18F-FDG-PET/CT imaging as an Early Survival Predictor in Patients with Primary High Grade Soft Tissue Sarcomas undergoing Neoadjuvant Therapy

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Running head 18F-FDG-PET for survival prediction in STS

Key Words Sarcoma, PET/CT, Neoadjuvant Therapy, Treatment Monitoring, Outcome

Research Support: UCLA ICMIC (5 P50 CA086306) and the UCLA DOE (DE-FG02-06ER64249) grants.

Previous Presentation: none.
Statement of Translational Relevance.

We previously reported that $^{18}$F-FDG-PET imaging identified histopathologic treatment responders at the end of (1) and after a single cycle (2) of neoadjuvant therapy. Here we demonstrate that FDG-PET permits survival predictions after the initial cycle of neoadjuvant chemotherapy in patients with STS. FDG PET can therefore serve as early intermediate endpoint biomarker in research and clinic. Such information cannot be derived from CT based serial tumor size measurements.

The ability to assess treatment response early during the course of therapy can potentially guide management decisions. Treatment could be switched from neoadjuvant therapy to immediate surgery in non-responding patients while it would be continued in responders. Such risk adapted therapy could reduce treatment associated morbidity and costs. Further prospective trials will determine whether early PET based changes in patient management result in improved patient outcome.
Abstract

PURPOSE: Neoadjuvant therapy is associated with considerable toxicity and limited survival benefits in patients with soft tissue sarcoma (STS). We prospectively evaluated whether 18F-FDG PET/CT imaging after the initial cycle of neoadjuvant therapy could predict overall survival in these patients.

EXPERIMENTAL DESIGN: 39 patients underwent 18F-FDG PET/CT prior to and after one cycle of neoadjuvant therapy. 56 patients underwent end of treatment PET. Overall survival was, among others, correlated with changes of SUVpeak and histopathology.

RESULTS: One-, two- and five-year survival rates were 95±3.0%, 86±4.6% and 68±6.6%, respectively. Median time to death was 30.9 months (mean: 27.7; range: 6.9 – 50.1). Optimal cut-offs for early and late decreases in SUV peak (26% and 57%, respectively) were significant predictors of survival in univariate survival analysis (p=0.041, HR=0.27 95%CI: 0.08 to 0.95, and p=0.045, HR=0.31 95%CI: 0.10 to 0.98). Seven/15 early PET non-responders but only 4/24 early PET responders died during follow up (p=0.068). The only other significant survival predictor was surgical margin positivity (p=0.041, HR 3.31 95%CI: 1.05 to 10.42). By multivariable analysis early metabolic response (p=0.016) and positivity of surgical margins (p=0.036) remained significant survival predictors.
CONCLUSION: $^{18}$F-FDG-PET predicted survival after the initial cycle of neoadjuvant chemotherapy in patients with STS and can potentially serve as an intermediate endpoint biomarker in clinical research and patient care.
Introduction:

Assessing therapeutic responses early during the course of cancer therapy is important because non-responding patients can be switched to alternative management strategies including earlier surgical resection. This is of particular importance when patients undergo marginally beneficial treatments. One such example is the frequently employed but still controversial neoadjuvant chemo- or chemoradiation therapy of patients with soft tissue sarcoma (STS) (3).

STSs are associated with an overall 5 year survival rate of approximately 50% (4). Patient prognosis depends on tumor grade, size, histology, depth, surgical margins and the presence of metastasis at the time of diagnosis. Moreover, histopathological response to neoadjuvant chemo- or chemo/radiation therapy has also been shown to predict patient outcome (5, 6).

Only 20-30% of patients with STS achieve a significant histopathologic response to neoadjuvant treatment (1, 2). Intermediate endpoint biomarkers to identify treatment responders and non-responders early during therapy are therefore needed to reduce side effects and costs of ineffective treatments (7-9).

18F-FDG-PET imaging has been used to identify histopathologic treatment responders at the end of (1) and as early as after one cycle (2) of neoadjuvant therapy. Similar results were also reported from other institutions (10, 11).

Based on these encouraging findings we hypothesized that early and late changes in tumor FDG uptake might predict long term survival of patients with STS undergoing neoadjuvant therapy.
Patients and Methods:

Seventy-eight consecutive patients with high grade soft tissue sarcoma were enrolled in this prospective study between February 2005 and April 2008. Correlations between PET findings and histopathological response have been reported previously (1, 2). Exclusion criteria were patient age of < 18 years, chemotherapeutic and/or radiotherapy within 6 months prior to the baseline PET/CT scan, presence of a second malignancy, unresectable disease, and a diagnosis of gastrointestinal stromal tumor (GIST). In addition, 21/78 patients (27%) were excluded from this analysis as they presented with recurrent and/or metastatic disease at the time of the baseline scan (primary and concurrent metastatic disease in 8 patients, recurrent disease in 5 patients, and recurrent metastatic disease in 8 patients, respectively). Thus, the current study population consisted of 57 patients with primary, non-metastatic soft tissue sarcoma who underwent neoadjuvant therapy followed by surgery (Table 1). The study was approved by the UCLA IRB and all patients provided written informed consent for their participation.

Neoadjuvant therapy. The neoadjuvant treatments were ifosfamide- (n=52; 91%) or gemcitabine-based (n=5; 9%). Standard first-line ifosfamide-based chemotherapy consisted of two cycles of ifosfamide (14g/m²) followed by doxorubicin (60-90mg/m²). Standard gemcitabine-based chemotherapy consisted of two cycles of gemcitabine (900 mg/m² on day 1 and 8) and docetaxel (75-100 mg/m² on day 8).
Forty-six patients (81%) received neoadjuvant external beam radiation starting after the first cycle of chemotherapy and following the early follow up PET/CT scan. Eleven patients (19%) received no radiation therapy due to location or extent of the primary disease.

**PET/CT imaging.** All 57 patients underwent a baseline scan prior to initiation of chemotherapy. A second (early follow up) study was performed in 39 patients after the initial cycle of chemotherapy and prior to radiation treatment. 36 of these 39 patients had been previously studied for correlation between histopathological response and PET findings. Seventeen/18 patients not undergoing the early follow up scan were included into this study prior to January 2006. An end-of-treatment scan (late follow up) was performed in 56 patients. One patient had rapid clinical progression after the first cycle of chemotherapy and opted for surgery before undergoing the late follow up scan. 38 patients underwent both, the early and late follow up scans.

Emission scans started at median intervals of 92 min (mean: 96 ±22 min; interquartile range (IQR): 79 - 107 min) 69 min (mean: 78 ±27 min; IQR: 60 – 90 min) and 90 min (mean: 93 ±20 min; IQR: 80 – 104 min) at baseline, early and late follow up, respectively. This resulted in median time differences in tracer uptake between baseline, early and late follow-up scan of 18 min (mean: 28 ±26 min; IQR: 8 – 42 min) and 14 min (20 ±18 min; IQR: 7 – 25 min), respectively. Early and late follow up studies were performed 26.3±7.4 (median: 25.0) days
and 104.7±37.6 (median: 98.0) days respectively after the baseline PET/CT study. Median time from late follow up PET/CT to surgery was 7.0 days.

All PET/CT studies were performed using the Siemens® Biograph Duo. The image acquisition protocol was reported before (12). In brief, after a minimum fasting period of 6 hours serum glucose levels were below 180 mg/dl in all patients. Patients received 0.21 mCi/kg of $^{18}$F-FDG-PET intravenously. PET emission scans were acquired using a weight based protocol and during shallow breathing as reported previously (13-15). PET images were reconstructed using an iterative algorithm (OSEM two iterations, eight subsets). The CT acquisition parameters were 130 kVp, 120 mAs, 1-s tube rotation, 4-mm slice collimation, and a bed speed of 8-mm/s. The CT images were reconstructed using filtered back-projection, at 3.4 mm axial intervals to match the slice separation of the PET data. A previously published CT-based algorithm was used for attenuation correction (16).

**Image analysis.** $^{18}$F-FDG-PET images were analyzed by one observer who was aware of the clinical diagnosis but blinded to histopathological treatment response, and progression free and overall survival. All $^{18}$F-FDG-PET studies were analyzed quantitatively as previously described (17). SUVpeak was defined by the average pixel value within a 15 mm 2D ROI drawn around the highest radioactivity concentration in a single plane, which was determined in a 3D volume covering the total tumor area. This approach was used for baseline and follow up scans. SUVs are given as g/ml (SUV = activity concentration in the
tumor (Bq/ml) x body weight (g) / injected activity (Bq)). Intravenous contrast (Omnipaque®, Novaplus) for CT imaging was given in all patients on baseline and follow up scans at a rate of 2 ml per second 30 to 40 seconds before imaging commenced unless contraindicated. Physicians with multi-year experience in CT interpretation, blinded to histopathologic response and survival data, analyzed all CT images as follows: A soft tissue window was used to display tumor images on CT. Maximum tumor diameter was measured before treatment, after the initial cycle of chemotherapy, and after completion of chemotherapy. Anatomic tumor response was determined using RECIST1.0 (18).

**Outcome assessment.** Clinical follow-up of patients was performed at least every six months or at shorter intervals as clinically indicated, and consisted of standard evaluations including imaging (radiograph, CT and/or MRI). Disease progression was documented if new lesions appeared on follow up imaging. Overall survival for the total population was calculated from date of the baseline PET/CT study to the date of death or to the date of last follow-up. To account for different time points of response assessments (1st and 2nd metabolic response assessment and histopathological response) survival times were also calculated from the dates of the 1st- and 2nd follow up PET-assessment and the date of surgery.

**Metabolic response (PET response).** Changes of SUVpeak from baseline to early and late follow up were determined. ROC-analysis was performed to
establish the degree of change that provided the best survival prediction. This identified decreases in SUVpeak by 26% and 57% for the early and late time points, respectively, as the best survival predictors. Early metabolic response was therefore defined as a decrease of SUVpeak of greater than 26%, while tumors with decreases in SUVpeak of equal or less than 26% were categorized as metabolically non-responding. Late metabolic response was accordingly defined as a decrease of SUVpeak of greater than 57%.

**Histopathology.** All specimens were analyzed by one pathologist, who was blinded to PET and CT data. Each specimen was sectioned at 1 cm intervals and a gross assessment of tumor necrosis was recorded. Sections were submitted for histological analysis from all areas of the tumor, with careful attention to sampling areas with different gross appearances. At least one block per centimeter of largest tumor diameter was submitted, per standard protocol. Histopathologic response (% necrosis, fibrosis) was quantified as the fraction of necrotic or fibrotic tissue in the tumor to the nearest 5%. Patients with ≥95% pathologic necrosis or fibrosis were classified as histopathologic responders as suggested previously (8).

**Statistical analysis.** Quantitative data are presented as median, range, and mean ± SD. The Wilcoxon signed rank test and the Mann-Whitney test were used for paired and unpaired comparisons of quantitative parameters. The Chi square- or Fisher exact test was conducted for comparison of frequency data.
between independent subgroups. Receiver operating characteristic curves (ROC curves) were used to determine optimal cut-off values for defining metabolic response for the prediction of survival. Fisher’s exact test was used to assess association of two categorical variables. A multivariable logistic regression analysis was employed to test for association of early changes in SUVpeak and histopathologic response (≥95% vs. <95%) while controlling for radiotherapy. Survival probabilities were calculated according to the Kaplan-Meier method and the log-rank test was used for statistical comparison of survival curves between independent subgroups. Multivariable survival analysis was performed by Cox proportional hazard regression and corresponding hazard ratio estimates were provided with ninety-five percent confidence intervals.

Statistical analyses were performed using IBM© SPSS© Statistics software for Windows© (version 19.0, SPSS Inc., Chicago, USA). All statistical tests were performed two-sided and a p-value < 0.05 was considered to indicate statistical significance. No correction of p-values was applied to adjust for multiple tests (19).
Results:

Survival. Seventeen deaths occurred during a median follow-up period of 55 months (maximum follow-up: 76 months). The one-, two- and five-year survival rates were 95±3.0% (n=54), 86±4.6% (n=49) and 68±6.6% (n=14), respectively. Median time to death was 30.9 months (mean: 27.7; range: 6.9 – 50.1).

Baseline Tumor ¹⁸F-FDG-uptake. SUVpeak averaged 9.5±6.5 g/ml (median, 7.5; range, 2.5-30.7) and was similar in surviving and non-surviving patients (9.3±6.4 vs 10.1±7.0, p=0.8).

Early changes in tumor ¹⁸F-FDG uptake: 39 patients underwent an early ¹⁸F-FDG-PET after one cycle of chemotherapy. 85% of these received neoadjuvant chemoradiation therapy while 15% received only neoadjuvant chemotherapy. SUVpeak decreased by 16.5±73.1% (median: 29.3%) from 10.2±6.9 to 7.1±5.1 (p<0.001) (Figure 1). Decreases in SUVpeak did not differ significantly between surviving and non-surviving patients (-32.5% vs. -24.0%, p=0.132). Seven of 15 early PET non-responders but only 4/24 early PET responders died during follow up (p=0.068). The overall survival rate 5 years after the 1st follow up PET scan was 82%±8% in early metabolic responders but only 45%±16% in early metabolic non-responders.
Late changes in tumor $^{18}$F-FDG uptake: 56 patients underwent end-of-treatment $^{18}$F-FDG-PET studies. SUVpeak decreased by 44.8±3.6% from 9.6±6.5 to 4.6±3.4 (p<0.001) (Figure 1). Decreases in SUVpeak did not differ significantly between survivors and non-surviving patients (-50.7% vs. -29.9%; p=0.110). Twelve of 29 late PET non-responders but only 4/27 late PET responders died during follow up (p=0.028). The overall survival rate 5 years after the 2nd follow up PET-scan was 85%±7% in late metabolic responders but only 54%±10% in late metabolic non-responders.

Changes in tumor diameter. At baseline (n=57), tumor size averaged 10.7±4.5 cm (median, 10.2 cm; range, 3.6-21.4 cm). Tumor size remained essentially unchanged on early (11.1±5.6 cm vs. 10.7±4.6 cm; n=39) and late follow up scans (10.7±5.4 cm vs. 10.7±4.6 cm: n=56). By RECIST, 36 patients (92%) had stable disease at early follow up while three (8%) exhibited progressive disease. At late follow up 2/56 (4%) patients who completed therapy were classified as partial responders, nine had progressive disease (16%) and 45 (80%) had stable disease. All patients with progressive disease had local progression and proceeded to surgery regardless.

Histopathologic response. The extent of histopathologic necrosis and fibrosis in excised tumor tissue averaged 62±30% ranging from 5-99%. Fifteen patients (26%) exhibited ≥95% response in the resected specimen and were therefore classified as histopathologic responders (26% response rate).
The sarcoma subtype of histopathological responders included sarcoma not-otherwise specified (NOS; n=6), synovial sarcoma (n=2), liposarcoma (one each pleomorphic and dedifferentiated; n=2), rhabdomyosarcoma (pleomorphic; n=1), MPNST (n=1), leiomyosarcoma (non-uterine, n=1), angiosarcoma (n=1) and extra-osseous Ewing’s sarcoma (n=1).

Survival analysis. We have previously identified early and late SUVpeak reductions by 35% and 60% as the best predictors of histopathologic response. However, histopathologic response was not predictive of patient survival in the current study (p-value: log-rank test=0.401) (Figure 2). Therefore, we conducted ROC-analyses to assess the predictive value of early and late changes in SUVpeak for survival. The optimum thresholds for survival predictions by ROC-curve analysis were decreases of baseline SUVpeak (AUC=0.659) by 26% and 57 % for early and late time points, respectively (AUC=0.638).

Univariate analysis was performed comprising a wide range of different parameters as detailed later. For the multivariable analysis only parameters that reached statistical significance in the univariate analysis were used. As early and late responses are dependent parameters only one of the two was considered in the multivariable analysis to avoid multicolinearity.

Univariate survival analysis. In the univariate survival analysis (11 deaths in 39 patients for the early and 16 deaths in 56 patients for the late response evaluation respectively), early and late decreases in FDG tumor uptake (by ROC
curve analysis) were significant predictors of survival (log-rank test: p=0.030 and p=0.034, respectively) (Figure 2). In contrast, late RECIST was not predictive of survival (p=0.801 by log rank test) (Figure 2). According to early RECIST, none of the patients responded to therapy. Therefore, the log-rank test was not applicable.

Further univariate survival analyses included other parameters reportedly predictive for sarcoma outcome (18). These include age, gender, sarcoma location (extremity, abdominal and thoracic), initial tumor size (≤5 cm, 5-10 cm and >10 cm), histology (tumor subtype), histopathological response, type of neoadjuvant treatment (chemo- vs. chemoradiotherapy), depth of tumor invasion (superficial and deep) and resection margin (positive vs. negative).

The only significant survival predictors were positivity of margins (p=0.011, HR 3.61 95%CI: 1.26 to 10.4) and early (p=0.041, HR=0.27 95%CI: 0.08 to 0.93) and late metabolic response (p=0.045, HR=0.32 95%CI: 0.10 to 0.98) (Table 2).

**Multivariable survival analysis.** Since early and late metabolic responses are dependent parameters 2 separate analyses were performed using only one PET response parameter. When combining early metabolic response with margin positivity only early metabolic response remained a significant predictor (p=0.016, HR=0.21, 95%CI: 0.06 to 0.75).

When late metabolic response and positivity of margins were combined only margin positivity was a significant prognosticator (p=0.036, HR=3.54, 95%CI:
1.09 to 11.52) while late changes in SUVpeak only tended to be predictive (p=0.079, HR=0.36, 95%CI: 0.11 to 1.13).
Discussion:

This prospective study demonstrates that FDG-PET imaging after a single cycle of neoadjuvant therapy may serve as an early intermediate endpoint biomarker to predict the survival of patients with STS undergoing neoadjuvant therapy. The ability to assess treatment response early during therapy might potentially be used to guide management decisions. Treatment could be switched from neoadjuvant therapy to immediate surgery in non-responding patients while it would be continued in responders. Such risk adapted therapy could reduce treatment associated morbidity and potentially costs.

Given the costs, toxicity and marginal outcome benefits of neoadjuvant treatments in STS (7, 9) intermediate biomarkers to identify responders and non-responders early during therapy are needed. Univariate analysis revealed that only early and late PET response and surgical margin positivity were significantly associated with survival. The latter confirms previously published data (20-22).

Frequently used prognostic parameters (18) were not predictive. These included age, gender, site of the sarcoma, initial tumor size, histology, histopathological response, type of neoadjuvant treatment and depth of tumor.

Early changes of SUVpeak remained a significant independent survival predictor even after inclusion of margin positivity. In contrast, late changes of SUVpeak were not predictive by multivariable analysis. The early PET responses might potentially be the most relevant survival predictor as both margin positivity and late PET response only allow for much later changes in patient management.
The value of neoadjuvant therapy in patients with soft tissue sarcoma is controversial (3). In fact, there is no evidence that significant survival benefits are associated with this strategy. Therefore, if reliable early response markers (intermediate endpoint biomarkers) were to become available, non-responding patients could undergo immediate surgery while responding patients would continue the neo-adjuvant treatment. CT measurements cannot provide response assessments in soft tissue sarcoma (2). Thus, early response assessments with FDG-PET could potentially shorten the duration of ineffective chemotherapy and thereby potentially reduce costs, the number of hospitalizations due to side effects and the use of palliative interventions required to treat these side effects.

As previously shown in a cohort of more than 400 patients, histopathological response to neoadjuvant chemo- or chemoradiation therapy predicted patient survival (5, 6). This is in contrast to the findings of the current study and might be explained by the relatively small current sample size. We therefore modeled whether and under which conditions a larger sample size might have resulted in significant response predictions by histopathology. Here we assumed an accrual time of five years, a minimum follow-up of three years, and a five year-overall survival of 63% for histopathological non-responders and 80% for histopathological responders. We further assumed a 25% rate of histopathologic response (approximately the same response rate observed in the current study). Using these parameters a study population of 250 patients would have been required to achieve statistical significance at a power of 0.80.
RECIST responders and non-responders had comparable five year survival rates of 62% and 69%, respectively (p=0.80). Using the same parameters as for histopathological response, a study population of 2880 patients would have been required to achieve statistical significance at a power of 0.80. The failure of tumor size based response measurements to separate reliably between responding and non-responding STS may be caused among others by intratumoral hemorrhage, necrosis, and edema all of which may present as mass. It should be noted that in addition to the increasing acceptance of PET imaging as a valuable tool other imaging approaches are under investigation for response assessment in sarcoma and other cancers. These include diffusion weighted magnet resonance imaging (DW-MRI) (23), and dynamic contrast enhanced (DCE-) MRI (24), as well as new response criteria / analysis methods, e.g. the previously published Choi criteria. Future prospective multi-center trials need to address whether these cross sectional imaging derived criteria are superior to molecular imaging based response classification systems or provide additional prognostic information.

We and other groups have previously reported that histopathological treatment response can be predicted in sarcoma patients by changes of $^{18}$F-FDG-uptake after completion (1, 11), as well as after one (2, 11) and two cycles of chemotherapy (10). The early predictive changes in SUVpeak are strikingly similar to those reported for other tumors including ovarian cancer (20%) (25), Melanoma (30%) (26), GIST (25%) (27), Lung Cancer (20%) (28), squamous cell cancer of the
esophagus (20%) (29), as well as those reported in our previous studies in sarcoma (2). Moreover, late predictive changes are also comparable to those reported for other cancers including colorectal (62.5%) (30), squamous cell carcinoma of esophagus (52%) (31) and sarcoma (1). This suggests that previously proposed PET response criteria are useful across a wide variety of cancers, including soft tissue sarcoma. It also supports the notion that FDG-PET response criteria are applicable across a wide range of sarcoma subtypes and treatments.

Schuetze et al. reported that changes in SUVmax by 40% were the best cutoff for prediction of survival (34). The difference between this and the current threshold is not surprising since they measured changes in tumor FDG uptake at various times after start of treatment (2-4 cycles) and none of the patients received neoadjuvant radiotherapy.

Before translating our results into the clinic, a number of limitations have to be addressed. First, we used the simple, straight-forward SUV approach for assessment of therapy responses. The use of full kinetic analysis and/or 3D volumes of interest may have provided different results as recently shown in gastrointestinal cancers (32, 33). Secondly, the considerable intra- and inter-individual difference in uptake times of FDG-PET scans is an important limitation potentially affecting response assessments. However, differences in uptake time in this specific cohort with median uptake times >60 min for baseline, early and late PET scan are less relevant than if imaging would have been performed after 45 min since SUVs are more stable after longer uptake times. Third, patients
received two different chemotherapies which might have affected FDG tumor uptake differently. Fourth, patient management upon recurrence might have confounded the association between initial biomarkers and outcome in favor of non-responding patients. However, the degree of such bias could not be addressed in the current study. Finally, it is unknown whether the various sarcoma subtypes show comparable changes in FDG uptake in response to treatment.

In conclusion, the current study suggests that $^{18}$F-FDG-PET allows survival predictions after the initial cycle of neoadjuvant chemotherapy in patients with STS and might therefore potentially serve as early intermediate endpoint biomarker in research and clinic. Such information cannot be derived from CT based serial tumor size measurements. These findings support additional prospective trials to examine whether changes in $^{18}$F-FDG uptake early after start of treatment can be used to guide therapeutic decisions in sarcoma patients. The design of such study could mimic the MUNICON trial (34) in which glucose metabolic changes by $^{18}$F-FDG-PET were used to decide whether neoadjuvant treatment in patients with gastroesophageal cancer should be continued or discontinued two weeks after start of neoadjuvant therapy.
Table 1. Clinical, pathological and treatment characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=57) n (%)</th>
<th>Early Subgroup (n=39) n (%)</th>
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<tbody>
<tr>
<td><strong>Age (y)</strong></td>
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</tr>
<tr>
<td>Median (range)</td>
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<td>20 (51)</td>
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<td>5 (13)</td>
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<tr>
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<td>3 (8)</td>
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<tr>
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<td>≥95% (responder)</td>
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<tr>
<td>Median (range)</td>
<td>48.5 (6.9 – 76.4)</td>
<td>46.0 (6.9 – 64.4)</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (12)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Negative</td>
<td>50 (88)</td>
<td>35 (90)</td>
</tr>
</tbody>
</table>

Abbreviations: NOS, not-otherwise specified; MPNST, malignant peripheral nerve sheath tumor.
Table 2. Univariate survival analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-Value</th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>0.116</td>
<td>1.03</td>
<td>0.99</td>
<td>1.07</td>
</tr>
<tr>
<td>Gender*</td>
<td>0.774</td>
<td>1.15</td>
<td>0.44</td>
<td>2.98</td>
</tr>
<tr>
<td>Site*</td>
<td>0.107</td>
<td>1.65</td>
<td>0.88</td>
<td>3.07</td>
</tr>
<tr>
<td>Size**</td>
<td>0.817</td>
<td>0.79</td>
<td>0.10</td>
<td>5.97</td>
</tr>
<tr>
<td>Histology**</td>
<td>0.296</td>
<td>1.83</td>
<td>0.59</td>
<td>5.68</td>
</tr>
<tr>
<td>CTx vs. RCTx*</td>
<td>0.669</td>
<td>1.31</td>
<td>0.38</td>
<td>4.57</td>
</tr>
<tr>
<td>Pathological Response**</td>
<td>0.590</td>
<td>0.71</td>
<td>0.20</td>
<td>2.49</td>
</tr>
<tr>
<td>Depth**</td>
<td>0.560</td>
<td>0.05</td>
<td>0.00</td>
<td>1428.59</td>
</tr>
<tr>
<td>Margin Positivity**</td>
<td>0.041</td>
<td>3.31</td>
<td>1.05</td>
<td>10.42</td>
</tr>
<tr>
<td>Early Response***</td>
<td>0.041</td>
<td>0.27</td>
<td>0.08</td>
<td>0.95</td>
</tr>
<tr>
<td>Late Response****</td>
<td>0.045</td>
<td>0.31</td>
<td>0.10</td>
<td>0.98</td>
</tr>
<tr>
<td>RECIST late****</td>
<td>0.614</td>
<td>1.38</td>
<td>0.39</td>
<td>4.85</td>
</tr>
</tbody>
</table>

Abbreviations: HR, Hazard Ratio; CTx, chemotherapy; RCTx, radiochemotherapy. Survival times were calculated from *date of baseline, **date of surgery, ***date of 2nd PET/CT scan and ****date of 3rd PET/CT.
**Figure and Table Legends**

**Table 1.** Clinical, pathological and treatment characteristics of all 57 patients.

**Table 2.** Univariate analysis displaying level of significance (p-value) and hazard ratio (HR) as well the corresponding 95% confidence intervals.

**Figure 1.**

Panel A: 20 year-old female treatment responder with primary synovial sarcoma of the left thigh (diagnosis). Baseline SUVpeak decreased by 79% at early and 81% at late follow up. The largest tumor diameter increased by 1% and 4%, respectively (stable disease according to RECIST). Histopathology revealed 20% necrosis in excised tumor tissue (histopathological non-response). Patient was alive without disease at the last follow-up 44.4 months after inclusion into the study.

Panel B: 43 year-old female treatment non-responder with NOS of the right chest (diagnosis). Baseline SUV increased by 44 % at early and 11% at late follow up compared to baseline. The largest tumor diameter increased by 6% and 1%, respectively (stable disease according to RECIST). Histopathology revealed 25% necrosis in excised tumor tissue (histopathological non-response). Patient presented disease recurrence 17.0 months and died of the disease 37.8 months after inclusion into the study.
Figure 2. Kaplan-Meier Survival Curves comparing responders and non-responders of A) histopathological response (p=0.401), B) RECIST (p=0.801), C) early metabolic response (SUVpeak decrease >26%; p=0.027) and d) Late Metabolic Response (SUVpeak decrease >57%; p=0.035; all p-values according to log-rank test). Survival times were calculated from date of surgery (A), date of 2nd PET/CT scan (C), and date of 3rd PET/CT scan (B and D), respectively.


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Clin Cancer Res  Published OnlineFirst February 14, 2012.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-11-2139

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