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ORIGINAL ARTICLE – ENDOCRINE TUMORS

# $^{18}$F-FDG PET/CT Volumetric Parameters are Associated with Tumor Grade and Metastasis in Pancreatic Neuroendocrine Tumors in von Hippel–Lindau Disease

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## ABSTRACT

**Background.** Approximately 8–17 % of patients with von Hippel–Lindau (VHL) syndrome develop pancreatic neuroendocrine tumors (PNETs), with 11–20 % developing metastases. Tumor grade is predictive of prognosis.

**Objective.** The aim of this study was to determine if preoperative metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were associated with metastatic disease and tumor grade.

**Methods.** Sixty-two patients with VHL-associated PNETs prospectively underwent $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT). MTV, TLG, and maximum standardized uptake value (SUV$_{max}$) were measured using a semi-automatic method. Surgically resected PNETs were classified according to 2010 World Health Organization tumor grade classification. MTV, TLG, and SUV$_{max}$ were analyzed by metastatic disease and tumor grade using the Mann–Whitney test.

**Results.** A total of 88 PNETs were identified by CT and $^{18}$F-FDG PET/CT, 10 of which were non-FDG-avid. Histologic grading was available for 20 surgical patients. Patients with metastatic PNETs had a higher TLG (median 25.9 vs. 7.7 mean SUV [SUV$_{mean}$]*mL; $p = 0.0092$) compared with patients without metastasis, while patients with grade 2 PNETs had a higher MTV (median 6.9 vs. 2.6 mL; $p = 0.034$) and TLG (median 41.2 vs. 13.1 SUV$_{mean*}$mL; $p = 0.0035$) compared with patients with grade 1 PNETs. No difference in tumor size or SUV$_{max}$ was observed between the groups.

**Conclusions.** Patients with metastatic PNETs have a higher TLG compared with patients without metastasis. Grade 2 PNETs have a higher MTV and TLG compared with grade 1 PNETs. Tumor size and SUV$_{max}$ were not associated with grade. Volumetric parameters on $^{18}$F-FDG PET/CT may be useful in detecting higher grade PNETs with a higher malignant potential that may need surgical intervention.

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Von Hippel–Lindau (VHL) disease, an autosomal dominant disorder, results from an inactivating germline mutation in the VHL tumor suppressor gene.[1,2] Patients with VHL are predisposed to develop a variety of tumors and cysts, including hemangioblastomas of the central nervous system and retina, renal cell carcinoma, pheochromocytomas, pancreatic cysts and tumors, and endolymphatic sac neoplasms. The most common pancreatic manifestations of VHL are cystic lesions, which include asymptomatic simple and complex cysts (30–91 %) and serous cystadenomas (10–12 %).[3–6] These lesions are rarely symptomatic and do not have malignant potential. In contrast, pancreatic neuroendocrine tumors (PNETs), which occur in 8–17 % of patients with VHL over their lifetime,[1,6] are indolent and slow growing in nature, but approximately 11–20 % of patients have, or will develop, metastatic disease.[6,7]

The goal in the management of PNETs in patients with VHL is to resect malignant disease (metastatic) or potentially malignant disease.[8,9] Current criteria for surgical resection of PNETs in VHL are based on tumor size, with resection recommended for lesions >3 cm, based on larger tumors having a higher rate of metastases.[9] In addition to tumor size, Blansfield and colleagues found exon 3 mutation status and doubling time less than 500 days were also associated with a higher rate of metastatic disease.[10]

The histologic grade of PNETs is an important prognostic factor.[11–15] The grading system developed by the World Health Organization (WHO) in 2010 classifies PNETs into low grade (G1), intermediate grade (G2), and high grade (G3) based on the Ki67 index and mitotic count.[16] Morin and colleagues examined a cohort of 119 patients with sporadic and non-sporadic PNETs, and found that higher grade was significantly associated with progression-free survival (G1 vs. G2 vs. G3, median 79.3 vs. 144 vs. 21 months, respectively).[11] Similarly, Strosberg and colleagues found tumor grade, as defined by mitotic count, was prognostic for overall survival, showing that the 5-year survival rates for intermediate- (62 %) and high-grade tumors (7 %) were significantly worse compared with low-grade tumors (75 %).[13] Given the valuable prognostic information, investigators have suggested an endoscopic ultrasound (EUS)-guided biopsy of the lesion could help in selecting individuals for surgery. Hasegawa and colleagues evaluated Ki-67 index in EUS-guided fine-needle aspiration (EUS–FNA) specimens and found the concordance of EUS–FNA specimens and resected tumor was only 74.0 % due to tumor heterogeneity. Furthermore, of the 50 patients who underwent EUS–FNA, 18 % had insufficient sample, subjecting nearly one in five patients to a non-diagnostic invasive procedure.[17] An invasive biopsy has risks, including pancreatitis, abscess formation, fistulas, and hemorrhage, and may not provide an accurate assessment of the grade of the tumor due to heterogeneity of tumor tissue.[17–19]

Positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been shown to be a prognostic imaging modality in pancreatic,[20] lung,[21] head and neck,[22] and ovarian cancer.[23,24] In cases of sporadic PNETs,[18]F-FDG PET/CT parameters, such as maximum standardized uptake values ($SUV_{max}$) and tumor avidity have been associated with tumor aggressiveness and grade.[25–27] While $SUV_{max}$ provides single voxel information, volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), defined as the product of MTV and mean SUV ($SUV_{mean}$), provide a comprehensive assessment of the whole tumor.[28] These parameters have been utilized to predict the prognosis of esophageal,[29] multiple myeloma,[29] and small cell lung cancer.[30] Furthermore, these parameters

may predict treatment response in pancreatic[20,31] and non-small cell lung cancer.[32] Automatic and semi-automatic methods have been developed to decrease inter- and intraobserver variation in tumor volume delineation, which allows data to be more accurate.[33]

The objective of this study was to determine whether volumetric parameters measured on ^{18}F-FDG PET/CT predict the metastatic potential and WHO histologic grade in VHL-associated PNETs, and can thus serve as a tool to better inform surgical intervention for patients with VHL.

## METHODS

### Patients

A retrospective analysis was performed on 62 of 314 patients with VHL-associated PNETs who were prospectively evaluated by ^{18}F-FDG PET/CT at the National Institutes of Health (NIH) Clinical Center (NCT00062166). Twenty-seven patients underwent an operation. Seven of the surgical patients were excluded due to the lack of histologic information or a > 1-year interval between ^{18}F-FDG PET/CT and surgical intervention. The decision to undergo surgical resection was based on our institutional operative criteria ($\geq 2$ cm in the head of the pancreas or $\geq 3$ cm in the body or tail of the pancreas by anatomical imaging). Patients with tumors <2 cm in the head and <3 cm in the body or tail by imaging (median follow-up 33.3 months, range 7.9–42.4 months) and patients with surgically resected tumors without evidence of regional lymph node metastases or distant metastases to the liver or lung (median follow-up 25.6 months, range 2.9–42.8 months) were classified as patients without evidence of metastatic disease. Patients with imaging suggestive of metastatic disease, as well as patients with surgically resected tumors with evidence of regional lymph node metastases or distant metastases to the liver, were classified as patients with metastatic disease. All patients gave written informed consent to participate in the imaging protocol, and the study was approved by the Institutional Review Board.

### Pathology and Histology

Tumors were reviewed by board-certified pathologists and were classified according to the WHO 2010 tumor grade classification system: G1: Ki67 <2 % and/or <2 mitoses per 10 high-power fields (hpf); G2: Ki67 3–20 % and/or 2–20 mitoses/10 hpf; G3: Ki67 > 20 % and/or > 20 mitoses/10 hpf. The greatest diameter of each pancreatic lesion was recorded for each patient.

**TABLE 1** Patient characteristics

| Patient characteristics | Entire cohort | Non-surgical cohort | Surgical cohort[a] |
|---|---|---|---|
| Patients [n] | 62 | 35 | 20 |
| Female | 44 | 24 | 15 |
| Male | 18 | 11 | 5 |
| Age, years [mean (SD)] | 44.7 (13.2) | 44.5 (13.2) | 45.7 (14.8) |
| Mutation in exon 3 [n (%)] | 26 (42) | 14 (40) | 11 (55) |
| No. of pancreatic lesions per patient [mean (range)] | 1.4 (1–4) | 1.4 (1–4) | 1.5 (1–4) |
| No. of lesions on imaging | | | |
| CT | | | |
| Pancreatic | 88 | 46 | 33 |
| Lymph node | 7 | – | 2 |
| Liver | 10 | – | 6 |
| ^{18}F-FDG PET/CT | | | |
| Pancreatic | 78 | 42 | 29 |
| Lymph node | 3 | – | 2 |
| Liver | 5 | – | 5 |
| Tumor volume of lesions on imaging[b] | | | |
| MTV, mL [median (IQR)] | 2.8 (2.0–5.2) | 2.4 (1.6–3.5) | 3.7 (2.4–10.6) |
| TLG, $SUV_{mean}$*mL [median (IQR)] | 9.6 (5.3–17.1) | 5.9 (4.2–10.9) | 15.5 (7.5–43.5) |

*SD* standard deviation, *CT* computed tomography, [18]*F-FDG* ^{18}F-fluorodeoxyglucose, *PET/CT* positron emission tomography/computed tomography, *MTV* metabolic tumor volume, *IQR* interquartile range, *TLG* total lesion glycolysis, $SUV_{mean}$ mean standardized uptake value

[a] A total of 27 patients underwent surgical intervention. Pathology and imaging for analysis were available for 20 of the 27 patients

[b] Pancreatic lesions only

### Positron Emission Tomography/Computed Tomography Imaging

^{18}F-FDG PET/CT scans were performed approximately 1 h following intravenous administration of 10 mCi of ^{18}F-FDG for patients with a body weight <90 kg, and 15 mCi for patients with a body weight >90 kg. Patients were required to fast 4–6 h before the scan was performed. Blood glucose levels, measured before administration of the radiotracer, were confirmed to be <200 mg/dL. Patients were scanned from the base of the skull to the mid-thigh. A low-dose non-contrast CT scan was used for anatomical localization and attenuation correction, and an estimate of the patient's lean body mass, body on weight, height and sex, was used to calculate SUVs.

### Image Analysis

^{18}F-FDG PET/CT images were analyzed using custom software written in IDL (Excelis Visual Information Solutions, Boulder, CO, USA). A semi-automated method was used to delineate tumors with post-construction smoothing with a Gaussian filter (FWHM, 5 mm) in an operator-defined region of interest (ROI). Tumor boundaries were determined using a threshold of 45 % of the voxel of maximum filtered value within the ROI. Areas of physiologic uptake were excluded in order to limit measurements to the tissue of interest. MTV, $SUV_{max}$ and mean $SUV_{mean}$ (SUV lean body mass) were measured for each tumor lesion, and TLG was determined as a product of MTV and mean $SUV_{mean}$. Tumor doubling time was calculated based on measurements of the largest pancreatic lesions from two sequential CT scans 1 year apart. The following equation was used: $T_i \times \log2/3 \times \log(D_i/D_0)$, where $T_i$ is the time interval, $D_i$ is the initial diameter, and $D_0$ is the final diameter.[34]

### Statistical Analyses

Differences in MTV and TLG between groups were assessed using the Mann–Whitney test, cut-off values to differentiate grades were calculated using receiver operator characteristic (ROC) curves, and associations were assessed using Spearman rank correlation coefficients. Statistical significance was defined as a *p* value < 0.05. Outliers were identified and removed using the ROUT method.[35] All calculations were performed using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA).

### RESULTS

The cohort consisted of 62 patients with VHL-associated PNETs who underwent ^{18}F-FDG PET/CT and CT scan with intravenous contrast (Table 1). The majority of
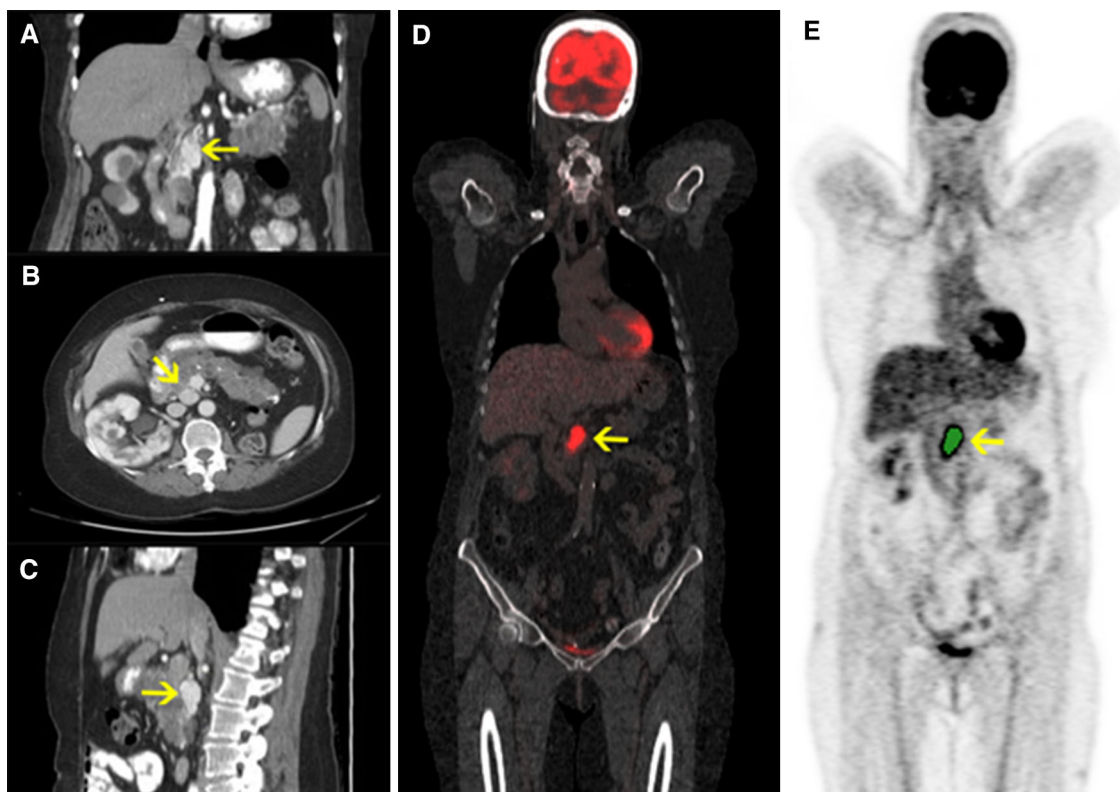
**FIG. 1** Enhancing solid pancreatic lesions on **a** coronal, **b** axial, and **c** sagittal CT that was **d** FDG-avid on $^{18}$F-FDG PET/CT and **e** measured for metabolically active portions. $^{18}$F-FDG $^{18}$F-fluorodeoxyglucose, *PET/CT* positron emission tomography/computed tomography
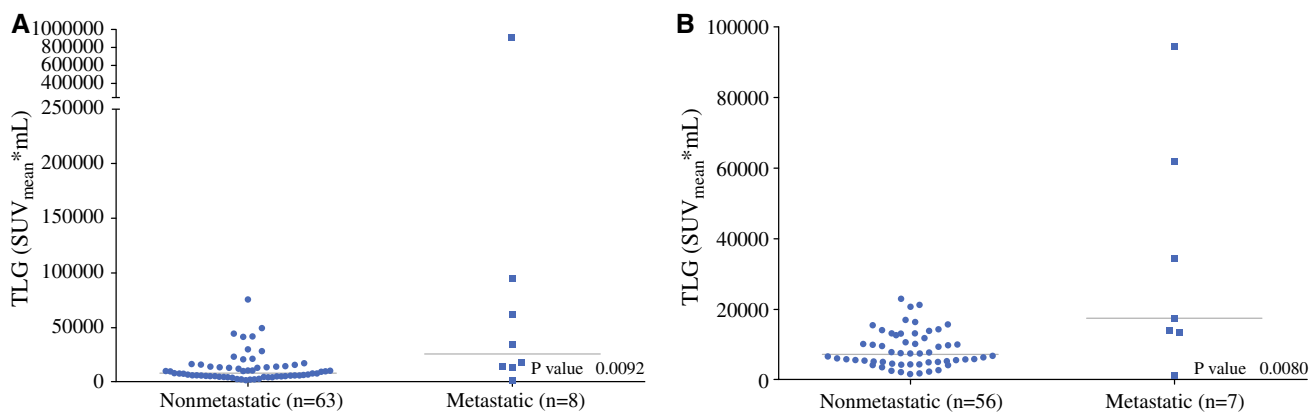


**FIG. 2** Comparison of PNETs not associated with metastatic disease and PNETs associated with metastatic disease by **a** TLG ($p = 0.0092$), and **b** TLG after outlier analysis ($p = 0.0080$). *PNETs* pancreatic neuroendocrine tumors, *TLG* total lesion glycolysis, $SUV_{mean}$ mean standardized uptake value

patients in the cohort were female (female:male ratio 44:18) and the mean age was 44.7 years. A total of 88 solid pancreatic lesions were identified on CT, of which 78 were found to be $^{18}$F-FDG-avid. The MTV and $SUV_{max}$ were measured for each pancreatic lesion identified on $^{18}$FDG PET/CT (Fig. 1). The median MTV and TLG of all pancreatic lesions was 2.8 mL (interquartile range [IQR] 2.0–5.2) and 9.6 $SUV_{mean}$*mL (IQR 5.3–17.1), respectively. In patients who did not undergo surgical

intervention, the median MTV and TLG of pancreatic lesions was 2.4 mL (IQR 1.6–3.5) and 5.9 $SUV_{mean}$*mL (IQR 4.3–10.9).

Thirty-five patients in the non-surgical cohort and 14 patients in the surgical cohort without metastatic disease at the time of operation had a total of 63 PNETs identified by $^{18}$F-FDG PET/CT. Four patients with metastatic disease had four PNETs associated with metastatic disease and two patients with metastatic disease had two

**TABLE 2** Surgical cohort characteristics

| Patient characteristics | Surgical cohort |
|---|---|
| TNM stage[a] [n] | |
| T1, <2 cm | 6 |
| T2, limited to pancreas >2 cm | 12 |
| T3, beyond pancreas, no involvement of SMA and celiac | 2 |
| T4, beyond pancreas with involvement of SMA and celiac | 0 |
| N1 | 4 |
| M1 | 2 |
| Clinical Staging [n] | |
| IA | 5 |
| IB | 8 |
| IIA | 1 |
| IIB | 0 |
| III | 4 |
| IV | 2 |
| Type of surgery [n] | |
| Total pancreatectomy | 3 |
| Whipple procedure | 5 |
| Distal pancreatectomy | 4 |
| Enucleation | 8 |
| Number of surgically resected lesions, total [n (%)] | 26 |
| Head | 13 (50) |
| Uncinate | 6 (23) |
| Tail | 6 (23) |
| Body | 1 (4) |
| Number of lesions by WHO classification[b] [n (%)] | |
| G1 | 13 (50) |
| G2 | 13 (50) |

*SMA* superior mesenteric artery, *$^{18}$F-FDG* $^{18}$F-fluorodeoxyglucose, *PET/CT* positron emission tomography/computed tomography

[a] Clinical TNM staging based on the American Joint Committee on Cancer, 7th ed. (2010)

[b] All lesions identified on $^{18}$F-FDG PET/CT were correlated to pathology

PNETs per patient associated with metastatic disease. A total of eight PNETs were associated with metastatic disease and were identified by $^{18}$F-FDG PET/CT. Sixty-three PNETs not associated with metastatic disease by imaging were compared with the eight PNETs associated with metastatic disease. PNETs associated with metastatic disease had a significantly higher TLG (median 25.9 SUV$_{mean}$*mL vs. 7.7 SUV$_{mean}$*mL; $p = 0.0092$) [Fig. 2a]. An outlier analysis was completed showing a continued difference between the two groups ($p = 0.0080$) [Fig. 2b]. No statistical difference was observed between PNETs not associated with metastatic disease and PNETs associated

with metastatic disease when comparing the groups by MTV and SUV$_{max}$.

Twenty-seven patients underwent surgical resection of their PNETs, 20 of whom had histological tumor grade and imaging data (Table 2). A total of 33 pancreatic lesions were identified on CT, of which 29 were found to be $^{18}$F-FDG-avid (four lesions were non-avid, detected by intraoperative ultrasound, and not resected). Of these 29 pancreatic lesions, 26 were resected and graded according to 2010 WHO classifications, with 13 lesions (50 %) classified as G1 and 13 lesions (50 %) classified as G2.

G2 lesions resected from the pancreas had a significantly higher MTV (median 6.9 vs. 2.6 mL; $p = 0.034$) [Fig. 3a], and TLG (median 41.2 SUV$_{mean}$*mL vs. 13.1 SUV$_{mean}$*mL; $p = 0.0035$) [Fig. 3b]. There was no difference in tumor size (median greatest diameter 2.5 vs. 2.0 cm; $p = 0.09$) or SUV$_{max}$ (median SUV$_{max}$ 8.4 vs. 9.0; $p = 0.54$) between G1 and G2 lesions. After an outlier analysis, TLG remained significantly higher in G2 lesions compared with G1 lesions (median 39.4 SUV$_{mean}$*mL vs. 13.3 SUV$_{mean}$*mL; $p = 0.0073$) and there was a trend for MTV (median 2.6 vs. 6.3 mL; $p = 0.0510$).

MTV, TLG, and tumor size had an area under the curve (AUC) of 0.75, 0.83, and 0.73, respectively, when determining grade. The positive predictive values (PPV) and negative predictive values (NPV) for G2 lesions were 75 and 71.4 % for MTV (cut-off 3.59 mL), 76.9 and 76.9 % for TLG (cut-off 17.2 SUV$_{mean}$*mL), and 57.1 and 83.3 % for tumor size (cut-off >3 cm), respectively. Metastatic disease, exon 3 mutational status, and tumor doubling time <500 days were not associated with higher MTV or TLG. Finally, no correlation was observed between whole-body MTV or TLG with preoperative serum chromogranin A levels.

## DISCUSSION

TLG measured on $^{18}$F-FDG PET/CT was found to be higher in PNETs with metastatic disease compared with PNETs without metastatic disease. MTV and TLG measured on $^{18}$F-FDG PET/CT were found to be higher in G2 PNETs compared with G1 PNETs in patients with VHL, while SUV$_{max}$ showed no significant difference. The findings of this study demonstrate that volumetric parameters on $^{18}$F-FDG PET/CT may be able to predict the metastatic potential and grade of PNETs. These findings may help determine whether patients have high-risk PNETs that would benefit from surgical intervention in VHL-associated PNETs.

Tumor grade is an important prognostic factor in patients with PNETs.[11–15] The WHO classification system developed in 2010 reflects these findings, classifying
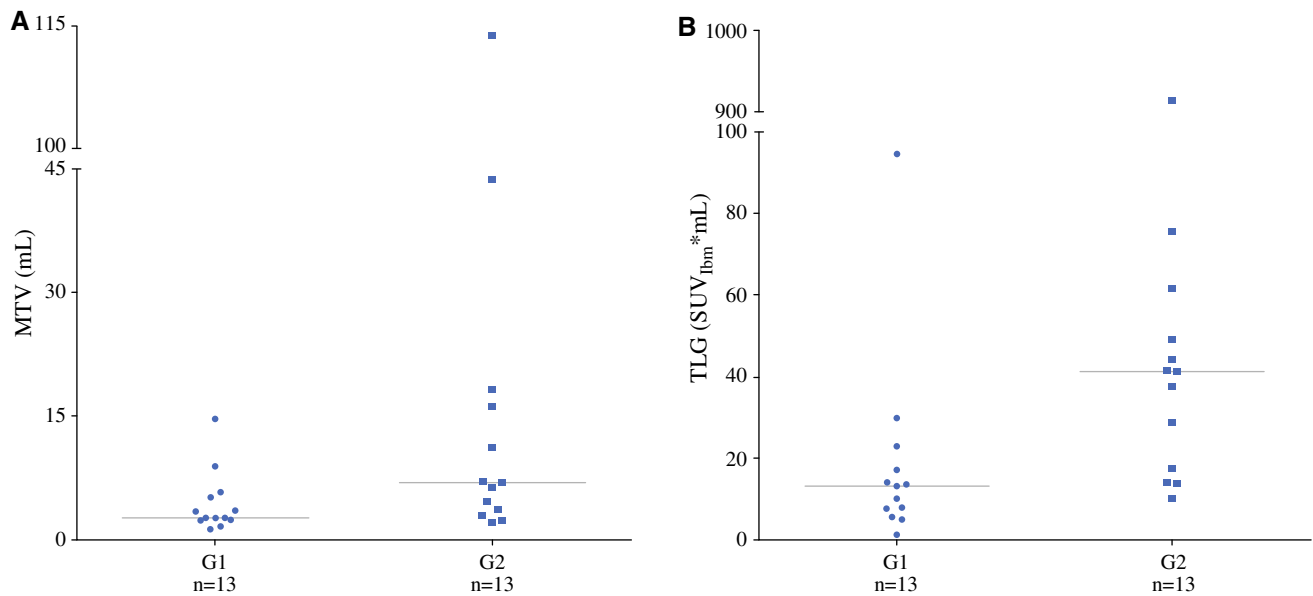
**FIG. 3** Comparison of G1 and G2 PNETs by **a** MTV ($p = 0.034$), and **b** TLG ($p = 0.0035$). *G1* grade 1, *G2* grade 2, *PNETs* pancreatic neuroendocrine tumors, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis, $SUV_{lbm}$ standardized uptake value normalized to lean body mass

PNETs based on mitotic count and/or Ki67 index, which has been validated by multiple studies.[14,36,37] The findings of our study suggest that ^{18}F-FDG PET/CT volumetric parameters may be useful in determining the grade of PNETs, and may provide a non-invasive method of detecting higher-grade lesions. The current 2010 WHO grading classification requires the examination of a large number of cells for the determination of grade due to high intratumoral heterogeneity within PNETs; however, it is often difficult to obtain sufficient cells on biopsy for a comprehensive analysis for tumor grade.[38,39] Studies assessing the use of EUS–FNA for the diagnosis of PNETs have further found that there is often discordance in cytology and histology findings for G2 tumors in samples obtained by EUS–FNA.[17,40] Thus, the ability to accurately detect tumor grade using ^{18}F-FDG PET/CT without the need for biopsy may be valuable for the management of PNETs.

Studies on sporadic PNETs have shown ^{18}F-FDG PET/CT to be clinically useful in the determination of tumor grade and overall survival; however, the utility of parameters such as $SUV_{max}$ has produced conflicting results.[41,42] In comparison, our study of VHL-associated PNETs found that there was no association between $SUV_{max}$ and grade, yet MTV and TLG were significantly different between G1 and G2 tumors. This reveals the advantage of using volumetric parameters that may better reflect the biology of the tumor. To our knowledge, this is the first time the utility of volumetric parameters on ^{18}F-FDG PET/CT have been shown to be associated with VHL-associated PNET WHO tumor grade.

Metabolic volumetric parameters were analyzed to identify if these could differentiate between patients with and without metastatic disease, and potentially identify patients who would benefit from earlier intervention. Several factors have been proposed for PNETs, including stage, exon 3 mutation status, serum chromogranin A levels, and doubling time associated with metastatic disease.[11,13] There was no association between tumor doubling time and exon 3 mutation status and metastatic disease in this study. Blansfield and colleagues used these two criteria, in addition to tumor size, to develop their treatment algorithm for VHL-associated PNETs. A lesion is defined as having high metastatic potential only if it meets two or more criteria.[10] An association of TLG was seen with metastatic disease and this may be explained by tumors with higher metabolic activity being more aggressive. A combination of tumor size and TLG may better select patients who would benefit from surgical intervention for potential metastatic disease, but this needs to be confirmed. Analyzing a change in either MTV or TLG with two discrete ^{18}F-FDG PET/CT scans may also identify patients with metastatic potential.

There are several limitations to this study. The study cohort consisted of 20 patients with histologically classified PNETs imaged on ^{18}F-FDG PET/CT, which is a relatively small sample size. ^{18}F-FDG PET/CT, while increasingly found to be useful in the evaluation of PNETs, is not the standard imaging modality for detection.[43,44] Newer modalities such as the -[68]Gallium-DOTATATE scan may be more accurate than our study and will require further study. Another limitation is that pancreatic solid

lesions identified on CT are not –always avid on $^{18}$F-FDG PET/CT. On the other hand, pancreatic lesions such as microcystic serous cystadenomas can also take up $^{18}$F-FDG and can be mistaken for PNETs.[45]

## CONCLUSIONS

The results from our study indicate that preoperative $^{18}$F-FDG PET/CT volumetric parameters such as MTV and TLG may be useful in the differentiation of G1 and G2 PNETs, and TLG may be useful in determining the metastatic potential of VHL-associated PNETs. Therefore, $^{18}$F-FDG PET/CT may play an important role in determining grade and metastatic potential in selecting patients with VHL-associated PNETs who would benefit from surgical intervention.

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