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REVIEW / *Nuclear medicine*

18F-FDG PET/CT in pancreatic adenocarcinoma: A role at initial imaging staging?

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Abstract Pancreatic ductal adenocarcinoma represents 90% of all pancreatic tumors. The only hope for prolonged survival in patients with this condition still remains surgery with complete R0 resection. Initial imaging has a pivotal role to identify patients who are eligible to curative surgery and those who may benefit of neoadjuvant chemotherapy. This review provides an analysis of the recent literature on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in pancreatic adenocarcinoma. Performances of FDG PET in the detection of lymph node involvement and metastatic spread at initial staging and those in the assessment of response to treatment are described.

Pancreatic ductal adenocarcinoma (PDAC) represents 90% of all pancreatic tumors and is considered to be the second cause of death due to cancer in Europe in 2030 [1]. Its incidence grew twofold in men and threefold in women from 1980 to 2012 [2]. It is one of the most lethal gastrointestinal cancers [3], and surgery offers the only potential chance for long-term survival. Radical surgery offers 10—29% overall 5-year survival whereas incomplete resection provides no benefits in terms of survival [4]. However, only 10% to 20% of patients have localized and resectable tumors at diagnosis. For patients with localized disease, surgical resection is always considered, followed or preceded by systemic chemotherapy. For locally advanced tumors without distant metastases at initial staging, multimodality treatment strategies are proposed, and patients could benefit from induction therapy to make the pancreatic lesion resectable. In this context, a precise initial staging is crucial to select patients who will benefit from surgery initially or after induction therapy. Until now, international guidelines have recommended morphological imaging during the

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initial staging of PDAC [5,6]. At initial staging, a minimal routine workup including at least a 3-phase contrast-enhanced multidetector computed tomography (CT) within 4 weeks of operation is generally performed. Magnetic resonance imaging (MRI) with cholangiopancreatography, 18F-fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT), or endoscopic ultrasonography in addition to fine-needle aspiration, are generally left to the surgeon's discretion. It is well established that morphological imaging is superior to FDG PET/CT for local assessment of PDAC and particularly for vascular invasion [5,6]. Until now, the exact value of FDG PET/CT remained unclear [5,7,8], but is used in many reference specialized institutions in conjunction with cross sectional imaging [9]. We pointed its importance and recommended FDG PET/CT at initial staging of PDAC in the recent published recommendations of good clinical practice for the use of PET in oncology [10]. We detail herein a recent literature analysis to determine the place of FDG PET/CT in the initial imaging workup of patients with PDAC. The present review used French HAS/INCA (Haute Autorité de santé/Institut National du Cancer) methodology and consisted of a systematic review of literature performed with Medline database analysis from 2005 to 2019 and based on search equation defined by INCA experts. Each selected article was analyzed on the basis of a critical reading principle [11].

18F-fluorodeoxyglucose positron emission tomography (FDG PET/CT)

FDG PET/CT technique

Glucose intolerance is frequently encountered in patients with pancreatic adenocarcinoma. It has been demonstrated that FDG PET/CT must be performed in patients with a plasma glucose level of less than 200 mg/dL (<11 mmole/L) at the time of the FDG injection [12,13]. Acquisition parameters of FDG PET/CT are realized in accordance with current guidelines [14]. Some authors found that contrast-enhanced FDG PET/CT allows a more precise assessment of distant metastasis, especially for supraclavicular lymph nodes and peritoneal metastases [15]. Some authors have pointed the potential of delayed FDG PET/CT images to improve assessment of uptake in PDAC but this was not confirmed and generalized [16].

FDG PET parameters on primary pancreatic tumor

The uptake of FDG has been related to pancreatic tumor aggressiveness in terms of pathological grade, with a significant correlation of SUVmax (standardized uptake value) and pathologic grades in 102 patients with histologically proven pancreatic adenocarcinoma [17]. Several studies have suggested that the intensity of FDG tumoral uptake could predict outcome, and tumors with a higher SUVmax are associated with shorter survival [18—24]. However, SUVmax cutoff values differed among studies, ranging from 3 to 10 [17—24]. In the meta-analysis of Zhu et al., which included 16 studies and 1146 patients, pretreatment FDG PET/CT parameters, such as SUVmax and volumetric parameters (metabolic tumoral volume and total lesion glycolysis), were significantly correlated with prognosis, including event-free survival and overall survival [25]. In the retrospective study of Pergoloni et al., the combination of SUVmax $\geq$ 6.0 and CA19.9 serum level $\geq$ 200 U/mL correlated significantly with worse disease-free survival (8 vs. 20 months, $P < 0.001$) in 46 patients operated for PDAC [22]. Pimiento et al. demonstrated that low FDG uptake by tumor in 164 patients who underwent pancreatic resection for stage I and II PDAC correlated with improved overall survival and disease-free survival [21]. These studies suggest that high FDG uptake could serve as an additional tool to consider patients with high-risk PDAC and could orientate disease management (Fig. 1).

Lymph node assessment

Three levels of lymph node metastases are described in PDAC: peripancreatic, along the hepatic hilum or main arteries (superior mesenteric artery, celiac axis, splenic artery) and para-aortic for level 1, 2 and 3 respectively. An increase in metastatic node level is associated with a corresponding decrease in prognosis. In most published studies, FDG PET/CT has limited role for lymphatic involvement assessment of PDAC [26,27]. In the meta-analysis of Wang et al. [26], among 101 patients and four studies, FDG PET (FDG PET alone) revealed a sensitivity of 64% for lymphatic involvement detection. In the retrospective study of Wang et al., the sensitivity and accuracy of FDG PET/CT for lymphatic involvement were 53% and 57%, respectively, as opposed to 17% and 41%, respectively, for thoracic and abdominal computed tomography [28]. More recent studies achieved better performance for FDG PET/CT, especially for level 3 lymphatic involvement (Fig. 2) [28—30]. In the study of Crippa et al., in seven of the eight patients with a pattern of level 3 lymph node metastases on FDG PET/CT, nodal metastases were confirmed by histological examination performed after a more extensive lymphadenectomy [29]. Identifying these level lymph node metastases is crucial, as celiac/para-aortic lymph node metastases are associated with poor prognosis in PDAC and could be considered as systemic metastases [31].

Distant metastases

The prevalence of liver metastases in PDAC is highlighted in the epidemiologic study of Oweira et al., analyzing 13,233 patients who had PDAC with metastases at diagnosis [32]. In this study, distant metastatic sites included liver (77%), lung (20%), distant lymph nodes (9%), bone (7%), and brain (1%) [32]. However, the prevalence of peritoneal carcinomatosis was not detailed in this study. The performance of FDG PET/CT to detect distant metastases is excellent in most studies, with sensitivity ranging from 85% to 89% and specificity from 55% to 100% [26—29,33—37,15,38].

FDG PET/CT detects occult distant metastases not visible on CT performed during initial staging. The rate of these distant occult metastases increased up to 33% in the retrospective study of Chang et al. performed in 388 patients with locally advanced PDAC without metastases on morphological imaging at diagnosis [37]. There was a single metastatic

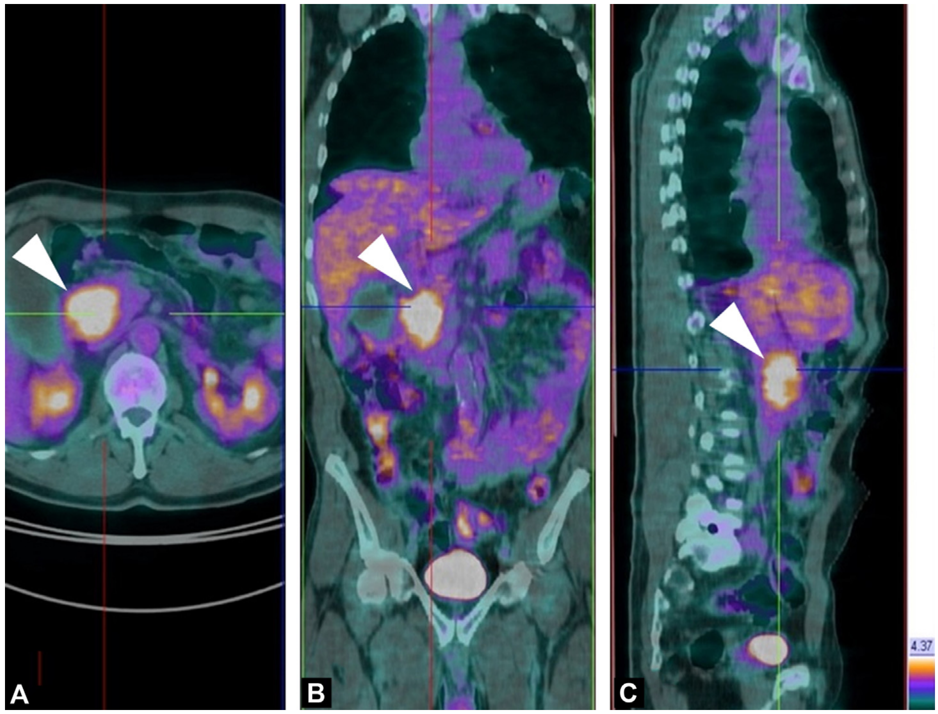

Figure 1. 56-year-old man with locally advanced ductal adenocarcinoma of the pancreatic head at initial staging. Fused 18F-fluorodeoxyglucose (18F-FDG) PET/CT images in the axial (A), coronal (B) and sagittal (C) planes show intense focal tumoral uptake of 18F-FDG (arrowheads). Maximum standardized uptake value (SUV max) of pancreatic adenocarcinoma is 12.

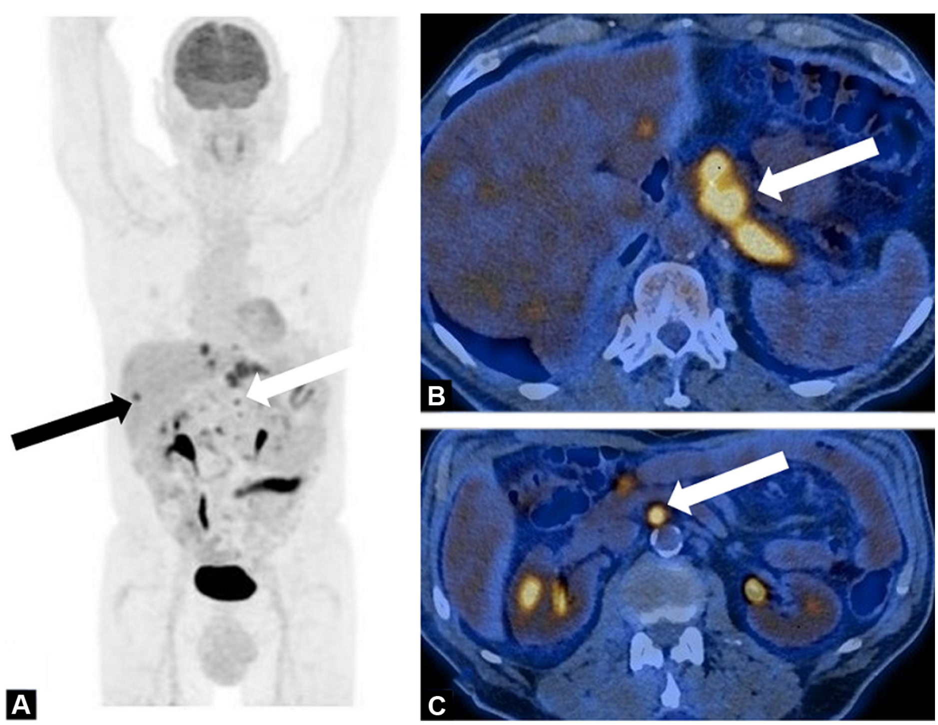

Figure 2. 67-year-old man with pancreatic ductal adenocarcinoma at initial staging. Maximum intensity projection (A) and fused transaxial 18F-fluorodeoxyglucose PET/CT (B, C) images show hypermetabolic para-aortic lymph node (white arrows) and liver metastases (black arrow). Standardized uptake value (SUV max) of pancreatic adenocarcinoma is 9. (Aknowlegments Mathieu Gauthe. Department of Nuclear Medicine, Tenon Hospital, Paris France).

site in 61% of patients. Distant metastatic sites were liver (56% of patients), bone (21%), supraclavicular lymph node (18%), pleura/lung (13%), peritoneum (13%), mediastinal lymph node (7.8%), pelvic cavity (5.5%), and others (4.7%). It must be noted that the high distant metastasis rate in this study is explained by characteristics of patients harboring only locally advanced PDAC. Similar metastatic sites were found in studies of Strobel et al. and Wang et al. [28,39]. In the study of Strobel et al., distant metastases were histologically proven in 10 of the 18 patients, and metastases were confirmed by radiologic appearance or progression on follow up in eight other patients [39]. In this latter study, authors highlighted the superiority of enhanced as opposed to unenhanced PET/CT, especially for liver and peritoneal lesions. In the prospective study of Burge et al. FDG PET/CT identified occult metastases or doubtful metastases on morphological initial imaging in 9/56 patients (16%) with operable pancreatic adenocarcinoma [40]. Liver metastases were present in 5 patients, and in three patients, metastases were detected in lymph nodes above the diaphragm (mediastinum/neck). Bone metastases were detected in one patient.

When compared to CT imaging, the performance of FDG PET/CT is superior [28,35,37,41] or equal [38] to that of CT. However, CT acquisition parameters were not detailed in these studies and this could have explained suboptimal performances of CT. In the retrospective study by Wang et al., performed in 79 patients with PDAC, the sensitivity and accuracy of FDG PET/CT to detect distant metastases was 60% and 88%, respectively, and 24% and 77% for morphological imaging (CT and chest X-ray) [28]. In this latter study, extra hepatic metastases (two patients with supraclavicular lymph nodes and six patients with peritoneal metastases) were detected only with FDG PET/CT [28].

In the retrospective study of Farma et al. involving 82 patients with potentially resectable PDAC, FDG PET/CT detected metastases in 14 of the 82 patients, and in 7 patients, metastases present in FDG PET/CT were not found on morphological imaging (supraclavicular lymph node, $n = 2$ patients; liver, $n = 2$ patients; peritoneal carcinomatosis, $n = 2$ patients; peri-esophageal lymph node, $n = 1$ patient) [35].

Recent studies have suggested that MRI including diffusion-weighted sequences was superior to CT to detect liver metastases [42,43]. In one prospective study including 118 patients, MRI showed liver metastases in 10% of patients with resectable PDAC in whom CT was considered as normal [42]. In one comparative retrospective study enrolling 167 patients [43], preoperative selection by CT plus MRI ($n = 65$) was associated with a better median overall survival (25 vs. 12 months, $P = 0.020$) and disease-free survival (10.0 vs. was 8.5 vs. 10.0 months, $P = 0.016$) than observed in the 102 patients operated after selection by CT alone. It must be pointed that there are presently no sufficient available data comparing FDG PET/CT and MRI for liver metastasis detection in PDAC [41]. In a recent study, no statistical differences were found between FDG PET/MRI and the association of FDG PET/CT and MDCT for distant metastatic assessment in 35 patients with PDAC [44]. There are also no sufficient available data concerning correlation between FDG PET/CT findings and the CA19-9 serum level in PDAC.

Impact on therapeutic management

Patients with distant metastases on FDG PET/CT could be spared from unnecessary harmful treatment. FDG PET/CT performed at the time of diagnosis of PDAC induced a change in the therapeutic plan in approximately 10% of patients [28,29,34,40]. Therapeutic plan change involved 16% of patients in the prospective study of Heinrich et al., which included 59 patients with operable PDAC [34]. FDG PET/CT findings resulted in surgery cancellation for 8/7979 patients (10%) Wang et al. study [28] and for 8/72 patients (11%) in Crippa et al. study [29]. In the multicenter prospective study of Ghaneh et al., FDG PET/CT changed the staging of pancreatic cancer in 56 of 261 patients ($P = 0.001$) and stopped resection in 58 patients who should have undergone surgery [45].

Furthermore, it must be emphasized that in the retrospective study of Chang et al. [37], among the 260 selected patients with PDAC without distant metastases on FDG PET/CT at staging, the incidence of early distant metastases after the completion of chemoradiation therapy was relatively low (13.1%), with longer survival (median overall survival, 14.6 months) and better locoregional control when compared to published data [46].

Therapeutic evaluation

For potentially resectable or borderline PDAC, induction neoadjuvant treatment is frequently performed to make the pancreatic lesion resectable. Several studies have highlighted the difficulty to precisely assess the efficacy of induction therapy and secondary resectability with morphological imaging [47—49]. FDG PET/CT demonstrated adequate performance in the evaluation of metabolic response after induction treatment for locally advanced pancreatic adenocarcinoma and can serve as a tool to assist the surgical decision [49—52]. In 40 patients with operable PDAC, decrease in SUVmax of more than 46% on pancreatic tumors between initial and end-of-treatment FDG PET/CT was associated with adequate pathological response [51]. In the retrospective study of Akita et al., decrease in SUVmax of more than 50% on pancreatic tumor between initial and end-of-treatment FDG PET/CT was associated with complete pathological response and a better outcome after surgery [53]. Volumetric parameters (metabolic tumoral volume and total lesion glycolysis) on primary tumors on FDG PET/CT upon completion of preoperative chemoradiotherapy were statistically lower in responders as opposed to non-responder patients in the retrospective study of Sakane et al. [52]. All authors emphasize the need to respect a delay of at least eight weeks to perform FDG PET/CT after completion of radiotherapy to avoid uptake due to inflammatory process.

Conclusion

FDG PET/CT has adequate performance for the initial staging of PDAC, especially for the depiction of distant lymph node and occult metastases. However, further studies are needed to compare FDG PET/CT with MRI for liver metastases detection. FDG PET-CT additionally demonstrates favorable performance to evaluate metabolic response after induction treatment. Today, it can be reasonably proposed at diagnosis, in addition to morphological imaging, in a subgroup of patients with locally advanced and potentially resectable PDAC before treatment to exclude occult metastases and as an additional tool for therapeutic response after induction treatment prior to surgery.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

All authors M. Wartski and A. Sauvanet have contribute to the present paper:

- conceptualization;
- formal analysis;
- methodology;
- project administratio;
- supervision;
- validation;
- writing original draft and review.

Disclosure of interest

The authors declare that they have no competing interest.

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