PET/CT in Pancreatic Malignancies

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Ameya D. Puranik, Archi Agrawal, Sneha Shah,
Nilendu Purandare, and Venkatesh Rangarajan

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7.1 Introduction

Pancreatic adenocarcinoma (PAC) accounts for about 85% of cases of pancreatic malignancies [1], and the term "pancreatic cancer" is sometimes used to refer only to that type. Imaging plays a central role in the management of this disease. Imaging facilitates establishing diagnosis, determining staging, monitoring treatment response, and detecting recurrence following surgery. Multiple modalities are involved, including computed tomography (CT), magnetic resonance imaging

A.D. Puranik (✉) • A. Agrawal • S. Shah • N. Purandare • V. Rangarajan
Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Mumbai, Maharashtra, India
e-mail: ameya2812@gmail.com

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(MRI), positron emission tomography with computed tomography (PET/CT), and endoscopic ultrasound (EUS). PET/CT combines functional information of PET with detailed anatomic information of multidetector CT [2]. Although the role of PET/CT in the diagnostic evaluation of patients with various abdominal malignancies is established, its role in pancreatic imaging is still evolving.

7.2 Imaging Modalities in Pancreatic Cancer

Abdominal ultrasonography is the first imaging modality for patients presenting with pancreaticobiliary symptoms or nonspecific abdominal pain. Diagnostic sensitivity of 90% has been reported by Karlson et al.; however, the retroperitoneal location of the pancreas obscured often by bowel gas, as well as the operator-dependent nature of the investigation precludes its use as an accurate diagnostic modality [3]. Multidetector CT (MDCT) is the modality of choice for diagnosis and staging of pancreatic cancers. PACs typically manifest as ill-defined hypoattenuating masses, with nearly 11% being isoattenuating on pancreatic and hepatic phase [4, 5]. MDCT has high sensitivity for detection of pancreatic cancers, ranging from 89 to 97%. Degree of vascular involvement and peritoneal and hepatic metastases on CT determine resectability of primary tumor [6]. MRI and MRCP are currently used as problem-solving tools for patients with PACs. There are specific situations where MRI is superior to CT: small tumors, hypertrophied pancreatic head, isoattenuating pancreatic cancer, and focal fatty infiltration of the parenchyma [7]. In small tumors, less than 3 cm, EUS is considered as an accurate modality for detecting these focal lesions; in addition, histological evidence can also be obtained by EUS-FNA [8, 9].

7.3 PET/CT in Pancreatic Cancer

7.3.1 Diagnosis and Staging

CECT is the modality of choice for diagnosis and staging; however, for tumors less than 2 cm, sensitivity significantly falls (approximately 83%). Moreover, tumors more than 2 cm in size and isoattenuating on CT account for almost 10% of PACs; these lesions are often missed on conventional CECT imaging [10]. Well-differentiated PACs are FDG-avid tumors, and hence metabolic imaging with FDG PET/CT picks up the primary site, while CT provides the morphological correlate. Okano et al. reported sensitivity of 100% and 40% for FDG PET and CT, respectively, for detecting lesions less than 2 cm [11]. As far as imaging pattern is concerned, focal FDG uptake is predictive of malignant etiology warranting further investigation [12]. Higher SUV (standardized uptake value) increases the sensitivity for depicting PACs, at the cost of specificity, as some of the infective and inflammatory lesions can sometimes show high SUV values. At the same time, ductal adenocarcinomas and mucinous/signet ring cell variants show low SUV values; a pattern typical for nonmalignant pancreatic lesions [13].

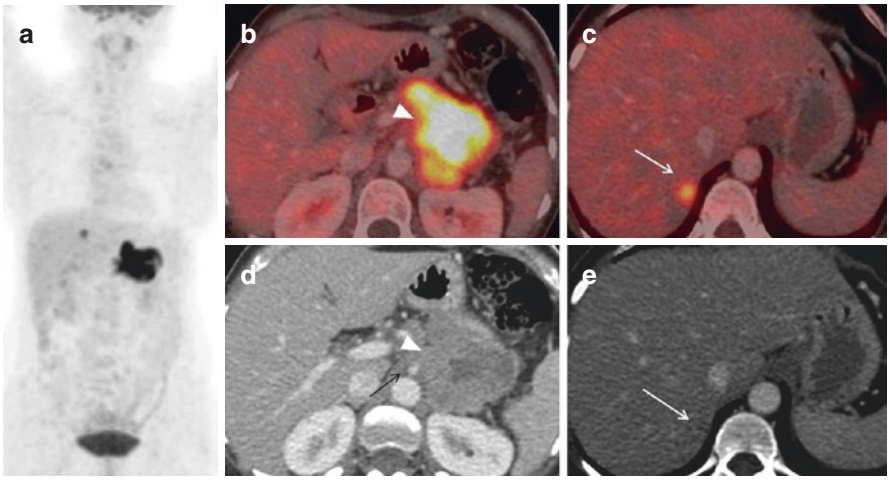

Fig. 7.1 FDG PET/CT in staging of pancreatic adenocarcinoma: MIP image (**a**) shows large area of tracer concentration in the mid-abdomen with focal tracer uptake in the liver. Axial PET/CT (**b**) shows FDG-avid large soft tissue mass in the body of pancreas with encasement of superior mesenteric artery on venous phase CT component (**c**-*arrow*) of PET/CT. There is intense desmoplastic reaction (**c**-*arrowhead*) with FDG uptake (**b**) delineating the actual tumor. Axial PET/CT (**d**-*arrow*) shows FDG-avid lesion in the liver which is seen as subtle hypodensity on CT (**e**-*arrow*) image suggestive of metastatic involvement

7.3.2 Local Staging

Pancreatic phase CECT (CT angiography phase) images of the aorta and the superior mesenteric artery (17–25 s after the start of contrast injection), pancreatic phase (35–50 s after the start of contrast injection), and portal venous phase images (55–70 s after the start of contrast injection), when acquired as a part of PET/CT protocol (Fig. 7.1b, c—arrow), provides best information about vascular involvement in terms of cross-sectional circumference, which determines operability [14].

PET, with its metabolic dimension, provides the actual site of disease, since PACs are often accompanied by a dense desmoplastic reaction (Fig. 7.1b, c—arrowheads). This, in addition, provides accurate site for biopsy and tissue sampling [15]. In actual clinical practice, most patients undergo triphasic CT for diagnosis and are further referred for PET/CT imaging in locally advanced or borderline respectable scenarios to rule out the liver and other sites of distant metastases.

7.3.3 Nodal Staging

Some studies reported modest improvement in the performance of FDG PET compared with CECT in patients with pancreatic masses, with sensitivity and specificity ranging from 30% to 49% and 63% to 93%, respectively, for evaluation of lymph nodes. Lesser tumor volume in affected lymph nodes and strong photon scatter from

the primary tumor (penumbra effect) may partially explain the poor performance of FDG PET for lymph node staging [16, 17]. Metabolic information of FDG PET may complement that of CT for nodal staging, because even low-grade metabolic activity on fused imaging in a rounded centimeter-or-more-sized node may be indicative of nodal metastases.

7.4 Liver Metastases

FDG uptake in hepatic lesions strongly favors metastatic involvement; also the absence of FDG uptake in suspicious liver lesions seen on conventional imaging rules out metastases [18]. This dilemma arises mostly in case of solitary focal liver lesion that appears suspicious on triphasic CT/ultrasonography; here FDG uptake is a clincher as the presence of uptake favors malignancy (Fig. 7.1d, e, arrows) and further can be managed by liver-specific interventions.

In a study comparing the performance of hepatobiliary contrast-enhanced MR imaging and FDG PET, MR imaging was more accurate in depicting small liver metastases, with a reported accuracy of 97.1% compared with 85.3% for FDG PET [19].

7.5 Other Distant Metastases

Small volume disease in the form of nodular peritoneal implants often seen as stranding and rarely as frank "caking" pose a diagnostic challenge on CT, with reported sensitivity of 65–88% and specificity of 38–63% [20]. Peritoneal implants were found at staging laparoscopy in 7% of patients with locally unresectable pancreatic cancer and no evidence of metastasis at CECT [21].

Since PET/CT imaging is a whole body study, it is the best modality for detecting distant metastases at any site.

Most of the centers incorporate breath-hold plain CT of chest in PET/CT protocol, for detection of metastatic lung nodules. This is because detection of subcentimeter-sized nodules is beyond the resolution of even modern-day PET scanners, and hence plain thin-section breath-hold CT serves the purpose.

Thus, PET/CT impacts management change in patients deemed "operable" on conventional imaging, by detecting distant metastases, thus avoiding the cost of futile surgery.

7.6 PET/CT to Detect Disease Recurrence

PACs are naturally aggressive cancers, and following the natural history, after surgery, 72–92% of pancreatic adenocarcinomas recur locally within 2 years [22]. Locally recurrent tumors are usually not resectable; however, radiation therapy or

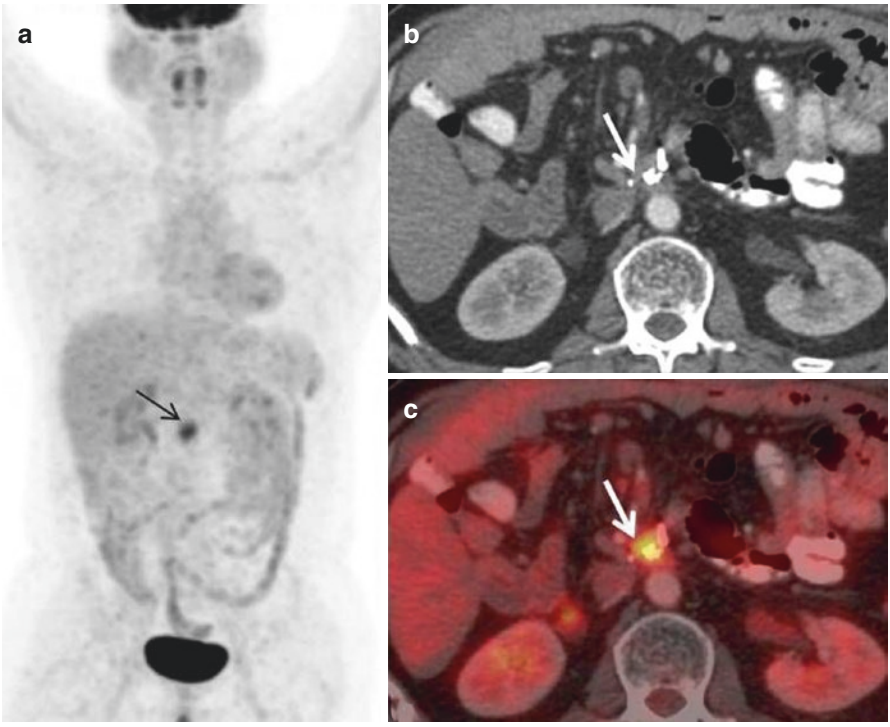

Fig. 7.2 FDG PET/CT for restaging. A 56-year-old female underwent Whipple's procedure for pancreatic adenocarcinoma involving body, followed by adjuvant chemotherapy; 6 months later, presented with rising CA19.9 levels, and hence was referred for PET/CT imaging. MIP image shows focal tracer uptake in the mid-abdomen (*arrow*), which corresponds to FDG-avid soft tissue (**b**-*arrow*) at the level of SMA origin (**c**-*arrow*) from abdominal aorta, thus representing local recurrence, with this being a typical pattern of local site recurrence

local ablation either with radiofrequency or cryoablation may be a palliative option. Postoperative changes in the surgical bed and early tumor recurrence have overlapping morphologic characteristics, as a result, differentiating between them is difficult on CECT. Moreover, it is often difficult to obtain an adequate tissue sample because desmoplastic reaction is known to be associated with pancreatic cancers. The use of FDG PET to depict tumor recurrence is promising, particularly when CT findings are equivocal [23, 24]. Increased FDG uptake in the surgical site at 3 months following surgery is usually indicative of recurrence (Fig. 7.2). The reported sensitivity of FDG PET for depicting tumor recurrence is 96% compared with 39% for CT and MR imaging [23]. Moreover, after resection, tumor relapse is depicted at FDG PET earlier than it is at CT, with higher sensitivity (98%) and specificity (90%) [24].

7.7 PET/CT to Detect Treat Response

PET combined with CECT plays a role in monitoring response to chemo- and radiation therapy in patients with unresectable pancreatic cancer [25, 26]. Significant reduction in FDG uptake may precede volumetric reduction at CT and may be proportional to the change in tumor size at subsequent follow-up examinations (Fig. 7.3). Therefore, earlier depiction of tumor response to therapy at FDG PET could influence the continuation or withdrawal of treatment [27]. Moreover, some recently published studies reported that FDG PET/CT might have prognostic value because tumors with a higher baseline SUV_{max} are more likely to recur in the early post-operative period. SUV_{max} is also an independent predictor for overall survival in patients with locally advanced pancreatic cancer [28, 29]. Postoperative inflammatory changes in the pancreas, radiation therapy, or stent placement may also cause some FDG uptake. To minimize these false-positive results, it is recommended that follow-up PET or PET/CT be performed at least 6 weeks after surgery [30].

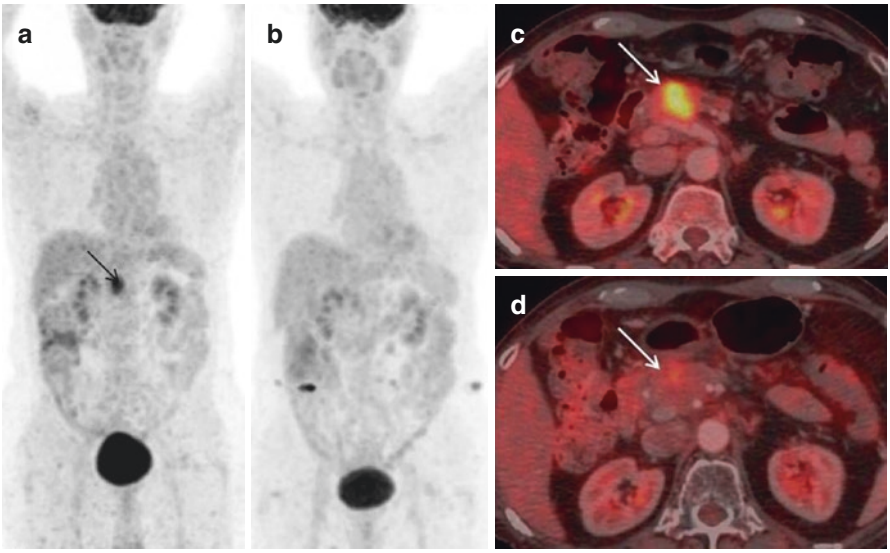

Fig. 7.3 FDG PET/CT in treatment response evaluation. A 46-year-old female patient presented with adenocarcinoma involving pancreatic head which was non-resectable received 6# chemotherapy; PET/CT study was performed to assess treatment response. MIP images (baseline-**a**, posttreatment-**b**) show regression in focal tracer uptake in mid-abdomen, which is seen as significant regression in size with near-complete metabolic regression at the primary pancreatic site (baseline, with no new lesions elsewhere, on axial PET/CT (**c**-baseline, **d**-posttreatment)

7.8 PET Tracers for Other Pancreatic Neoplasms

7.8.1 68Ga-DOTA-PET/CT

Neuroendocrine tumors represent 1–2% of all pancreatic neoplasms [31]; nonfunctioning tumors now account for 60–80% of such tumors [32]. Insulinoma and gastrinoma are the most common functioning islet cell tumors, accounting for about 32 and 9% of cases, respectively. Functioning tumors are detected earlier in their clinical course, when they are generally small in size.

As many as 90% of nonfunctioning tumors are malignant at the time of diagnosis, with more indolent biologic behavior than pancreatic adenocarcinoma [33]. Well-differentiated NETs, termed "carcinoids," often express somatostatin receptors (SSTR), whereas poorly differentiated variants express GLUT receptors making these tumors FDG avid. SSTR-specific radionuclides like Ga68-DOTA-TOC/NOC/TATE are the most sensitive radionuclides for this subset of tumors. Versari et al. [34] reported that 68Ga DOTA-TOC PET/CT has accuracy comparable to those of endoscopic US and multidetector CT for depicting primary neuroendocrine tumors in the duodenopancreatic area, with a sensitivity of 87% and specificity of 83%.

7.8.2 68Ga-DOTA-Exendin-4 PET/CT

The most common cause of endogenous hyperinsulinemic hypoglycemia in adults is an insulinoma. Endogenous hyperinsulinemic hypoglycemia is biochemically diagnosed by a prolonged supervised fasting test in an inpatient setting [35]. Small size of tumors is a limitation for localization by conventional imaging. Methods like intra-arterial calcium estimation and venous sampling are sensitive; however, their invasive nature poses risk of complications. Benign insulinomas have a high concentration of glucagon-like peptide-1 receptors (GLP R 1), which are good targets for in vivo imaging [36]. Early results with 68Ga-DOTA-exendin-4 PET/CT, which localizes to GLP-R-1, have shown good sensitivity for detection of these lesions [37].

7.8.3 18F–FDOPA PET/CT

The most frequent catecholamine-producing tumors are pheochromocytomas, which arise from chromaffin cells of the adrenal medulla (80–85%) or extra-adrenal paraganglia (15–20%). Imaging techniques are used to localize the primary tumor and to search for metastases. In case of pheochromocytomas, most tumors are benign, but 10–20% are malignant. The most specific agent which localizes to catecholamine precursor dopamine receptors is a F-18-labeled compound, fluoro-L-dihydroxyphenylalanine (F-DOPA) [38]. It has better resolution, imaging characteristics, and sensitivity than I-131 MIBG SPECT scintigraphy.

Key Points

- CECT is the modality of choice for diagnosis and staging.
- Well-differentiated PACs are FDG-avid tumors, and hence metabolic imaging with FDG PET/CT picks up the primary site, while CT provides the morphological correlate.
- For detection of lesions less than 2 cm, the sensitivity of FDG PET and CT is 100% and 40%, respectively.
- Ductal adenocarcinomas and mucinous/signet ring cell variants show low SUV values, a pattern typical for nonmalignant pancreatic lesions.
- In detecting nodal disease, there is modest improvement reported in the performance of FDG PET compared with CECT in patients with pancreatic masses.
- FDG uptake in hepatic lesions strongly favors metastatic involvement, but MR imaging is more accurate in depicting small liver metastases.
- The use of FDG PET to depict tumor recurrence is promising, particularly when CT findings are equivocal.
- Increased FDG uptake in the surgical site at 3 months following surgery is usually indicative of recurrence.
- The reported sensitivity of FDG PET for depicting tumor recurrence is 96% compared with 39% for CT and MR imaging.
- PET combined with CECT plays a role in monitoring response to chemo- and radiation therapy in patients with unresectable pancreatic cancer.

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