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

Ken Herrmann¹, Matthias R. Benz¹, Johannes Czernin¹, Martin S. Allen-Auerbach¹, William D. Tap², Sarah M. Dry³, Tibor Schuster⁶, Jeff J. Eckardt³, Michael E. Phelps¹, Wolfgang A. Weber¹,⁷, and Fritz C. Elber¹,⁴

**Abstract**

**Purpose:** Neoadjuvant therapy is associated with considerable toxicity and limited survival benefits in patients with soft tissue sarcoma (STS). We prospectively evaluated whether 2[18F]fluoro-2-deoxy-o-glucose (18F-FDG)-PET/computed tomographic (CT) imaging after the initial cycle of neoadjuvant therapy could predict overall survival in these patients.

**Experimental Design:** Thirty-nine patients underwent 18F-FDG-PET/CT before and after one cycle of neoadjuvant therapy. Fifty-six 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 cutoff values for early and late decreases in SUVpeak (26% and 57%, respectively) were significant predictors of survival in univariate survival analysis (P = 0.041; HR, 0.27; 95% confidence interval [CI], 0.08–0.95 and P = 0.045; HR, 0.31; 95% CI, 0.10–0.98). Seven of 15 early PET nonresponders but only four of 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, 1.05–10.42). By multivariable analysis, early metabolic response (P = 0.016) and positivity of surgical margins (P = 0.036) remained significant survival predictors.

**Conclusion:** 18F-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. *Clin Cancer Res; 18(7); 2024–31. ©2012 AACR.*

**Introduction**

Assessing therapeutic responses early during the course of cancer therapy is important because nonresponding 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. 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 cutoff values for early and late decreases in SUVpeak (26% and 57%, respectively) were significant predictors of survival in univariate survival analysis (P = 0.041; HR, 0.27; 95% confidence interval [CI], 0.08–0.95 and P = 0.045; HR, 0.31; 95% CI, 0.10–0.98). Seven of 15 early PET nonresponders but only four of 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, 1.05–10.42). By multivariable analysis, early metabolic response (P = 0.016) and positivity of surgical margins (P = 0.036) remained significant survival predictors.

**Conclusion:** 18F-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. *Clin Cancer Res; 18(7); 2024–31. ©2012 AACR.*

**Authors**

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**Affiliations:** ¹Department of Molecular and Medical Pharmacology, Ahmanson Translational Imaging Division, Divisions of ²Molecular Oncology, ³Orthopedic Oncology, and ⁴Surgical Oncology, ⁵Department of Pathology, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, California; ⁶Institute of Medical Statistics and Epidemiology, Technische Universität München, Munich; and ⁷Abteilung Nuklearmedizin, Universität Freiburg, Freiburg, Germany

**Corresponding Authors:** Fritz C. Elber, Division of Surgical Oncology, University of California at Los Angeles, 10833 Le Conte Avenue, Rm 54-140 CHS, Los Angeles, CA 90095. Phone: 310-825-7086; Fax: 310-825-7575; E-mail: fceilber@mednet.ucla.edu and Johannes Czernin, Department of Molecular and Medical Pharmacology. Phone: 310-206-322; E-mail: jczernin@mednet.ucla.edu

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Translational Relevance

We previously reported that [18F]fluoro-2-deoxy-D-glucose (18F-FDG)-PET imaging identified histopathologic treatment responders at the end of and after a single cycle of neoadjuvant therapy. Here, we show that 18F-FDG-PET permits survival predictions after the initial cycle of neoadjuvant chemotherapy in patients with soft tissue sarcoma. 18F-FDG-PET can, therefore, serve as an early intermediate endpoint biomarker in research and clinic. Such information cannot be derived from computed tomographic–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 nonresponding patients whereas 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.

Patients and Methods

Seventy-eight consecutive patients with high-grade STS were enrolled in this prospective study between February 2005 and April 2008. Correlations between PET findings and histopathologic response have been reported previously (5, 6). Exclusion criteria were patient age of less than 18 years, chemo- and/or radiotherapy within 6 months before the baseline PET/computed tomographic (CT) scan, presence of a second malignancy, unresectable disease, and a diagnosis of gastrointestinal stromal tumor (GIST). In addition, 21 of 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, nonmetastatic STS who underwent neoadjuvant therapy followed by surgery (Table 1). The study was approved by the University of California at Los Angeles (Los Angeles, CA) Institutional Review Board, 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 2 cycles of ifosfamide (14 g/m2) followed by doxorubicin (60–90 mg/m2). Standard gemcitabine-based chemotherapy consisted of 2 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 before initiation of chemotherapy. A second (early follow-up) study was conducted in 39 patients after the initial cycle of chemotherapy and before radiation treatment. Thirty-six of these 39 patients had been previously studied for correlation between histopathologic response and PET findings. Seventeen of 18 patients not undergoing the early follow-up scan were included into this study before January 2006. An end-of-treatment scan (late follow-up) was carried out 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. Thirty-eight patients underwent both, the early and late follow-up scans.

Emission scans started at median intervals of 92 minutes [mean, 96 ± 22 minutes; interquartile range (IQR), 79–107 minutes], 69 minutes (mean, 78 ± 27 minutes; IQR, 60–90 minutes), and 90 minutes (mean, 93 ± 20 minutes; IQR, 80–104 minutes) 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 minutes (mean, 28 ± 26 minutes; IQR, 8–42 minutes) and 14 minutes (20 ± 18 minutes; IQR, 7–25 minutes), respectively. Early and late follow-up studies were conducted 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 conducted 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 18F-FDG-PET intravenously. PET emission scans were acquired with a weight-based protocol and during shallow breathing as reported previously (13–15). PET images were reconstructed with an iterative algorithm (OSEM; 2 iterations, 8 subsets). The CT acquisition parameters were 130 kVp, 120 mAs, 1-second 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

18F-FDG-PET images were analyzed by one observer who was aware of the clinical diagnosis but blinded to histopathologic treatment response and progression free and overall survival. All 18F-FDG-PET studies were analyzed quantitatively as previously described (17). SUVpeak was defined by the average pixel value within a 15-mm 2-dimensional region of interest drawn around the highest radioactivity concentration in a single plane, which was...
Physicians with multiyear 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 carried out at least every 6 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 (first and second metabolic response assessment and histopathologic response), survival times were also calculated from the dates of the first and second 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. Receiver operating characteristic (ROC) analysis was conducted 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%, whereas tumors with decreases in SUVpeak of equal or less than 26% were categorized as metabolically nonresponding. 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 histologic 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% or more 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 U test were used for paired and unpaired comparisons of quantitative parameters. The χ² or Fisher exact test was conducted for comparison of frequency data between

### Table 1. Clinical, pathologic, and treatment characteristics

| Characteristics                  | All patients (N = 57, n (%)) | Early subgroup (N = 39) n (%)
|---------------------------------|-----------------------------|-----------------------------
| Age, y                          | 53 (20–86)                  | 53 (20–78)                  |
| Sex                             | 28 (49)                     | 19 (49)                     |
| Male                            |                             |                             |
| Female                          | 29 (51)                     | 20 (51)                     |
| Site                            | 46 (81)                     | 31 (79)                     |
| Extremity                       |                             |                             |
| Retro/abdominal                 | 5 (9)                       | 3 (9)                       |
| Chest/trunk                     | 6 (10)                      | 5 (13)                      |
| Tumor size, cm                  |                             |                             |
| <5                              | 4 (7)                       | 3 (8)                       |
| 5–10                            | 24 (42)                     | 16 (41)                     |
| >10                             | 29 (51)                     | 20 (51)                     |
| Histology                       |                             |                             |
| NOS                             | 19 (33)                     | 17 (44)                     |
| Synovial                        | 6 (11)                      | 3 (8)                       |
| Myxofibrosarcoma                | 7 (12)                      | 6 (15)                      |
| Liposarcoma                     | 10 (18)                     | 5 (13)                      |
| Leimyosarcoma                   | 6 (11)                      | 3 (8)                       |
| MPNST                           | 3 (5)                       | 1 (3)                       |
| Other                           | 6 (11)                      | 4 (10)                      |
| Grade                           |                             |                             |
| High                            | 57 (100)                    | 39 (100)                    |
| Radiotherapy                    |                             |                             |
| Yes                             | 46 (81)                     | 33 (85)                     |
| No                              | 11 (19)                     | 6 (15)                      |
| Pathologic response             |                             |                             |
| ≥95% (responder)                | 15 (26)                     | 8 (21)                      |
| <95% (nonresponder)             | 42 (74)                     | 31 (79)                     |
| Recurrence/progression          |                             |                             |
| Yes                             | 24 (42)                     | 17 (44)                     |
| No                              | 33 (58)                     | 22 (56)                     |
| Death                           |                             |                             |
| Yes                             | 17 (30)                     | 11 (28)                     |
| No                              | 40 (70)                     | 28 (72)                     |
| Time of follow-up, mo           |                             |                             |
| Median (range)                  | 55.1 (38.0–76.4)            | 50.6 (38.0–64.9)            |
| Survival, mo                    |                             |                             |
| Median (range)                  | 48.5 (6.9–76.4)             | 46.0 (6.9–64.4)             |
| Margins                         |                             |                             |
| Positive                        | 7 (12)                      | 4 (10)                      |
| Negative                        | 50 (88)                     | 35 (90)                     |

determined in a 3-dimensional 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) × body weight (g)/injected activity (Bq)]. Intravenous contrast (Omnipaque; Nova-plus) 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 contraindi-
Independent subgroups. ROC curves were used to determine optimal cutoff values for defining metabolic response for the prediction of survival. The Fisher exact test was used to assess association of 2 categorical variables. A multivariable logistic regression analysis was employed to test for association of early changes in SUV_peak 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 conducted by Cox proportional hazard regression, and corresponding HR estimates were provided with ninety-five percent confidence intervals (CI).

Statistical analyses were conducted with IBM SPSS Statistics software for Windows (version 19.0, SPSS Inc.). All statistical tests were conducted 2-sided, and a P value less than 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 1-, 2-, and 3-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

SUV_peak averaged 9.5 ± 6.5 g/mL (median, 7.5; range, 2.5–30.7) and was similar in surviving and nonsurviving patients (9.3 ± 6.4 vs. 10.1 ± 7.0, P = 0.8).

Early changes in tumor 18F-FDG uptake

Thirty-nine patients underwent an early 18F-FDG-PET after one cycle of chemotherapy. Eighty-five percent of these received neoadjuvant chemoradiation therapy whereas 15% received only neoadjuvant chemotherapy. SUV_peak decreased by 16.5% ± 73.1% (median, 29.3%) from 10.2 ± 6.9 to 7.1 ± 5.1 (P < 0.001; Fig. 1). Decreases in SUV_peak did not differ significantly between surviving and nonsurviving patients (–32.5% vs. –24.0%, P = 0.132). Seven of 15 early PET nonresponders but only 4 of 24 early PET responders died during follow-up (P = 0.068). The overall survival rate 5 years after the first follow-up PET scan was 82% ± 8% in early metabolic responders but only 45% ± 16% in early metabolic nonresponders.

Late changes in tumor 18F-FDG uptake

Fifty-six patients underwent end-of-treatment 18F-FDG-PET studies. SUV_peak decreased by 44.8% ± 3.6% from 9.6 ± 6.5 to 4.6 ± 3.4 (P < 0.001; Fig. 1). Decreases in SUV_peak did not differ significantly between survivors and nonsurviving patients (–50.7% vs. –29.9%; P = 0.110). Twelve of 29 late PET nonresponders but only 4 of 27 late PET responders died during follow-up (P = 0.028). The overall survival rate 5 years after the second follow-up PET scan was 85% ± 7% in late metabolic responders but only 54% ± 10% in late metabolic nonresponders.

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 vs. 10.7 ± 4.6 cm; n = 39) and late follow-up scans (10.7 ± 5.4 vs. 10.7 ± 4.6 cm; n = 56).

By Response Evaluation Criteria in Solid Tumors (RECIST), 36 patients (92%) had stable disease at early follow-up whereas 3 (8%) exhibited progressive disease. At late follow-up 2 of 56 (4%) patients who completed therapy were classified as partial responders, 9 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% to 95%. Fifteen patients (26%) exhibited 95% or more response in the resected specimen and were therefore classified as histopathologic responders (26% response rate).

The sarcoma subtype of histopathologic responders included sarcoma not otherwise specified (NOS; n = 6), synovial sarcoma (n = 2), liposarcoma (one each...
pleomorphic and dedifferentiated; \( n = 2 \)), rhabdomyosarcoma (pleomorphic; \( n = 1 \)), malignant peripheral nerve sheath tumor (MPNST; \( n = 1 \)), leiomyosarcoma (nonuterine, \( n = 1 \)), angiosarcoma (\( n = 1 \)), and extraosseous Ewing’s sarcoma (\( n = 1 \)).

Survival analysis

We have previously identified early and late SUV\(_{\text{peak}}\) 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 = 0.401, log-rank test; Fig. 2). Therefore, we conducted ROC analyses to assess the predictive value of early and late changes in SUV\(_{\text{peak}}\) for survival. The optimum thresholds for survival predictions by ROC curve analysis were decreases of baseline SUV\(_{\text{peak}}\) [area under curve (AUC = 0.659)] by 26% and 57% for early and late time points, respectively (AUC = 0.638).

Univariate analysis was conducted 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 2 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 (\( P = 0.030 \) and \( P = 0.034 \), respectively, log-rank test; Fig. 2). In contrast, late RECIST was not predictive of survival (\( P = 0.801 \), log-rank test; Fig. 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, 5–10, and >10 cm), histology (tumor subtype), histopathologic 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 (\( P = 0.011; \text{HR, 3.61; 95\% CI, 1.26–10.4} \)) and early (\( P = 0.041; \text{HR, 0.27; 95\% CI, 0.08–0.93} \)) and late

![Figure 2. Kaplan–Meier survival curves comparing responders and nonresponders of (A) histopathologic response (\( P = 0.401 \)), (B) RECIST (\( P = 0.801 \)), (C) early metabolic response (SUV\(_{\text{peak}}\) decrease >26%; \( P = 0.027 \)), and (D) late metabolic response (SUV\(_{\text{peak}}\) decrease >57%; \( P = 0.035 \); all \( P \) values according to log-rank test). Survival times were calculated from date of surgery (A), date of second PET/CT scan (B), and date of third PET/CT scan (C and D), respectively.](https://clincancerres.aacrjournals.org/content/18/7/2028/F2.large.jpg)
metabolic response ($P = 0.045$; HR, 0.32; 95% CI, 0.10–0.98; Table 2).

**Multivariable survival analysis.** Because early and late metabolic responses are dependent parameters, 2 separate analyses were conducted 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, 0.06–0.75).

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, 1.09–11.52) whereas late changes in SUV$_{peak}$ only tended to be predictive ($P = 0.079$; HR, 0.36; 95% CI, 0.11–1.13).

**Discussion**

This prospective study shows that $^{18}$F-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 nonresponding patients whereas 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 nonresponders 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, histopathologic response, type of neoadjuvant treatment, and depth of tumor.

Early changes of SUV$_{peak}$ remained a significant independent survival predictor even after inclusion of margin positivity. In contrast, late changes of SUV$_{peak}$ 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 STS 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, nonresponding patients could undergo immediate surgery whereas responding patients would continue the neoadjuvant treatment. CT measurements cannot provide response assessments in STS (2). Thus, early response assessments with $^{18}$F-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, histopathologic response to neoadjuvant chemoradiation therapy predicted patient survival (3, 4). 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 5 years, a minimum follow-up of 3 years, and 5-year overall survival rates of 63% for histopathologic nonresponders and 80% for histopathologic 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.

**Table 2. Univariate survival analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$P$</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age$^a$</td>
<td>0.116</td>
<td>1.03 (0.99–1.07)</td>
</tr>
<tr>
<td>Gender$^a$</td>
<td>0.774</td>
<td>1.15 (0.44–2.98)</td>
</tr>
<tr>
<td>Site$^b$</td>
<td>0.107</td>
<td>1.65 (0.88–3.07)</td>
</tr>
<tr>
<td>Size$^b$</td>
<td>0.817</td>
<td>0.79 (0.10–5.97)</td>
</tr>
<tr>
<td>Histology$^b$</td>
<td>0.296</td>
<td>1.83 (0.59–6.68)</td>
</tr>
<tr>
<td>CTx vs. RCTx$^d$</td>
<td>0.669</td>
<td>1.31 (0.38–4.57)</td>
</tr>
<tr>
<td>Pathologic response$^b$</td>
<td>0.590</td>
<td>0.71 (0.20–2.49)</td>
</tr>
<tr>
<td>Depth$^b$</td>
<td>0.560</td>
<td>0.05 (0.00–1.42859)</td>
</tr>
<tr>
<td>Margin positivity$^b$</td>
<td>0.041</td>
<td>3.31 (1.95–10.42)</td>
</tr>
<tr>
<td>Early response$^e$</td>
<td>0.041</td>
<td>0.27 (0.08–0.95)</td>
</tr>
<tr>
<td>Late response$^d$</td>
<td>0.045</td>
<td>0.31 (0.10–0.98)</td>
</tr>
<tr>
<td>RECIST late$^d$</td>
<td>0.614</td>
<td>1.38 (0.39–4.85)</td>
</tr>
</tbody>
</table>

**NOTE:** Univariate analysis displaying level of significance ($P$ value) and HR as well the corresponding 95% CI. Abbreviations: CTx, chemotherapy; RCTx, radiochemotherapy.

Survival times were calculated from $^a$date of baseline, $^b$date of surgery, $^c$date of second PET/CT scan, and $^d$date of third PET/CT.
response criteria/analysis methods, for example, the previously published Choi criteria. Future prospective multicenter 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 histopathologic treatment response can be predicted in sarcoma patients by changes of $^{18}$F-FDG uptake after completion (5, 11), as well as after one (6, 11) and 2 cycles of chemotherapy (10).

The early predictive changes in SUVpeak are strikingly similar to those reported for other tumors including ovarian cancer (20%; ref. 25), melanoma (30%; ref. 26), GIST (25%; ref. 27), lung cancer (20%; ref. 28), squamous cell cancer of the esophagus (20%; ref. 29), as well as those reported in our previous studies in sarcoma (6). Moreover, late predictive changes are also comparable with those reported for other cancers including colorectal (62.5%; ref. 30), squamous cell carcinoma of esophagus (52%; ref. 31), and sarcoma (5). This suggests that previously proposed PET response criteria are useful across a wide variety of cancers including STS. It also supports the notion that $^{18}$F-FDG-PET response criteria are applicable across a wide range of sarcoma subtypes and treatments.

Schuetze and colleagues reported that changes in SUVmax by 40% were the best cutoff points for prediction of survival (32). The difference between this and the current threshold is not surprising as 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 3-dimensional volumes of interest may have provided different results as recently shown in gastrointestinal cancers (33, 34). Second, the considerable intra- and interindividual difference in uptake times of $^{18}$F-FDG-PET scans is an important limitation potentially affecting response assessments. However, differences in uptake time in this specific cohort with median uptake times more than 60 minutes for baseline, early, and late PET scan are less relevant than if imaging would have been carried out after 45 minutes as SUVs are more stable after longer uptake times. Third, patients received 2 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 nonresponding 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 patients with sarcoma. The design of such study could mimic the MUNICON trial (35) 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 2 weeks after start of neoadjuvant therapy.

Disclosure of Potential Conflicts of Interest

W. A. Weber has a commercial research grant from Bayer and Philips. No potential conflicts of interest were disclosed by the other authors.

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18F-FDG-PET for Survival Prediction in STS


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

Ken Herrmann, Matthias R. Benz, Johannes Czernin, et al.


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