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^{18}F-FLT PET/CT as a prognostic imaging biomarker of disease specific survival in patients with primary soft tissue sarcoma

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ABSTRACT

Purpose: The purpose of this study was to evaluate ^{18}F-FLT PET/CT as an early prognostic imaging biomarker of long-term overall survival (OS) and disease-specific survival (DSS) in soft tissue sarcoma (STS) patients treated with neoadjuvant therapy (NAT) and surgical resection.

Methods: This is a 10-year follow up of a previous, single-center, single-arm, prospective clinical trial. Patients underwent ^{18}F-FLT PET/CT prior to treatment (PET1) and after NAT (PET2). Post-treatment pathology specimens were assessed for tumor necrosis / fibrosis as well as Ki-67 and TK1 expression. Maximally selected cut-offs for PET and histopathologic factors were applied. Survival was calculated from the date of subject consent to the date of death or last follow-up.

Results: The study population consisted of 26 patients who underwent PET1, 16/26 primary STS underwent PET2. Thirteen deaths occurred during a median follow up period of 104 months. In the overall cohort, OS was longer in patients with low versus high PET1 tumor SUVmax (dichotomized by SUVmax ≥ 8.5 vs. < 8.5; not yet reached vs. 49.7 months; p = 0.0064). DSS showed a trend toward significance (p = 0.096). In a sub-analysis of primary STS, DSS was significantly longer in patients with low versus high PET1 tumor SUVmax (dichotomized by SUVmax ≥ 8 vs < 8; p = 0.0034). There were no significant ^{18}F- FLT PET response thresholds corresponding to DSS or OS following NAT at PET2.

Conclusion: ^{18}F-FLT PET may serve as prognostic baseline imaging biomarker for DSS in patients with primary STS.

INTRODUCTION

Soft tissue sarcomas (STS) comprise approximatly 1% of adult cancers (*1*), but constitute a family of more than 50 histiotypes (*2*) that present quite differenly in biologic characteristis and clinical behaviour.

Histologic tumor grading by the French Federation of Cancer Centers Sarcoma Group (FNCLCC) is regarded as the “gold-standard” for prognostication and guides the clincal management of STS patients (*3*). Low, intermediate and high grade is determined by three parameters: differentiation, mitotic activity, and the extent of tumor necorisis. However, the FNCLCC system has several limitations including: lack of applicability to all sarcoma histiotypes, inherent difficulty in reproducibly assessing sarcoma differentiation and under-sampling from core needle biopsy (*4,5*). In addition, the FNCLCC system was developed on untreated tumors. Grading on post- post-neoadjuvant therapy (NAT) resections in STS is not advised since tumor necosis can not be distinguished from NAT induced necrosis.

Genomic tests might in the future replace or complement current histologic grading in STS (*6*). The complexity index in sarcomas (CINSARC) is a prognostic gene expression signature which comprises 67 genes involved in pathways of mitosis control and chromosome segregation (*7*). CINSARC has been identified as a better prognostic factor of metastases free survival (MFS) than the FNCLCC system, irrespective of the STS histiotypes (*7*).

Proliferative activity dependent accumulation of 3′-deoxy-3’-fluorothymidine (^{18}F-FLT) has been demonstrated for a variety of solid and hematologic neoplasms, however

varying degrees of correlation between ^{18}F-FLT uptake and histological markers of proliferation, such as Ki-67, have been (*8,9*) reported.

In the current study we correlated ^{18}F-FLT uptake at pre- and post-NAT PET, changes in ^{18}F-FLT uptake and post-NAT histologic variables (% tumor necrosis, Ki-67 and TK1 expression) with OS and DSS in patients previously enrolled in a prospective, single center, single arm, exploratory study. The hypothesis was that ^{18}F-FLT PET might be used as a prognostic imaging biomarker of disease specific survival in patients with STS.

PATIENTS AND METHODS

Study design and patients

Between October 2008 and September 2009, 26 patients with high-grade STS and 1 patient with osteosarcoma were enrolled in a prospective, single-center, single arm, exploratory study which investigated the cell proliferation response to NAT as measured by ^{18}F-FLT-PET/CT (IRB 07-03-110) (*8*). This previous study enrolled adult patients (≥18 years) who were scheduled to undergo NAT prior to surgical resection of a biopsy proven sarcoma. Exclusion criteria were unresectable disease, performance status preventing the initiation of NAT, systemic therapy within 6 months of study participation, synchronous second malignancy, and the inability to tolerate a PET/CT study. For the purpose of the current study the patient with osteosarcoma was excluded; therefore, the current study population consists of 26 patients; nineteen/26 patients (73%) had primary disease and 7/26 patients (27%) had recurrent/residual disease. Two

of the 19 patients with primary disease had a contemporary history of a secondary malignancy (hepatocellular carcinoma and breast cancer).

All 26 patients underwent a ^{18}F-FLT PET/CT before initiation of NAT and 20 patients (77%) after completion of NAT. Six patients did not undergo PET2: Two patients exhibited low SUVmax at PET1 (SUVmax 1.7 and 2.0), further diagnostic workup after PET1 revealed unresectable disease in 2 patients, 1 patient had a synchronous secondary malignancy at the time of PET 1 (hepatocellular carcinoma), and 1 patient declined to undergo PET2.

The median time interval between treatment initiation and PET1 and between PET1 and PET2 was 0.7 weeks (IQR, 0.1 - 1.5) and 11 weeks (IQR, 10 - 16.7), respectively. The patient demographics and clinical characteristics are summarized in Table 1.

The follow up of patients previously enrolled in the trial IRB 07-03-110 was approved by the University of California Los Angeles (UCLA) Institutional Review Board (IRB), and the necessity for outcome specific consent was waived by the IRB (IRB 20-001899).

^{18}F-FLT PET/CT imaging and analysis

Of the 46 ^{18}F-FLT-PET/CT scans, 43 (93%) were performed on a Siemens Biograph 64 TruePoint PET/CT scanner and 3 (7%) on a Siemens Emotion Duo PET/CT approximately one hour after a median injected activity of 247.9 MBq (IQR, 229.4 – 255.3 MBq). Intravenous and oral contrast media was administered in 33 / 46 (72%) and 36 / 46 (78%) scans, respectively.

Several SUV parameters were assessed on PET 1 and PET2: SUVmax, SUVpeak, SUVmean and total lesion FLT (SUVTLF) with a 40, 50, 60 and 80% cut-off of SUVmax. Since SUVmax proved to be equal or superior over the other PET parameters we selected SUVmax for further analyses. ^{18}F-FLT-PET/CT images were interpreted by one reader (MRB). The reader was aware of the sarcoma diagnosis but blinded to the treatment regimen, other clinical and outcome data.

Post-treatment pathology specimens were assessed by tumor necrosis and / or fibrosis as well as Ki-67 and TK1 expression as described previously (*8*).

Treatment

Neoadjuvant: 23 / 26 patients (88%) underwent neoadjuvant therapy followed by complete surgical resection. Ten patients (38%) underwent neoadjuvant ifosfamide-based treatments, 5 patients (19%) had gemcitabine-based therapy, 1 patient (4%) underwent treatment with Adriamycin (doxorubicin; 75 mg/m^2), 1 patient (4%) was treated with Taxol (paclitaxel; 175 mg/m^2) and bevacizumab, 1 patient (4%) was treated with ridaforolimus as part of a phase II clinical trial. Standard chemotherapy administrations were previously reported [8]. Gastrointestinal stromal tumors (GISTs; n = 3; 12%) were treated with imatinib at a dose of 400 mg p.o. per day. Two patients (8%) received neoadjuvant external beam radiation only. Ten patients (38%) underwent neoadjuvant chemoradiation therapy. Adjuvant and recurrent treatment regimens are listed in Table 1.

Histopathology

Pathology specimens were reviewed by a pathologist with expertise in sarcoma pathology, as reported previously (*8*).

Statistics

Quantitative variables are presented as median and interquartile range (IQR), or mean and standard deviation (SD) where appropriate. Statistics were performed using R 4.0.2 (R Core Team 2020). SUV Cutoffs were delineated using maximally selected rank statistics as implemented in the maxstat R package (http://cran.r-project.org/web/packages/maxstat/index.html). Maximally selected rank statistics evaluated the log-rank comparisons of survival along the continuous absolute SUVmax spectrum. Selected cut-offs represent the defined highest threshold for statistical discrimination between values along the SUVmax spectrum. Dichotomizations via median SUVmax was not included as the maximally selected SUVmax value 8.5 was equivalent to the median SUVmax 8.7 with low (n=7) and high (n=10) for both. Changes in SUVmax between PET1 and PET2 were dichotomized at a threshold of 60%. Post-NAT tumor necrosis, Ki-67, and TK1 expression were dichotomized at a threshold of ≥95%, 50%, and 18%, respectively. Survival was calculated from the date of subject consent to the date of death or last follow-up. Deaths included in the survival analysis were categorized as disease specific death or all-cause mortality, which entailed non-disease specific death and unknown cause of death. Survival was estimated using the method of Kaplan and Meier. A p value less than 0.05 was considered to indicate statistical significance.

RESULTS

Outcome assessment

The cut-off date for last follow up was January 21st, 2021. The median follow up period was 104 months (maximum follow up, 144.8 months). The median overall survival was 106 months (95%CI, 31.9 – not yet reached (NYR)).

11 patients (42%) had no evidence of disease, 10 patients (38%) died of disease, 2 (8%) were alive with disease, and 3 (12%) died of another cause. The median follow up time in patients alive at last follow-up date was 104 months (IQR, 27.8 - 141.1).

Imaging characteristics

Tumor *SUVmax of all patients averaged 6.6 ± 3.7 (median 7.1, range 1.7 - 16.1) and 3.6 ± 2.1 (median 3.4, range 0.9 - 7.9), at PET1 and PET2, respectively (**Figure 1**).* Tumor SUVmax of primary STS averaged 8.1 ± 4.3 (median 8.7, range 1.7 – 17.5) and 2.8 ± 2.4 (median 2.3, range 0 – 6.9), at PET1 and PET2, respectively.
Tumor size of all patients averaged 8 ± 5 cm (median 6.4 cm, range 1.2 - 20.6 cm) at baseline and decreased to 6.9 ± 3.4 cm (median, 6.1 cm, range 1.7 - 14.5 cm) at PET2."

Imaging biomarkers

PET1: OS was significantly longer in patients with low versus high tumor SUVmax (dichotomized by SUVmax ≥ 8.5 vs. < 8.5; NYR (not yet reached) vs. 49.7 months; p = 0.0064) (Figure 2a). DSS showed a trend toward significance (NYR vs. 49.7 months; p = 0.096) (Figure 2b).

In a sub-analysis of primary STS (17/26 patients), DSS was significantly longer in patients with low versus high tumor SUVmax (dichotomized by SUVmax ≥ 8 vs < 8; NYR vs. NYR months; $p = 0.0034$) (Figure 3).

PET2 and changes between PET1 and PET2: In primary STS who underwent PET2 (n = 16/17), neither absolute PET2 tumor SUVmax (dichotomized by SUVmax ≥ 5 vs < 5; NYR vs. 20.4 months; $p = 0.25$), nor decreases in SUVmax ≥ 60% between PET1 and PET2 were significantly correlated with DSS survival (NYR vs. NYR months; $p = 0.56$).

Histopathologic biomarkers

DSS was not significantly different in primary STS patients (16/26 patients) with histopathologic response in the resected specimens post-NAT (n=3) versus patients without post-NAT histopathologic response (n=13) (dichotomized by tumor necrosis and fibrosis ≥ 95% vs. < 95%; NYR vs. NYR months, $p = 0.86$).

Ki-67 expression was available in 14/17 primary STS patients. DSS showed a trend towards prolonged DSS in patients with low (n=11) versus high post-NAT Ki-67 expression (n=3) (dichotomized by Ki-67 ≥ 50% vs. < 50%; 27.5 vs. NYR months, $p = 0.057$) (supplemental Figure 1).

TK1 expression was available in 14/17 primary STS patients. DSS was not significantly different in patients with low (n=4) versus high post-NAT TK1 expression (n=10) (dichotomized by TK1 ≥ 18% vs. < 18%; NYR vs. NYR months, $p = 0.25$).

DISCUSSION

In this post-hoc analysis of patients with soft tissue sarcoma, low pre-treatment ^{18}F-FLT uptake served as an early prognostic imaging biomarker of long-term survival. The prognostic value of ^{18}F-FLT uptake at initial diagnosis has been reported for several malignancies such as lymphoma (*10*), NSCLC (*11*), and pancreatic cancer (*12*). Here we report the first long-term outcomes, predicted by baseline ^{18}F-FLT uptake in STS who underwent neoadjuvant treatment.

As ^{18}F-FLT uptake in other tumors has frequently been associated with the proliferation rate of cancer cells, therapy-induced alterations in intratumoral ^{18}F-FLT uptake have been proposed as an early imaging biomarker for therapy response and outcome (6-8). However, in this study ^{18}F-FLT uptake after neoadjuvant treatment and changes in ^{18}F-FLT uptake across treatment did not significantly correlate with improved survival.

Recent literature surrounding the application of ^{18}F-FLT illustrates that ^{18}F-FLT accumulation is not solely a correlate of tumor cell proliferation rate (*13,14*). ^{18}F-FLT is a substrate for thymidine kinase 1 (TK1), a proximal mediator of the pyrimidine salvage pathway which functions in parallel with the de novo pathway to produce dTTP for DNA replication and repair (*15*). Thus, ^{18}F-FLT avidity is influenced by the relative activity of de novo and salvage pathways which are in turn regulated by substrate abundance, gene expression and oncogene/tumor suppressor activity (*15,16*). Uptake of ^{18}F-FLT is not solely isolated to tumor cells and is impacted by the active proliferation of T-cells after removal of CTLA-4 checkpoint inhibition (*17*). More recently, ^{18}F-FLT uptake in tumors has been shown to be elevated alongside interferon signaling-driven thymidine

phosphorylase (TYMP) expression in preclinical xenograft models (*18,19*). Given that innate and adaptive immune cells are a dominant source of interferon, ^{18}F-FLT uptake could also reflect intratumoral immune cell infiltration and elevated cytokine signaling.

An additional potential reason for discordant ^{18}F-FLT PET findings after NAT in the current study might be the late timing of PET2 12 weeks after the start of NAT. The low ^{18}F-FLT uptake at PET2 might in part not represent cytotoxic treatment effect but viable tumor with low ^{18}F-FLT uptake due to restricted tracer delivery, internalization, and trapping. All considered, future studies investigating ^{18}F-FLT should integrate clinical observations with a detailed molecular and cellular assessment of biopsy tissue which could enable the identification of molecular mechanisms driving PET probe accumulation.

Several potential limitations of our study merit consideration. First, this is a small pilot study; therefore, it was not adequately powered to detect small differences. For example, patients with low post-NAT Ki-67 (≤ 50%) and low post-NAT TK1 (≤ 18%) showed a trend towards a prolonged DSS, but the significance of this finding needs further evaluation. Second, imaging cutoffs were not predefined but maximally selected. Third, patients with a variety of sarcoma subtypes were included in this study.

In conclusion, the current study demonstrates that low ^{18}F-FLT uptake at initial diagnosis correlates with long-term survival in primary soft tissue sarcoma and may be useful in determining treatment strategies. ^{18}F-FLT uptake at post-NAT PET does not improve outcome prediction.

KEY POINTS

Questions: Can 3′-deoxy-3’-fluorothymidine (^{18}F-FLT) PET/CT be used as a prognostic imaging biomarker of disease specific survival in patients with soft tissue sarcoma?

Pertinent findings: In the current study we report the first long term outcomes (the median follow up period was 104 months), predicted by ^{18}F-FLT PET/CT, before initiation of neoadjuvant therapy in patients with soft tissue sarcoma.

Implication for patient care: Pre-treatment tumor grading guides clinical decision making and prognostication of soft tissue sarcoma patients. However, given that “standard” histopathologic grading of soft tissue sarcomas has its limitations, new biomarkers are needed to improve clinical management and prognostication, and as predictive factors for treatment response.

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Figure 1a.

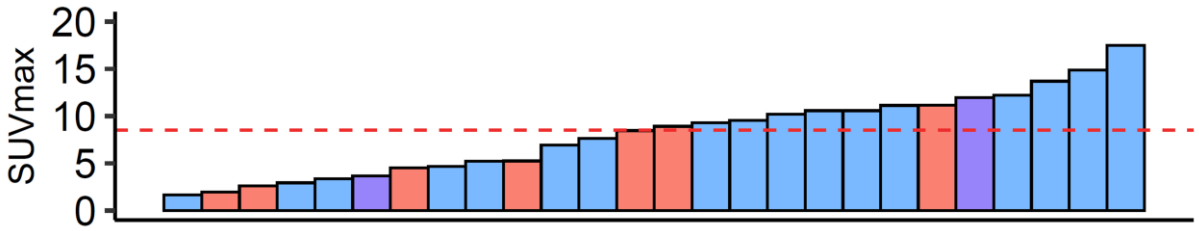

Figure 1b.

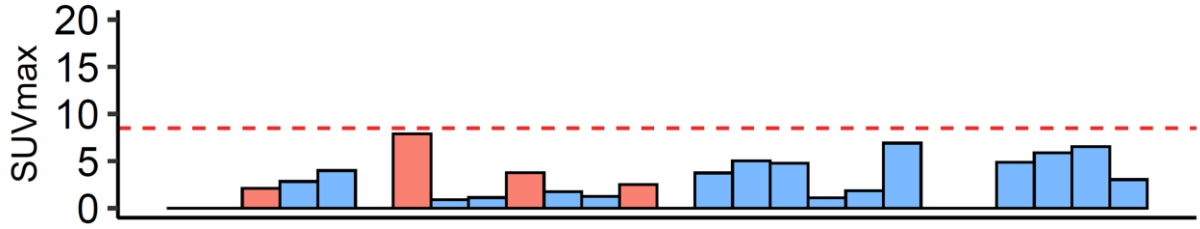

Figure 1: Waterfall diagram of SUVmax at PET1 (a) and PET2 (b). Primary tumors are depicted in blue, recurrent/residual tumors in red, and patients with a history of a secondary malignancy in purple. The red dotted line indicates the maximally selected SUVmax cut-off of 8.5 to dichotomize patients into low and high baseline FLT uptake.

Figure 2a.

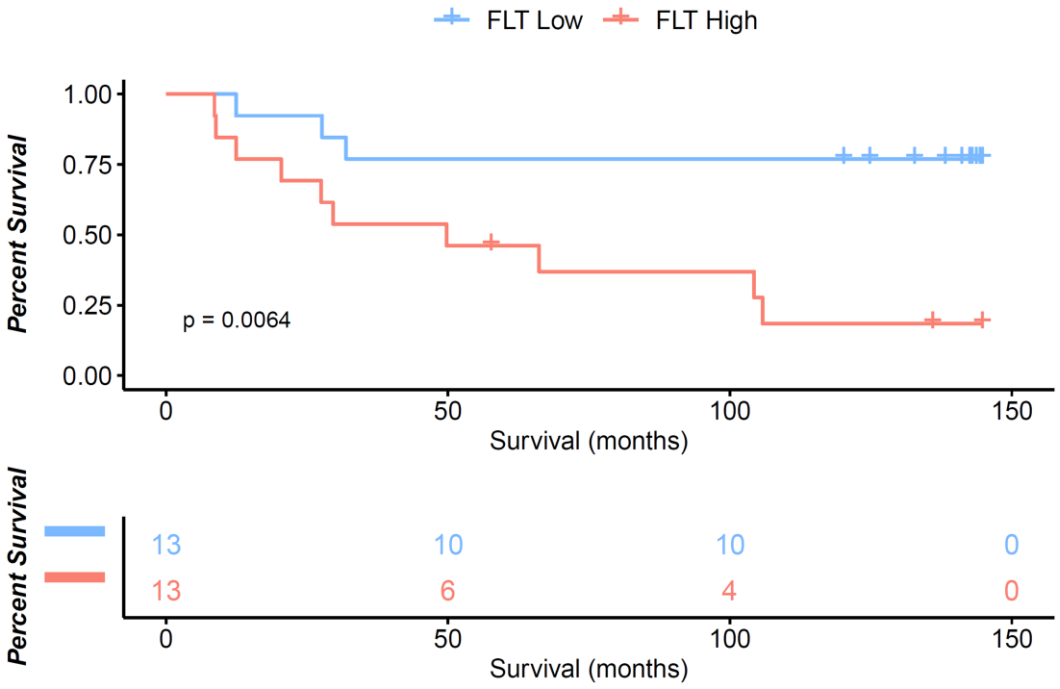

Figure 2b.

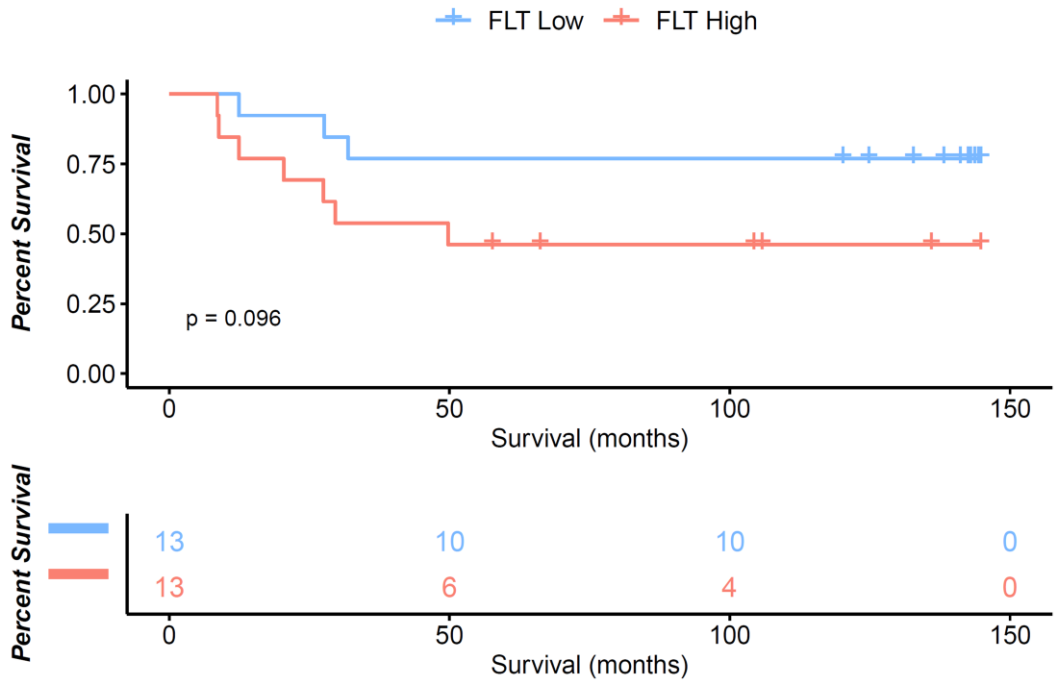

Figure 2: Kaplan Meier curves for overall survival (a) and disease specific survival (b) in all patients (n = 26) dichotomized by SUVmax ≥ 8.5 vs < 8.5 at PET1.

Figure 3.

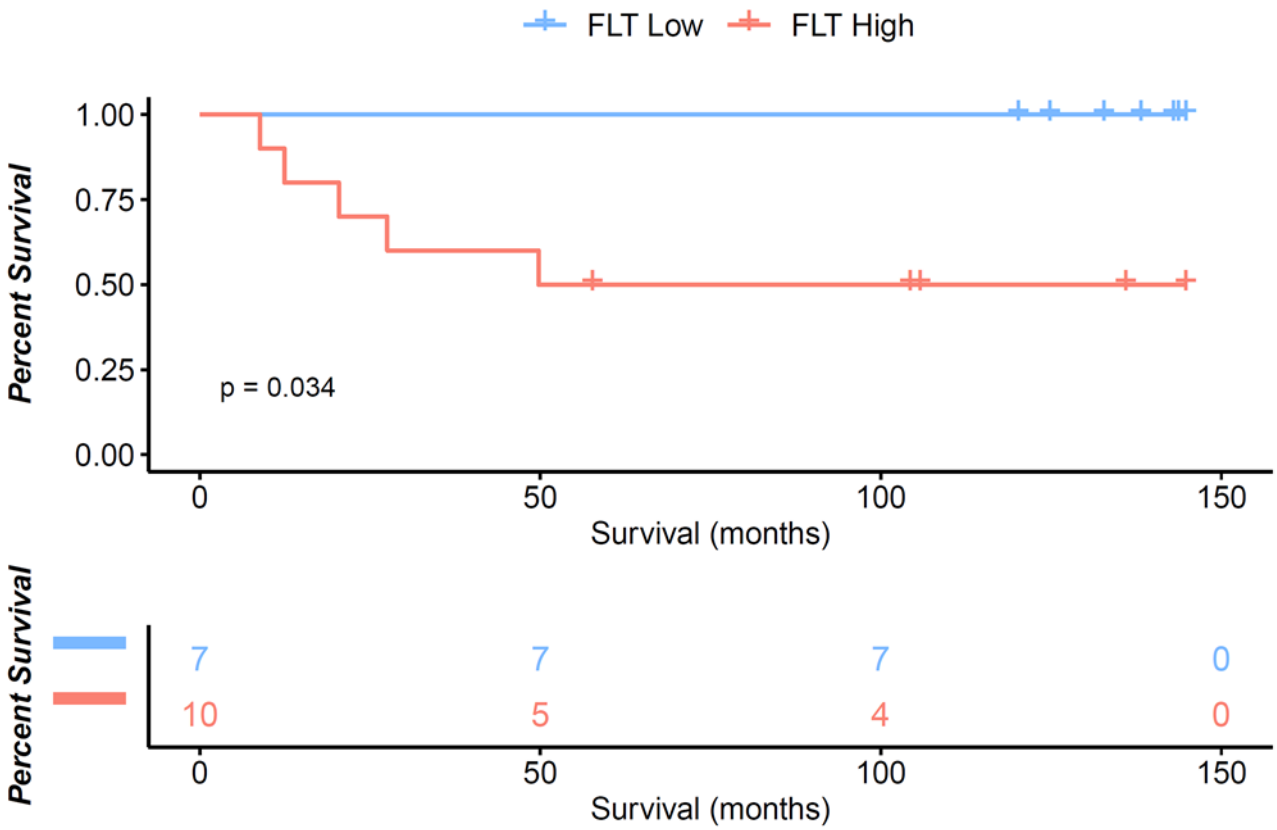

Figure 3: Kaplan Meier curves for disease specific survival in primary soft tissue sarcomas (17/26 patients) dichotomized by SUVmax ≥ 8.5 vs < 8.5 at PET1.

Supplemental Figure 1.

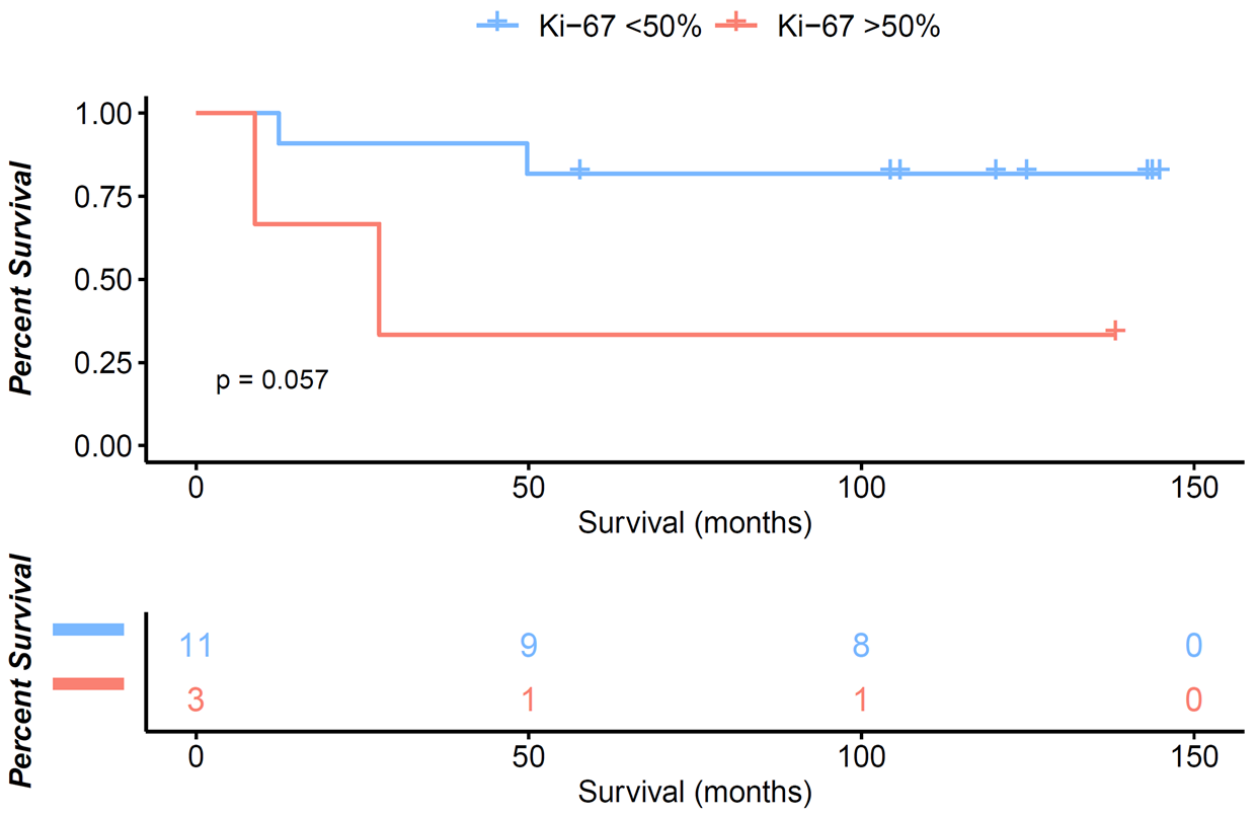

Figure 1: Kaplan Meier curves for DSS survival dichotomized by Ki-67 ≥ 50% vs < 50% post-NAT.

Table 1. Clinical, pathologic, and treatment characteristics (n=26)	
Characteristics	**n (%)**
Age (y)	
Median (range)	63 yrs (26 – 94 yrs)
Sex	
Male	13 (50%)
Female	13 (50%)
Site	
Extremity	12 (46%)
Chest/Trunk	8 (31%)
Retroperitoneal/Abdominal	6 (23%)
Presentation status	
Primary	17 (65%)
Primary + contemporary history of secondary malignancy	2 (8%)
Recurrent/residual	7 (27%)
Tumor Size	
<5 cm	6 (23%)
5-10 cm	13 (50%)
>10 cm	7 (27%)
Histology	
NOS	7 (27%)
MPNST	3 (12%)
GIST	3 (12%)
Angiosarcoma	2 (8%)
Leiomyosarcoma	5 (19%)
Fibromyxoidsarcoma	3 (12%)
Pleomorphic liposarcoma	1(4%)
Dedifferentiated liposarcoma	1 (4%)
Synovial sarcoma	1 (4%)
Neoadjuvant Therapy	
CTX (incl. Gleevec)	11 (42%)
CRTx	10 (38%)
RTx	2 (8%)
No neoadjuvant	3 (12%)
Surgery	24 (92%)
Adjuvant Therapy	
CTx	11 (42%)
CRTx	3 (12%)
RTx	2 (8%)
No adjuvant therapy	6 (23%)
Incomplete records	4 (15%)
Recurrent Therapy	
CTx	3 (12%)
Surgery	3 (12%)
Surgery + CTx	2 (8%)
Surgery + RTx	1 (4%)
Surgery + CRTx	1 (4%)
Recurrence with incomplete records of re-treatment	7 (27%)
Incomplete records of recurrence / re-treatment	3 (12%)
No recurrence	6 (23%)
Pathologic	
Responder	3 (13%)

Non-responder	21 (87%)

Abbreviations: CTx, chemotherapy; CRTx, chemoradiation therapy, MPNST, malignant peripheral nerve sheath tumor; NOS, sarcoma not otherwise specified; RTx, radiation therapy.

Graphical abstract.