The role of preoperative \(^{18}\)F-fluorodeoxyglucose positron emission tomography/computed tomography (\(^{18}\)F-FDG PET/CT) in retroperitoneal sarcoma

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Abstract

$^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) scan was used to predict pathologic grade based on the maximum standardized uptake value (SUVmax) in soft tissue sarcoma and bone sarcoma. In retroperitoneal sarcoma (RPS), the effectiveness of PET scan was not well known. This study is designed to investigate the association of SUVmax with histopathologic grade and usefulness of 18 F-FDG PET/CT scan preoperatively. Patients undergoing primary surgery for retroperitoneal sarcoma with preoperative $^{18}$F-FDG PET/CT imaging were investigated between January 2001 and February 2020 at Samsung Medical Center. The relationship between SUVmax and histologic features was assessed. The association of SUVmax with overall survival (OS), local recurrence (LR), and distant metastasis (DM) was studied. Of the total 129 patients, the most common histologic subtypes were liposarcoma (LPS, 68.2%) and leiomyosarcoma (LMS, 15.5%). The median value of SUVmax was 4.5 (range, 1-29). The value of SUVmax was correlated with higher tumor grade ($p < 0.001$, Spearman coefficient 0.627) and mitosis ($p < 0.001$, Spearman coefficient 0.564) and showed a higher value in LMS (12.04±6.73) than in dedifferentiated liposarcoma (DDLPS, 6.32±4.97, $p = 0.0054$). The optimal threshold to distinguish high tumor grade was 4.8. High SUVmax group based on the above threshold showed poor prognosis in OS, LR, and DM ($p < 0.001$). SUVmax was correlated with pathologic parameters (tumor grade, mitosis) in RPS and was higher in the LMS group than DDLPS group. In addition, prognosis (OS, LR, DM) was poor at high SUVmax values ($p < 0.001$). The value of SUVmax 4.8 is the optimal threshold to rule out high-grade tumors and predict prognosis.

Introduction

Retroperitoneal sarcomas (RPS) are rare neoplasm of mesenchymal origin derived from connective tissue. The incidence of RPS is 1% of all human malignancies $^{1}$. The most common histologic types are liposarcoma and leiomyosarcoma, which account for 70% of all retroperitoneal sarcomas $^{2,3}$. Surgical resection including that of adjacent organs is the most important treatment for RPS $^{4-6}$. Research on preoperative radiotherapy and adjuvant chemotherapy is ongoing, but the effectiveness of these has not been determined. Therefore, most patients require only surgery with multi-organ resection. However, in cases of patients with locally advanced and high-risk primary sarcomas, neoadjuvant chemotherapy can improve the likelihood of negative resection margins, which are associated with reduced local recurrence $^{7,8}$. Preoperative diagnosis is becoming increasingly important as preoperative radiotherapy and adjuvant chemotherapy research continues. Percutaneous biopsy is a very good preoperative diagnosis method and can safely classify histologic subtype $^{9,10}$. In confirming the metastasis of retroperitoneal sarcoma, computed tomography (CT) scans are sufficient to screen for presence. Since sufficient preoperative information can be obtained through CT and percutaneous biopsy $^{3}$, the role of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) has not been defined.
There have been several studies on the use of $^{18}$F-FDG PET/CT in sarcomas, but most of those studies included both bone sarcoma and soft tissue sarcoma$^{11,12}$. Alternatively, whole soft tissue sarcomas not specific to RPS were targeted$^{13,14}$. Previously, our research team conducted a study on the association between maximum standardized uptake value (SUVmax) and retroperitoneal liposarcoma (LPS)$^{15}$. However, there was a limitation that only LPS was included.

In this study, we aimed to investigate prognostic significance of SUVmax in RPS and preoperative usefulness of $^{18}$F-FDG PET/CT imaging.

Results

Clinicopathologic data. In total, 136 patients who underwent primary surgery for RPS from 2001 to 2016 and underwent preoperative $^{18}$F-FDG PET/CT to determine the presence of metastasis were identified. Three patients with Ewing’s sarcoma were excluded. Four patients were excluded due to insufficient pathological data such as mitosis and necrosis. After excluding these patients, data from a total of 129 patients were investigated. The histologic subtypes were dominantly LPS (68.2%) and LMS (15.5%). DDLPS accounted for 68% of the LPS patients, followed by well-differentiated liposarcoma (WDLPS) and pleomorphic liposarcoma (PLS). The distribution of tumor grades was similar for the three grades. Demographic and clinicopathological details are shown in Table 1.
Table 1
Characteristics of patients.

| Variable                          | Value                |
|-----------------------------------|----------------------|
| Age, years                        | 56.4 ± 12.2          |
| Gender (%)                        | F 67 (51.9)          |
|                                   | M 62 (48.1)          |
| BMI, kg/m²                        | 23.5 ± 3.0           |
| Underlying disease                |                      |
| DM                                | Yes 11               |
|                                   | No 118               |
| HTN                               | Yes 39               |
|                                   | No 90                |
| COPD                              | Yes 1                |
|                                   | No 128               |
| Chronic renal disease             | Yes 1                |
|                                   | No 128               |
| Histologic subtype (%)            | Well-differentiated liposarcoma 24 (18.6) |
|                                   | Dedifferentiated liposarcoma 60 (46.5) |
|                                   | Pleomorphic liposarcoma 4 (3.1) |
|                                   | Leiomyosarcoma 20 (15.5) |
|                                   | Malignant peripheral nerve sheath tumor 4 (3.1) |
|                                   | Perivascular epithelioid cell tumor 1 (0.8) |
|                                   | Other 16 (12.4)      |
| FNCLCC grade (%)                  | 1 29 (22.5)          |
|                                   | 2 36 (27.9)          |
|                                   | 3 64 (49.6)          |
| SUVmax (median [range])           | 4.5 [0.4, 29.0]      |
| Tumor size, mm                    | 166.4 ± 101.3        |
| Variable                                      | Value         |
|----------------------------------------------|---------------|
| Multifocality (%)                            | Yes 23 (17.8) |
|                                              | No 106 (82.2) |
| Necrosis (%)                                 | Absent 60 (46.5) |
|                                              | <50% 60 (46.5) |
|                                              | ≥50% 9 (7.0)  |
| Mitosis (%)                                  | <9/10 HPF 95 (73.6) |
|                                              | 10-19/10 HPF 24 (18.6) |
|                                              | ≥20/10 HPF 10 (7.8) |
| Local recurrence (%)                         | Yes 54 (41.9) |
|                                              | No 75 (58.1)  |
| Distant metastasis (%)                       | Yes 17 (13.2) |
|                                              | No 112 (86.8) |
| Follow up months after primary surgery, mean | 46.8 ± 34.1   |

**Correlation between SUVMmax and pathologic details.** The median value of SUVmax was 4.5 (range, 0.4-29). Tumor SUVmax was correlated with higher tumor grade (p < 0.001, Spearman coefficient 0.627) and mitosis (p < 0.001 Spearman coefficient 0.564). The SUVmax value was different depending on histologic subtype. The LPS group showed a lower SUVmax value than did the LMS group. When comparing the SUVmax of the three groups, values were obtained in this order: WDLPS (2.32 ± 0.89), DDLPS (6.32 ± 4.97), and LMS (12.04 ± 6.73). The differences were statistically significant (Fig. 1).

**Prognostic factors of RPS and SUVmax.** The univariate analysis of prognostic factors associated with OS was performed on all patients with RPS. The factors significantly associated with OS were high-grade tumor (grade III, p = 0.003), SUVmax (p < 0.001), mitosis [≥ 20/10 high power fields (HPF), p < 0.001], and necrosis (≥50%, p < 0.001). On multivariate analysis, SUVmax (p = 0.004) was determined to be the only significant associated factor. When analyzing the prognostic factors of OS by histologic subtype, tumor grade (grade III, p = 0.011) and SUVmax (p < 0.001) were significant prognostic factors in the LPS group, consistent with RPS. However, there was no statistically significant risk factor in the LMS group. The details of analyses are shown in Table 2.
| Variables                  | Univariate |         |         | Multivariate |         |
|---------------------------|------------|---------|---------|--------------|---------|
|                           | HR (95% CI)| p value | HR (95% CI)| p value      |         |
| Male                      | 1.9 (0.98,3.66) | 0.057  |         |              |         |
| Age                       | 1.03 (1.106)  | 0.033  |         |              |         |
| SUVmax                    | 1.11 (1.07,1.16) | < 0.001 |         | 1.09 (1.03,1.15) | 0.004  |
| FNCLCC grade : ref. = 1   |            |         |         |              |         |
| 2                         | 0.93 (0.19,4.61) | 0.926  |         | 0.76 (0.15,4.01) | 0.749  |
| 3                         | 6.06 (1.84,19.98) | 0.003  |         | 4.4 (0.83,23.45) | 0.083  |
| Necrosis : ref. = Absent  |            |         |         |              |         |
| <50%                       | 3.26 (1.46,7.28) | 0.004  |         | 0.81 (0.24,2.74) | 0.74   |
| ≥50%                       | 6.49 (2.1,20.02) | 0.001  |         | 1.37 (0.33,5.73) | 0.666  |
| Mitosis : ref. = <9/10 HPF |            |         |         |              |         |
| 10-19/10 HPF              | 2.26 (1.06,4.81) | 0.035  |         | 0.7 (0.26,1.9)  | 0.484  |
| ≥20/10 HPF                | 4.63 (1.83,11.7) | 0.001  |         | 0.77 (0.21,2.81) | 0.69   |

The univariate analysis of prognostic factors for LR was performed on all RPS patients. The significantly associated factors were SUVmax (p < 0.001), high tumor grade (p < 0.001), mitosis (≥ 20/10 HPF, p = 0.024), and necrosis (≥ 50%, p < 0.001). On multivariate analysis, the only factors independently associated with LR were high tumor grade (p = 0.013) and necrosis (≥ 50%, p = 0.028). However, in the analysis conducted by histologic subtypes, SUVmax (p < 0.001) and high tumor grade (p = 0.002) were the main factors for LR in LPS groups (Table 3).
**Table 3**

Univariate and multivariate analyses of risk factors associated with local recurrence.

| Variables                  | Univariate                  | Multivariate                |
|----------------------------|-----------------------------|-----------------------------|
|                            | HR (95% CI) p value         | HR (95% CI) p value         |
| Male                       | 1.14 (0.67,1.95) 0.632      |                             |
| Age                        | 1.01 (0.99,1.03) 0.503      |                             |
| SUVmax                     | 1.08 (1.04,1.12) < 0.001    | 1.03 (0.96,1.09) 0.416      |
| FNCLCC grade: ref. = 1     |                             |                             |
| 2                          | 8.43 (1.93,37.39) 0.005     | 7.24 (1.56,33.67) 0.012     |
| 3                          | 15.38 (3.69,64.04) < 0.001  | 8.16 (1.55,42.96) 0.013     |
| Necrosis: ref. = Absent    |                             |                             |
| <50%                       | 3.35 (1.77,6.33) < 0.001    | 1.36 (0.59,3.14) 0.473      |
| ≥50%                       | 13.9 (5.38,6) < 0.001       | 4.01 (1.16,13.87) 0.028     |
| Mitosis: ref. = <9/10 HPF  |                             |                             |
| 10-19/10 HPF               | 3.38 (1.79,6.39) < 0.001    | 1.57 (0.73,3.41) 0.25       |
| ≥20/10 HPF                 | 2.99 (1.15,7.75) 0.024      | 1.25 (0.31,4.99) 0.751      |

**Optimal threshold to distinguish high grade sarcoma.** The ROC curve analysis demonstrated that the AUC for high tumor grade (Grade III) was maximal when the threshold SUVmax was 4.8. The AUC for high tumor grade at the cut-off SUVmax was 0.820 (p < 0.001). At this threshold, the values of sensitivity and specificity were 0.77 and 0.80, respectively (Fig. 2).

**Prediction of outcome with optimal SUVmax threshold.** The SUVmax threshold was divided into a high SUVmax group and a low SUVmax group based on a cut off of 4.8; and survival analysis was performed for OS, LR, and DM. In analysis of the entire RPS group, the high SUVmax group showed poor prognosis in OS, LR, and DM (p < 0.001). When analyzed by histologic subtype, the liposarcoma group's high SUVmax subgroup showed poor prognosis in OS (p < 0.001) and LR (p = 0.004). However, there was no difference in the LMS group (Fig. 3).

**Discussion**

This study analyzed the relationship between SUVmax and the pathologic details of RPS and the usefulness of SUVmax for prediction of prognosis. We showed that SUVmax is associated with the high-grade portion of RPS. In addition, we demonstrated that the range of SUVmax varies according to histologic subtype.
Distinction between DDLPS and LMS. Our key finding was that LMS (12.04±6.73) showed the higher range of SUVmax value than DDLPS (6.32±4.97). DDLPS and LMS have potential for neoadjuvant chemotherapy; micro-metastasis potential is lowered and unresectable tumor can be reduced in size before surgery. In adjuvant chemotherapy, anthracycline-based chemotherapy is the cornerstone of first-line treatment in localized soft tissue sarcoma. However, based on many retrospective studies, different histology-driven-chemotherapy can be applied to DDLPS and LMS. In addition, multi-center prospective study (STRASS-2) is ongoing to determine whether these treatments affect the prognosis. The distinction between high grade LPS and LMS is becoming increasingly important through these studies. Our finding suggests that ¹⁸F-FDG PET/CT can be useful in distinguishing these two histology subtypes preoperatively.

Detecting the high-grade portion through ¹⁸F-FDG PET/CT imaging. Due to its multifocal nature and large size, RPS can be difficult to target accurately during biopsy at the time of detection. In addition, preoperative biopsies tend to underestimate the final grade probably due to sampling error. For example, in LPS, when solid portion and fatty portion exist together, the high-grade portion is likely to be the solid portion. However, when there are several solid portions, prediction of only the high-grade portion is difficult with CT. Because of these difficulties, the TARPSWG guideline suggests that ¹⁸F-FDG PET/CT be available for defining biopsy target areas. The current study demonstrated that SUVmax of tumors was correlated with higher tumor grade (p < 0.001, Spearman coefficient 0.627) and mitosis (p < 0.001 Spearman coefficient 0.564). This result is similar to other studies showing the association between pathologic details and SUVmax. These results support the suggestion of using the TARPSWG guideline to set SUVmax as the biopsy target areas.

Prognosis prediction with SUVmax. A previous study conducted by our research team demonstrated an SUVmax cutoff > 4.5 to be associated with a higher grade and worse prognosis in RPS. In this study, only LPS was used, and there was a limitation in that SUVmax was performed on heterogenous populations including metastatic and recurrent tumors. Subramaniam et al. also reported that when the SUVmax value was higher than 5.0, the prognosis was poor, and the high SUVmax value and grade were related. This study investigated the homogenous population; only the DDLPS and LMS groups were studied. However, the small number of patients was mentioned as a limitation. In both studies referenced above, OS and relapse free survival (RFS) were mentioned in the analysis of SUVmax and prognosis.

The current study investigated a relatively large number of patients given the low prevalence of RPS, excluding metastatic and recurrent tumors. In addition, the study showed a correlation between SUVmax and DM, which was not shown in other studies. The cut-off value of SUVmax (4.8) was a good measure for predicting prognosis but showed relatively low sensitivity (0.77) for predicting tumor grade and was not particularly useful in the LMS group. Therefore, ¹⁸F-FDG PET/CT is considered to be useful as a measure of prognosis of LPS patients or to rule out high-grade tumors by utilizing relatively high specificity (0.8).
Limitations. The current study is limited by its retrospective nature and small number of LMS patients. A large-volume study is needed to find the SUVmax value that can differentiate between DDLPS and LMS and to study the role of $^{18}$F-FDG PET/CT in recurrent and metastatic tumors.

Conclusion

Tumor SUVmax was correlated with pathologic parameters (tumor grade, mitosis) in RPS and was higher in LMS than DDLPS. In addition, the prognosis (OS, LR, DM) was poor at high SUVmax values ($p < 0.001$). The value of SUVmax 4.8 is the optimal threshold to rule out high grade tumors, and the prognosis can be predicted through this value.

Methods

Patients. We retrospectively investigated patients undergoing primary surgery for retroperitoneal sarcoma with preoperative $^{18}$F-FDG PET/CT imaging at Samsung Medical Center between January 2001 and February 2020. The diagnoses were determined according to the World Health Organization (WHO) 2013 classification by pathologists specialized in sarcoma through specimens after surgery. Patients excluded were: 1) pediatric patients (under 19 years); 2) patients diagnosed with another malignant disease; 3) patients who received additional treatment like chemo-radiation therapy before obtaining PET imaging; and 4) patients diagnosed with visceral sarcoma (tumors that clearly originated from a visceral organ, such as uterine sarcoma and sarcoma of the prostate, bladder, vesicles), benign tumor, carcinosarcoma, and gastrointestinal tumor.

Data on underlying diseases, gender, BMI, and surveillance [overall survival (OS), local recurrence (LR), and distant metastasis (DM)] were investigated through medical records. Tumor histologic subtype, size, mitosis, necrosis, and multifocality were investigated through pathology records. Tumor grade was determined using the French Federation of Cancer Centers Sarcoma Group Grading System (FNCLCC).

$^{18}$F-FDG PET/CT imaging. All patients fasted for at least 6 hours before the PET/CT study. Blood glucose level was required to be less than 200 mg/dL. Whole-body PET and unenhanced CT images were acquired using a PET/CT scanner (Discovery STE, GE Healthcare, Waukesha, WI, USA). Whole-body CT was performed using a 16-slice helical CT with 30 to 170 mAs adjusted to the patient's body weight at 140-kVp and 3.75-mm section width. After the CT scan, an emission scan was performed from the thigh to the basal skull for 2.5 min per frame in three-dimensional mode 60 minutes after intravenous injection of $^{18}$F-FDG (5.0 MBq/kg). PET images were reconstructed using CT for attenuation correction with the ordered subsets expectation maximization algorithm (20 subsets, 2 iterations) with a $128 \times 128$ matrix and voxel size of $3.9 \times 3.9 \times 3.3$ mm. SUVmax was normalized to patient body weight. For measurement of SUVmax, we placed a spherical volume of interest of 3 cm in diameter at a location where the tumor tissue had highest metabolic activity on PET imaging using volume viewer software (Advantage Workstation 4.4, GE Healthcare).
**Statistical analysis.** Factors affecting the prognosis of RPS were analyzed through univariate and multivariate Cox regression models. The Cox proportional hazard model was used to evaluate prognostic variables, and an estimated hazard ratio (HR) with 95% confidence interval (95% CI) was presented. P < 0.05 was considered statistically significant.

The receiver-operating characteristic (ROC) methodology was used to calculate the ideal threshold to distinguish high-grade sarcoma. The area under the curve (AUC) was calculated for each parameter using the non-parametric method to represent the overall predictive or prognostic performance.

For survival analysis, Kaplan-Meier estimates and the log-rank test were used. OS, LR, and DM were analyzed using time-to-event regression. OS was calculated from the date of surgery to the date of death. LR was defined a tumor was found on CT scan, and the duration was calculated based on the CT scan date. When late identification of recurrence occurred because of progression at follow-up, not initial, testing, the date was calculated as the date of the first discovery. DM was defined as a tumor found in organs such as liver, lung, brain, and bone, and the date was calculated as when the tumor was detected by clinical symptoms or imaging tests. All analyses were performed using R 4.0.4 software (The R Core Team, Vienna, Austria).

**Declarations**

**Ethical approval.** The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2021-09-062-001)

**Informed consent.** The need for informed consent was waived by the institutional review board of Samsung Medical Center due to the retrospective nature of the study

**Author contributions**

Sung Jun Jo : Investigation, methodology, writing -original draft, writing – review & editing

Kyeong Deok Kim : Investigation, resources

So Hee Lim : Data curation, investigation

Jinseob Kim : Data curation, validation, visualization

Seung Hyup Hyun : Writing – review & editing, investigation

Jae Berm Park : Project administration, resources

Kyo Won Lee : Investigation, methodology, writing – review & editing

**Competing interests**
The authors declare no competing interests.

**Conflicts of interest and sources of funding:** none declared.

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**Figures**
Figure 1

Comparison of median SUVmax with histologic subtypes.
Figure 2

Receiver Operation Characteristic (ROC) curve for SUVmax.
Figure 3

Kaplan-Meier survival graph compared to the SUVmax threshold of 4.8. (a) OS, LR, DM in RPS group, (b) OS, LR, DM in LPS group.