Original article

Role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in diagnosis and management of pancreatic cancer; comparison with Multidetector Row Computed Tomography, Magnetic Resonance Imaging and Endoscopic Ultrasonography

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A R T I C L E   I N F O

Article history:
Received 9 May 2013
Accepted 30 August 2013
Available online 17 October 2013

Keywords:
18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
Pancreatic cancer Diagnosis Staging

A B S T R A C T

Objectives: We aimed to analyze the contribution of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging to the diagnosis and management of pancreatic cancer compared with multidetector row computed tomography (MDCT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS).

Material and methods: We retrospectively scanned the data of 52 patients who were referred for FDG PET/CT imaging for evaluation of pancreatic lesions greater than 10 mm. The diagnostic performances of 4 imaging methods and the impact of PET/CT on the management of pancreatic cancer were defined.

Results: Pancreatic adenocarcinoma was diagnosed in 33 of 52 patients (63%). 15 patients had benign diseases of pancreas (29%), and 4 patients were normal (8%). Sensitivity and NPV of EUS and PET/CT were equal (100%) and higher than MDCT and MRI. Specificity, PPV and NPV of PET/CT were significantly higher than MDCT. However, sensitivities of two imaging methods were not significantly different. There was no significant difference between PET/CT and MRI and EUS for these values. When the cut-off value of SUVmax was 3.2, the most effective sensitivity and specificity values were obtained. PET/CT contributed to the management of pancreatic cancer in 30% of patients.

Conclusion: FDG PET/CT is a valuable imaging method for the diagnosis and management of pancreatic cancer especially when applied along with EUS as first line diagnostic tools.

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Papel de 18F-Fluorodeoxiglucosa por emisión de positrones/tomografía computarizada en el diagnóstico y tratamiento de cáncer de páncreas; una comparación con la tomografía computarizada multidector, la resonancia magnética y la ecografía endoscópica

R E S U M E N

Objetivo: El objetivo fue analizar la contribución de la PET/TC con 18F-FDG (FDG PET/TC) en el diagnóstico y tratamiento del cáncer de páncreas en comparación con la tomografía computarizada multidetector (TCMD), la resonancia magnética (RM) y la ecografía endoscópica (EUS).

Material y métodos: Se revisaron retrospectivamente 52 pacientes que fueron remitidos para la evaluación de lesiones pancreáticas mayores de 10 mm mediante FDG PET/TC. Se definieron los hallazgos diagnósticos de los 4 métodos de imagen y el impacto de la FDG PET/TC en el tratamiento del cáncer de páncreas.

Resultados: En 33 de los 52 pacientes (63%) se diagnosticó un adenocarcinoma pancreático; 15 pacientes tenían enfermedades benignas del páncreas (29%) y 4 pacientes no mostraron enfermedad pancreática (8%). La sensibilidad y el valor predictivo negativo (VPN) del EUS y la FDG PET/TC fueron iguales (100%) y superior a la TCMD y a la RM. La especificidad, el valor predictivo positivo y el VPN de la FDG PET/TC fueron significativamente mayores que la TCMD; sin embargo, la sensibilidad de 2 métodos de imagen no fue significativamente diferente. No hubo diferencias significativas entre la FDG PET/TC, RM y EUS. Con un punto de corte de SUVmax igual a 3.2 se obtuvieron los valores más efectivos de sensibilidad y de especificidad. La FDG PET/TC contribuyó al manejo clínico del cáncer de páncreas en 30% de los pacientes.

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http://dx.doi.org/10.1016/j.remn.2013.08.005
Introduction

Pancreatic ductal adenocarcinoma is one of the leading causes of cancer death. Five-year survival rate is less than 5% in newly diagnosed patients. Surgical resection still remains the only curative treatment; however only 15–20% of the tumors are resectable at time of diagnosis. Thus, discriminating the malignant lesions from benign lesions or normal pancreatic tissue and also evaluating the dissemination of the malignant disease accurately is very important in order to assess the option of operation.

Suspicious pancreatic cystic or solid lesions are usually defined by abdominal ultrasonography or computed tomography. About a quarter of examined pancreata show cystic lesions and neoplastic cysts comprise 60–70% of all pancreatic cystic lesions. More than 90% of solid lesions of pancreas represent ductal adenocarcinomas, while 2–5% are neuroendocrine and acinar tumors and benign entities.

Multidetector row computed tomography (MDCT) is the most common diagnostic tool for diagnosis and staging of pancreatic cancer. Invasion of the vascular structures and peripheral tissues in addition to metastases to peritoneum and liver can be demonstrated by MDCT. Magnetic resonance imaging (MRI) has nearly same impact on diagnosis and staging of pancreatic cancer as MDCT. Endoscopic ultrasonography (EUS) gives detailed information about pancreatic head and body, and permits fine needle aspiration biopsy for diagnosis. However all these methods may be insufficient for the determination of the benign and malignant lesions since only anatomic information is obtained, and also the accurate staging of the pancreatic cancer may not be possible since the distant metastases can be missed by abdominal imaging.

Functional imaging with FDG PET/CT can provide accurate determination of benign versus malignant lesions since malignant cells show increased uptake of FDG. Also the whole body images obtained by PET/CT can reveal the possible distant metastases and change the stage and management of the disease. Although there are encouraging results of studies defining the role of FDG PET/CT in diagnosis and staging of the pancreatic cancer, the number of studies comparing the efficacy of PET/CT with conventional imaging methods, such as MDCT, MRI and EUS is very limited.

In this retrospective study, we aimed to analyze the contribution of FDG PET/CT to differential diagnosis of benign and malignant lesions of pancreas and management of disease by evaluating the extent of pancreatic cancer.

Material and methods

Patients

We retrospectively analyzed the data of 52 patients in two different nuclear medicine physicians who were referred to FDG PET/CT imaging for evaluating the pancreatic cystic and solid lesions greater than 10 mm in diameter which had been detected by ultrasonography or computed tomography. FDG PET-CT images of all patients and also the images or interpretations of conventional diagnostic tools which had been performed within 1 month of PET/CT were scanned and re-evaluated for differentiation of benign and malignant lesions of pancreas and management of the disease. This study was approved by the local ethic committee.

PET/CT imaging

All of the 52 patients underwent FDG PET/CT imaging using the same protocol in two different high resolution PET scanners with integrated 6 and 16-slice multidetector CT (Siemens Biograph PET/CT, Illinois, USA), respectively. Prior to FDG injection, glucemia was measured in well hydrated patients who fasted at least 4h before their appointment. 296–703 MBq FDG was administered intravenously to the patients with a glucemia level below 150 mg/dl. Following injection, patients were left to rest in a peaceful and comfortable room for 60 min in order to let FDG to complete its biodistribution throughout the body. At the end of this waiting period, patients void their urinary bladders and they were instructed to lie down at supine position on the PET/CT scanner bed. PET scans were completed with acquisition of 7–8 bed positions with 3–4 min of acquisition time per position from vertex-to-upper thigh. PET/CT images were visually and semiquantitatively assessed by an experienced nuclear medicine physician. The reconstructed images were visually assessed in the standard axial, coronal, and sagittal views. The accumulation of FDG outside the physiologic uptake areas was considered pathologic. For semiquantitative analysis, a region of interest was carefully drawn around the site of increased FDG uptake and the maximum standardized uptake value (SUVmax) of the lesions were used for this analysis. The SUV was calculated using the following formula: SUV = Tissue concentration (Bq/g)/[Injected dose (Bq)/Body weight (g)].

Conventional imaging modalities

Archival data of 52 patients were analyzed and findings of one or more conventional imaging modalities like MDCT, MRI and EUS performed within 1 month of PET/CT examination were re-evaluated either with the images or the interpretations which could be obtained. Solid and hypodens lesions with irregular margins in MDCT were considered as malignant. The low or heterogeneous contrast enhancement of the lesion and dilatation of the pancreatic duct were malignancy criteria for both MDCT and MRI. Solid and hypoechogenic mass lesions were considered as malignant or highly suspicious for malignancy in EUS. EUS-guided fine needle aspiration biopsy was performed in 21 patients for diagnosis.

Diagnostic accuracy of PET/CT and other imaging modalities

The final diagnosis of the patients was obtained by histopathology (surgery or biopsy) or serial follow ups for 6–12 months. The clinical outcome was assessed by reviewing the medical record.

Pancreatic cancers with distant metastasis and locally advanced disease were considered as unresectable. Locally advanced diseases included invasion of major arteries (celiac trunk, superior mesenteric artery, hepatic artery) and long segment involvement of the portal vein and superior mesenteric vein.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET/CT, MDCT, MRI and EUS were evaluated for diagnosis of malignant pancreatic tumors and benign pathologies. A Chi-square test was performed to compare the findings of these imaging modalities. A p<0.05 was considered...
Table 1
Patient characteristics.

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Male</th>
<th>Female</th>
<th>Age years (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>24</td>
<td>28</td>
<td>63.4 ± 11.7</td>
</tr>
</tbody>
</table>

Lesion characteristics:
- Cystic: 9
- Solid: 38
- Semisolid: 5

Diagnostic imaging modalities:
- PET/CT: 52
- MDCT: 40
- MRI: 34
- EUS: 35
- MDCT, MRI, EUS, PET-CT: 15

Assessment of diagnosis:
- Surgery: 5
- Biopsy: 30
- Follow-up, median 9 months (range 6–12)

Final diagnosis:
- Adenocarcinoma: 33 (2 surgery, 22 biopsy, 9 follow-up)
- Chronic pancreatitis: 1 (biopsy)
- Pseudocyst: 5 (4 follow-up, 1 biopsy)
- Benign IPMN: 4 (2 surgery, 1 biopsy, 1 follow-up)
- Mucinous cystic neoplasm: 2 (1 biopsy, 1 follow-up)
- Insulinoma: 3 (1 surgery, 2 biopsy)
- Normal (no pathology in follow-up): 4

Table 2
SUVmax values of lesions.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Minimum SUVmax</th>
<th>Maximum SUVmax</th>
<th>Mean SUVmax (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign or normal</td>
<td>0.5</td>
<td>18.0</td>
<td>3.0 (±4.7)</td>
</tr>
<tr>
<td>(n=19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>4.9</td>
<td>35.4</td>
<td>11.9 (±7.0)</td>
</tr>
<tr>
<td>(n=33)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUVmax values of the lesions are shown in Table 2. ROC analysis was performed to evaluate the SUVmax levels of the benign and malignant lesions (Fig. 1). When the cut-off value of SUVmax was statistically significant. A receiver operating characteristic analysis (ROC) was performed to find the cut-off value of SUVmax with the most efficient sensitivity and specificity.

Results

Patient characteristics are represented in Table 1. Pancreatic adenocarcinoma was diagnosed in 33 of 52 patients (63%), 15 patients had benign diseases of pancreas (29%), and 4 patients were normal (8%). All of the 9 patients with cystic lesions in pancreas were diagnosed with benign diseases; intraductal papillary mucinous neoplasm (IPMN) (n=3), pseudocyst (n=4), mucinous cystic neoplasm (n=2). Five patients with semisolid lesions were diagnosed as insulinoma (n=2), adenocarcinoma (n=2) and pseudocyst (n=1). In 38 patients with solid lesions, adenocarcinoma (n=31), insulinoma (n=1), chronic pancreatitis (n=1), and IPMN (n=1) were diagnosed. The 4 patients for whom suspicious solid lesions had been reported in previous imaging findings were followed up and no pathological lesions were defined in later imaging, so considered as normal.

Differentiation of benign and malignant lesions

SUVmax values of the lesions are shown in Table 2. ROC analysis was performed to evaluate the SUVmax levels of the benign and malignant lesions (Fig. 1). When the cut-off value of SUVmax was 3.2, the sensitivity of PET/CT was 100% and specificity was 89.5% for discriminating the benign and malignant lesions.

PET/CT showed the malignant disease truly in all of the 33 patients diagnosed with pancreatic ductal adenocarcinoma. There were 2 false positive findings in PET/CT; one of them was an acute exacerbation of chronic pancreatitis in a 64-year-old woman. A mass lesion with intense FDG uptake (SUVmax = 18.0) was observed in pancreatic head, and also smaller FDG uptake foci were seen in pancreatic body which were interpreted as metastatic lesions. The other 3 imaging tools had also false positive results for this patient at the beginning. After treatment of pancreatitis a significant regression in lesion size was seen in serial MDCT imaging.

Four patients were diagnosed with benign IPMN. Three of the lesions showed low SUVmax values (1.4, 2.0, 3.2) and 2 adenomas and 1 borderline lesion were diagnosed. However 1 patient, considered falsely positive in PET/CT examination had high SUVmax (14.9) in pancreatic head and histopathology defined borderline IPMN. In this patient other three imaging methods also had false positive findings.

The sensitivity, specificity, PPV and NPV of PET/CT, MDCT, MRI and EUS for discriminating benign diseases from adenocarcinoma are represented in Table 3. PET/CT has had the highest values of specificity and PPV in comparison to other imaging modalities. Sensitivity and NPV of EUS and PET/CT were equal (100%) and higher than MDCT and MRI. The Chi-square test results comparing the sensitivity, specificity, PPV and NPV of PET/CT with conventional

Table 3
Detection of pancreatic cancer.

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>MDCT</th>
<th>MRI</th>
<th>EUS</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>92</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity</td>
<td>50</td>
<td>75</td>
<td>88</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>PPV</td>
<td>77</td>
<td>80</td>
<td>90</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>NPV</td>
<td>78</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>

Table 4
Statistical analysis of PET/CT performance compared to other methods.

<table>
<thead>
<tr>
<th></th>
<th>PET/CT vs. MDCT</th>
<th>PET/CT vs. MRI</th>
<th>PET/CT vs. EUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Specificity</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PPV</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NPV</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, nonsignificant; p>0.05.
imaging methods for lesion discrimination are in Table 4. Specificity, PPV and NPV of PET/CT were significantly higher than MDCT ($p = 0.012, p = 0.046, p = 0.042$, respectively); however sensitivity of two imaging methods was not significantly different ($p = 0.105$). There was no significant difference between PET/CT and MRI and EUS for these values.

**Impact of PET/CT on management of malignant disease**

In 10 patients from 33 patients with ductal adenocarcinoma (30%), PET/CT imaging had an impact on the management of disease. Nine of the patients were upstaged after PET/CT by showing the distant metastases which were not shown with other three imaging tools; liver ($n = 5$), lung ($n = 4$), brain ($n = 2$), mesentery ($n = 1$) and adrenal gland ($n = 1$). The findings of PET/CT defining the distant metastases were confirmed by advanced imaging methods and follow-up imagings after therapies. One patient was downstaged after PET/CT by showing the lack of FDG uptake in a suspected lesion in spleen which was described as a metastatic mass lesion in MDCT and MRI.

**Discussion**

Since the pancreatic cancer is one of the neoplasms with poor prognosis, early diagnosis and accurate management of treatment is very important. Evaluating the stage of the malignant disease correctly is crucial for using the surgical options.5,6 On the other hand, the discrimination of benign and malignant lesions of the pancreas should be performed carefully in order to avoid aggressive and unnecessary surgery for benign disease.

In the current study, the diagnostic performance of FDG PET/CT for differentiating benign versus malignant lesions of pancreas is found to be effective with sensitivity of 100%, specificity of 89%, PPV of 94% and NPV of 100% and superior than three conventional imaging methods; MDCT, MRI and EUS. Also in 30% of the patients diagnosed with ductal adenocarcinoma, PET/CT findings changed the stage of the disease and had important impact on the management.

One of the first studies about the role of FDG PET in diagnosis and management of pancreatic carcinoma conducted by Delbeke et al. had found that using a cut-off level of 3.0 for SUV, FDG PET had higher sensitivity and specificity than CT in correctly diagnosing pancreatic carcinoma (92% and 85% vs. 65% and 61%). In that study diagnostic performance of PET was superior to CT and application of PET to the preoperative imaging tools had altered the management in 43% of patients.2 In our study when the cut-off value was considered 3.2, the best sensitivity and specificity values were obtained.

In a recent study the NPV of PET/CT for excluding pancreatic cancer was found 75%. The 25% of the patients with negative PET/CT findings (14/56) were diagnosed with adenocarcinoma and it was suggested that a negative interpreted PET/CT imaging does not exclude pancreatic cancer.7 However in our study, all of the 17 patients who were evaluated as nonmalignant in PET/CT were diagnosed with benign diseases or normal and NPV was 100%. Chronic pancreatitis is one of the conditions that FDG PET can be falsely positive since inflammatory cells also accumulate FDG as malignant cells. Autoimmune pancreatitis, a subtype of chronic pancreatitis represents the majority of the benign diseases that mimic pancreatic cancer.8,9 In one study comparing the FDG PET findings of autoimmune pancreatitis and pancreatic cancer showed that there is no significant difference between SUVmax values of two kind of lesions in either early or delayed phase.8 One of the 2 false positive cases of our study was an acute exacerbation of chronic pancreatitis showing intense FDG uptake and interpreted as pancreatic cancer (Fig. 2a–c).

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are neoplasms that originate from the main duct or branch of the pancreatic duct epithelium with mucin hypersecretion. These lesions can be classified as adenoma, borderline, carcinoma in situ and invasive carcinoma. Malignant IPMNs usually consist of carcinoma in situ and invasive carcinoma, while adenomas and borderline lesions are considered as benign IPMNs.10 The anatomic imaging methods like MDCT and MRI and even also EUS may be insufficient to discriminate the benign and premalignant or malignant IPMNs considering the size of the tumor, presence of the nodules or irregular septa and thickness of the wall. It has been reported in some studies that comparing with other imaging tools, PET/CT has better sensitivity, specificity and accuracy values for defining malignant disease.10–12 One of the 2 false positive cases in our study was a borderline IPMN showing avid FDG uptake as a malignant lesion (Fig. 2d–f).

Pancreatic neuroendocrine tumors (PNET) may be categorized as functional and nonfunctional tumors and insulinomas are the most common type of the functional PNETs. The use of FDG PET in PNETs is controversial. Increased FDG uptake was reported in less differentiated tumors with high proliferative activity.13 Three of our patients with two semisolid and one solid lesions, were diagnosed with insulinoma. SUVmax values of the lesions were 0.7, 1.1
Fig. 3. FDG PET/CT images of a 69-year-old man with pancreatic cancer showing intense FDG uptake (a, b). Left adrenal gland (c, d), mediastinum and lung parenchyma (e, f) and brain (g, h) metastases.

and 1.7. Since insulinoma is a well differentiated, functional tumor low SUVs of the lesions are inevitable. However in a recent study in 2 patients with PNET significantly high SUVs were found and differentiation of the benign and malignant lesions were reported to be difficult with PET/CT.14

In a prospective study by Kauhanen et al. comparing the efficacy of FDG PET/CT with MDCT and MRI, the diagnostic accuracy of PET/CT for pancreatic malignancy was 89%, compared with 76% and 79% for MDCT and MRI, respectively. In patients with advanced pancreatic carcinoma all three methods had low sensitivity for N-staging (30%), while sensitivity of PET/CT for M-staging was significantly higher than MDCT and MRI, 88% and 38%, respectively. In this study the clinical management was altered after FDG PET/CT in 26% of the patients.2 In the current study we did not evaluate the role of PET/CT for T and N staging of the 33 patients with adenocarcinoma, since it is a well-known truth that non-contrast enhancer CT images and PET images with low spatial resolution of the PET/CT imaging are not sufficient for assessing T and N staging of the pancreatic tumor. In previous studies it was also shown that there is no correlation between the SUV and the maximum tumor diameter (pTS factor).15,16 However, 9 of 33 malignant tumors which were upstaged after PET/CT imaging were considered as resectable according to the other imaging findings (Fig. 3).

In one of the recent studies evaluating the contribution of FDG PET/CT to staging and management of the pancreatic cancer, the diagnostic accuracy rates of contrast-enhanced (CE) PET/CT were reported as greater than 80% for T staging, 42% for N staging and 94% for M staging in stage IVa resectable patients and the PET/CE-CT imaging was suggested as useful for assessing T and M factors in pancreatic cancer but not very useful for assessing the N factor.14 Another recent study has revealed that, after conventional staging that included MDCT, PET/CT results changed the management plan in only 2.6% of the patients.17 However, in our study the impact of PET/CT to management of the malignant disease was 30% (10/33).

Endoscopic ultrasonography has been a widely accepted imaging modality for screening the gastrointestinal and pancreatic cancers. EUS can be used for both diagnosis and treatment by giving opportunity to fine needle aspiration (FNA) biopsy and also having options like drug delivery, biliary drainage, celiac neurolysis and brachytherapy.18 In diagnosing pancreatic lesions <3 cm, EUS is reported to be superior to CT.19 A recent meta-analysis assessing the diagnostic capability of EUS in pancreatic solid lesions has reported that EUS-FNA is a highly accurate diagnostic test with a sensitivity of 85% and specificity of 98% in detecting the malignancy.20 Also in T and N staging of pancreatic cancer EUS may be effective showing the pancreatic head and peripancreatic region closely. However since EUS is an operator-depending imaging tool, interobserver differences can make this method unreliable.

De Witt et al. compared MDCT and EUS for detecting and staging of pancreatic cancer and they reported that EUS is superior for tumor detection and staging but similar for nodal staging and resectability of preoperatively suspected nonmetastatic pancreatic cancer.21 Shami et al. have reported that EUS and MRI are marginally correlated for staging of pancreatic cancer and therefore both tests should be performed for accurate staging.18 Schick et al. performed a prospective study comparing FDG PET/CT with endosonography, endoscopic retrograde cholangio-pancreatography with intraductal ultrasonography and abdominal ultrasound.3 They found that there were no significant differences between sensitivity, specificity, PPV and NPV as obtained by PET/CT in comparison to US, EUS, ERCP; however additional clinical diagnosis were derived from concomitant whole-body PET/CT imaging. In our study findings of EUS and PET/CT were highly correlated for differentiating benign versus malignant lesions with sensitivities and NPVs of 100%. Specificity and PPV of PET/CT were nonsignificantly higher than EUS (89% vs. 88% and 94% vs. 90%).

In conclusion, despite the limitations of retrospective design, non-contrast enhanced PET/CT imaging and missing of a blinded reading of another nuclear medicine physician, our results show that FDG PET/CT can play an important role in evaluation of suspicious cystic and solid pancreatic lesions greater than 10 mm. In this study FDG PET/CT and EUS revealed highly correlated findings for differentiating benign versus malignant lesions of pancreas and were more effective than MDCT and MRI. In patients with pancreatic adenocarcinoma PET/CT changed the therapy planning in 30% of the patients. In diagnosis and management of pancreatic cancer, application of FDG PET/CT along with EUS as first line diagnostic tools can provide the most accurate and effective results with functional and anatomic imaging together also obtaining histopathological findings and whole body evaluation.

Conflict of interest

The authors have no conflict of interest to declare.

References


