Predictive and prognostic factors associated with soft tissue sarcoma response to chemotherapy: a subgroup analysis of the European Organisation for Research and Treatment of Cancer 62012 study

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Introduction

Soft tissue sarcomas (STS) are a group of rare aggressive tumours of mesenchymal origin, separated into over 50 different subtypes by histological and molecular classifications. Chemotherapy is the mainstay of treatment for patients with unresectable metastatic disease, and is usually administered with palliative intent. Doxorubicin and ifosfamide have single-agent activity in STS [JCO 1995 13:1537-45, EJC 2002 38:2397-406], but the role of combination doxorubicin-ifosfamide has been less certain. The European Organisation for Research and Treatment of Cancer (EORTC) 62012 study was a multi-centre randomised phase III trial of first-line single-agent doxorubicin vs intensified doxorubicin-ifosfamide chemotherapy for young, fit patients with advanced intermediate or high grade STS [Lancet Oncol 2014 15:415-23]. Combination chemotherapy was associated with a significantly higher tumour response rate (complete + partial response, 26% vs 14%; $p<0.0006$) and improved progression free survival (PFS, hazard ratio (HR) 0.74, 95% confidence intervals (CI) 0.60 – 0.90; $p=0.003$), but overall survival (OS) was not significantly different (HR 0.83, 95% CI 0.67 – 1.03; $p=0.076$). Furthermore, combination chemotherapy was associated with significantly more toxicity (Grade 3-4 febrile neutropenia 46% vs 13%; $p<0.0001$). The study authors concluded that single-agent doxorubicin was appropriate for the majority of patients with advanced STS, however combination chemotherapy was justified for selected patients in whom the primary aim of treatment was tumour shrinkage, to alleviate symptoms or to enable local disease control by subsequent surgery or radiotherapy.

A previous meta-analysis of seven heterogeneous EORTC-led clinical trials of first-line anthracycline-based chemotherapy for advanced STS reported younger age, good performance status (PS) and absence of liver metastases as prognostic of both improved tumour response to chemotherapy and OS [JCO 1999 17:150-7]. High tumour grade and liposarcoma histology were other factors associated with improved tumour response to chemotherapy, whilst low tumour grade and increased time

between initial sarcoma diagnosis and commencing first-line palliative chemotherapy were associated with improved OS.

We performed a subgroup analysis of the EORTC 62012 study to validate factors prognostic of tumour response to chemotherapy and OS in patients with advanced STS treated in a contemporary prospective randomised phase III clinic trial. We then explored tumour histology and tumour grade as predictive factors to identify patient subtypes more likely to benefit from treatment with combination chemotherapy.

Methods

Patients included in the subgroup analysis:

455 patients were recruited to the EORTC 62012 study. The detailed eligibility criteria for the EORTC 62012 study have previously been published [Lancet Oncol 2014 15:415-23], including age ≤60 years, WHO performance status (PS) 0 or 1, intermediate or high grade by local pathology opinion. Patients who received at least one cycle of chemotherapy were eligible for the subgroup analysis. A central pathology review of histology and tumour grade was performed by six expert STS pathologists. Cases without central pathology review were excluded from the subgroup analysis. Patients without sarcoma histology, or where tumour grade was low or not assessable by central pathology review, were also excluded from the subgroup analysis. Patients who did not meet other eligibility criteria for the main study were also excluded (figure 1). The subgroup analysis study population consisted of 310 patients with similar characteristics to the main study population (table 1).

Gender, age, PS, time from first presentation with sarcoma to starting palliative chemotherapy, tumour grade, histological subtype, and sites of metastases were assessed as potential predicitve factors for tumour response to chemotherapy and their relationship to prognosis, i.e. OS. Patients were included in the analysis based on central pathology review. Histological subtype and tumour grade were then assessed as factors predictive of improved tumour response and OS with combination chemotherapy. In this exploratory analysis, histological subtype and tumour grade were analysed according to local and central pathology assignment.

Statistics:

Prognostic factor analyses were performed using univariate logistic regression models for tumour response to chemotherapy, and cox regression models for OS. Factors included in the final multivariate models were identified using a reduced stepwise selection procedure. A significance

level of 0.15 was required to include a factor within the multivariate model, and a significance level of 0.05 was required for a factor to stay in the model.

Results

Central pathology review of tumour histology was available for 354/455 cases (78%). Discordance with local assessment was observed in 118 cases (33%), including six patients who did not have STS histology on central review. Central pathology review of tumour grade was available for 339/455 cases (75%). Discordance with local assessment was observed in 141 cases (42%). After excluding patients that failed other eligibility criteria, 310 patients were included in the subgroup analysis. Consistent with the main study results, combination chemotherapy was associated with improved tumour response (odds ratio (OR) 2.44, 95% CI 1.38 – 4.31; p=0.002), but OS was not significantly different (HR 0.82, 0.63 – 1.06; p=0.128).

In multivariate analysis, gender, age, PS, time from first presentation with sarcoma to starting palliative chemotherapy, tumour grade, histological subtype, and sites of metastases were assessed as potential factors predictive of tumour response to chemotherapy and improved OS. Central pathology review of histology and tumour grade were used for this analysis.

Patients with liposarcoma had improved tumour response to chemotherapy compared to other histological subtypes (p=0.014), whilst patients with metastases other than lung, liver or bone had a poorer tumour response (OR 0.42, 95% CI 0.23 – 0.78; p=0.006) (table 2). Patients with high grade tumours had an improved tumour response to chemotherapy, but this was not statistically significant (OR 1.43, 95% CI 0.76 – 2.67). Liposarcoma and other metastatic disease sites were retained as factors predictive of tumour response to chemotherapy in the final multivariate model.

PS 1 (HR 1.37, 95% CI 1.06 – 1.77; p=0.017), shorter time to palliative chemotherapy from initial STS presentation (HR 1.49, 95% CI 1.08 – 2.07; p=0.014), and presence of bone metastases (HR 1.44, 95% CI 1.00 – 2.07; p=0.052) were associated with reduced OS (table 3). In the final multivariate model, only bone metastases remained statistically significant (HR 1.56, 95% CI 1.16 – 2.09; p=0.003).

Tumour grade and histological subtype, grouped into liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS), or 'other', were assessed as predictive factors. Outcomes differed dependent on local or central pathology assignment of histological subtype (table 4). By local pathology assessment of histology, synovial sarcomas and 'other' subtypes had a higher response rate (complete + partial response) with combination chemotherapy compared to single-agent doxorubicin (43.5% vs 11.1% (OR 6.15, 95% CI 1.43 – 26.39) and 29.0% vs 10.5% (OR 3.48, 95% CI 1.27 – 9.53) for synovial sarcoma and 'other' respectively), whilst tumour response rates for liposarcoma, leiomyosarcoma and UPS subtypes did not differ significantly by treatment arm. In contrast, by central pathology assessment, the UPS subtype had a higher response rate with combination chemotherapy than with single-agent doxorubicin (42.3% vs 6.9% (OR 9.90, 95% CI 1.93 – 50.7)), but response did not differ significantly between treatment arms for liposarcoma, leiomyosarcoma, synovial sarcoma or 'other' subtypes. Analysis of OS by local pathology assessment showed no interaction between histological subtype and treatment arm, whilst patients with UPS by central pathology review had improved OS with combination chemotherapy compared with single-agent doxorubicin (HR 0.44, 95% CI 0.26 – 0.79) (figure 2),.

Irrespective of local or central pathology assessment, high grade tumours had an improved response rate with combination chemotherapy compared with single-agent doxorubicin (OR 2.93, 95% CI 1.30 – 6.61 and 3.64, 95% CI 1.72 – 7.70 by local and central pathology assessment respectively). Response rate in intermediate grade tumours by either local or central pathology assessment did not differ significantly by treatment arm. No interaction between treatment arm and tumour grade was identified in OS analysis, irrespective of local or central pathology assessment of grade.

Discussion

We observed a substantial discordance between local pathology assessment and central pathology review of histological subtype and tumour grade. This degree of discordance is consistent with levels reported by other STS studies [Lancet Oncol 2012 13(10):1045-54; Br J Cancer 1991 64(2):315-20; JCO 1989 7(12):1845-551; JCO 1986 4(11):1658-61]. Sarcoma. 2014;2014:686902. doi: 10.1155/2014/686902. Epub 2014 Aug 5.Histopathological diagnostic discrepancies in soft tissue tumours referred to a specialist centre: reassessment in the era of ancillary molecular diagnosis.Thway K[1], Wang J[1], Mubako T[1], Fisher C[1]., *OR* Sarcoma. 2009;2009:741975. doi: 10.1155/2009/741975. Epub 2009 May 27.Histopathological diagnostic discrepancies in soft tissue tumours referred to a specialist centre.Thway K[1], Fisher C. STS pathology is highly complex, and the classifications of STS subtypes are constantly evolving. Despite the growing role of molecular pathology to facilitate diagnosis, the identification of STS subtypes is still largely reliant on interpretation of tumour morphology and immunohistochemistry. Central pathology review therefore fulfils an important role in verifying the diagnosis. In contrast to local pathology opinion, which may be refined by access to additional tumour samples and clinical and radiological correlates, central pathology assessment was wholly dependent on the specimen submitted for review. As STS tumours contain areas of heterogeneity, this explains some of the discordance observed between local and central pathology opinions.

The eligibility criteria of previous clinical trials in STS frequently included patients with a variety of different histological subtypes. However, as treatments of individual subtypes are progressively refined, clinical trials increasingly recruit STS patients with specific histological subtypes. The EORTC 62043 study, a single-arm phase II trial of pazopanib in patients with advanced STS, for example, assessed treatment response in four histological cohorts of STS (leiomyosarcoma, liposarcoma, synovial sarcoma and 'others') [JCO 2009 27(19):3126-32]. On the basis of this study, patients with liposarcoma were excluded from the subsequent phase III PALETTE trial [Lancet Oncol 2012 379(9829):1879-86]. Different conclusions could be drawn from our subgroup analysis of histological subtype as a predictive factor of response to combination chemotherapy, dependent on whether local pathology or central pathology assessment of tumour histology was used. This analysis was exploratory, and was limited by small numbers of patients in each histological subgroup, but it

highlights the importance of accurate pathology classification in STS studies, and suggests a role for incorporating mandatory prospective central pathology review into future trial protocols. This should become practical as shared digital platforms become increasingly common.

The subgroup analysis suggests that synovial sarcoma, 'others' and UPS were most likely to respond to treatment with combination chemotherapy. Only UPS by central review classification had improved OS with combination chemotherapy. The lack of OS advantage with combination chemotherapy in synovial sarcoma and 'others' despite improved tumour response rates is consistent with a separate analysis of the EORTC 62012 study, which demonstrated that the absence of tumour progression not the extent of disease remission defines prognosis in STS [EJC 2015 51(S3):S688]. Synovial sarcomas are considered to be chemosensitive tumours. Previous studies have suggested synovial sarcomas have higher responses rates to chemotherapy than other STS subtypes, including improved response rates to regimens containing ifosfamide [EJC 2010 46:72-78]. UPS are aggressive high grade tumours with no discernable histological differentiation [Modern Pathology 2014 27:S39-45]. They are diagnosed by exclusion of other pleomorphic subtypes, including leiomyosarcoma and liposarcoma. Samples identified as UPS on central pathology review therefore include poorly differentiated STS subtypes, which have been re-classified on the basis of the submitted specimen. Such poorly differentiated tumours may have aggressive tumour biology that benefit more from combination chemotherapy. This would support the parallel observation that high grade tumours were more likely to respond to combination chemotherapy than intermediate grade lesions, although tumour grade did not influence OS.

We used central pathology assessment of tumour histology and tumour grade for the predictive factor analysis, as this had been undertaken by a small panel of expert sarcoma pathologists. The predictive factor analysis identified an improved tumour response rate for liposarcomas compared to other STS subtypes. Previous studies have also suggested that liposarcomas are associated with a higher response rate (J Clin Oncol 1999 17(1):150-7). Liposarcomas are a group of disparate tumours

including de-differentiated liposarcoma, pleomorphic liposarcoma and myxoid liposarcoma. Myxoid liposarcomas are considered chemosensitive, whilst de-differentiated liposarcomas are considered relatively insensitive to chemotherapy. Unfortunately, data were not collected on the proportion of liposarcoma subtypes recruited to the EORTC 62012 study.

PS is a well-established prognostic factor [BJC 2011 104:1544-50]. The EORTC 62012 study recruited patients aged ≤60 with WHO PS 0 or 1. It is therefore striking that PS was prognostic of OS despite eligibility criteria restricting the study population to young fit patients. Time between initial diagnosis of sarcoma and commencing palliative chemotherapy has previously been identified as prognostic [JCO 1999 17(1):150-7]. Patients with a shorter time to starting palliative chemotherapy from initial diagnosis (3 – 12 months) had worse OS. This cohort consisted of patients with poor tumour biology and rapidly progressive disease. A longer interval between initial diagnosis and starting chemotherapy (>12 months) implied less aggressive disease and was associated withimproved OS, whilst patients presenting with metastatic disease (interval from initial diagnosis <3 months) represented a mix of these two patient populations. The presence of bone metastases was the only factor prognostic for OS in the final multivariate model. Bone metastases were reported in 44/310 (14.1%) patients included in the subgroup analysis. A previous multi-centre retrospective analysis identified bone metastases as a poor prognostic feature, and suggested routine use of bisphosphonate therapy for patients with metastatic bone disease to delay the onset of skeletal related events (e.g. pathological fracture, spinal cord compression, or hypercalcaemia) [ClinCancer Res 2013 3:6].

In summary, we performed a subgroup analysis of the EORTC 62012 study, a large phase III trial of single-agent doxorubicin versus a doxorubicin-ifosfamide combination for advanced STS. This subgroup analysis highlights the importance of the sarcoma pathologist to the assessment of clinical trial outcomes. Single-agent doxorubicin remains standard of care first-line chemotherapy for patients with advanced soft tissue sarcoma. However, combination doxorubicin-ifosfamide is

indicated for selected patients, and this analysis suggests combination treatment may be most appropriate to consider in young fit patients with high grade, poorly differentiated tumours including UPS.

Fig 1

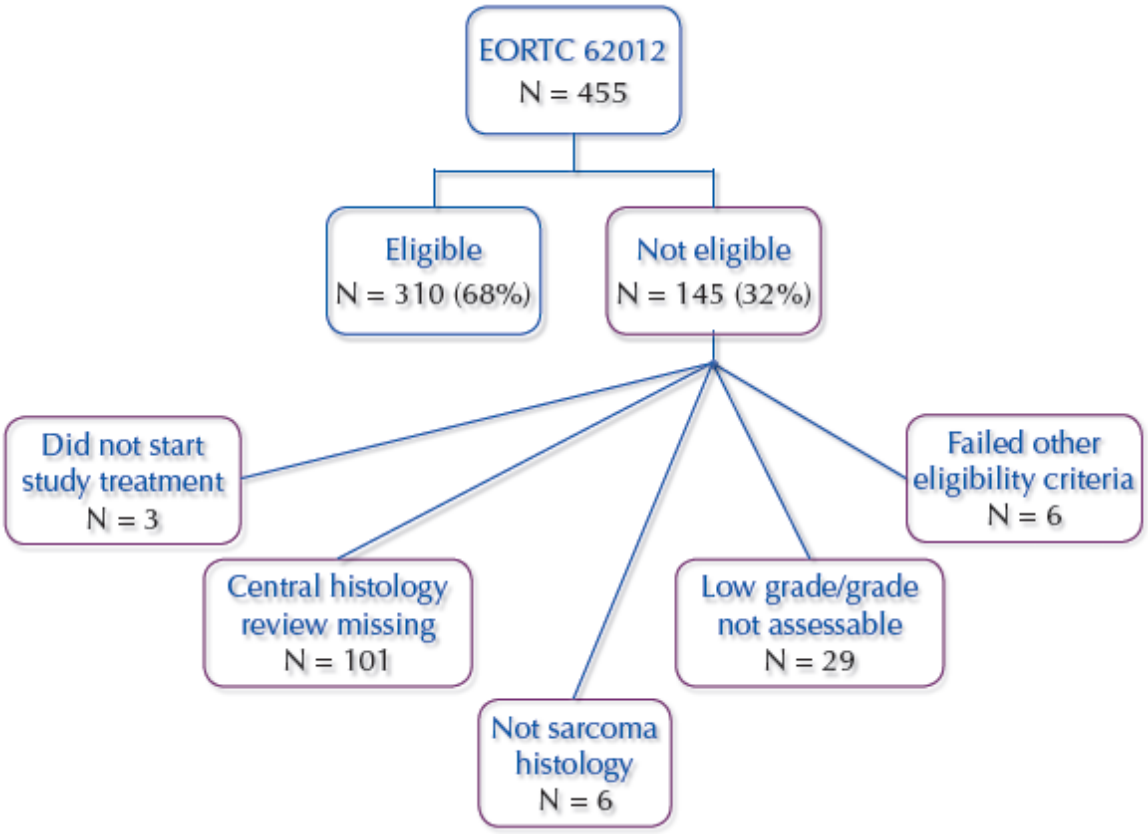

Figure 2

FIGURE 2 Interaction of histological subtype (**central** review) with treatment on overall survival

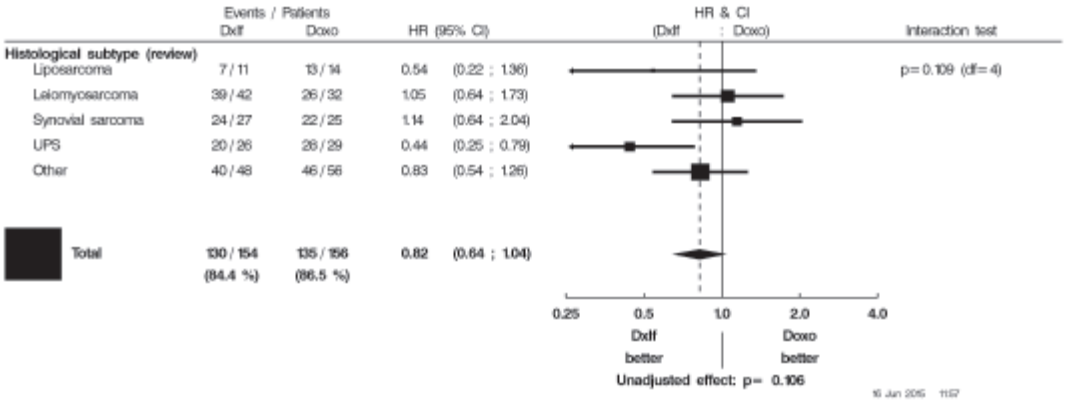

FIGURE 3 Interaction of histological subtype (**local** assessment) with treatment on overall survival

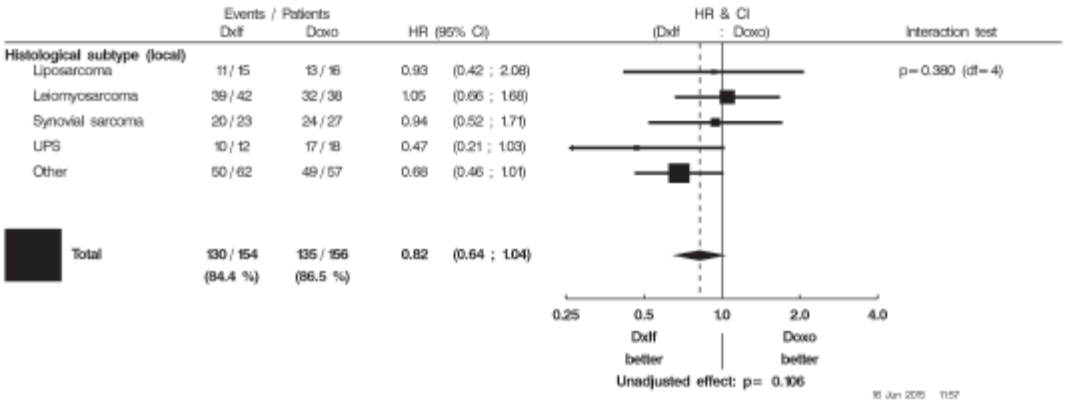

Table 1

		Analysis population	
		All patients (N=455)	All eligible patients (N=310)
		N (%)	N (%)
Treatment	Doxorubicin	228 (50.1)	156 (50.3)
	Doxorubicin + Ifosfamide	227 (49.9)	154 (49.7)
Gender	Male	217 (47.7)	148 (47.7)
	Female	238 (52.3)	162 (52.3)
Age	< 40 yrs	112 (24.6)	73 (23.5)
	40-49 yrs	148 (32.5)	94 (30.3)
	≥ 50 yrs	195 (42.9)	143 (46.1)
Performance status	0	252 (55.4)	176 (56.8)
	1	201 (44.2)	134 (43.2)
	2	2 (0.4)	0 (0.0)
Time since initial diagnosis	< 3 m	156 (34.3)	95 (30.6)
	3 - 12 m	128 (28.1)	96 (31.0)
	> 12 m	171 (37.6)	119 (38.4)
Tumor grade (review)	Low	18 (4.0)	0 (0.0)
	Intermediate	131 (28.8)	128 (41.3)
	High	190 (41.8)	182 (58.7)
	Not assessed / Unknown	116 (25.5)	0 (0.0)
Histological subtype (review)	Liposarcoma	34 (7.5)	25 (8.1)
	Leiomyosarcoma	85 (18.7)	74 (23.9)
	Synovial sarcoma	54 (11.9)	52 (16.8)
	UPS	58 (12.7)	55 (17.7)
	Other	117 (25.7)	104 (33.5)
	Not a sarcoma	6 (1.3)	0 (0.0)
	Missing	101 (22.2)	0 (0.0)
Liver metastases		80 (17.6)	53 (17.1)
Lung metastases Liver		310 (68.1)	227 (73.2)
Bone metastases		65 (14.3)	44 (14.2)
Other metastases		360 (79.1)	239 (77.1)

UPS = Undifferentiated Pleomorphic Sarcoma

Table 2

TABLE 2 Prognostic factors for best overall response (CR + PR) Multivariate analysis stratified by treatment

Parameter	Levels	Odds Ratio (95% CI)	P-value
Gender	Male	1.00	0.223 (df=1)
	Female	1.47 (0.79, 2.74)	
Age	< 40 yrs	1.00	0.752 (df=2)
	40-49 yrs	1.14 (0.49, 2.67)	
	>= 50 yrs	0.87 (0.37, 2.05)	
Performance status	0	1.00	0.907 (df=1)
	1	0.96 (0.53, 1.76)	
Time since initial diagnosis	< 3 months	1.00	0.728 (df=2)
	3-12 months	0.76 (0.34, 1.66)	
	> 12 months	0.98 (0.46, 2.07)	
Histological grade (review)	Intermediate	1.00	0.267 (df=1)
	High	1.43 (0.76, 2.67)	
Histological subtype (review)	Liposarcoma	1.00	0.004 (df=4)
	Leiomyosarcoma	0.14 (0.04, 0.45)	
	Other	0.12 (0.04, 0.36)	
	Synovial sarcoma	0.19 (0.06, 0.63)	
	UPS	0.20 (0.06, 0.62)	
Liver metastases	No	1.00	0.180 (df=1)
	Yes	0.53 (0.21, 1.35)	
Lung metastases	No	1.00	0.140 (df=1)
	Yes	1.85 (0.82, 4.19)	
Bone metastases	No	1.00	0.317 (df=1)
	Yes	1.56 (0.65, 3.72)	
Other metastases	No	1.00	0.020 (df=1)
	Yes	0.44 (0.22, 0.88)	

UPS = Undifferentiated Pleomorphic Sarcoma

Table 3

TABLE 3 Prognostic factors analysis for OS
Multivariate stratified by treatment

Parameter	Levels	Odds Ratio (95% CI)	P-value
Gender	Male	1.00	0.064 (df=1)
	Female	0.78 (0.60, 1.01)	
Age	< 40 yrs	1.00	0.502 (df=2)
	40-49 yrs	1.17 (0.80, 1.71)	
	>= 50 yrs	1.25 (0.86, 1.82)	
Performance status	0	1.00	0.017 (df=1)
	1	1.37 (1.06, 1.77)	
Time since initial diagnosis	< 3 months	1.00	0.014 (df=2)
	3-12 months	1.49 (1.08, 2.07)	
	> 12 months	0.99 (0.72, 1.35)	
Histological grade (review)	Intermediate	1.00	0.240 (df=1)
	High	1.17 (0.90, 1.50)	
Histological subtype (review)	Liposarcoma	1.00	0.257 (df=4)
	Leiomyosarcoma	1.78 (1.04, 3.02)	
	Other	1.74 (1.05, 2.90)	
	Synovial sarcoma	1.60 (0.90, 2.86)	
	UPS	1.77 (1.02, 3.07)	
Liver metastases	No	1.00	0.230 (df=1)
	Yes	1.23 (0.88, 1.73)	
Lung metastases	No	1.00	0.712 (df=1)
	Yes	1.06 (0.79, 1.42)	
Bone metastases	No	1.00	0.052 (df=1)
	Yes	1.44 (1.00, 2.07)	
Other metastases	No	1.00	0.198 (df=1)
	Yes	1.23 (0.90, 1.69)	

UPS = Undifferentiated Pleomorphic Sarcoma

Table 4

TABLE 1 - Interaction of histological subtype (**local** pathology assessment) on response to treatment

Histological subtype (local)	Total (N=310) N (%)	Doxo Responders (N=22) N (row %)	Total (N=156) N (column %)	Dxlf Responders (N=44) N (row %)	Total (N=154) N (column %)	OR (95% CI)
Liposarcoma	31 (10)	6 (37.5)	16 (10.3)	5 (33.3)	15 (9.7)	0.83 (0.19, 3.64)
Leiomyosarcoma	80 (26)	4 (10.5)	38 (24.4)	9 (21.4)	42 (27.3)	2.32 (0.65, 8.27)
Synovial sarcoma	50 (16)	3 (11.1)	27 (17.3)	10 (43.5)	23 (14.9)	6.15 (1.43, 26.39)
UPS	30 (10)	3 (16.7)	18 (11.5)	2 (16.7)	12 (7.8)	1.00 (0.14, 7.10)
Other	119 (38)	6 (10.5)	57 (36.5)	18 (29.0)	62 (40.3)	3.48 (1.27, 9.53)

TABLE 2 - Interaction of histological subtype (**central** pathology assessment) on response to treatment

Histological subtype (central)	Total (N=310) N (%)	Doxo Responders (N=22) N (row %)	Total (N=156) N (column %)	Dxlf Responders (N=44) N (row %)	Total (N=154) N (column %)	OR (95% CI)
Liposarcoma	25 (8)	7 (50.0)	14 (9.0)	5 (45.5)	11 (7.1)	0.83 (0.17, 4.06)
Leiomyosarcoma	74 (24)	4 (12.5)	32 (20.5)	8 (19.0)	42 (27.3)	1.65 (0.45, 6.05)
Synovial sarcoma	52 (17)	4 (16.0)	25 (16.0)	9 (33.3)	27 (17.5)	2.63 (0.69, 9.98)
UPS	55 (18)	2 (6.9)	29 (18.6)	11 (42.3)	26 (16.9)	9.90 (1.93, 50.7)
Other	104 (33)	5 (8.9)	56 (35.9)	11 (22.9)	48 (31.2)	3.03 (0.97, 9.47)

UPS = Undifferentiated Pleomorphic Sarcoma