S. N. Reske

FDG-PET and PET/CT in Pancreatic Cancer

Pancreatic cancer, the fourth most common cause of cancer deaths, has a very poor prognosis, with a 3% 5-year survival rate [1], accounting for 30,000 deaths yearly in the USA [2]. The majority of patients present with advanced disease, resulting in a low resection rate, especially if the patient is seen outside of regional specialist units [3]. Without resection, the overall median survival is 4–6 months, with an estimated 5-year survival rate of 0.4–5% [4]; chemotherapy has only a modest effect, improving survival by just a few weeks or months [5]. High mortality rates are related to the highly aggressive nature of the tumor, the nonspecific symptoms leading to late presentations, and the diagnostic limitations of current imaging modalities [6]. Patients who undergo pancreatic resection demonstrate a median survival of 10–18 months and a 5-year survival rate of 17–24%. The late presentation is responsible in part for the poor overall survival and poor long-term survival rates. Since pancreatic tumors may have a better prognosis when detected at an early stage, before metastases occur, imaging studies that can detect small isolated lesions could be valuable.

Standards of Care

Currently, the standard of care for patients with suspected pancreatic cancer includes imaging with ultrasonography, endosonography, and computed tomography (CT), and then either needle biopsy sampling or open laparoscopy depending upon whether the mass appears malignant or benign. Masses that appear malignant and resectable may undergo laparoscopy, while masses that appear rather benign or malignant but unresectable undergo biopsy. Biopsy, although safer then laparoscopy, is associated with complications, the most concerning of which is acute pancreatitis. Approximately 5% of individuals will have minor complications and the diagnostic yield of endoscopic ultrasound-guided biopsy is about 68%.

Imaging Techniques

The limitations of CT in detecting pancreatic carcinoma include difficulty in identifying small lesions in the pancreas (false negatives), difficulty in differentiating pancreatic carcinoma from mass-forming pancreatitis (false positives), and indeterminate results. Mass-forming pancreatitis occurs when the inflammation associated with pancreatitis affects only a portion of the pancreas, creating the appearance of a mass on imaging tests. As chronic pancreatitis is a risk factor for pancreatic carcinoma, mass-forming pancreatitis is not uncommon in the patient population being investigated. Adjunct testing with an imaging study that relies upon a different imaging technique has been suggested as a way to address these limitations of CT. The use of [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET; FDG-PET) has several theoretical advantages over conventional imaging. FDG-PET uses a radiotracer-labeled glucose analogue, FDG, to monitor the functional activity of specific regions of interest and to compare it with the baseline background activity of a nearby area. The pancreas typically has a very low uptake of FDG, while pancreatic adenocarcinoma has a high uptake due to the upregulated expression of glucose transporters at the cellular membrane of pancreatic cancer cells (Fig. 11.1) [7]. In addition, pancreatic carcinoma cells lack the enzymes to break down FDG, essentially resulting in storage of FDG within the tumor tissue, further enhancing its signal intensity as compared with the normal surrounding areas (Fig. 11.2). As FDG-PET relies upon detection of functional activity rather than lesion size, it may possess an advantage in the differentiation of benign from malignant pancreatic lesions. For these reasons, it has been suggested that FDG-PET should be added as an adjunct to CT to reduce the overall false-positive, false-negative, and indeterminate rates [8–17]. Reducing the false-positive rate prevents unnecessary laparoscopy and/or biopsy; reducing the false-negative rate may permit earlier detection of small,

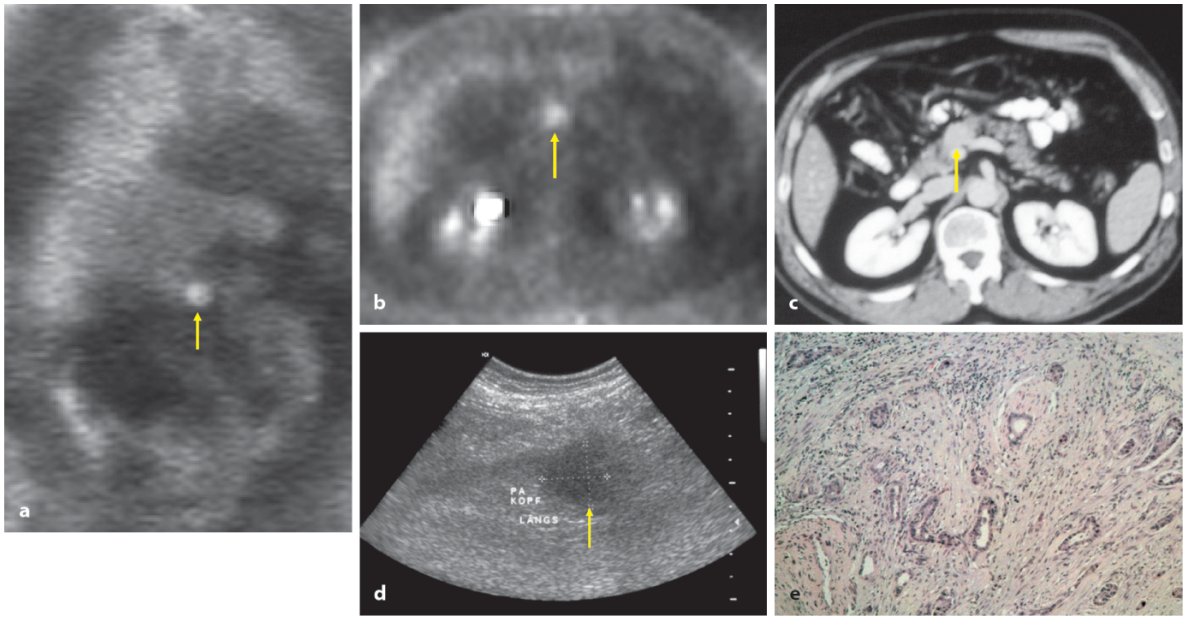

Figure 11.1

Ductal pancreatic adenocarcinoma pT2. [18F]fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) shows focally increased FDG uptake in the head of the pancreas (*arrows*,**a**,**b**) corresponding to CT lesion (*arrow*,**c**) and ultrasonography (*arrow*, **d**). Histology (hematoxylin and eosin stain) shows adenocarcinoma of the pancreas (e)

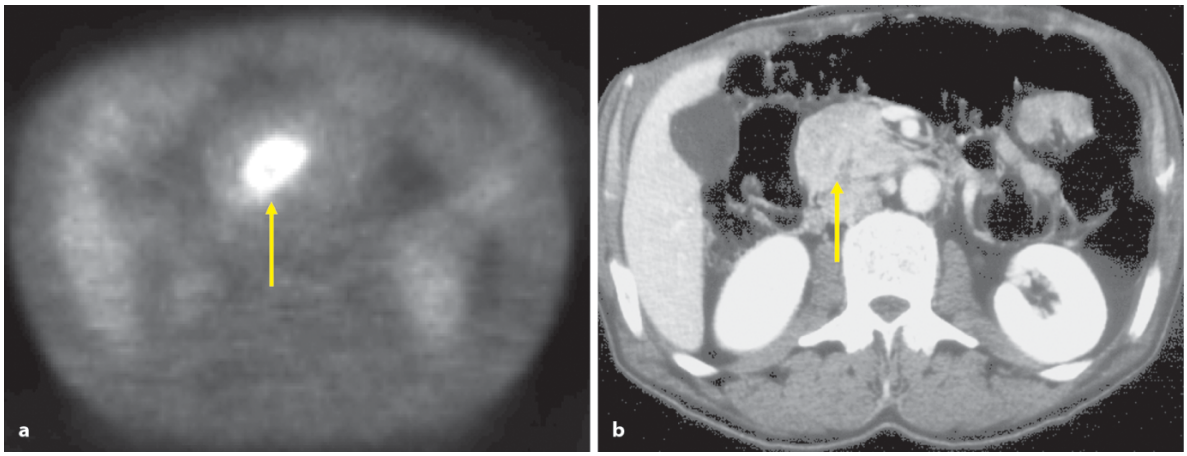

Figure 11.2

FDG-PET (**a**) and corresponding CT (**b**), transverse sections. Large mass seen on CT (*arrow*) in the head of the pancreas with intensive FDG uptake within the central part of the lesion (*arrow*)

localized tumors during a period when they may be more amenable to cure; and reducing the indeterminate rate has the benefits of both reducing the false-positive and false-negative rates.

Comparison of CT and FDG-PET

Several studies have been performed comparing FDG-PET to CT for the differentiation of benign from malignant pancreatic lesions (Table 11.1). The most relevant studies up to the publication year of 2001 have been summarized in a recent meta-analysis [18]. The pooled sensitivity and specificity for CT across

Table 11.1. Description of studies included in analysis [18]. *PET* Positron emission tomography, *CT* computed tomography

Author	Year	PET total	CT total	Population	PET sensitivity[a]	PET specificity[a]	CT sensitivity[a]	CT specificity
Delbeke et al. [16]	1999	65	65	Suspected carcinoma	92% (81–96)	58% (34–79)	64% (51–78)	62% (32–85)
Nakamoto et al. [22]	2000	47		Suspected carcinoma	100% (87–100)	80% (56–93)		
Zimny et al. [15]	1997	105		Suspected carcinoma	89% (79–95)	53% (35–70)		
Diederichs et al. [9]	1999	122	101	Referred resection	88% (74–94)	87% (75–94)	95% (84–99)	91% (78–97)
Bares et al. [25]	1994	40	40	Mass or pancreatitis	89% (70–97)	85% (54–97)	100% (87–100)	23% (6–54)
Ho et al. [17]	1996	14	14	Mass or pancreatitis	100% (63–100)	67% (24–94)	25% (5–64)	100% (54–100)
Keogan et al. [26]	1998	37	37	Mass of dilated duct	88% (68–97)	83% (51–97)	75% (53–89)	93% (51–97)
Bares et al. [20]	1993	15	15	Mass	92% (62–100)	100% (16–100)	95% (75–100)	50% (3–97)
Kalady et al. [27]	2002	54	54	Mass	88% (73–95)	92% (62–100)	65% (39–85)	87% (72–95)
Kato et al. [28]	1995	24		Mass	93% (66–100)	78% (40–96)		
Koyoma et al. [29]	2001	86	86	Mass	82% (70–90)	81% (58–94)	91% (80–96)	38% (19–61)
Sendler et al. [21]	2000	42	42	Mass	81% (52–85)	64% (32–87)	74% (55–87)	73% (40–93)
Imdahl et al. [30]	1999	48	48	Known Ca or pancreatitis	96% (79–100)	100% (84–100)	50% (35–65)	44% (15–77)
Inokuma et al. [31]	1995	46	46	Clinical symptoms	94% (80–99)	82% (48–97)	89% (72–96)	73% (40–93)
Papos et al. [32]	2001	22	22	Clinical symptoms	100% (54–100)	88% (61–98)	100% (54–100)	56% (31–79)
Rajput et al. [33]	1998	13	13	Clinical symptoms	82% (48–97)	100% (16–100)	73% (40–93)	0% (0–84)
Kasperk et al. [34]	2001	103	103	Suspected carcinoma	92% (83–96)	58% (34–79)	85% (75–91)	89% (66–98)

[a] Sensitivity and specificity are reported as the calculated value with the 95% confidence interval

Table 11.2. Results of PET and CT for individuals with a false positive (*FP*) or false negative (*FN*) on either imaging test [18]. *NA* Not available

Study	No without cancer	CT false positives (FP) CT FP correctly dx by PET/CT FP	PET false positives (FP) PET FP correctly dx by CT/PET FP	No with cancer	CT false negatives (FN) CT FN correctly dx by PET/CT FN	PET false negatives (FN) PET FV correctly dx by CT/PET FN
Delbeke et al. [16]	13	2/5	0/3	52	18/18	0/0
Keogan et al. [26]	12	0/2	0/2	22	2/2	0/1
Kalady et al. [27]	13	4/5	01	41	1/4	3/5
Koyoma et al. [29]	21	6/8	3/5	65	4/6	5/7
Sendler et al. [21]	11	NA/3	3/4	31	7/8	8/9
Imdahl et al. [30]	21	4/4	0/0	27	5/5	1/1
Inokuma et al. [35]	11	3/3	2/2	35	2/4	0/2
Papos et al. [32]	16	5/7	0/2	6	0/0	0/0
Rajput et al. [33]	2	2/2	0/0	11	3/3	2/2

all studies was 81% (95% confidence interval, CI, 72–88%) and 66% (95% CI 53–77%), respectively. When combining the nine studies from Table 11.2, the pooled sensitivity and specificity for PET in those with a positive CT was 92% (95% CI 87–95%) and 68% (95% CI 51–81%), respectively, and in those with a negative CT those figures were 73% (95% CI 50–88%) and 86% (95% CI 75–93%), respectively. The areas under the ROC curve for PET were higher in both those with a positive CT (0.94) and a negative CT (0.93) than for CT alone (0.82), suggesting that the addition of PET as an adjunct test would improve the ability to discriminate between patients with and without pancreatic cancer. The sensitivity was 92% and the specificity 88% for the abnormal prior imaging group, and 86% and 89%, respectively for the normal prior imaging group. There was a strong trend toward a lower test performance for PET in individuals with a negative CT.

Other Findings

In the five studies [14, 15, 19–21] that evaluated the effect of hyperglycemia on the sensitivity and specificity of PET, all concluded that hyperglycemia increased the number of false-negative results (Fig. 11.3). The average sensitivity for detecting pancreatic cancer decreased by 4%, from 92 to 88% in individuals with hyperglycemia [18].

Several studies on FDG-PET in pancreatic cancer have been published since 2001, covering new imaging technologies such as PET/CT, technical-software-based fusion imaging, technically improved data acquisition and analysis, response to chemotherapy, and diagnosis of relapse.

In general, diagnostic studies comparing CT, magnetic resonance tomography (MRT) or endoscopic ultrasonography (EUS) and PET have found increased sensitivity of CT, MRT, or EUS imaging compared to earlier studies, probably related to improved imaging equipment used in these studies (Table 11.3). Although the specificity of FDG-PET has generally improved compared to standard imaging technology, most authors found little additional value of FDG-PET for the diagnosis of pancreatic cancer, given the lack of information regarding T-staging and resectability through FDG-PET.

It appears, however, that virtually all studies excluding one case report, did not use PET/CT equipment, which is now regarded as a standard PET imaging procedure in oncology. It is therefore believed that the value of FDG-PET/CT in the diagnosis and staging of pancreatic cancer is currently unknown and needs to be prospectively studied.

Beyond use of adequate imaging technology, PET-based imaging of pancreatic cancer may be improved by delayed imaging (i.e., 2 h instead of 1 h post-FDG injection) due to increased detectability of primaries, and liver and lymph node metastases [22, 23], and normalization to tumoral FDG uptake to blood glucose concentration.

In a recent report, the value of FDG-PET (n=31) for the diagnosis of recurrent pancreatic cancer was compared to CT (n=14) or MRI (n=17) [24]. All 31 patients relapsed and 25/31 patients had local relapse; 23 of the 25 relapsing patients relapsed early after surgery. FDG-PET detected 22/23 (96%) patients with "initial" relapse; that number for CT/MRI was 9/23 (39%). FDG-PET detected 5/12 (42%) liver metastases and CT/MRT detected 11/12 (92%). PET detected 7/9 ab-

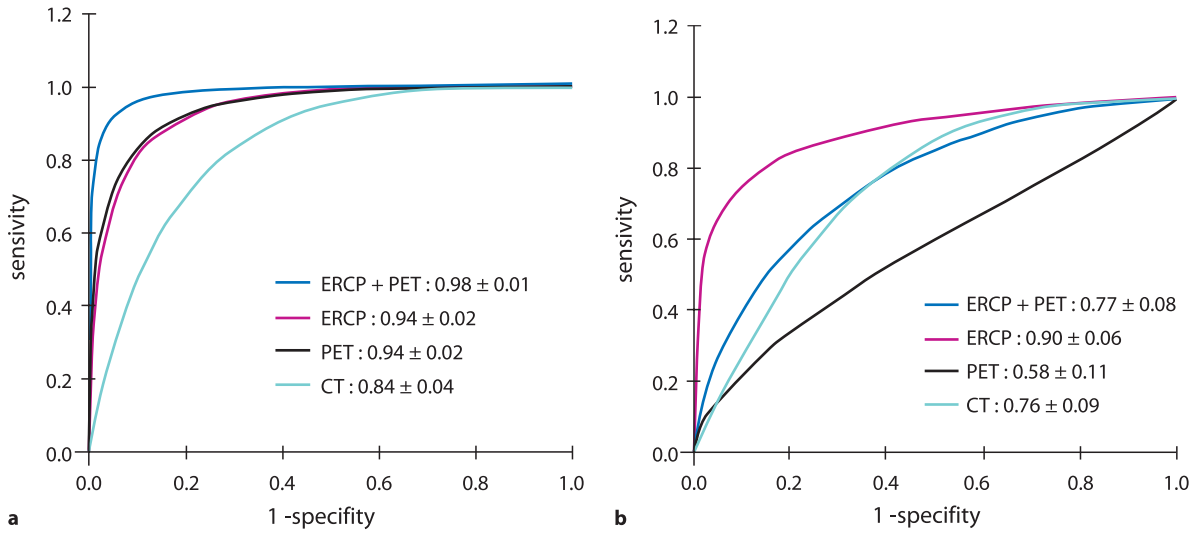

Figure 11.3

ROC analysis of CT, endoscopic retrograde cholangiopancreatography (*ERCP*) and FDG-PET in pancreatic cancer. Comparison of CT, ERCP, and FDG-PET in euglycemic (a) and hyperglycemic (b) patients. Note the markedly reduced performance of FDG-PET in hyperglycemic patients [19]

Table 11.3. FDG-PET in the diagnosis of pancreatic cancer – recent publications. *sens* Sensitivity, *spec* specificity, *SUV* standardized uptake value [41], *EUS* endoscopic ultrasonography, *MRT* magnetic resonance tomography

Author	Publication Year	CT *N*	CT sens (%)	CT spec (%)	PET *N*	PET sens (%)	PET spec (%)	
Koyoma and Okamura [36]	2001	86	94	62	86	82	81	SUV≥2.2
		(MRT 86)	79	70	86	91	76	
Papós and Takacs [32]	2002	22	100	50	22	100	88	
Valinas and Barrier [37]	2002				22	64		Gamma camera, PET
Rasmussen and Sorensen [38]	2004				20	75	80	SUV≥3.5
					20	92	75	
Borbath et al. [39]	2005	59	MRT 97.5		59	87,5		
		59	EUS 98					
Lytras et al. [40]	2005	112	89	65	112	73	60	
		small-volume metastases 112	20	94	112	22	91	
Ruf et al. [24]	2005	focal relapse 31	39		31	96		
			92		12	42		
		liver metastases 12						

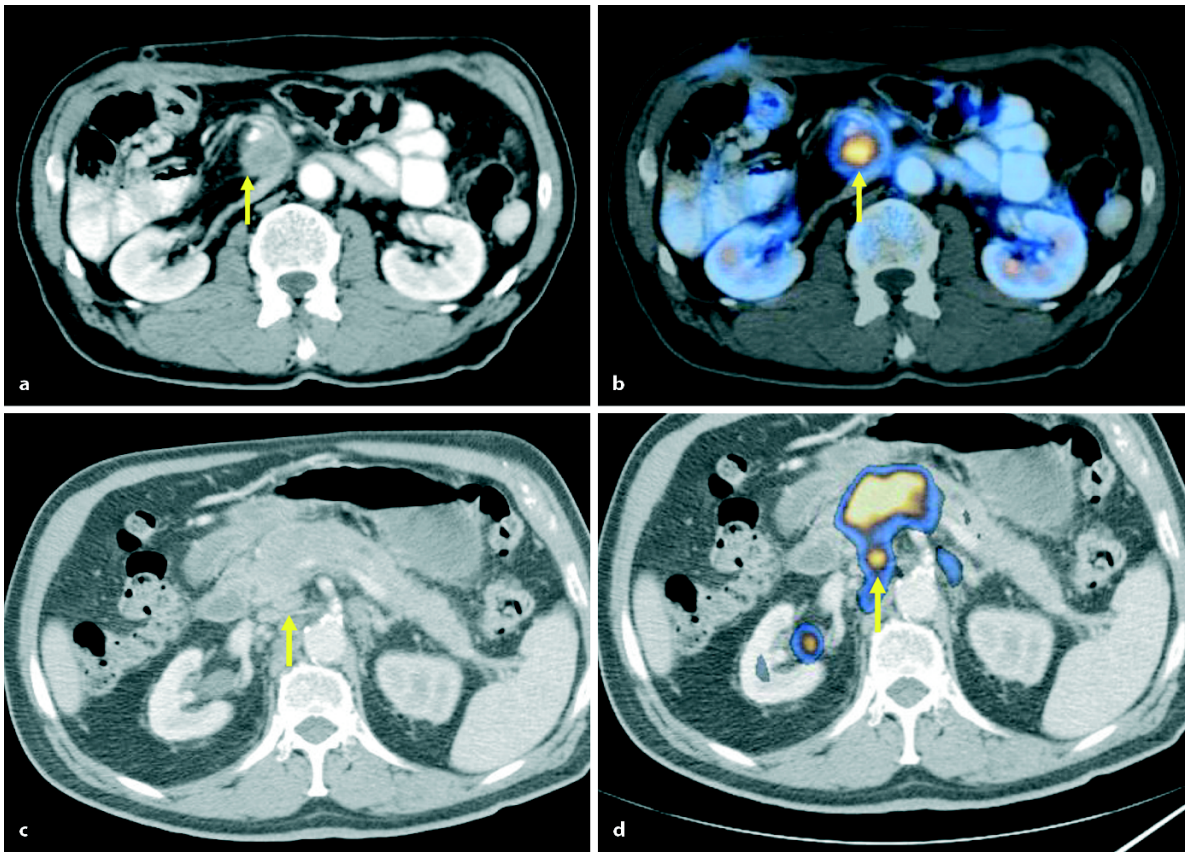

Figure 11.4

FDG-PET/CT in adenocarcinoma of pancreatic head (*arrow*, CT **a**, PET/CT fusion imaging **b**) with regional nodal involvement (*arrows*, CT **c**, PET/CT fusion imaging **d**)

dominal lesions and CT/MRT detected none [24]. The authors concluded that FDG-PET was much more sensitive for detecting local relapse of pancreatic cancer and was advantageous for showing nonlocoregional abdominal deposits, whereas CT/MRT was more sensitive for detecting liver metastases. The preliminary results of an ongoing study in our institution basically confirmed these data, when FDG-PET/CT is used (Figs. 11.4–11.6).

It must be kept in mind, however, that at present, standard imaging techniques such as EUS, spiral CT and magnetic resonance cholangiopancreatography are not able to reliably detect small cancer lesions (<1 cm). Furthermore, even small pancreatic carcinomas (<1 cm) are frequently incurable. Detection of pancreatic intraepithelial neoplasia (PanIN) is virtually impossible with the standard diagnostic modalities. Thus new diagnostic tools using novel technology for targeting of cancer (or PanIN)-specific genetic changes are urgently needed, in particular for the screening of high-risk populations. Development of novel diagnostic approaches using up-to-date genetic analyses and molecular and diagnostic imaging technology is currently being pursued in a large EU-sponsored consortium of basic and clinical scientists (MolDiag-Paca: Novel molecular diagnostic tools for the prevention and diagnosis of pancreatic cancer. EU Contract no.: PL018771).

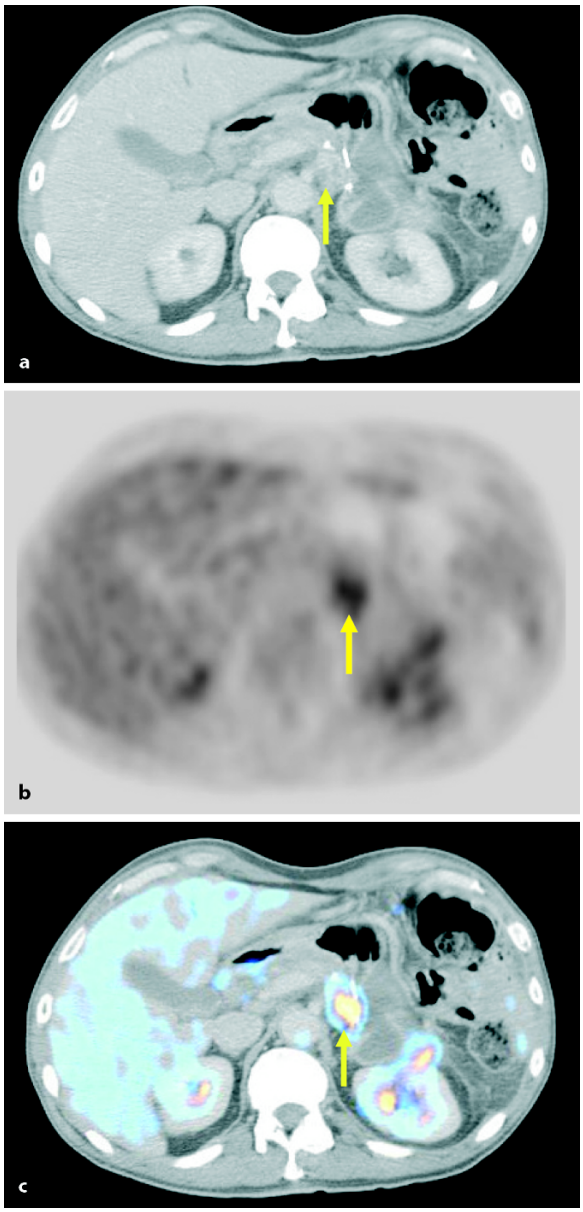

Figure 11.5

Local relapse of pancreatic adenocarcinoma in an indeterminate mass, as judged from CT (*arrow*, **a**). FDG-PET shows a focal hypermetabolic mass (*arrow*, **b**). PET/CT fusion imaging localizes the hypermetabolic mass just below the clip material within the mass seen on CT (*arrow*, **c**) indicative of local relapse, which was confirmed by resection

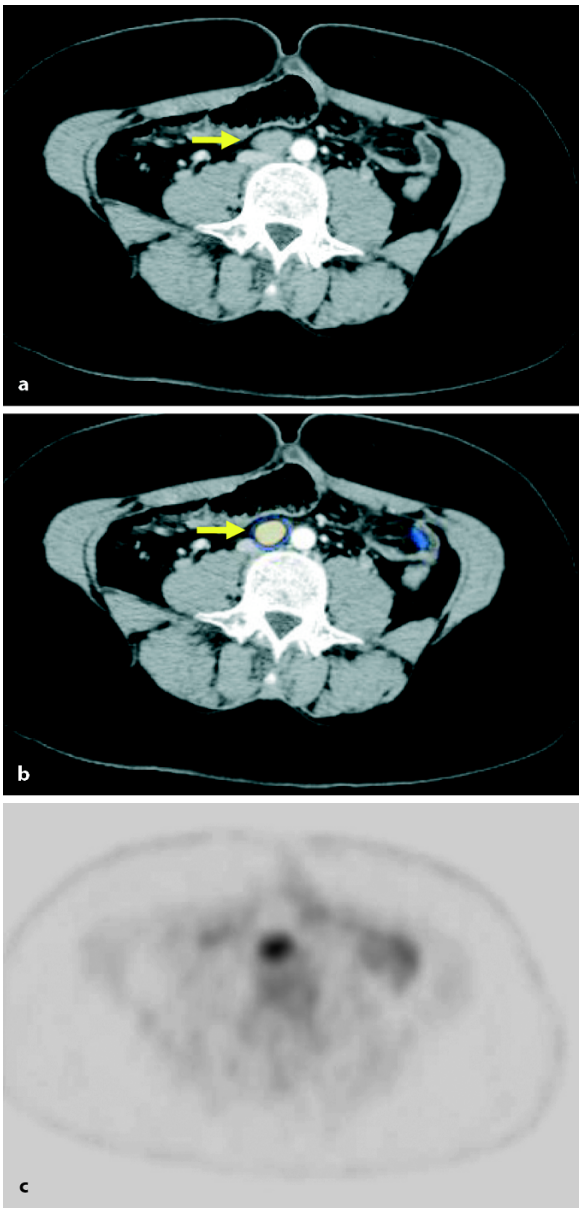

Figure 11.6

Nodal relapse in a para-aortic lymph node after Whipple's resection of pancreatic cancer. Highly increased focal FDG uptake (*arrow*, **a**) precisely localized in an enlarged aortocaval lymph node seen on CT (*arrow*, **b** and PET/CT (*arrow*, **c**)

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