Research Article

Prediction of Histologic Subtype and FNCLCC Grade by SUVmax Measured on $^{18}$F-FDG PET/CT in Patients with Retroperitoneal Liposarcoma

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This study aimed to evaluate the usefulness of maximum standardized uptake value (SUVmax) on $^{18}$F-fluorodeoxyglucose positron emission tomography with computed tomography ($^{18}$F-FDG PET/CT) in differentiating the subtypes and tumor grades of retroperitoneal liposarcoma (RPLS). The data of RPLS patients who underwent surgical resection from November 2013 to December 2019 at the sarcoma center of our institute were reviewed. The demographics, clinical features, and SUVmax of 84 patients who underwent preoperative $^{18}$F-FDG PET/CT scans were analyzed. Of these, 19 patients (22.6%) were with well-differentiated liposarcoma (WDLPS), 60 patients (71.4%) were with dedifferentiated liposarcoma (DDLPS), and 5 patients (6.0%) were with pleomorphic liposarcoma (PMLPS). The median SUVmax of WDLPS, DDLPS, and PMLPS groups was 2.8 (IQR: 1.9–3.2), 6.2 (IQR: 4.1–11.3), and 4.5 (IQR: 4.0–7.4). The ROC curve suggested 3.8 as an approximate cutoff value of SUVmax for distinguishing WDLPS and non-WDLPS (sensitivity = 0.769; specificity = 0.895). The median SUVmax for FNCLCC Grades 1, 2, and 3 of RPLS was 2.5 (IQR: 1.9–3.2), 4.5 (IQR: 3.2–6.7), and 9.0 (IQR: 6.0–13.3). The ROC curves suggest that SUVmax of ≤3.8 and >5.3 can be used for predicting FNCLCC Grades 1 and 3, respectively. The result showed that $^{18}$F-FDG PET/CT exhibited high sensitivity and specificity for identifying the subtypes and FNCLCC grades of RPLS. Additionally, $^{18}$F-FDG PET/CT might be a useful complementary imaging modality for guiding suitable biopsy location of RPLS.

1. Introduction

Retroperitoneal sarcomas (RPSs) are rare tumors, with an expected incidence of 3 new cases per 1,000,000 people each year in mainland China [1]. Surgical resection is the mainstay of curative therapy for treating RPS. Previous studies have proved that histologic subtype and tumor grade of RPS are considered as significant predictors of survival [2, 3]. Liposarcoma is the most common type of sarcomas that arises in the retroperitoneum. However, the difficulties in resection of tumors with wide clear margins and predilection for postoperative local recurrence contributed to the complexity of surgical treatment of retroperitoneal liposarcoma (RPLS).

Anatomic imaging including computed tomography (CT) and magnetic resonance imaging (MRI) are widely employed in the diagnosis, staging, and follow-up of RPLS, but both these were associated with limited capabilities in evaluating biological activity and malignant capacity of tumors. The $^{18}$F-fluorodeoxyglucose positron emission tomography with computed tomography ($^{18}$F-FDG PET/CT) combines anatomic localization by CT with functional PET imaging and has a promising role in the diagnosis and treatment of many solid tumors. It is associated with high
sensitivity, specificity, and safety in evaluating glucose metabolism of tumors for staging and restaging. The maximum standardized uptake value (SUVmax) refers to the radioactivity concentration of imaging agent in the tumor, which is the most widely used semi-quantitative parameter. However, there are only a few studies on the use of 18F-FDG PET/CT in RPLS due to its rarity and low incidence [4–6].

Therefore, a monoinstitutional series of RPLS in differentiating the subtypes and tumor grades by SUVmax by using 18F-FDG PET/CT was conducted.

2. Materials and Methods

2.1. Study Design. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent form, and the study protocol was approved by the Institutional Ethics Committee of the Peking University Cancer Hospital (approval no. 2019KTJ19). A retrospective review of our institutional RPS database and patients’ clinical charts was conducted.

The following formula for estimating the sample size of this study was used:

\[
N = \frac{Z_{\alpha/2}^2 \times P \times (1 - P)}{\delta^2},
\]

where \(\delta = 0.1\) and for \(\alpha = 0.05\), \(Z_{\alpha/2}\) is inserted by 1.96. The sample size was calculated to be 47 or 65 when the value of \(P\) is defined as sensitivity (85.7%) or specificity (78.3%) as reported in the previous study [6]. Thus, the study requires enrollment of at least 65 patients for obtaining adequate sensitivity/specificity.

The inclusion and exclusion criteria were as follows: (1) patients who underwent operations with curative intent of resection and whose postoperative pathological diagnoses were RPLS were included; (2) patients who underwent excisional biopsies by open and laparoscopic procedures were excluded as the biopsied specimen might not reflect the histology of RPLS due to its heterogeneity; (3) patients with incomplete resection from November 2013 to December 2019 at the sarcoma center of our institute were enrolled in this study. All patients did not accept any antitumor therapy before undergoing the PET/CT scan. Complete resection was achieved in 69 patients (82.1%), and incomplete resection was performed in 15 patients (17.9%). All patients received concomitant resection of a median of five additional organs (range: 1–10). The clinicopathological features of 84 patients are shown in Table 1. The median interval between PET/CT scan and surgery was 8 (IQR: 6–14.5) days. Forty-six patients (56.0%) had primary RPLS, and the remaining 37 patients

2.2. PET/CT Examinations. Patients were instructed to fast for at least 6 hours prior to undergoing PET/CT scan. The images were acquired approximately 60 minutes after an injection of 3.7 MBq/kg 18F-FDG. A whole-body acquisition was commenced in 6–8 bed positions (1 min/bed) using a hybrid system (Gemini TF 16 PET/CT, Philips, Netherlands), covering the base of the skull to the upper thigh. CT was conducted using the following parameters: 120 kV, 100 mAs, and slice thickness of 3 mm for attenuation correction and anatomic localization. Two experienced nuclear medicine physicians who were blinded to the findings of clinical and prognostic information have reported 18F-FDG-PET/CT images by reaching consensus. The SUVmax generated from each patient was used in the final analysis.

2.3. Statistical Analysis. Statistical analysis was performed using IBM SPSS Statistics (IBM Corp., Released 2019, IBM SPSS Statistics for Windows, Version 26.0., Armonk, NY) and MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). The measurement data with normal distribution were expressed as means and standard deviation and compared by independent sample’s t-test. Data with non-normal distribution were presented in median and interquartile range (IQR), and the differences in median SUVmax across groups were evaluated using the Mann–Whitney U test for 2 groups or the Kruskal–Wallis test for more than 2 groups as appropriate. Two-sided \(p\) values of <0.05 were considered significant. Categorical variables were compared using the Pearson chi-square test or Fisher’s exact test (when there are one or some cells with expected frequencies less than 5). Using the statistically significant data obtained from the above parameters, the receiver operating characteristic (ROC) curves were generated and areas under the curves (AUCs) were calculated. The cutoff SUVmax for differentiation was determined based on the maximum Youden index. The corresponding sensitivity and specificity were calculated.

3. Results

3.1. Demographic and Clinical Features. A total of 84 RPLS patients (women = 37; men = 47) who underwent surgical resection from November 2013 to December 2019 at the sarcoma center of our institute were enrolled in this study. All patients did not accept any antitumor therapy before undergoing the PET/CT scan. Complete resection was achieved in 69 patients (82.1%), and incomplete resection was performed in 15 patients (17.9%). All patients received concomitant resection of a median of five additional organs (range: 1–10). The clinicopathological features of 84 patients are shown in Table 1. The median interval between PET/CT scan and surgery was 8 (IQR: 6–14.5) days. Forty-six patients (56.0%) had primary RPLS, and the remaining 37 patients
and 9.0 (IQR: 6.0–13.3) for Grades 1, 2, and 3 groups. The median SUVmax was 2.5 (IQR: 1.9–3.2), 4.5 (IQR: 3.2–6.7), and 9.0 (IQR: 6.0–13.3) for Grades 1, 2, and 3 groups, respectively. Diagnostic Value for Predicting FNCLCC Grade. The ROC curve suggested 3.8 as an appropriate cutoff value of SUVmax for distinguishing FNCLCC Grade 3 from Grades 1 and 2, with sensitivity and specificity of 80.7% and 71.7%, respectively. The AUC was calculated to be 0.878 (CI: 0.789–0.939, p < 0.001). By setting the cutoff point as SUVmax of 3.8, the sensitivity and specificity were calculated to be 75.0% and 93.8%, respectively. The ROC curve of SUVmax for predicting FNCLCC Grade 1 is shown in Figure 6. The AUC was calculated to be 0.825 (CI: 0.727–0.899, p < 0.001). By setting the cutoff point as SUVmax of 5.3, the sensitivity and specificity were calculated to be 80.7% and 71.7%, respectively.

4. Discussion

Accurate preoperative assessment of RPS has always been a critical issue. Contrast-enhanced CT scan is the preferred imaging study for diagnosis and staging of RPS. MRI on the other hand has superior contrast resolution and provides better tissue characterization [8]. Both CT and MRI are frequently used in clinical practice and, indeed, can provide detailed information with regard to tumor location, size, morphology, and structural changes. But neither of these can provide adequate information about tumor biology and malignant behavior. The combination of these two imaging technologies (18F-FDG PET/CT) provides information with regard to the location and metabolism of tumor. This in turn provides a whole-body imaging, detects the most aggressive portion of the tumor, and demonstrates the biological behavior of the tumor and therefore has a predictive value. These features are extremely important in detecting sarcomas that are commonly heterogeneous and pleomorphic.

In some reports, 18F-FDG PET/CT demonstrated high clinical efficacy for initial diagnosis, staging, guiding the appropriate site for biopsy, restaging, and predicting the prognosis and response assessment to therapy for the management of soft tissue sarcomas [9–14]. Additionally, previous studies have shown a significant correlation between SUVmax and tumor grading and have the ability in differentiating low-grade from high-grade sarcomas in
Figure 1: PET/CT images of a WDLPS patient with an SUVmax of 1.4 (white arrow).

Figure 2: Continued.
suitable subtypes [15]. But most of these studies have limitations of inclusion of heterogeneous histological types and were mainly conducted on sarcomas that originated from the extremities and trunk. Only a few studies have been published on the role of 18F-FDG PET/CT in the diagnoses of RPS so far [4–6].

In this study, liposarcoma, which is the predominant histological type of RPS, was focused on. The results showed a high predictability of SUVmax for the subtype and

**Figure 2**: PET/CT images of a DDLPS patient with an SUVmax of 32.5 (white arrow).

**Figure 3**: Distribution of SUVmax by histologic subtype.

**Figure 4**: ROC curve for SUVmax for distinguishing WDLPS and non-WDLPS.
FNCLCC grade. In general, the CT scan features of WDLPS or non-WDLPS are typical. Most of the WDLPS consisted of predominant fatty or large-area soft tissue density masses with uniform density and integrity margins containing minimal nodular nonlipomatous component and thin septa [8]. WDLPS usually has hypovascularity or slight enhancement, without visible calcification [16]. DDLPS is visualized as a predominant nonlipomatous mass, has frequent satellite nodules, and is sometimes presented as a dedifferentiated component within a WDLPS. About one quarter of DDLPS patients exhibited calcification or ossification within the tumor, which corresponded to metaplastic patterns of dedifferentiation [17, 18]. As an infrequent but highly malignant subtype, PMLPS had similar radiological features with that of DDLPS. PMLPSs often appear as large heterogeneous masses with areas of hemorrhage and necrosis and without any visible fat, making the imaging diagnosis difficult as they look like any other sarcoma [19]. Compared to DDLPS or PMLPS, cystic/necrotic areas were less commonly observed than in WDLPS [8, 16, 18]. Although the CT findings demonstrated different appearances between the subtypes, there were no unique characteristics observed.

As an effective diagnostic tool for evaluating both primary and locally or metastatic recurrent soft tissue sarcoma, the use of 18F-FDG PET/CT increases the accuracy in diagnosing different histological types and tumor grades of RPS. In this study, the result suggested SUVmax ≤ 3.8 as an appropriate cutoff value for diagnosing WDLPS and FNCLCC G1. Our study confirmed the results by MD Anderson cancer center, which included 14 DDLPS and 12 WDLPS with an SUVmax of 4.0 as a proper cutoff (area under the curve (AUC) = 0.875) for distinguishing WDLPS versus DDLPS [5]. Notably, the sample size of our study is quite larger than that of the MD Anderson series. In addition, our study also suggested an SUVmax of > 5.3 as a proper cutoff value for predicting FNCLCC Grade 3 of RPLS. This result is similar to that of the previous Korean report that used SUVmax > 4.5 as a cutoff point (AUC = 0.877) for diagnosing FNCLCC Grade 3 [6].

Although 18F-FDG PET/CT scan alone is not competent in diagnosing RPLS without contrast-enhanced CT or MRI, if a retroperitoneal tumor is suspected to be RLPS in CT or MRI scan, then 18F-FDG PET/CT scan can add valuable information with regard to the aggressiveness of the tumor. It is noteworthy that percutaneous biopsy has relatively low
accuracy (36.5%) in diagnosing retroperitoneal DDLPS according to the previous report [20]. Accurate biopsy and adequate representative sampling in huge masses with heterogeneous components are sometimes difficult by conventional imaging modalities such as CT and MRI [21]. DDLPS is often presented as a dedifferentiated component within a WDLPS. If a sample is obtained only from the well-differentiated component of the mass, then the histologic diagnosis will probably be WDLPS. Our data suggest that $^{18}$F-FDG PET/CT for large heterogeneous RPLS provides guidance with regard to the presence of dedifferentiation and helps select most of the suitable biopsy sites. This study also supported the performance of $^{18}$F-FDG PET/CT in the initial diagnostic strategy for RPLS patients.

However, there are some limitations in this study. Firstly, there is an obvious selection bias. All the investigated patients underwent resection with definitive post-operative histological diagnosis. Many of the unresectable RPLS patients who underwent PET/CT were excluded as they had distant metastases or multifocal intra-abdominal spread at the time of initial diagnosis. As a result, this study might not reflect the characteristics of the entire RPLS group. The unresectable RPLS patients with definitive histologic diagnosis should be enrolled to determine a more reliable result. Secondly, majority of the cases (94%) in this study are WDLPS and DDLPS. As an infrequent subtype, only five cases with PMLPS were enrolled in this study, and limited sample size is considered as a major confounding factor. Thirdly, 82.1% of the patients underwent complete resection and 17.9% of the patients underwent incomplete resection. In the latter group, accurate pathological diagnosis of some part of the samples might be missed, but the SUV index was measured for the whole tumor. Therefore, a potential mismatch is inevitable. Fourthly, only SUVmax was used to predict the subtype and tumor grade of RPLS. However, some parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been reported to be useful for predicting the proliferative potential and prognosis of soft tissue sarcoma [22, 23]. Therefore, this study should be considered as a preliminary finding, and further studies are warranted to investigate the predictive value of MTV and TLG with regard to RPLS assessment.

In conclusion, this study is the largest Chinese monoinstitutional case-series of RPLS that presented high sensitivity and specificity by PET/CT for identifying the subtypes of RPLS, with an SUVmax cutoff of 3.8 to help differentiate between WDLPS and more aggressive histological types (DDLPS and PMLPS). Our study also suggested that SUVmax ≤3.8 and >5.3 can be used to predict FNCLCC Grades 1 and 3 of RPLS separately. These findings suggest that $^{18}$F-FDG PET/CT might be a useful complementary imaging modality for predicting the histologic subtype and tumor grade and guide suitable biopsy location in of RPLS. Based on the SUVmax of retroperitoneal sarcoma that is suspected to be liposarcoma, individualized surgical plans should be developed preoperatively according to the possible histological subtype.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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