**Absence of progression, not extent of tumour shrinkage defines prognosis in soft tissue sarcoma – an analysis of the EORTC 62012 study of the EORTC STBSG**

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**Abstract:**

**Background:** Anthracycline-based chemotherapy remains the mainstay of first-line treatment in metastatic or advanced soft tissue sarcoma (STS). Age, performance status, tumour histology and tumour grade are recognised prognostic factors, however the prognostic value of tumour response and tumour shrinkage is ill-defined.

**Methods:** Patients recruited to the European Organisation for Research and Treatment of Cancer (EORTC) 62012 trial with advanced intermediate or high grade STS, who received at least one cycle of chemotherapy and one tumour assessment of response were eligible for this study. Kaplan-Meier estimates of overall survival (OS) by tumour response were computed using a landmark approach after 2, 4, and 6 cycles of chemotherapy. The prognostic role of the kinetics of tumour response was analysed by Cox proportional hazards.

**Results:** 389 patients were included in this study. Compared to stable or responding patients, patients with progressive disease (PD) after 2, 4 and 6 cycles of chemotherapy achieved a worse OS (Hazard ratio (HR) 2.62 (95%CI 1.72-4.00), p<0.001; HR 2.23 (95%CI 1.4-3.56), p=0.0001; and HR 3.16 (95%CI 1.96-5.08), p=0.0001 respectively). However, patients with stable or responding disease achieved similar OS outcomes. Correspondingly, patients with an increase in tumour size by 10% or more correlated with a worse OS in Cox proportional hazard analysis.

**Conclusions:** No association between prognosis and amount of tumor shrinkage was detected. Interestingly, an increase in tumour size by at least 10% correlated with a worse OS, but re-defining PD as a ≥10% increase in tumour size did not translate into a better discrimination of survival outcomes for responders vs. stable disease. Disease control rather than tumour response is a valuable endpoint in advanced or metastatic STS receiving palliative anthracycline-based chemotherapy, supporting the use of time to event endpoints in future STS trials.

**Introduction**

Anthracycline-based chemotherapy remains the mainstay of therapy in soft tissue sarcomas (STS) since its introduction into the treatment algorithm in the 70’s [1]. Numerous studies have explored whether the combination of anthracyclines with other agents such as ifosfamide, cyclophosphamide, vincristine or dacarbazine had additional benefit [2-4]. However, none were able to show an improvement in overall survival (OS). A dose-response relationship has been reported for ifosfamide, and combinations were reported to produce response rates as high as 50-60% in small studies [3,5-7]. These results were not validated in larger data sets and many of the early studies tested agents at doses which are now considered inadequate for optimal efficacy.

The European Organisation for Research and Treatment of Cancer (EORTC) 62012 study compared single agent doxorubicin with a combination of full dose doxorubicin and ifosfamide, a contemporary dosing regimen. The combination achieved a significant increase in response rate compared to doxorubicin alone (26 vs. 14%), but failed to attain a significant OS difference [8].

Several large retrospective studies analysed pooled patient data from EORTC-led clinical trials investigating prognostic factors associated with chemotherapy response and overall survival in patients with advanced soft tissue sarcoma [9,10]. These studies identified age, performance status and tumour histology as prognostic factors. While high-grade tumours showed an increased chance of tumour response, low-grade tumours were associated with a greater overall survival. However, these retrospective analyses have not directly correlated tumour response with survival or whether the extent and speed of tumor shrinkage has prognostic value. In other neoplasms, depth of remission has been shown to have prognostic value [11,12].

The aim of this study was to assess the prognostic value of early tumour response and whether the kinetics of tumour shrinkage influences OS.

**Methods**

**Inclusion criteria**

Patients with advanced STS who were recruited to the EORTC 62012 (NCT00061984) and received at least one cycle of chemotherapy were eligible for this analysis. Patients with unconfirmed high or intermediate grade STS by central pathology review were excluded. For the analysis correlating tumour response to survival, the inclusion criteria were extended to include measurable disease with at least one follow-up assessment. The principal inclusion and exclusion criteria of the EORTC 62012 study were previously reported [8]. A detailed list for ineligibility criteria applied is depicted in the supplement (Table S1).

**Assessment of tumour response**

Tumour measurements in the EORTC 62012 study were collected and assessed by local treatment centres every other chemotherapy cycle (every six weeks) by CT scan, according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 [13]. Measurable lesions were specified at baseline and followed during the course of treatment for changes in tumor size. Each lesion was measured uni-dimensional requiring at least 10 mm at its longest diameter. Objective response (OR) reflects the locally recorded best response from the start of the treatment, after 2, 4 and 6 cycles of chemotherapy (i.e. end of treatment), or until treatment discontinuation for disease progression/recurrence or unacceptable toxicity. OR was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Unscheduled assessments in between intervals were considered as response of the next scheduled imaging. Patients who received surgical resection of residual disease were censored at the time of surgery.

**Categorization of tumour shrinkage**

The sum of the largest diameter (SLD) of target lesions was assessed for tumor shrinkage, and calculated as the percentage change of SLD from baseline measurements. Negative values represent tumour shrinkage, positive values represent tumour growth. A confirmation of response was not mandated. Patients were grouped according to changes of tumor size:

≥-50, -50 to -30, -30 to -20, -20 to -10, - 10 to 0%, or 0 to +10, +10 to +20, and >+20%.

**Overall survival**

OS was computed from the date of randomization to the date of death. Patients still alive at the time of the analysis were censored at their last follow-up date or the clinical cut-off date, whichever occurred first.

OS was landmarked after 2, 4 and 6 cycles of chemotherapy. In this case overall survival was computed as above, starting from the date of end of cycle 2, 4 and 6 till date of death.

**Statistical analysis**

Patient and tumour characteristics were summarized by eligibility status. Survival data was estimated by the Kaplan–Meier method.

The prognostic factor analyses were performed based on Cox proportional hazard models for OS.

Response assessments after 2, 4 and 6 cycles of chemotherapy were correlated with OS using a landmark approach to avoid guarantee-time bias [14].

**Results**

*Patient characteristics*

Of 455 eligible patients from the EORTC 62012 study (NCT00061984), a total of 389 met inclusion criteria for the current analysis. At the landmarks post 2, 4, and 6 cycles of chemotherapy, a total of 344, 234, and 193 patients were assessable for response (Figure 1). Patient numbers decreased at each landmark because some patients discontinued treatment early, in most cases either due to progressive disease or unacceptable toxicity. Baseline parameters were similarly distributed between the EORTC 62012 study population and those used in this analysis (Table 1), except for those parameters, which have been specifically excluded (performance status 2, low grade sarcoma, unknown grade or histology).

*Objective response*

In eligible patients, the overall objective response rate (CR+PR) was 20.3%, SD was 51.7%, and PD 25.2% (Table 2). The proportion of patients responding to treatment increased over time. After 2, 4, and 6 cycles of chemotherapy 10.1, 24.4, and 37.7% achieved either CR or PR, while the fraction of patients with PD showed decreasing numbers (25.4, 12.2, and 13.0%, respectively) (Table 2). Only 5 patients (1.3%) received secondary resection and were not assessable for response.

*Overall survival according to objective response*

Patients were grouped according to RECIST-defined response criteria (CR+PR, SD, or PD) and OS estimates were plotted after 2 (Figure 2a), 4 (Figure 2b), and 6 cycles of chemotherapy (Figure 2c). Comparison of patients with CR+PR and SD as best response after 2 cycles of chemotherapy achieved a hazard ratio (HR) of 0.94 (95% confidence interval (CI) 0.63-1.39), whereas patients with PD had worse outcome (HR 2.62 (95%CI 1.72-4.00); overall *P* <0.001). Results remained consistent when assessed after 4 (SD: HR 0.86 (95%CI 0.62-1.21); PD: HR 2.23 (95%CI 1.4-3.56); overall *P*=0.0001) and 6 cycles of chemotherapy (SD: HR 0.82 (95%CI 0.57-1.17); PD: HR 3.16 (95%CI 1.96-5.08); overall *P*=0.0001) respectively. Overall, tumour response (CR+PR) was not associated with improved OS expectations compared to patients with SD.

*Tumor shrinkage and clinical outcome*

To further dissect the prognostic value of tumour shrinkage, OS was assessed according to changes in tumour size after 2 and 4 cycles of chemotherapy. Patients with an increase in tumour size of 0-10% were used for reference. Survival estimates revealed a similar outcome pattern for patients with increase in tumor size of ≤10% or tumor shrinkage of any category after 2 and 4 cycles of chemotherapy (Figure 3A, 3B). However, patients with an increase in size by >10% had the poorest OS. Cox proportional hazard analysis confirmed OS estimates, i.e. an increase by 10-20% or >20% in tumour size was associated with a poor prognosis (HR 1.97 (95%CI 1.26-3.07) and 2.94 (95%CI 1.99-4.36); overall *P*<0.001, respectively; Table 3).

*Modified definition of progression*

A 10% threshold for PD was explored as a novel definition for progression in STS. A total of 34 patients showed a 10-20% increase in tumor size after 2 cycles of chemotherapy. However, only 18 patients were exclusively captured by this method, because RECIST-defined progression also includes non-target progression or development of new lesions. Therefore, OS estimates did not change substantially by setting a 10% increase in tumour size as the threshold for disease progression (SD: HR 0.90 (95%CI 0.60-1.34); PD: HR 2.44 (95%CI 1.61-3.69); *P*<0.001); Figure 1S).

**Discussion**

The use of anthracycline-based chemotherapy is the mainstay of treatment in STS. During the past decades, intensification of therapy has been explored in numerous trials using different dosing regimens, but none was able to show a survival benefit compared to single agent treatment. The EORTC 62012 study compared single agent doxorubicin with a contemporary dose combination of doxorubicin plus ifosfamide. While combination chemotherapy improved tumour response rates from 14 to 27%, and progression free survival (PFS, 4.6 vs. 7.4 months), the study failed its primary endpoint (10% improvement in 1-year survival) [8].

Formerly, the role of tumour response and tumour shrinkage on prognosis has not been assessed in advanced STS. In other malignancies, tumour shrinkage has been shown to have prognostic value. In renal cell carcinoma, the depth of remission correlated with OS [11], and early tumor shrinkage of at least 10% after 6 weeks of treatment with a tyrosine kinase inhibitor was also able to predict prognosis [15]. Similar findings were reported in KRAS wild-type metastatic colorectal and advanced non-small cell lung cancer treated with targeted agents [16,17].

The role of changes in tumour size in response to chemotherapy seems to be different. A recent study of the RECIST working group of the EORTC was not able to show a major prognostic value of tumour response in more than 3700 patients with breast, lung, or colorectal cancer [18]. It seems conceivable that changes in tumour size may have distinct impacts on prognosis in different diseases, and may vary between molecularly targeted and conventional cytotoxic chemotherapy.

Our data support this notion. In advanced or metastatic sarcoma patients treated with anthracycline-based first line chemotherapy, neither achievement of an objective tumour response nor the extent of tumor shrinkage of target lesions was prognostically relevant, although the number of patients achieving a CR or going on to surgical resection of residual disease were small. However, an increase in tumour size by more than 10% or RECIST-defined disease progression correlated with poor OS, indicating that absence of progression is a key parameter for clinical outcome in sarcoma.

Our data supports the notion that time to event endpoints are crucial for capturing clinical activity in STS - a concept which was implemented in 2002, when PFS rate was suggested as an efficacy read-out of early clinical trials in STS [19]. Future treatment strategies should focus on disease control as an important endpoint for efficacy of palliative chemotherapy in STS, which may be captured by PFS as a surrogate for OS.

The major strength of our study is its prospective data collection on contemporary palliative chemotherapy regimens across Europe, which includes pre-specified time points for tumour imaging. The major limitation of our study is its *post-hoc* nature, which was not previously specified. Furthermore, re-imaging per se is prone to observer divergence thereby adding variability to our analysis.

Given the role of disease control in advanced or metastatic STS, the concept of maintenance therapy may become more appealing. Instead of increasing toxicities by administration of combination therapy, maintenance and sequential treatment may improve patient outcomes whilst minimizing toxicities. A recent study showed that PFS was improved by maintenance treatment with ridaforolimus, an inhibitor of the mammalian target of rapamycin (mTOR) [20]. However, the increment delivered was not considered clinically meaningful, and it failed to gain a license in STS. Outstanding questions in relation to that study include the efficacy of mTOR inhibitors in different STS subtypes.

In conclusion, our data show that absence of progression and not extent of tumor shrinkage is a surrogate for survival in advanced STS treated with palliative first line anthracycline-based chemotherapy. This observation may be important for future treatment concepts in sarcoma, such as maintenance therapy for metastatic patients. Clearly, these data should not be extrapolated to localized disease, which is treated with curative intent.

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**Conflict of interest**

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