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The utility of 18F-FDG PET/CT in the diagnosis, staging of non-functioning pancreatic neuroendocrine tumors

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Abstract

Background: The non-functional PNETs are often discovered incidentally, they are commonly malignant and commonly present at a late stage with large size. We evaluate in this study the usefulness of 18F-FDG PET/CT in the detection and staging of non-functioning PNETs.

Results: Thirty patients with non-functioning PNETs were involved in this prospective study over a period starting from September 2016 to March 2021. Age ranged from 33 to 79 years. 18F-FDG PET/CT detected 26 patients had SUV max ≥ 2.5 of primary lesions and 4 lesions had SUV max < 2.5. There was no statistical significant between the site of the lesions and the type of grading of the tumors. 32 distant metastatic lesions were detected which show SUVmax ≥ 2.5 and only 9%where below 2.5. Of 30 patients, 4 patients (13.3%) of well differentiated tumor had altered their clinical strategies according to the results of PET/CT examinations. 18F-FDG PET/CT upstaged 1 patient with stage IB and 3 patients with IIA and B to stage IV.

Conclusion: The increased use of 18F-FDG PET/CT in the investigation of patient with PNETs allows for more accurate staging and therefore more appropriate management decision.

Keywords: Nonfunctional pancreatic neuroendocrine tumor, 18F-FDG PET/CT

Background

Pancreatic cancer is characterized by abnormal growth of pancreatic cells 0.95% of pancreatic cancer developed from the exocrine cells, the remaining 5% originate from the endocrine cells, the so-called neuroendocrine tumors or islet-cell tumors [1].

Pancreatic neuroendocrine tumors (PNETs) are classified according to their clinical manifestation into functioning and non-functioning tumors. 90% of PNETs tumors are non-functioning tumors. Contrary to functioning PNETs as insulinoma or gastrinoma, non-functioning PNETs are commonly malignant and presenting at late stage with large size with surrounding mass effect causing abdominal pain, weight loss as well as local invasion and distant metastasis [2].

PNETs are classified according to its differentiation, the grading system is based on the rate of tumor proliferation which is defined by the mitotic count according to the 2017 WHO classification, low grade tumors are characterized by low proliferative indices while high grades have high proliferative indices, and are thus very aggressive [3].

Imaging plays a crucial role in the work-up of the 1ry tumor, in diagnosis, staging, monitoring and prediction of response therapeutic regimen and tumor recurrence. CT and MRI have been routinely used for assessing the tumor type, extent and invasion of the surrounding structures and vasculatures [4, 5]. However the current imaging approaches still misdiagnose some possibly curable pancreatic cancers and do not provide prognostic information or inform ideal management strategies. 18F-FDG

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PET/CT is a powerful and a common functional imaging technique that can afford typical information about the functional and metabolic features of malignant tumors, its staging, therapeutic response and recurrence. Furthermore it permits anatomic correlation and exact localization of the lesions [6].

Unlike functioning PNETs which commonly displays as well differentiated and slowly growing, small sized mass lesion, the non-functional PNETs are often discovered incidentally, they are commonly malignant and often present at a late stage with mass effect on the surrounding structures, vascular invasion or metastatic spread the challenge of imaging is not to detect the pancreatic tumor, that is more often large but, to differentiate it from ductal pancreatic adenocarcinoma or from other tumors and to determine their extent and their potential of resect ability [7].

Therefore it is worth wise to evaluate the usefulness of 18F-FDG PET/CT in the detection and staging of non-functioning PNETs and this was the aim of the present study.

Methods

Patient preparation

Thirty patients with non-functioning PNETs were involved in this prospective study. Age ranged from 33 to 79 years (mean age = 56). 20 male and 10 female were involved in this study. Patients were examined at our radiology department during the period starting from September 2016 to March 2021.

Table 1 Patient characteristics

	No of patients $n = 30$	SUV max < 2.5	SUVmax ≥ 2.5
Male	20	1	19
Female	10	1	9
Tumor site			
Head	18	2	16
Body and tail	12	–	12
Tumor size			
≤ 3 cm	8	2	–
≥ 3 cm	22	–	26
Grade of the tumor	$n = 26$		
G1	3 (10.7%)	2	1
G2	16 (57%)	1	15
G3	7 (25%)	–	7
Stage of the tumor			
IA	3	2	1
IB	2	2	-
IIA	6		6
IIB	6		6
III, IV	9, 4		9, 4

All patients underwent 18F-FDG PET/CT as requested, they were asked to fast for 6 h before the examination, normal glucose plasma levels were confirmed < 160 mg/dl. All metals were removed and bladder was empty.

Patients were instructed to rest in a quiet room and avoid any kind of vigorous activity and talking prior to the examination and following injection of the radioactive tracer to avoid physiological muscle uptake of FDG.

The study protocol was approved by the ethical committee of the university. Written informed consent was received from all the patients participating in this study.

Technique

18F-FDG PET/CT is obtained using PET/CT scanner (Discovery STE, GE Healthcare, and Boston, USA). I.V injection of 3–7 MBq/kg of 18F-FDG PET/CT was done 45–90 min before the exam. A PET emission scan was performed over various bed positions from 5 to 7 for 2 min per bed position with axial field of view of 21.6 cm per bed position and in plane spatial resolution of 2 mm from the base of the skull caudally to the mid-thigh at 2 min per bed position.

Diagnostic CT was performed using the subsequent diameters, 120 kV, 350 mAs, 0.5 s tube rotation, slice thickness 5 mm, 8 mm table feed, and 3 mm incremental reconstruction. Reconstructed trans-axial PET and CT images were fused. These are then converted into coronal and sagittal images, and data were generated. The maximum SUV in the volume of interest was considered as the SUV max for the purpose of analysis.

Image interpretation

Two expertise radiology consultants with more than 10 years of experience independently assessed the data. The readers were blinded to each other and reports were compared with the histopathology results at surgery or with serial imaging and clinical follow-up.

Any focus of elevated FDG uptake (SUVmax ≥ 2.5) which could not be located at areas of normal FDG uptake was considered positive. The quantitative measures of its metabolic activity was acquired and measured using the SUV max for each lesion.

Statistical analysis

The lesions characteristics regarding the location, size, TNM staging, grades and SUV max were compared using Fisher, s exact probability test. Statistical significance was set at p value of < 0.05. Data were coded and entered using the statistical package for social sciences (SPSS version 22).

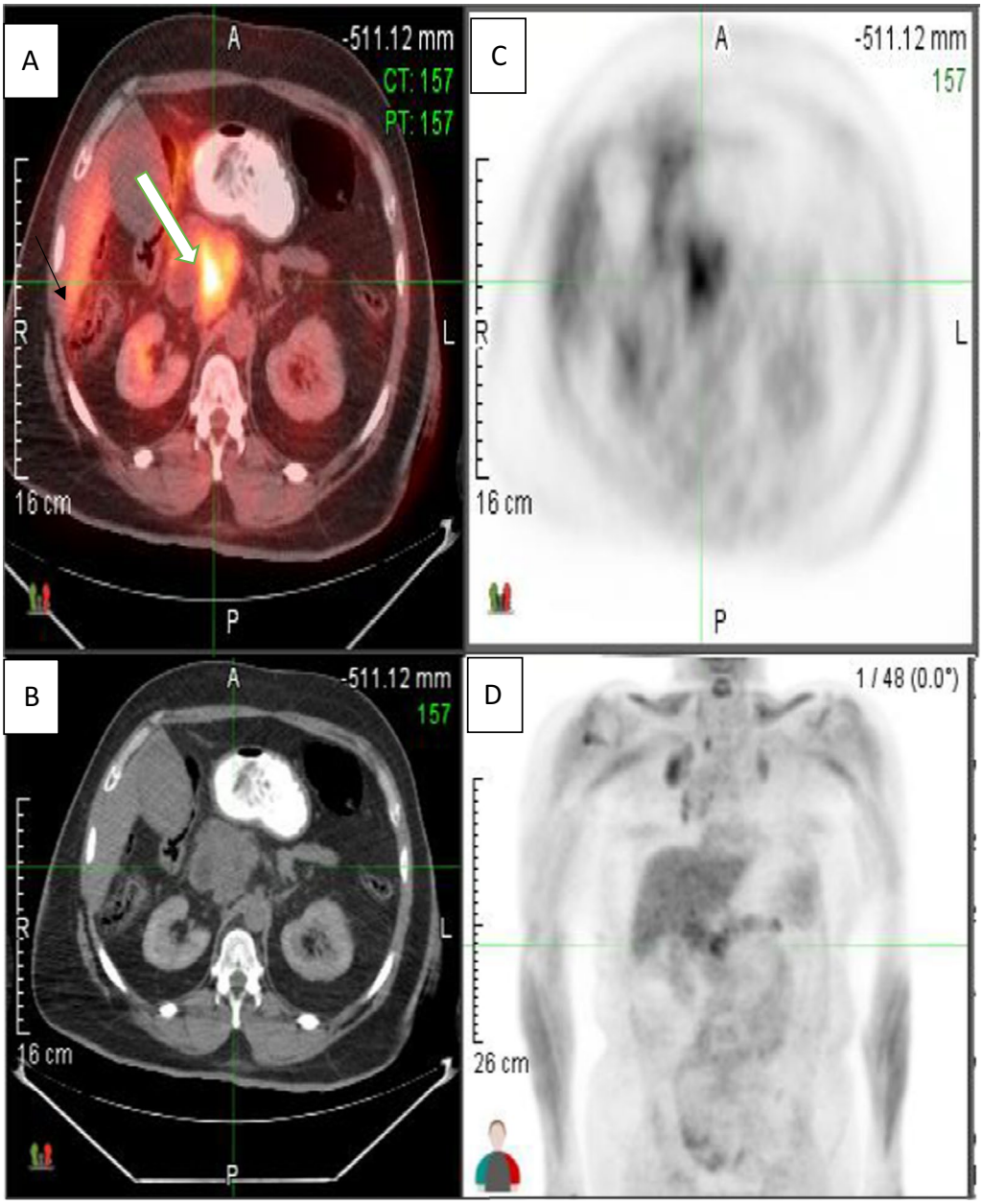

Fig. 1 56-year-old male patient with 4 × 4 cm pancreatic head FDG avid mass with SUVmax 3.9 (white block arrow) G3PNET which is histopathologically proved.In addition, there is slightly accentuated activity with SUVmax 2.4 in the inferior right hepatic lobe potentially represent liver metastasis (black arrow). **A** Fused Axial PET/CT, **B** Axial CT, **C**, **D** PET

Results

Thirty patients with non-functioning PNETs were involved in this prospective study. Age ranged from 33 to 79 years (mean age = 56), 20 male and 10 female patients were involved in this study. Patients were examined at our radiology department during the period starting from September 2016 to March 2021.

18F-FDG PET/CT detected 26 patients had SUV max ≥ 2.5 of primary lesions and 4 lesions had SUV max < 2.5. There was 12 lesions detected at the head of pancreas, 18 at the body and tail.

According to the size of the lesions, 8 were equal or below 3 cm in size, while 22 lesions were more than 3 cm in size.

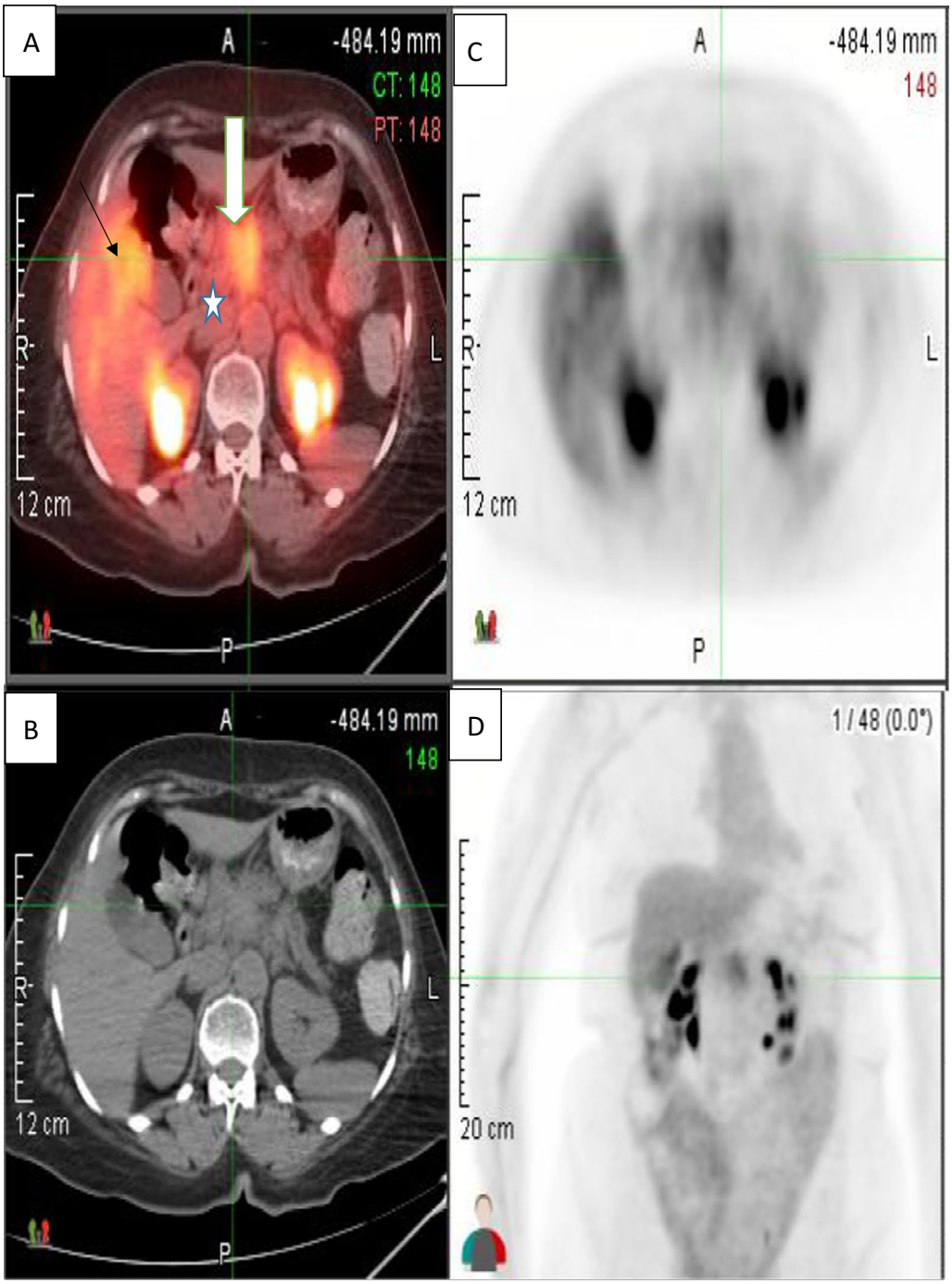

Fig. 2 71-year-old female patient with 3 × 2.5 cm pancreatic FDG avid mass in the pancreatic neck and proximal body with SUV max 2.9 (white block arrow) G2 PNET, which is histopathologically proved, producing downstream atrophy of the pancreatic body with dilatation of the pancreatic duct (star). Medial segment of the left liver lobe near the gall bladder fossa shows metastatic lesion measuring 5 × 2 cm with SUV max 3.2 (black arrow). Physiologic uptake in the urinary tract is noted. **A** Fused Axial PET/CT, **B** Axial CT, **C**, **D** PET

Lesions with Grade 1 were $n=3$ with no lymph node metastasis and the most common location was in the body or tail of pancreas (54%) $p=0.470$.

Grade 2 lesions $n=16$ where located equally at the head, body and tail of pancreas.

All the lesions of Grade 3 $n=7$ where located at the head of pancreas ($p=0.554$).

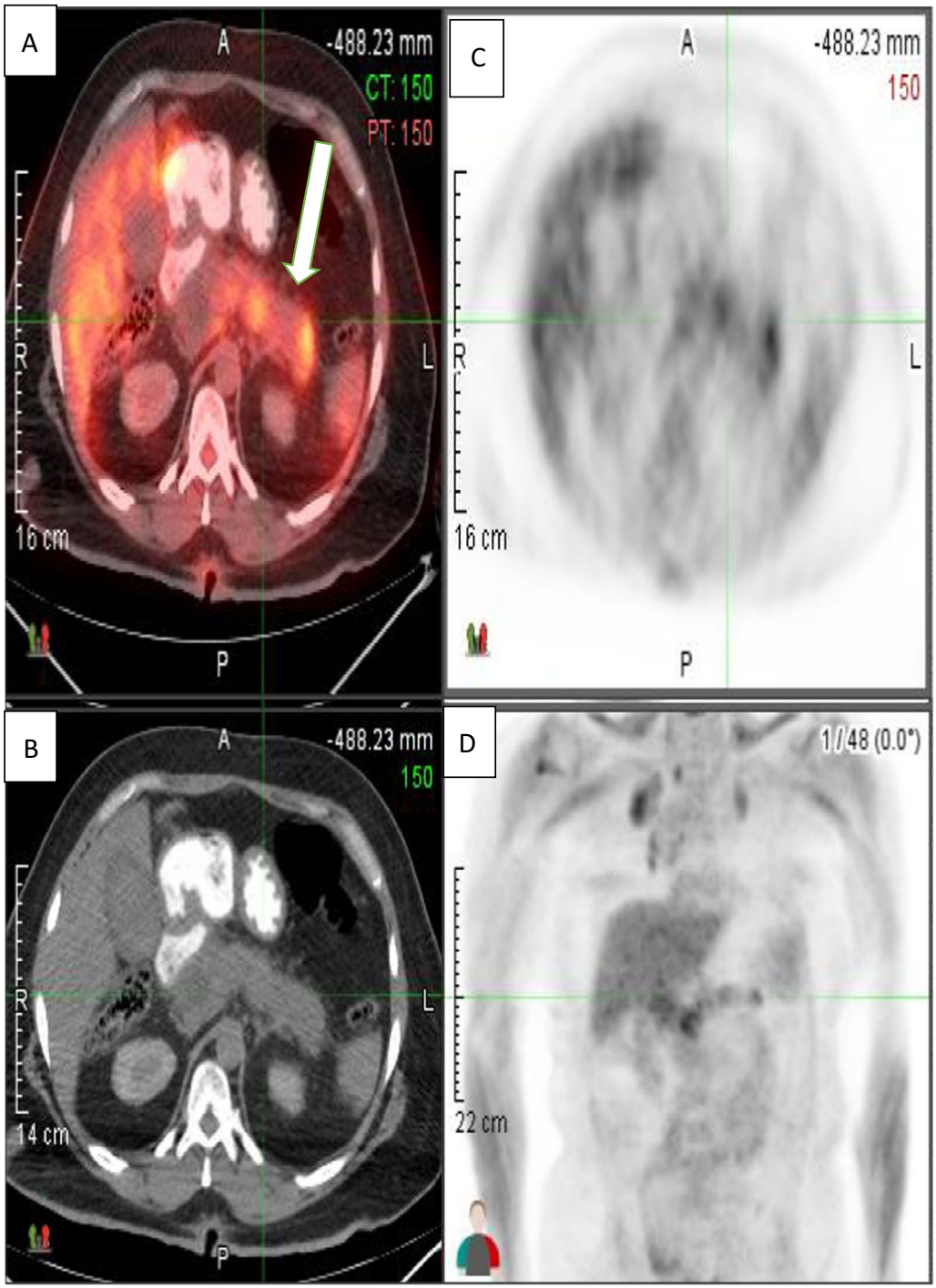

Fig. 3 65-year-old male patient with two avid FDG activity lesions in the body and tail of the pancreas, measuring 2 × 2 cm and 3.5 × 2 cm respectively with SUVmax 2.8(white block arrow) G1 PNET, which is histopathologically proved. There is infiltration of the fat surrounding the pancreatic body and tail, revealed neoplastic involvement. **A** Fused Axial PET/CT, **B** Axial CT, **C**, **D PET**

There was no statistical significant between the site of the lesions and the type of grading of the tumors.

Correlation between grades of the tumor and FDG uptake

FDG with SUVmax ≥ 2.5 was in 26 lesions analyzed on 30 patients.

Grade 1 tumor in 3 cases, Grade 2 in 16 cases and Grade 3 in 7 cases.

There was statistically significant between FDG uptake and the grade of tumor $p = 0.021$.

Grade 1 tumors SUVmax ranges as follows, 2 patients were below 2.5 and one above 2.5. One patient of Grade 2 was below 2.5 while 15 patients were above 2.5. All Grade 3 patients were above 2.5 (Table 1).

Lymph node status

3 lymph node metastasis were seen in patients with Grade 2 and 3 in Grade 3, they were histopathologically confirmed.

Distant metastasis

32 metastatic lesions were detected distantly. They were confirmed by biopsy or serial imaging and clinical follow-up. The most common site, the liver with 64% and 36%for all other sites as peritoneum, lung and distant lymph nodes. Most of the distant metastasis show SUVmax $\geq$ 2.5 and only 9% where below 2.5

Correlation between FDG uptake and the tumor staging

According to the American Joint Cancer Committee (AJCC) TNM staging system, Stage I in 5 patients with 4 patients with stage I had SUVmax < 2.5.

Stage II in 12 patient.

Stage III and IV in 13 patients.

All the remaining 26 patients had SUVmax $\geq$ 2.5.

Of 30 patients, 4 patients (13.3%) of well differentiated tumor had modified their clinical strategies according to the results of PET/CT examinations.

18F-FDG PET/CT upstaged 1 patient with stage IB and 3 patients with IIA and B to stage IV.

Discussion

Recent developments in pancreatic cancer imaging, are rapidly changing the field [8]. The main concern of this study was to evaluate, if the nonfunctioning PNETS could be detected with 18F-FDG PET/CT.

FDG is a glucose analog that accumulate in the tumor cells proportionally to their glucose metabolic activity, allowing cell to be detected by 18F-FDG PET/CT images [9].

In the present study we found that 86.7% of nonfunctioning PNETS can be detected by 18F-FDG PET/CT, 26 of 30 patients have SUVmax above 2.5 while 4 patients were below 2.5.

This was in concordant with Luo et al. [10] who revealed that 90.3%of nonfunctioning PNETS can be visualized by PET/CT, suggesting that 18F-FDG PET/CT can be used to detect nonfunctioning PNETS.

Many published researches [11, 12] reported that tumors with increase FDG accumulation seem more aggressive and correspond to bad prognosis as the majority of nonfunctioning PNETS are undifferentiated with high proliferative activity.

In the present study we analyze the effect of the tumor size, grade, and the TNM stage of the lesion on the FDG uptake of PET/CT.

Our results show positive correlation between the tumor size and the tumor uptake of FDG, as tumors with avid FDG were larger in size than the poorly avid one.

These agree with Partelli et al. [13] who concluded that the uptake of FDG in NF PNETs was significantly related with tumor size.

Further in our study we found significantly associated correlation between tumor grade and the FDG uptake of the tumor and this correlation maintained significant with the rate of tumor proliferation ($p = 0.554$). Our results show that 10.7% of patients were Grade 1, 57% were Grade 2 and 25% were Grade 3. In addition, we also examined the TNM stage, which was found to be significantly associated with the FDG uptake ($p = 0.021$).

Majala et al. [14] prospectively investigated well differentiated metastatic NETs and reported that FDG is positively correlated with decreased progression and overall survival. They found 20% of Grade 1 were PET/CT positive compared with 76% of Grade 2.

Our results show that increased FDG uptake is significantly associated with poorly differentiated tumor nature. 4 of stage I patients show SUV max below 2.5 while 26 patients have SUV max more than 2.5, as follows Grade 1 tumor manifested in 3 cases, Grade 2 in 16 cases and Grade 3 in 7 cases.

Diletta et al. [15] and Asagi et al. [16], found that the significance of 18F-FDG PET/CT altered the treatment plan of the nonfunctioning PNETS patients as it detects 90.5% of distant metastasis, suggesting that it can be utilized to stage non-functioning PNETs.

The results of our study show, that the 18F-FDG PET/CT enables the detection of aggressive tumors with avid SUVmax more than 2.5 among the well differentiated NF-PNETs. Thus it could supplement the evaluation of the tumor nature and tailor more appropriate management decisions, however false negative imaging findings should be considered. In addition, involvement of 18F-FDG PET/CT in clinical management of NF PNETs was found to restage the primary tumor.

This agree with our results as we found that of 30 patients, 4 patients of well differentiated tumor had altered their clinical strategies according to the results of PET/CT examinations.

18F-FDG PET/CT upstaged 1 patient with stage IB and 3 patients with IIA and B to stage IV (Fig. 1, 2, 3).

Limitations

We encountered some limitations in this study as small sample size of patients with non-functioning PNETs. Most patients present in late stage of this disease.

Conclusion

18F-FDG PET/CT is a valuable method to detect stage and control surveillance of non-functioning PNETs.

The increased use of 18F-FDG PET/CT in the investigation of patient with PNETs allows for more accurate staging and therefore more appropriate management decision. This may improve patient outcomes and increased cost effectiveness by avoiding futile therapy plans.

A multicentric study with large study patients will be needed to obtain more accurate results.

Abbreviations

18 F-FDG PET/CT: 18F fluorodeoxyglucose positron emission tomography/computed tomography; SUVmax: Maximum standardized uptake value; PNET: Pancreatic neuroendocrine tumor; NF-PNET: Nonfunctional pancreatic neuroendocrine tumor; WHO: World Health Organization.

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Authors' contributions

The single author is solely responsible to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine at October 6 University, reference number not applicable. All patients gave written informed consent to participate in this study which was approved by the Research Ethics Committee of the Faculty of Medicine at October 6 University.

Consent for publication

All patients included in this study gave informed consent to publish the data contained within this study.

Competing interests

The author declares that she has no competing interests.

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