagnosis of sarcoma and registration					<0.001
<6 mon	233 (70.8)	416 (34.6)	650 (69.0)	1299 (52.5)	
6-12 mon	32 (9.7)	190 (15.8)	80 (8.5)	302 (12.2)	
1-2 yrs	22 (6.7)	238 (19.8)	82 (8.7)	342 (13.8)	
>=2 yrs	40 (12.2)	352 (29.3)	118 (12.5)	510 (20.6)	
Median (months)	1.9	11.8	2.3	6.3	<0.001[a]
Range (months)	0.0 - 222.8	0.0 - 346.5	0.0 - 198.7	0.0 - 346.5	
Q1-Q3 (months)	0.8 - 9.2	4.3 - 28.5	0.9 - 9.5	1.4 - 19.1	
Unknown	2 (0.6)	6 (0.5)	12 (1.3)	20 (0.8)	
Treatment					
Anthracyclines	137 (41.6)	461 (38.4)	369 (39.2)	967 (39.1)	
DOX+IFO	129 (39.2)	432 (35.9)	394 (41.8)	955 (38.6)	
IFO ALONE	53 (16.1)	206 (17.1)	125 (13.3)	384 (15.5)	
Other	10 (3.0)	103 (8.6)	54 (5.7)	167 (6.8)	
Primary site involved					
No	0 (0.0)	1202 (100.0)	0 (0.0)	1202 (48.6)	
Yes	329 (100.0)	0 (0.0)	942 (100.0)	1271 (51.4)	
Lung metastases					
No	329 (100.0)	316 (26.3)	361 (38.3)	1006 (40.7)	
Yes	0 (0.0)	886 (73.7)	581 (61.7)	1467 (59.3)	
Bone metastases					
No	329 (100.0)	1071 (89.1)	810 (86.0)	2210 (89.4)	
Yes	0 (0.0)	131 (10.9)	132 (14.0)	263 (10.6)	
Liver metastases					
No	329 (100.0)	979 (81.4)	745 (79.1)	2053 (83.0)	
Yes	0 (0.0)	223 (18.6)	197 (20.9)	420 (17.0)	

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
Other metastases					
No	329 (100.0)	709 (59.0)	532 (56.5)	1570 (63.5)	
Yes	0 (0.0)	493 (41.0)	410 (43.5)	903 (36.5)	

Table 1 continued

[a]Kruskal-Wallis test

1 **Table 2 Overall response rate**

	Disease stage			
	Locally advanced (N=329) N (%)	Metastases only (N=1202) N (%)	Both (N=942) N (%)	Total (N=2473) N (%)
Best overall response				
Complete Response (CR)	16 (4.9)	34 (2.8)	16 (1.7)	66 (2.7)
Partial Response (PR)	47 (14.3)	226 (18.8)	133 (14.1)	406 (16.4)
Stable Disease (SD)	145 (44.1)	482 (40.1)	362 (38.4)	989 (40.0)
Progressive Disease (PD)	77 (23.4)	385 (32.0)	347 (36.8)	809 (32.7)
Not Evaluable	44 (13.4)	75 (6.2)	84 (8.9)	203 (8.2)
Responders				
Failure	266 (80.9)	942 (78.4)	793 (84.2)	2001 (80.9)
Responders (CR+PR)	63 (19.1)	260 (21.6)	149 (15.8)	472 (19.1)

2

3 **Table 3 results of univariate analysis for prognostic factors for overall survival**

Overall Survival – stratified by treatment							
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Performance status	PS 0	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)
	PS 1	1.62 (1.21, 2.17)		1.60 (1.39, 1.83)		1.49 (1.28, 1.74)	
	PS 2+	2.38 (1.55, 3.65)		3.37 (2.46, 4.61)		1.91 (1.45, 2.50)	
Gender	Male	1.00	0.712	1.00	0.387	1.00	0.125
	Female	1.05 (0.80, 1.38)		0.94 (0.83, 1.08)		0.89 (0.77, 1.03)	
Age	< 40 yrs	1.00	0.030 (df=3)	1.00	0.206 (df=3)	1.00	0.028 (df=3)
	40-50 yrs	1.36 (0.90, 2.04)		1.13 (0.93, 1.37)		1.04 (0.84, 1.28)	
	50-60 yrs	1.40 (0.94, 2.06)		1.19 (0.99, 1.42)		1.31 (1.08, 1.60)	
	>=60 yrs	1.77 (1.21, 2.59)		1.22 (1.00, 1.49)		1.15 (0.93, 1.42)	
Histological cell type	Leiomyosarcoma	1.00	0.005 (df=3)	1.00	0.004 (df=3)	1.00	0.043 (df=3)
	Synovial	0.55 (0.30, 1.00)		0.82 (0.66, 1.00)		0.83 (0.63, 1.11)	
	Liposarcoma	0.51 (0.31, 0.84)		0.66 (0.52, 0.85)		0.66 (0.49, 0.89)	
	Other	1.03 (0.76, 1.41)		0.96 (0.83, 1.12)		0.91 (0.78, 1.07)	
Grade	Grade I	1.00	0.071 (df=3)	1.00	0.004 (df=3)	1.00	<0.001 (df=3)
	Grade II	1.25 (0.77, 2.02)		1.33 (1.02, 1.73)		1.34 (0.99, 1.82)	
	Grade III	1.71 (1.08, 2.70)		1.55 (1.19, 2.00)		1.87 (1.38, 2.53)	
	Unknown	1.61 (1.00, 2.57)		1.52 (1.16, 2.00)		1.59 (1.17, 2.16)	
Tumour site	Other	1.00	0.001 (df=2)	1.00	0.131 (df=2)	1.00	0.085 (df=2)
	Extr	0.41 (0.25, 0.67)		0.87 (0.75, 1.01)		0.82 (0.69, 0.98)	
	Unknown	1.05 (0.75, 1.48)		0.87 (0.73, 1.05)		0.95 (0.78, 1.16)	
Time since initial diagnosis	<6 mon	1.00	0.002 (df=3)	1.00	<0.001 (df=3)	1.00	0.002 (df=3)
	6-12 mon	2.05 (1.34, 3.16)		1.05 (0.86, 1.27)		1.05 (0.81, 1.36)	
	1-2 yrs	1.21 (0.71, 2.08)		0.84 (0.70, 1.01)		1.02 (0.79, 1.31)	
	>=2 yrs	0.74 (0.47, 1.15)		0.63 (0.53, 0.74)		0.65 (0.52, 0.82)	

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Table 4 Multivariate analysis for prognostic factors for overall survival

		Locally advanced disease	Distant metastatic disease	Both
Parameter	**Levels**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Performance status	PS 0	1.00	1.00	1.00
	PS 1	1.71 (1.27, 2.31)	1.62 (1.41, 1.86)	1.44 (1.24, 1.69)
	PS 2+	2.40 (1.51, 3.81)	3.52 (2.56, 4.84)	1.77 (1.33, 2.34)
		***P*<0.001 (df=2)**	***P* <0.001 (df=2)**	***P* <0.001 (df=2)**
Histology	Leio	1.00	1.00	
	Lipo	0.62 (0.37, 1.04)	0.64 (0.50, 0.83)	
	Other	1.17 (0.85, 1.62)	0.95 (0.81, 1.10)	
	Synov	0.76 (0.41, 1.42)	0.82 (0.66, 1.00)	
		***P* =0.047 (df=3)**	***P* =0.003 (df=3)**	
Site of tumour	Other	1.00		1.00
	Extr	0.40 (0.24, 0.66)		0.77 (0.65, 0.92)
	Unknown	*0.78 (0.54, 1.12)*		*0.90 (0.73, 1.10)*
		***P* =0.001 (df=2)**		***P* =0.016 (df=2)**
Time since initial diagnosis	<6 mon	1.00	1.00	1.00
	6-12 mon	2.03 (1.31, 3.14)	1.16 (0.95, 1.41)	1.09 (0.84, 1.42)
	1-2 yrs	1.56 (0.89, 2.74)	0.91 (0.76, 1.10)	0.95 (0.74, 1.23)
	>=2 yrs	0.90 (0.57, 1.42)	0.69 (0.58, 0.82)	0.67 (0.53, 0.85)
		***P* =0.006 (df=3)**	***P* <0.001 (df=3)**	***P* =0.008 (df=3)**
Gender	Male			1.00
	Female			0.84 (0.72, 0.97)
				***P* =0.019 (df=1)**
Age	< 40 yrs			1.00
	40-50 yrs			1.05 (0.85, 1.31)
	50-60 yrs			1.44 (1.18, 1.77)
	>=60 yrs			1.17 (0.94, 1.46)
				***P* =0.002 (df=3)**
Histologic grade	Grade I			1.00
	Grade II			1.32 (0.97, 1.80)
	Grade III			1.76 (1.30, 2.39)
	Unknown			*1.45 (1.06, 1.98)*
				***P* <.001 (df=3)**

Table 5 Univariate analysis for prognostic factors for progression free survival

Progression free survival – stratified by treatment							
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Performance status	PS 0	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)	1.00	0.006 (df=2)
	PS 1	1.39 (1.07, 1.80)		1.26 (1.12, 1.43)		1.23 (1.07, 1.42)	
	PS 2+	2.14 (1.44, 3.17)		1.83 (1.35, 2.48)		1.34 (1.03, 1.74)	
Gender	Male	1.00	0.510	1.00	0.999	1.00	0.471
	Female	0.92 (0.72, 1.18)		1.00 (0.89, 1.12)		0.95 (0.83, 1.09)	
Age	< 40 yrs	1.00	0.197 (df=3)	1.00	0.273 (df=3)	1.00	0.045 (df=3)
	40-50 yrs	1.26 (0.87, 1.82)		1.12 (0.94, 1.33)		1.06 (0.87, 1.29)	
	50-60 yrs	1.39 (0.98, 1.96)		1.11 (0.94, 1.32)		1.28 (1.06, 1.55)	
	>=60 yrs	1.40 (1.00, 1.97)		1.20 (1.00, 1.43)		1.19 (0.97, 1.46)	
Histological cell type	Leiomyosarcoma	1.00	0.047 (df=3)	1.00	0.001 (df=3)	1.00	0.013 (df=3)
	Synovial	0.60 (0.35, 1.01)		0.75 (0.63, 0.91)		0.70 (0.54, 0.91)	
	Liposarcoma	0.99 (0.66, 1.49)		0.68 (0.55, 0.84)		0.73 (0.57, 0.94)	
	Other	1.18 (0.88, 1.59)		0.86 (0.75, 0.99)		0.87 (0.75, 1.01)	
grade	Grade I	1.00	0.798 (df=3)	1.00	0.165 (df=3)	1.00	0.014 (df=3)
	Grade II	1.10 (0.72, 1.68)		1.17 (0.93, 1.48)		1.31 (0.99, 1.72)	
	Grade III	1.20 (0.79, 1.81)		1.27 (1.01, 1.60)		1.53 (1.16, 2.01)	
	Unknown	1.20 (0.79, 1.83)		1.26 (0.99, 1.59)		1.43 (1.08, 1.89)	
Tumour site	Other	1.00	0.076 (df=2)	1.00	0.006	1.00	0.642 (df=2)
	Extr	0.66 (0.44, 0.99)		0.81 (0.71, 0.92)		0.93 (0.79, 1.09)	
	Unknown	1.10 (0.81, 1.50)		0.91 (0.77, 1.07)		0.99 (0.82, 1.19)	
Time since initial diagnosis	<6 mon	1.00	0.001 (df=3)	1.00	<0.001 (df=3)	1.00	0.153 (df=3)
	6-12 mon	2.10 (1.41, 3.14)		1.05 (0.88, 1.25)		1.08 (0.85, 1.37)	
	1-2 yrs	1.78 (1.09, 2.89)		0.96 (0.81, 1.13)		1.23 (0.97, 1.55)	
	>=2 yrs	1.08 (0.74, 1.58)		0.70 (0.61, 0.82)		0.88 (0.72, 1.08)	

Table 6 Multivariate analysis for prognostic factors for progression free survival

		Locally advanced disease	Distant metastatic disease	Both
Parameter	**Levels**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Performance status	PS 0	1.00	1.00	1.00
	PS 1	1.43 (1.10, 1.87)	1.28 (1.13, 1.45)	1.20 (1.04, 1.39)
	PS 2+	2.11 (1.41, 3.17)	1.90 (1.40, 2.57)	1.24 (0.95, 1.62)
		***P* <.001 (df=2)**	***P* <.001 (df=2)**	***P* =0.031 (df=2)**
Histology	Leio		1.00	1.00
	Lipo		0.69 (0.55, 0.85)	0.77 (0.60, 1.00)
	Other		0.86 (0.75, 0.99)	0.85 (0.73, 0.99)
	Synov		0.77 (0.64, 0.93)	0.70 (0.54, 0.92)
			***P* =0.002 (df=3)**	***P* =0.024 (df=3)**
Time since initial diagnosis	<6 mon	1.00	1.00	
	6-12 mon	1.92 (1.28, 2.88)	1.11 (0.93, 1.33)	
	1-2 yrs	2.07 (1.26, 3.39)	1.01 (0.85, 1.19)	
	>=2 yrs	1.08 (0.74, 1.58)	0.74 (0.64, 0.87)	
		***P* =0.001 (df=3)**	***P* <.001 (df=3)**	
Histologic grade	Grade I			1.00
	Grade II			1.31 (0.99, 1.73)
	Grade III			1.50 (1.14, 1.98)
	Unknown			*1.41 (1.07, 1.87)*
				***P* =0.029 (df=3)**

Table 7 Univariate analysis for prognostic factors for overall response rate (a lower odds ratio indicates a higher change for good response)

Response rate – stratified by treatment							
		Locally advanced tumour		Metastases only		Both	
		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Performance Status	PS 0	1.00	0.161 (df=2)	1.00	0.801 (df=2)	1.00	0.572 (df=2)
	PS 1	0.73 (0.40, 1.32)		1.07 (0.79, 1.43)		0.83 (0.57, 1.21)	
	PS 2+	2.02 (0.65, 6.29)		1.24 (0.60, 2.56)		0.79 (0.40, 1.55)	
Gender	Male	1.00	0.856 (df=1)	1.00	0.053 (df=1)	1.00	0.225 (df=1)
	Female	1.05 (0.60, 1.86)		1.32 (1.00, 1.76)		0.80 (0.56, 1.15)	
Age	< 40 yrs	1.00	0.445 (df=3)	1.00	0.137 (df=3)	1.00	0.043 (df=3)
	40-50 yrs	1.33 (0.60, 2.95)		1.44 (0.96, 2.16)		0.79 (0.49, 1.27)	
	50-60 yrs	1.79 (0.81, 3.92)		1.39 (0.95, 2.04)		1.58 (0.95, 2.62)	
	>=60 yrs	1.66 (0.78, 3.54)		1.59 (1.04, 2.43)		1.26 (0.74, 2.16)	
Histological cell type	Leiomyosarcoma	1.00	0.289 (df=3)	1.00	<0.001 (df=3)	1.00	0.772 (df=3)
	Synovial	0.41 (0.14, 1.14)		0.42 (0.27, 0.66)		0.78 (0.39, 1.56)	
	Liposarcoma	1.20 (0.42, 3.40)		0.32 (0.20, 0.53)		0.77 (0.39, 1.51)	
	Other	0.84 (0.42, 1.67)		0.67 (0.47, 0.96)		0.83 (0.54, 1.25)	
Grade	Grade I	1.00	0.418 (df=3)	1.00	0.180 (df=3)	1.00	0.022 (df=3)
	Grade II	1.30 (0.43, 3.90)		1.27 (0.71, 2.24)		1.93 (0.90, 4.12)	
	Grade III	0.67 (0.25, 1.81)		0.87 (0.50, 1.50)		0.87 (0.44, 1.75)	
	Unknown	0.85 (0.31, 2.37)		1.14 (0.64, 2.04)		1.10 (0.54, 2.23)	
Tumour site	Other	1.00	0.597 (df=2)	1.00	<0.001 (df=2)	1.00	0.742 (df=2)
	Extr	0.84 (0.36, 2.00)		0.44 (0.31, 0.60)		0.98 (0.63, 1.51)	
	Unknown	0.71 (0.36, 1.40)		0.78 (0.52, 1.18)		0.83 (0.52, 1.33)	
Time since initial diagnosis	<6 mon	1.00	0.180 (df=3)	1.00	0.447 (df=3)	1.00	0.510 (df=3)
	6-12 mon	1.90 (0.63, 5.70)		1.42 (0.91, 2.22)		0.88 (0.47, 1.63)	
	1-2 yrs	1.67 (0.47, 5.98)		1.21 (0.81, 1.80)		0.76 (0.42, 1.37)	
	>=2 yrs	3.23 (0.95, 10.96)		1.12 (0.79, 1.60)		1.40 (0.73, 2.66)	

Tables 8a Multivariate analysis for overall response rate for metastatic disease only (a lower odds ratio indicates a higher change for good response)

Parameter	Levels	Odds Ratio (95% CI)	P-value
Histology	Leio	1.00	0.002 (df=3)
	Lipo	0.40 (0.24, 0.66)	
	Other	0.80 (0.56, 1.16)	
	Synov	0.58 (0.36, 0.93)	
Site of tumour	Other	1.00	0.001 (df=2)
	Extr	0.51 (0.36, 0.73)	
	Unknown	0.80 (0.53, 1.22)	

Tables 8b Multivariate analysis for overall response rate for patients with both locally advanced and metastatic disease (a lower odds ratio indicates a higher change for good response)

Parameter	Levels	Odds Ratio (95% CI)	P-value
Grade	GRADE I	1.00	0.022 (df=3)
	GRADE II	1.93 (0.90, 4.12)	
	GRADE III	0.87 (0.44, 1.75)	
	Unknown	1.10 (0.54, 2.23)	

Supplementary tables and figures

Supplementary table 1 Included studies and study treatments

Supplementary table 2 Inclusion per year

Supplementary table 3 Histologic subtypes included

Supplementary figure 1 Consort diagram

Supplementary analysis: patients included in studies after 1999

Supplementary table 1 Included studies and study treatments

Study	Phase & design	Trt Arm A (N)	Trt arm B (N)	Trt Arm C (N)	N contributing to this substudy Total = 2473
1. EORTC 62761	**R. Ph II**	CYVADIC FU (191)[#]	CYVADIC Cy (121)[#]		-
2. EORTC 62801	**R. Ph II/III**	DOX 75 (106)	EPI 75 (104)		184
3. EORTC 62842	**Ph II**	DOX 50 + IFO 5000 (203)			189
4. EORTC 62851	**R. Ph III**	DOX 75 (295)	DOX 50 + IFO 5000 (297)	CYVADIC FU (157)[#]	512
5. EORTC 62883	**Ph II**	DOX 75 + IFO 5000 (111)[#]			-
6. EORTC 62901	**R. Ph II/III**	DOX 75 (112)[#]	EPI 3*50 (111)[#]	EPI 1*150 (111)[#]	-
7. EORTC 62903	**R. Ph III**	DOX 50 + IFO 5000 (157)	DOX 75 + IFO 5000 (157)		293
8. EORTC 62912	**R. ph II**	IFO 5000 (93)	IFO 3*3000 (89)		100
9. EORTC 62941	**R. Ph II**	DOX 75 (42)	DOCETAXEL (44)[#]		40
10. EORTC 62953	**Ph II**	IFO 12 (124)			91
11. EORTC 62962	**R. Ph II**	DOX 75 (45)	Caelyx (50)		88
12. EORTC 62971	**R. Ph III**	DOX 75 (110)	IFO 3*3000 (109)	IFO 5000 (107)	292
13. EORTC 62012	**R. Ph III**	DOX 75 (228)	DOX 75 + IFO 10 (227)		435
14. EORTC 62061	**R. Ph II**	DOX 75 (39)	Brostallicin (N=79)		116
15. EORTC 62091	**R. Ph II**	DOX 75 (43)	Trabectedin 3hrs (N=47)	Trabectedin 24hrs (N=43)	133

R. randomized, Ph phase, CYVADIC cyclophosphamide, vincristine, doxorubicin, dacarbazin, DOX doxorubicin, EPI epirubicin, IFO ifosfamide, given dose is in mg/m^2

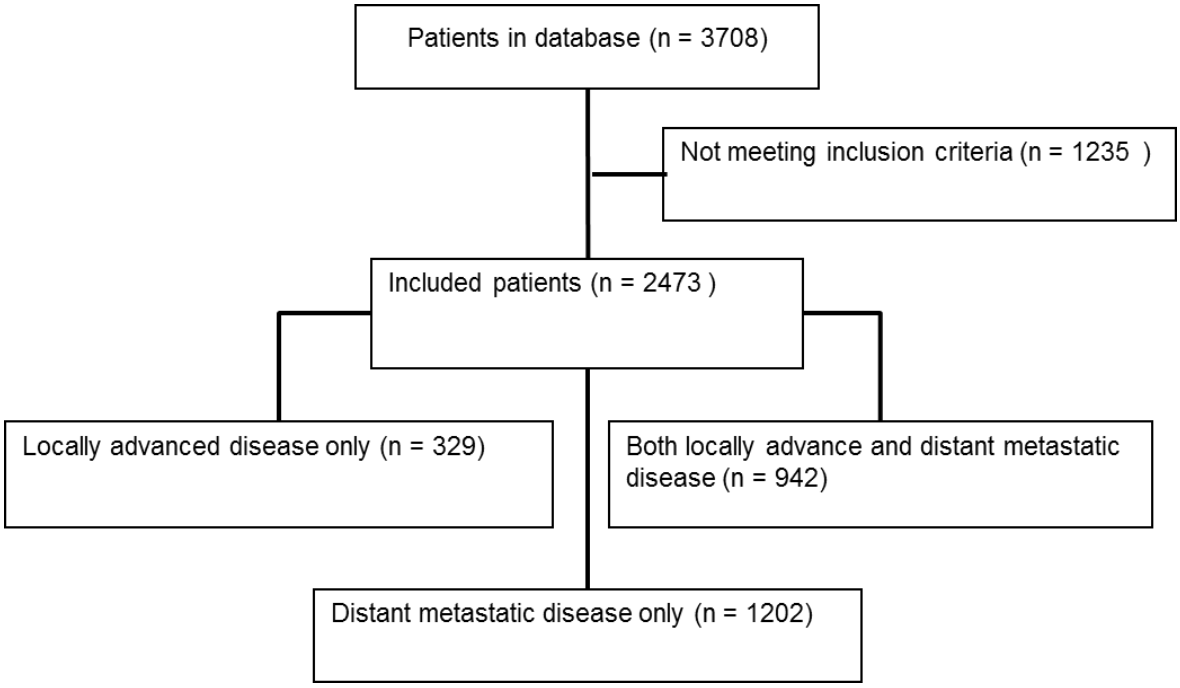
[#] Treatment arms that were excluded

Supplementary table 2 Inclusion per year

YEAR	Protocol												
Frequency	62012	62061	62091	62801	62842	62851	62903	62912	62941	62953	62962	62971	Total
1980	0	0	0	4	0	0	0	0	0	0	0	0	4
1981	0	0	0	84	0	0	0	0	0	0	0	0	84
1982	0	0	0	72	0	0	0	0	0	0	0	0	72
1983	0	0	0	24	0	0	0	0	0	0	0	0	24
1984	0	0	0	0	74	0	0	0	0	0	0	0	74
1985	0	0	0	0	114	11	0	0	0	0	0	0	125
1986	0	0	0	0	1	123	0	0	0	0	0	0	124
1987	0	0	0	0	0	122	0	0	0	0	0	0	122
1988	0	0	0	0	0	146	0	0	0	0	0	0	146
1989	0	0	0	0	0	95	0	0	0	0	0	0	95
1990	0	0	0	0	0	15	0	0	0	0	0	0	15
1992	0	0	0	0	0	0	48	0	0	0	0	0	48
1993	0	0	0	0	0	0	123	0	0	0	0	0	123
1994	0	0	0	0	0	0	105	13	0	0	0	0	118
1995	0	0	0	0	0	0	17	66	24	0	0	0	107
1996	0	0	0	0	0	0	0	21	16	28	0	0	65
1997	0	0	0	0	0	0	0	0	0	63	40	0	103
1998	0	0	0	0	0	0	0	0	0	0	48	49	97
1999	0	0	0	0	0	0	0	0	0	0	0	106	106
2000	0	0	0	0	0	0	0	0	0	0	0	86	86
2001	0	0	0	0	0	0	0	0	0	0	0	51	51
2003	10	0	0	0	0	0	0	0	0	0	0	0	10
2004	55	0	0	0	0	0	0	0	0	0	0	0	55
2005	68	0	0	0	0	0	0	0	0	0	0	0	68
2006	63	3	0	0	0	0	0	0	0	0	0	0	66
2007	59	71	0	0	0	0	0	0	0	0	0	0	130
2008	63	42	0	0	0	0	0	0	0	0	0	0	105
2009	86	0	0	0	0	0	0	0	0	0	0	0	86
2010	31	0	0	0	0	0	0	0	0	0	0	0	31
2011	0	0	27	0	0	0	0	0	0	0	0	0	27
2012	0	0	106	0	0	0	0	0	0	0	0	0	106
Total	435	116	133	184	189	512	293	100	40	91	88	292	2473

Supplementary table 3 Histologic subtypes included

	Disease stage			
	Locally advanced (N=173)	Metastases only (N=516)	Both (N=497)	Total (N=1186)
	N (%)	N (%)	N (%)	N (%)
Histological cell type for other				
Malignant fibrous histiocytoma	41 (23.7)	124 (24.0)	90 (18.1)	255 (21.5)
Fibrosarcoma	12 (6.9)	37 (7.2)	40 (8.0)	89 (7.5)
Rhabdomyosarcoma	10 (5.8)	17 (3.3)	29 (5.8)	56 (4.7)
Angiosarcoma	12 (6.9)	28 (5.4)	45 (9.1)	85 (7.2)
Neurogenic sarcomas	25 (14.5)	50 (9.7)	34 (6.8)	109 (9.2)
Miscellaneous	47 (27.2)	210 (40.7)	180 (36.2)	437 (36.8)
Unclassified	26 (15.0)	50 (9.7)	79 (15.9)	155 (13.1)



Supplementary figure 1 Consort diagram

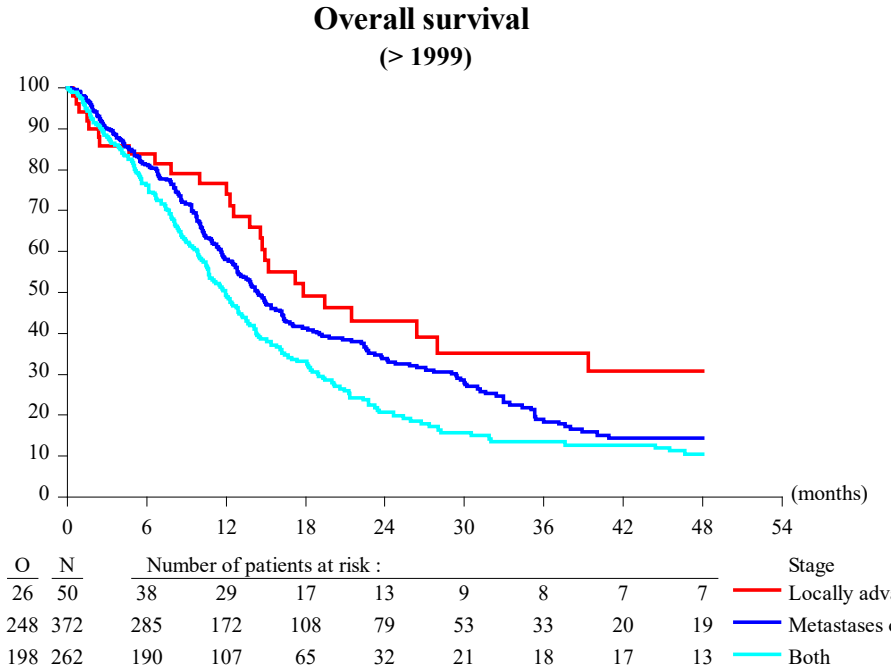
Supplementary analysis: patients included in studies after 1999

Patient's characteristics				
	Disease stage			
	Locally advanced (N=50)	Metastases only (N=372)	Both (N=262)	Total (N=684)
	N (%)	N (%)	N (%)	N (%)
Gender				
Male	22 (44.0)	172 (46.2)	129 (49.2)	323 (47.2)
Female	28 (56.0)	200 (53.8)	133 (50.8)	361 (52.8)
Performance status				
PS 0	28 (56.0)	225 (60.5)	119 (45.4)	372 (54.4)
PS 1	22 (44.0)	145 (39.0)	143 (54.6)	310 (45.3)
PS 2+	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)
Age (years)				
< 40 yrs	13 (26.0)	54 (14.5)	49 (18.7)	116 (17.0)
40-50 yrs	4 (8.0)	88 (23.7)	68 (26.0)	160 (23.4)
50-60 yrs	19 (38.0)	131 (35.2)	85 (32.4)	235 (34.4)
>=60 yrs	14 (28.0)	99 (26.6)	60 (22.9)	173 (25.3)
Median	54	54	51	53
Range	21 - 78	18 - 84	19 - 88	18 - 88
Q1-Q3	36 - 60	44 - 60	43 - 59	44 - 60
Prior radiotherapy				
No	26 (52.0)	110 (29.6)	143 (54.6)	279 (40.8)
Yes	2 (4.0)	116 (31.2)	38 (14.5)	156 (22.8)
Missing	22 (44.0)	146 (39.2)	81 (30.9)	249 (36.4)
Prior Surgery				
Unknown	50 (100.0)	372 (100.0)	262 (100.0)	684 (100.0)
histology				
Leiomyosarcoma	10 (20.0)	107 (28.8)	69 (26.3)	186 (27.2)
Synovial sarcoma	3 (6.0)	53 (14.2)	23 (8.8)	79 (11.5)
Liposarcoma	16 (32.0)	44 (11.8)	37 (14.1)	97 (14.2)
Other	21 (42.0)	168 (45.2)	133 (50.8)	322 (47.1)
Histopathological grade				
GRADE I	4 (8.0)	15 (4.0)	12 (4.6)	31 (4.5)
GRADE II	19 (38.0)	123 (33.1)	98 (37.4)	240 (35.1)
GRADE III	16 (32.0)	170 (45.7)	113 (43.1)	299 (43.7)
Missing	11 (22.0)	64 (17.2)	39 (14.9)	114 (16.7)
Site of primary tumor				
Other	40 (80.0)	183 (49.2)	183 (69.8)	406 (59.4)
Extr	10 (20.0)	176 (47.3)	76 (29.0)	262 (38.3)
Missing	0 (0.0)	13 (3.5)	3 (1.1)	16 (2.3)
Time between the initial diagnosis of sarcoma and registration				
<6 mon	31 (62.0)	121 (32.5)	175 (66.8)	327 (47.8)
6-12 mon	7 (14.0)	60 (16.1)	21 (8.0)	88 (12.9)
1-2 yrs	6 (12.0)	64 (17.2)	26 (9.9)	96 (14.0)
>=2 yrs	6 (12.0)	127 (34.1)	40 (15.3)	173 (25.3)
Median	2.3	12.3	2.6	8.1
Range	0.0 - 117.7	0.2 - 249.8	0.0 - 198.7	0.0 - 249.8
Q1-Q3	1.1 - 11.9	5.2 - 33.5	1.2 - 12.2	1.9 - 24.6

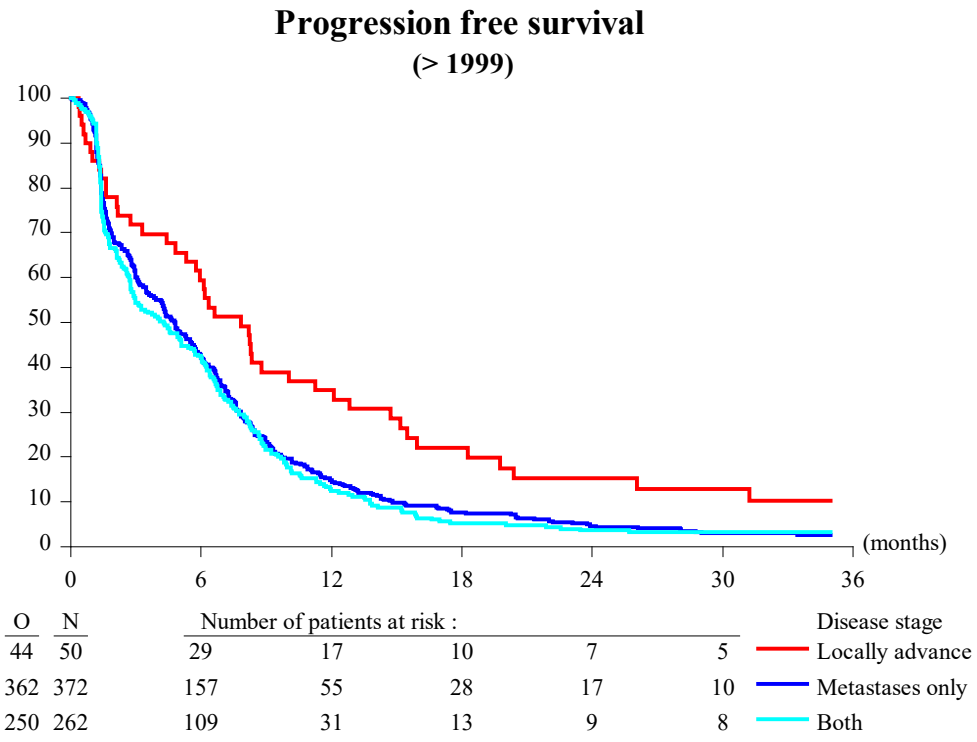
	Disease stage			
	Locally advanced (N=50)	Metastases only (N=372)	Both (N=262)	Total (N=684)
	N (%)	N (%)	N (%)	N (%)
Treatment				
Anthracyclines	25 (50.0)	159 (42.7)	115 (43.9)	299 (43.7)
DOX+IFO	15 (30.0)	110 (29.6)	93 (35.5)	218 (31.9)
Other	10 (20.0)	103 (27.7)	54 (20.6)	167 (24.4)
Primary site involved				
No	0 (0.0)	372 (100.0)	0 (0.0)	372 (54.4)
Yes	50 (100.0)	0 (0.0)	262 (100.0)	312 (45.6)
Lung metastases				
No	50 (100.0)	86 (23.1)	80 (30.5)	216 (31.6)
Yes	0 (0.0)	286 (76.9)	182 (69.5)	468 (68.4)
Bone metastases				
No	50 (100.0)	323 (86.8)	213 (81.3)	586 (85.7)
Yes	0 (0.0)	49 (13.2)	49 (18.7)	98 (14.3)
Liver metastases				
No	50 (100.0)	300 (80.6)	211 (80.5)	561 (82.0)
Yes	0 (0.0)	72 (19.4)	51 (19.5)	123 (18.0)
Other metastases				
No	50 (100.0)	148 (39.8)	89 (34.0)	287 (42.0)
Yes	0 (0.0)	224 (60.2)	173 (66.0)	397 (58.0)

Post 1999 subgroup analysis: protocols 62012, 62061, 62091

Limited subgroup (N =684) of which the majority belongs to 62012 (435) – phase 3 and two smaller phase 2 studies



Disease stage	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 2 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Locally advanced	50	26	17.84 (13.80, 39.39)	43.0 (27.0, 58.1)	1.00	<0.001 (df=2)
Metastases only	372	248	14.36 (12.81, 16.26)	33.8 (28.3, 39.3)	1.51 (1.01, 2.27)	
Both	262	198	11.93 (10.51, 13.47)	20.6 (15.3, 26.5)	1.99 (1.32, 3.01)	



Disease stage	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 1 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Locally advanced	50	44	7.85 (5.29, 11.24)	34.9 (22.0, 48.1)	1.00	0.002 (df=2)
Metastases only	372	362	4.78 (3.91, 5.59)	14.8 (11.4, 18.6)	1.65 (1.20, 2.28)	
Both	262	250	4.27 (2.89, 5.52)	12.4 (8.7, 16.8)	1.79 (1.29, 2.48)	

	Disease stage		
	Locally advanced (N=50)	Metastases only (N=372)	Both (N=262)
	N (%)	N (%)	N (%)
Best overall response			
Complete Response (CR)	0 (0.0)	6 (1.6)	1 (0.4)
Partial Response (PR)	4 (8.0)	77 (20.7)	30 (11.5)
Stable Disease (SD)	31 (62.0)	159 (42.7)	125 (47.7)
Progressive Disease (PD)	11 (22.0)	116 (31.2)	84 (32.1)
Not Evaluable	4 (8.0)	14 (3.8)	22 (8.4)
Responders			
Failure	46 (92.0)	289 (77.7)	231 (88.2)
Responders (CR+PR)	4 (8.0)	83 (22.3)	31 (11.8)

Multivariate analysis

- Very low power in locally advanced subgroup with only N=50

Overall survival – metastases only

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Performance status	PS 0	1.00	<.001 (df=2)
	PS 1	1.84 (1.42, 2.39)	
	PS 2+	9.52 (2.24, 40.47)	
Time since initial diagnosis	<6 mon	1.00	<.001 (df=3)
	6-12 mon	0.58 (0.40, 0.86)	
	1-2 yrs	0.59 (0.40, 0.86)	
	>=2 yrs	0.44 (0.32, 0.61)	
Gender	Male	1.00	0.034 (df=1)
	Female	0.76 (0.59, 0.98)	

Overall survival – both

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Performance status	PS 0	1.00	0.002 (df=1)
	PS 1	1.57 (1.18, 2.09)	

Progression free survival – mets only

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Performance status	PS 0	1.00	<.001 (df=2)
	PS 1	1.51 (1.21, 1.87)	
	PS 2+	3.22 (0.78, 13.19)	
Time since initial diagnosis	<6 mon	1.00	<.001 (df=3)
	6-12 mon	0.73 (0.53, 1.00)	
	1-2 yrs	0.66 (0.48, 0.90)	
	>=2 yrs	0.51 (0.39, 0.66)	

Progression free survival – both

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Grade	GRADE I	1.00	0.050 (df=3)
	GRADE II	1.21 (0.66, 2.22)	
	GRADE III	1.72 (0.94, 3.15)	
	Unknown	1.68 (0.83, 3.39)	

Response rate – mets only

Parameter	Levels	Odds Ratio (95% CI)	P-value
histology	Leio	1.00	0.001 (df=3)
	Lipo	0.26 (0.11, 0.62)	
	Other	1.36 (0.66, 2.81)	
	Synov	1.03 (0.40, 2.62)	
Site of tumor	Other	1.00	0.001 (df=2)
	Extr	0.31 (0.16, 0.59)	
	Unknown	0.21 (0.05, 0.87)	
Grade	GRADE I	1.00	0.013 (df=3)
	GRADE II	3.35 (0.90, 12.51)	
	GRADE III	2.20 (0.60, 8.07)	
	Unknown	0.66 (0.15, 2.80)	
SEX	Male	1.00	0.045 (df=1)
	Female	0.56 (0.32, 0.99)	

Response rate – both:

None significant