18F-FDG PET-CT in Cystic Tumors of the Pancreas

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Abstract: In order to plan treatment or follow-up of pancreatic cystic lesions, is crucial to distinguish benign from malignant cystic tumors with reliable, non-invasive methods. Despite evaluation with several preoperative investigations, a correct pathologic diagnosis rate does not exceed 68%. 2–[18F]–fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET-CT) has been found to be a highly sensitive and specific non-invasive procedure to detect malignancy in cystic tumors of the pancreas (CTP). The introduction of hybrid PET/CT scans allowed a more accurate localization of the foci of hypermetabolism. We reviewed 14 series (645 patients) with a CTP who underwent 18F-FDG PET-CT from 2001; four of these studies came from our group of investigators (226 patients). In the last studies, sensitivity in detecting malignancy ranged from 83 to 100% and specificity from 78 to 100%. 18F-FDG PET-CT for a long time was used only when conventional imaging was insufficient to rule out a cancer. In our experience, 18F-FDG PET-CT was found to be reliable to detect "cancer in situ" when no other investigations could detect it, so we stress the use of 18F-FDG PET-CT in the first assessment, as alternative to EUS with FNA, to exclude malignancy. We are lacking data about the use of 18F-FDG PET-CT and timing in the follow-up of patients (un)-operated. We suggest a regular use in the follow up of patients with intraductal papillary mucinous neoplasms (IPMN), due to their multifocality and to the high rate of extra-pancreatic cancers.

Keywords: 18F-FDG PET/CT, standardized uptake value (SUV), pancreas, pancreatic cystic neoplasm, intraductal papillary mucinous neoplasm (IPMN).

INTRODUCTION

The widespread use of high-resolution non-invasive abdominal imaging lead to an increasing detection of cystic tumors of the pancreas (CTP), and the prevalence of incidental pancreatic cystic lesion in adults ranges from 2.8 to 13.5% [1, 2]. Autopsy series report a CTP prevalence of 23.5%, ranging from 8% below 70 years of age to 35% in > 90 years old people, increasing also in number and size of the cystic lesions according to age [3]. CTP include a variety of neoplasms with different prognosis from benign to premalignant or malignant behavior [4]. Four types of neoplasms included in WHO 2010 classification [5] account for approximately 90% of all cystic tumors of the pancreas: intraductal papillary mucinous neoplasms (IPMNs), either main duct, branch duct or mixed, mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs), either microcystic or oligocystic variant, and pseudopapillary neoplasms.

Cystic feature of some types of CTPs (pseudopapillary neoplasms, neuroendocrine neoplasms, secondary tumors or, occasionally, ductal adenocarcinomas) is due to degenerative changes. Pseudocysts, cystic lymphangiomas and other rare non-neoplastic cysts may enter in the differential diagnosis with CTPs. Preoperative evaluation of pancreatic cystic lesions include abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS) with fine needle aspiration cytology (FNAC) and finally US-guided percutaneous FNAC. Despite these diagnostic tools and many evidence-based practice guidelines [6, 7, 8] have been published, size of the lesion, the presence of high-risk features [6], the role of different diagnostic techniques, and the accuracy of cyst fluid markers and cytology for CTP definition are still controversial issues. Actually, the correct preoperative diagnosis rate in CTP does not exceed 68% in operated patients [9].

POSITRON EMISSION TOMOGRAPHY

2–[18F]–fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) is a scintigraphy technique based on the detection of hypermetabolic lesions due to excess glucose consumption from the tumor cells.

Glycolysis in neoplastic cells is increased due to their ability in glucose transportation through the

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membrane and increased activity of the glycolytic enzymes. The glucose analogue (deoxyglucose) radiolabelled with 18F (a positron emitter), injected one hour before examination (350-450 Mbq) intravenously, in the patient fasted for six hours, is transported into the cell after binding with cell-membrane transporter proteins, and then is metabolized by hexokinase into FDG-6-phosphate. FDG-6-phosphate is not further metabolized in the glycolysis pathway then it remains trapped into the tumor cell. So the FDG-6 phosphate molecule labelled with the radiotracer (18F) may be detected using a gamma–camera. Details of the methods and equipment currently used in our Center, has been previously published [10]. The radioactivity detected by the gamma-camera is coupled with the imaging of a CT scan (hybrid system PET/CT), in order to give more accurate anatomical information on the site of hypermetabolism. To perform a quantitative analysis, the standardized uptake value (SUV) is calculated in the suspected cancer focus. For the SUV analysis a circular region of interest is placed over the area of maximal focal uptake and the mean radioactivity values are obtained. The upper normal limit of the SUV may vary in different centers. As described in our previous papers, in our Center the focal uptake with a SUV > 2.5 is considered positive [10, 11]. In order to avoid false negative results, patients with diabetes were tested just before FDG injection, having a glycaemia of 120-130 mg% (eventually adjusted with insulin). Use of 18-FDG-PET/CT for oncologic imaging is well established and widely accepted for many malignancies [12] including pancreatic cancer [13, 14].

FDG-PET IN CYSTIC TUMOR OF THE PANCREAS

The first report on the use of FDG-PET in evaluating the malignant potential of CTPs was published in 2001 from our Center. Since then, only 12 papers have been published in the Literature, including series with at least 30 patients investigated with PET, PET/CT and/or PET/MRI, in order to compare a significant number of cases of malignant versus benign CTPs. In Table **1** we reported the results in terms of sensitivity and specificity of either FDG-PET or PET/CT. The studies reported are heterogeneous in terms of case mixing of CTP, design of the study (most of them are retrospective), inclusion of pseudocysts in the benign group, and inclusion of histologically proven cases.

About 650 patients having a CTP were investigated in the series published in 14 years from the first study on FDG-PET scan; more than 400 cases had a confirmed histology with 164 malignant CTPs included in these studies. As shown in Table **1**, four of these studies came from our group of investigators accounting 35% of total number of cases published. The paper published from our group in 2011 [10] focusing on IPMN include all patients of the 2007 study [18] and 25 patients reported in the other 2 studies [11,

Table 1: Sensitivity and Specificity of FDG-PET, FDG-PET/TC and FDG-PET/CT in Differential Diagnosis between Malignant and Benign Pancreatic Cystic Lesions

Center	Ref.	Type of study	Year	Nr of pts.	Benign/ Malignant*	All CTP/ IPMN	Sensitivity %	Specificity %
Padova (Italy)	[11]	R, PET	2001	56	39/17	CTP	94	97
Padova (Italy)	[15]	P, PET	2005	50	33/17	CTP	94	94
New York (NY)	[16]	R, PET	2006	68	14/7	CTP	57	85
Indianapolis (IN)	[17]	R, PET	2007	30	23/7	CTP	57	65
Padova (Italy)	[18]	R, PET	2007	64	21/26	IPMN	92	95
Seoul (S Korea)	[19]	R, PET/CT	2010	31	15/16	IPMN	100	87
Osaka (Japan)	[20]	R, PET, PET/CT	2010	72	14/14	IPMN	93	100
Padova (Italy)	[10]	R, PET- PET/CT	2011	145	33/36	IPMN	83	100
Brescia (Italy)	[21]	P, PET/CT	2012	44	32/12	IPMN	83	100
Chiba (Japan)	[22]	R, PET/CT	2013	48	16/32	IPMN	88	88
Miyazaki-city (Japan)	[23]	R, PET/CT [PET/MRI]	2013	31	22/9	CTP	95.5 [100]	77.8 [77.8]
Turku (Finland)	[24]	P, PET/CT	2015	31	16/6	CTP	100	88

*Results expressed for patients (pts) with proven histology; [] results expressed for PET/MRI; P = Prospective; R = Retrospective; CTP = cystic tumors of the pancreas; IPMN = intraductal papillary mucinous neoplasm.

15]. Six papers were dealing with all variety of CPT (overall 266 patients evaluated of which 63 with proven malignancy).

Only two studies were prospective and only studies published after 2010 investigated patients with a PET/CT scan (hybrid equipment). When FDG-PET was compared with results of CT imaging in the Italian studies, contrast enhanced CT had lower sensitivity and specificity (65% and 87-88% respectively) irrespective of the use of multidetector CT equipment in the latter study. The two studies from USA found a 57% sensitivity with a specificity of 65 -85% respectively [16, 17]; however, they enrolled a low number of patients (57 of which 14 malignant) with smaller size of lesions.

In the last studies (data based on PET/CT imaging), sensitivity in detecting malignancy ranged from 83 to 100% and specificity from 78 to 100%. Six studies reported in Table **1** were dealing with IPMNs of the pancreas and the issue of detecting malignancy in this subset of patients. Most of the patients were studied with PET-CT equipment and compared results obtained by MRI and/or CT scan and in total 340 IPMN patients were investigated with 110 malignant ones. Sensitivity of FDG-PET/CT to distinguish malignant IPMN ranged from 83 to 100% and specificity from 87 to 100%; so 97/110 (88%) malignant IPMNs investigated had a positive FDG-PET/CT scan. Moreover when considering non invasive cancer in IPMNs (cancer in situ, CIS) reported in five of these papers, 22/32 cases (69%) had a positive FDG-PET/CT scan. It is noteworthy that in IPMNs with this technique, we can found most of cancers in early stage, not yet invasive, than potentially curable with surgical resection.

SEROUS CYSTIC NEOPLASMS AND FDG-PET

Serous cystadenomas (SCAs) account for about 16% of resected cystic tumors of the pancreas [25]. SCAs are benign, slow-growing tumors that affect mainly women (approximately 75%). Mean age of patients who underwent surgery for SCAs was 62 years in USA [26] and 52 and 58 years in Italian and French series [27, 28]. The typical SCA is formed by many tiny cysts and has a honeycomb appearance (microcystic tumor), having cysts < 2 cm in diameter. The cyst are filled of serous fluid, do not communicate with pancreatic ducts and are often arranged around a central dense fibrous scar with thin fibrous septa radiating to the periphery, occasionally calcified in the center [5]. A SCA variant, called (oligocystic or) macrocystic, has few cysts of more than 2 cm in size and is present in up to 24% of cases [25, 27]. They are difficult to differentiate on imaging with mucinous cystadenomas (MCA). Sixty-one% of SCA are asymptomatic and most are resected due to uncertain diagnosis or size increase [28].

In our Unit from 2004 to 2013 (published in part - [11, 15]) 46 SCAs had a PET study (20% of them had a macrocystic variant) and only 1 microcystic SCA (2%) had a positive PET scan. Therefore in case of difficult differential diagnosis between SCA and mucinous cyst, FDG-PET may help to establish the benign nature of the CTP at time of first assessment.

MUCINOUS CYSTIC NEOPLASMS AND FDG-PET

Mucinous cystic neoplasms (MCNs) account for up to 23% of CTP resected [29]. The risk of malignancy (Mucinous Cystadenocarcinoma) is 17.5-27 % of cases including carcinoma in situ or invasive cancer. They occur mainly in women and in the distal pancreas, being always a single lesion. The cyst (unilocular or with septa) do not communicate with the ductal system and occasionally shows calcifications. Mean age at diagnosis is 45 years [30] and in case of mucinous cystadenocarcinoma the age is 5-10 years older, and the tumor has larger cysts (more than 4 cm in size) and eventually mural nodules or egg-shell calcifications, thick wall or thick septa. Surgical resection is curative, except for invasive carcinomas with extracapsular growth.

In total, including the 2 studies published [11, 15] and cases unpublished (operated on from 2004 to 2012), in our Center 36 MCNs were collected, with three false negative on PET-scan out of 17 malignant MCN (82% sensitivity).

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS AND FDG-PET

Intraductal papillary mucinous neoplasms (IPMNs) are defined as macroscopic (cystic or mass forming) epithelial neoplasms with ductal differentiation that grow primarily within the ductal system of the pancreas [5]. These neoplasms are usually slow-growing and still asymptomatic when they are diagnosed. Histologically they are characterized by a papillary growth pattern, mucin production and they may progress from low-grade dysplasia up to invasive carcinoma. Small IPMNs are incidentally detected due to the use of MRI or CT imaging, and the incidence of IPMNs is

estimated to be more than 20% of total CTPs. IPMNs are more commonly detected in old population (mean age 66 years) [2], and IPMN-related invasive carcinoma occur in people 3 to 5 years older. Three variety of the tumor are recognized, according to the site of origin: main-duct type, branch-duct type, or, in case of main-duct and side-branch duct involvement, mixed type. Risk of malignancy in the main-duct type (or mixed type) is high, accounting for 45% of invasive carcinoma, and for 20% of cancer in situ. Symptoms related to main-duct IPMN are: abdominal pain (55%), weight loss (45%), jaundice (17%), and recurrent acute pancreatitis (15%). Surgical resection is mandatory in main-duct and mixed type. Indication for surgery in branch-duct IPMNs (BD-IPMNs) is mandatory in symptomatic patients, who occasionally may present with pancreatitis. CT/MRI features may vary a lot, including single small cysts up to multiple cystic lesions of different sizes scattered throughout the pancreas [31]. The risk of malignancy of BD-IPMNs is low, <2.5% in three years of follow up in patients who underwent surveillance [25]. In BD-IPMNs operated for suspected features (such as nodules, multiplicity, increasing in cyst size) the mean frequency of malignancy is as high as 25% [6].

FDG-PET CT (as reported above in Table **1**) is able to detect 88% of malignancy in 110 IPMNs, and it is still positive in 69% of cancer in situ (CIS). It is not surprising that a “functional” technique like the FDG-PET may detect a focal increase of glucose metabolism, even when the disease is limited to microscopic changes. It is an extraordinary chance to identify some high risk patients in which surgery is mandatory, achieving a curative resection before the overt spread of the disease.

In our experience [10] PET has an higher rate of positivity compared to other preoperative imaging techniques and even when compared to criteria established in the International Consensus Guidelines defined in Sendai Conference [32]. Than we concluded that FDG-PET scan may help in the first assessment of IPMNs. Moreover, in 24% of our patients with IPMN, a preoperative negative PET/CT scan allowed a more conservative pancreatic resection, ruling out the risk of dealing with a cancer when operating on these patients (often with multifocal disease).

Echo-ultrasound (EUS) and FNA are included and recommended in the Fukuoka guidelines for management of BD-IPMNs and MCN [6], but we think that the use of FDG-PET/CT represent a useful, less invasive alternative to EUS-FNA, operator-dependent technique that may have bias from inconclusive responses from cytology and uncertain results from tumor markers assay in the cyst fluid.

We reported 59 BD-IPMNs (diagnosis based on MRI and without histology) with a negative FDG-PET/TC placed under surveillance [10]; after a mean follow-up of 25 months no one developed malignancy, despite worrisome features according to Fukuoka Conference [6]. Therefore we suggest the use of FDG PET/CT in the first assessment of all IPMNs, particularly in those BD-IPMNs with worrisome features.

At present, we have no information about the use and timing of FDG-PET/CT in the follow-up of patients. From our experience, we suggest to repeat the investigation every three years, or in case of changes in morphology in MRI, rise in serum CA19-9, or symptoms. Due to the low-risk of malignancy, BD-IPMN with cyst < 1 cm can be managed only with MRI.

SOLID PSEUDOPAPILLARY NEOPLASMS AND FDG-PET

Solid pseudopapillary neoplasms (SPNs) of the pancreas are uncommon (< 5% of resected CPTs). SPNs occur in women (up to 90%) with median ages of 30-38 years [33] and a high peak of incidence below 20 years. SPNs appear as heterogeneous masses with solid and cystic components, are low-grade malignant neoplasms forming solid and pseudopapillary structures and frequently undergoing hemorrhagic cystic degeneration. SPNs are single and large masses (average size 8 cm) [5], and metastases occur in 5-15 % of cases in the liver or peritoneum. Surgical resection is curative in 90% of patients. Recently two papers dealing only with SPNs have been published [34, 35]. Irrespective to the real behavior, all the SPN appear to have a high metabolism (SUV max 8.9) with a direct relationship with the proliferative index (Ki-67) and tumor cellularity [34]. Kang *et al*. [35] reported a series of 37 cases studied with FDG PET/CT, and reviewed all the literature including report of single cases, collecting other 24 SPNs. Adding to these series 7 unpublished cases operated on in our Center, out of 69 total cases only 2 (3%) were PET negative. The high rate of FDG-PET positivity even in SPNs with benign behavior makes it useless in the differential diagnosis between benign and malignant (metastatic) neoplasms, however in those with distant metastases may help in the cancer staging.

CYSTIC PANCREATIC NEUROENDOCRINE NEOPLASMS (CPNNS) AND PET

Cystic pancreatic neuroendocrine neoplasms (CPNNs) represent about 8% of resected cystic tumors of the pancreas [29] and 10-17% of resected pancreatic neuroendocrine tumors [36, 37]. Most of them are incidental findings of nonfunctional tumors. They appear as cystic lesions at CT scan, with a hypervascular rim and occasionally containing septa or a solid component. Tumor size is not always related to malignancy, and surgical resection is recommended for all patients (long term survival >85%).

In our experience, FDG-PET was positive in 3 malignant CPNNs and negative in other 3 benign lesions. Despite the high rate of positivity of FDG-PET in pancreatic neuroendocrine tumors (pNETs) with aggressive behavior (78% sensitivity and 83% specificity in malignant pNETs, in our experience) [39, 40], this investigation has a little impact in the clinical practice to differentiate malignant versus benign pNETs. For PET investigations in pNETs, 68Gallium-tracers (DOTATOC and DOTANOC, used as somatostatin receptor agonist) have larger diffusion [41]. Gallium-PET is positive in 93-96% of NETs and represents nowadays the “standard” for staging the disease. Both in cystic and non-cystic lesions, Gallium-PET is able to differentiate malignant from benign lesions when lymph-nodes or distant metastases are detected.

CONCLUSION

The worldwide experience on the use of FDG PET-CT and its diagnostic role in cystic tumors of the pancreas is somehow limited. Only 12 reports have been published in the last 14 years, since our first paper in 2001 dealing with the diagnosis of malignancy in CTP [11]. Less than 700 patients with different variety of CTPs (including short series and personal unpublished data) have been submitted to PET studies and about 35% of them were studied in our Center.

From our first study the results in term of sensitivity, specificity and accuracy of FDG-PET were found to be better than conventional CT or MR imaging to detect malignancy in these heterogeneous neoplasms. In the last studies [10, 20-24], when PET/CT equipment was used, sensitivity in detecting malignancy ranged from 83 to 100% and specificity from 78 to 100%.

Diagnosis of malignancy is crucial in IPMNs, because most of them do not need resection but only surveillance, particularly BD-IPMNs that very often present with multifocal disease. In this case, the risk to overlook a cancer or a malignant non invasive lesion is relatively low, but once the tumor become invasive its behavior is similar to a ductal adenocarcinoma. In order to reduce this risk, an EUS and FNA is suggested [6], but only FDG-PET is able to detect even “cancer in situ” in IPMNs with high sensitivity, then we strongly recommend FDG-PET/TC as a non-invasive alternative to EUS and FNA to rule out the risk of a malignancy in IPMNs.

Currently, the Italian consensus guidelines for the diagnostic work-up and follow-up of CTPs [8] recommend the use of FDG PET/CT only when conventional imaging techniques are inconclusive to rule out a cancer diagnosis. On the basis of the results reported in this review, we believe that this indication should be extended to all patients with CTPs with suspected malignancy, undergoing operation or in follow up.

From 2007-2008 the improvement of the PET equipment with hybrid system PET/CT, allowed a better resolution, anatomical localization and imaging of the focus of hypermetabolism in the abdomen, and since then, the reports showing good results of FDG PET/CT in CTPs are coming from many Centers of Nuclear Medicine all over the world. The lacking of this facility close to Centers dealing with pancreatic surgery and the cost of this technique may be in part responsible of the low number of subjects with CTPs investigated.

There are few open questions about the use of FDG-PET/CT in the follow up of patients with IPMN or in patients already resected for CTP (particularly IPMNs and those with multifocal disease). We do not have data about the timing to repeat a FDG-PET/CT after the first one, or after surgery, since the risk of malignancy in BD-IPMN is unclear and the risk of recurrence after resection depends on the degree and extent of dysplasia left behind in the residual pancreas. We found reasonable to submit our patients (at risk) to a FDG-PET/CT every 3 years, according to imaging (worrisome) features, histology if available, age and general conditions of patients (most IPMNs are >80 years old). In patients with IPMNs a 21 to 30% prevalence of extra-pancreatic cancers has been reported, developed in the course of their lives [42, 43]. A FDG-PET/CT may be a good investigation to detect extra-pancreatic cancers, as they occur incidentally in

8% of our patients at first assessment or during a mean follow-up of 29 months.

Finally, in some variety of CTPs, the FDG–PET seems less important to define malignancy, for example in SPNs, that are strongly positive (with high SUV) at FDG-PET, independently from the real behavior of disease. In the rare CPNNs, the clinical value of FDG-PET/CT is limited to advanced cases, in which the FDG uptake with high SUV is related to poorly differentiated lesion(s) and may help to choose the therapeutic option (chemotherapy or Peptide Receptor Radionuclide Therapy, PRRT).

DISCLOSURE STATEMENT

The authors declare that there is no competing or other conflicting interest in relation to this paper.

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