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Abdominal Imaging PICTORIAL ESSAY

Imaging patterns of pancreatic cancer recurrence

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ABSTRACT

Pancreatic cancer is characterised by its aggressive biological behaviour and may relapse even after optimal resection. Early recognition of local recurrence or metastatic disease is important in order to achieve better patient survival. Post-surgical anatomic alterations and the fact that early recognition of tumour relapse on imaging is difficult make the diagnosis even more challenging for Radiologists. Although MDCT is the preferred follow-up imaging method, it seems that MRI offers some advantages in cases of equivocal liver lesions, liver steatosis and when the study of the biliary tree is primarily requested. FDG-PET is advantageous when anatomic imaging is non-conclusive, in cases with strong clinical suspicion of tumour relapse. Postoperative changes and findings related to early or late complications should not be mistaken as tumour relapse. This is why it is of paramount importance that the Radiologist is aware of what kind of surgery was performed, of any postoperative complications, as well as of all necessary information from the final pathology report. In this review paper, specific patterns of recurrence will be described that are related to tumour site, type of operation and histopathology concerning mainly resection margins. Important questions that are also related to imaging of early pancreatic cancer recurrence will be addressed.

KEY WORDS: Pancreatic adenocarcinoma/recurrence; CT/diagnosis; MR imaging/diagnosis

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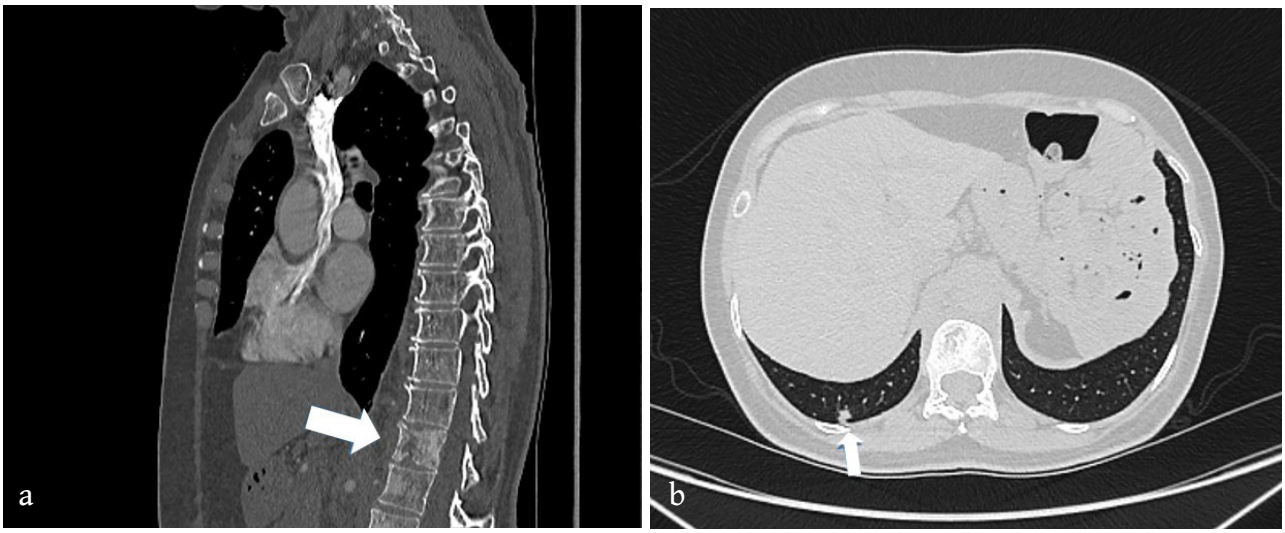

Fig. 1. *Spinal sclerotic metastasis (arrow in* ***1a****) together with lung metastasis in the right lower lobe (arrow in* ***1b****) are shown on CT images in a patient one year after pancreatectomy.*

Introduction

Pancreatic cancer ranks high among the list of poor prognosis cancers with an overall five year patient survival rate of 9% [1]. Approximately only 20% of patients presenting with pancreatic cancer are candidates for resection [2], which remains the treatment that allows longer survival. What is even more unfortunate is the fact that even after R0 resection the recurrence rate of pancreatic cancer is about 85% within the first two years [3, 4]. Adjuvant chemotherapy with gemcitabine ± paclitaxel has increased the disease free and overall survival of patients after R0 resection, while a modified FOLFIRINOX (leucovorin, fluorouracil [5-FU], irinotecan and oxaliplatin) regimen has recently been reported to lead to significantly longer survival than gemcitabine at the expense of a higher incidence of toxic effects [5].

Pancreatic cancers can recur either locoregionally or in the form of metastases. It has been suggested that patients with isolated local recurrence have a longer median survival if their disease is amenable to repeat resection (26.0 vs. 10.8 months, p=0.0104) [6]. One retrospective observational study has reported that the rates of local, metastatic and synchronous local/metastatic recurrent pancreatic cancers were 17%, 60% and 23%, respectively [7]. The majority of extra-pancreatic recurrences have been reported to develop in the liver, followed by the peritoneum and, to a lesser extent, in the lungs and retroperitoneum. Bone metastases and paraspinal masses can rarely be seen **(Fig. 1)**.

It was in one of the first descriptive papers on computed tomography (CT) of the abdomen after Whipple procedure back in 1990 that the most frequent site of pancreatic cancer recurrence is the liver and regional lymph nodes [8]. The same paper also emphasised how important it is for Radiologists to be familiar with the normal postoperative anatomy in order to assess for local recurrence.

Local recurrence of pancreatic cancer usually presents as an infiltrating tumour with perineural invasion and encasement of the mesenteric vessels [9]. Perivascular cuffing on the other hand is a normal postoperative finding which may be accompanied by some inflammatory stranding in the perivascular fat. The major clue suggestive of recurrent disease is the continuous, well-defined thickening of the fascial planes surrounding the mesenteric vessels and the alteration of the vessel lumen.

In a large recent study investigating recurrence pattern according to the primary pancreatic site (head versus body and/or tail) the most common recurrence type was found to be local recurrence (84.4%), followed by lymph node (15.5%), liver (14.4%), and lung metastasis (6.7%) [10]. The predominant site of local recurrence in pancreatic head tumours was along cardinal arteries, including superior mesenteric artery (SMA), common hepatic artery, and/or coeliac artery (57.4%), followed by the area defined by portal vein, inferior vena cava, and coeliac axis or SMA (31.2%). On the other hand, patients with pancreatic body and/or tail cancer had higher incidence of metastatic dis-

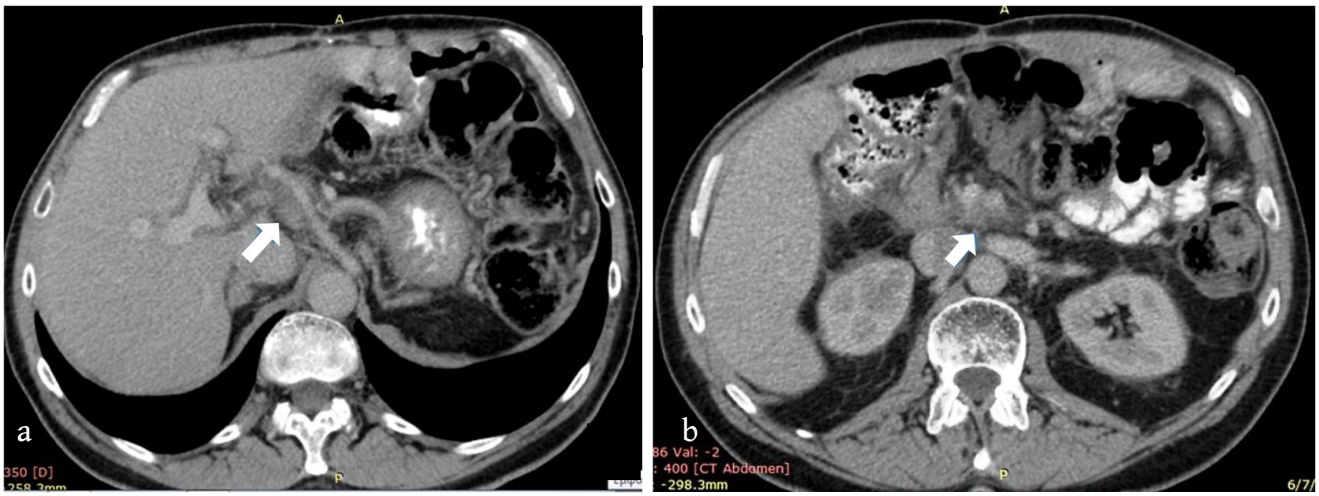

Fig. 2. *Contrast enhanced CT shows local recurrence of pancreatic cancer after total pancreatectomy along the hepatic artery (arrow in* ***2a****) and posterior to the mesenteric vessels (arrow in* ***2b****).*

ease, while resection margin was the most common site of local tumour recurrence, seen in 46.7% cases versus 8.2% of patients with pancreatic head tumours, demonstrating that the localisation of primary tumour influences the type of tumour relapse and the site of local recurrence [10]. This happens because pancreatic ductal adenocarcinoma (PDAC) of the head and uncinate process very early invades the lymphatic and nerve plexus of the arteries that often remain behind on the resection area versus pancreatic body and tail cancer that is removed together with the vessels, so the only place of local recurrence can be the resection margin and remaining lymph nodes.

Discussion

Important issues that have to be considered by Radiologists when assessing for pancreatic recurrence after surgical treatment are the following:

Who is more prone to local recurrence?

The histopathological report post-surgery has to be properly reviewed at the multidisciplinary Oncology meeting and all important information need to be extracted and discussed. Patients who do not get an R0 resection margin and who are found to have positive lymph nodes are considered of high risk for local recurrence, as well as patients with an advanced disease stage, who demonstrate perineural ± angiovascular invasion or have an initial CA 19-9>200 U/ml. The post-surgical clinical history of the patient also plays an important role, as patients who develop major postoperative complications such as fistula and haemorrhage are also reported to have a higher risk for early local recurrence [11].

Timing- when should we image?

Currently there is no strong evidence-based guideline for optimal surveillance after pancreatic cancer resection. Expert opinion guidelines provided by the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO), respectively are the only available sources providing information. The NCCN guidelines recommend a history and physical examination to be obtained every 3–6 months for two years in addition to serum cancer-associated antigen 19-9 (CA19-9) levels and CT scan of the abdomen and pelvis at the same time intervals [12]. After the initial two years, if patients are disease free, these tests are recommended annually.

The ESMO guidelines are based on the fact that there is no possibility for cure in the setting of local recurrence or metastasis, so the surveillance plan recommended is more individualised in order to minimise emotional stress and economic burden to the patient. In case CA19-9 levels are elevated preoperatively, the ESMO guidelines suggest measuring CA19-9 every three months for two years in addition to repeat CT scans of the abdomen and pelvis every six months [13].

It should be noted that elevation of CA 19-9 levels precedes clinical or radiological evidence of recurrence by 2-6 months. On the other hand in a small but significant proportion of population, around 14%, this carbohydrate

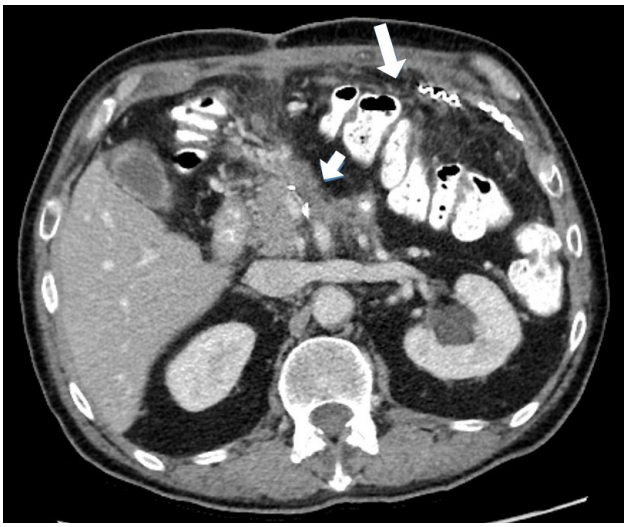

Fig. 3. *Contrast enhanced CT shows local recurrence at the borders of left pancreatectomy (short arrow) as well as tiny peritoneal infiltrations (long arrow). Metallic foreign bodies in the anterior aspect of the left upper quadrant, right posterior to the anterior abdominal wall, represent drainage tube remnants previously inserted to treat post-operative complication.*

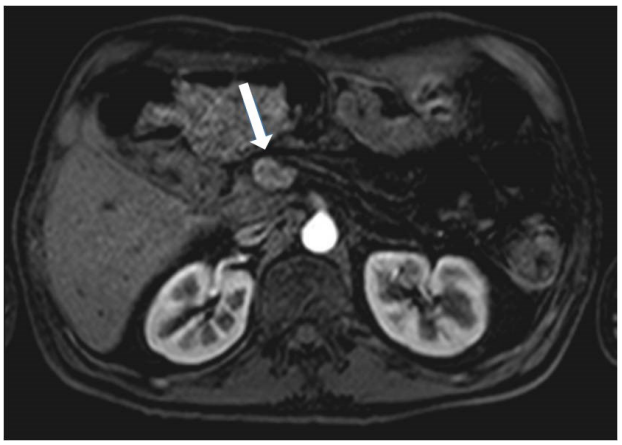

Fig. 4. *Heterogeneous metastatic lymph node at the surgical bed (arrow) is seen on axial fat suppessed contrast-enhanced T1W MR image.*

antigen is not expressed, and tumour recurrence may occur without serum marker elevation.

From a radiological point of view, dedicated pancreas centers worldwide have proposed obtaining a baseline multidetector CT (MDCT) examination at approximately 6-8 weeks after surgery, allowing for resolution of common immediate postoperative changes, to serve as a baseline [14]. Careful comparison of surveillance follow-up MDCT studies with a postoperative baseline MDCT examination will certainly aid in the detection of early recurrent pancreatic cancer.

What to look for

Patients post Whipple procedure tend to have three anastomoses to different jejunal sites: a pancreaticojejunostomy, a choledochojejunostomy and a gastrojejunostomy, while regional lymph nodes will have typically been removed. In case a pylorus- preserving procedure is performed, the gastric antrum and the 1st portion of the duodenum will have remained intact and a duodenojejunostomy will have been performed. In case of initial involvement of the superior mesenteric vein (SMV) upon removal, a jugular venous interposition graft might be found in place [15].

As mentioned earlier most common sites of recurrence are along the SMA and coeliac trunk, and between them and the portal vein-splenic vein-SMV (PV-SV-SMV) confluence to these vessels at the aortocaval space **(Fig. 2)**. The reason for this is that pancreatic adenocarcinoma spreads along neurovascular bundles. For primary cancer of the pancreatic head the SMA seems to be the main leading structure for disease propagation [16]. In cases of R1 status post-surgery the remaining tumour cells will regrow along the same vascular structures [17].

A second site of recurrence is the resection margin of the residual pancreatic parenchyma, because of R1 resection or intraparenchymal lymph or vascular infiltration which is microscopic and not detected initially, followed by the mesenteric root **(Fig. 3)**.

Imaging findings suspicious for local recurrence are the following: a) presence of new lymph nodes **(Fig. 4)**, b) size increase of pre-existing nodes in the surgical resection area or even in the pre-and para-aortic space as well as c) presence of newly-formed tissue at the site of pancreatectomy or in the retroperitoneum **(Fig. 5)** [16]. Indirect signs that should be taken into consideration are pancreatic duct or bile duct dilatation **(Fig. 6)**, if not present during the immediate post-operative period due to oedema at the pancreaticojejunostomy, distension of adjacent bowel loops **(Fig. 7)** and non-fibrotic vessel stenosis or thrombosis **(Fig. 8)**. Mild dilatation of the pancreatic duct can also persist indefinitely, but significant dilatation or progressing dilatation should raise concern for locally recurrent tumour [18].

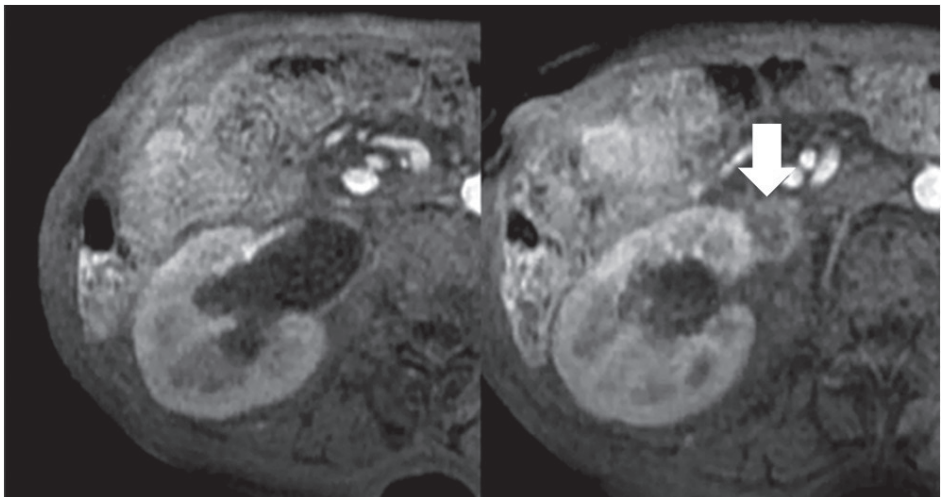

Fig. 5. *Axial fat suppressed contrast-enhanced T1W MR images show retroperitoneal tumour relapse, resulting in infiltration and dilatation of the right renal pelvis.*

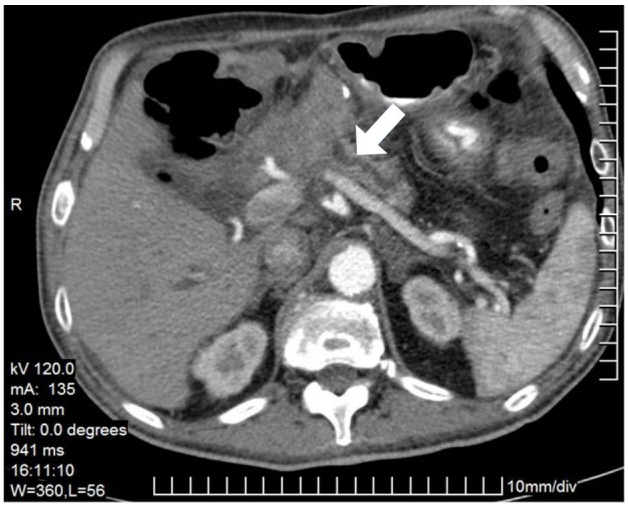

Fig. 6. *Contrast enhanced CT shows pancreatic duct dilatation of pancreatic remnant (arrow), which was not evident on immediate follow up CT examination post Whipple operation. This is a sign of tumour relapse.*

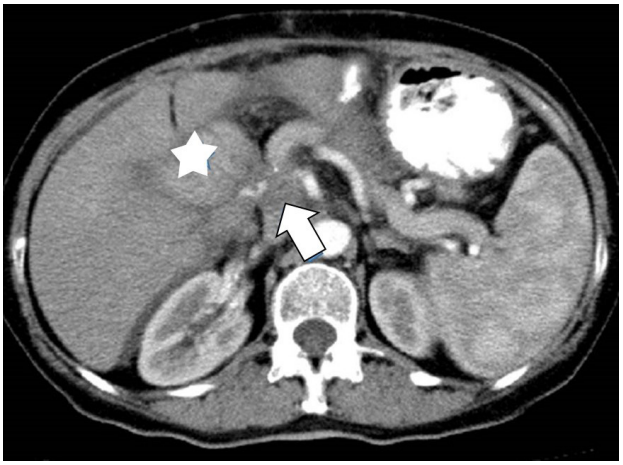

Fig. 7. *Contrast enhanced CT shows bowel dilatation close to the porta hepatis (asterisk), due to the relapsing mass on the right side of the superior mesenteric artery (arrow).*

Potential imaging pitfalls

Postoperative fibrosis especially around the PV or the hepatic artery is commonly seen and may mask tumour recurrence or mimic cancer relapse **(Fig. 9)**. The presence of unopacified anastomotic bowel loops in the porta hepatis region can also be mistaken for local recurrence, lymphadenopathy, or fluid collections.

Normal reactive lymphadenopathy may be present, consisting of small lymph nodes with a short axis <1 cm. Last but not least, at the early post-operative period, considerable oedema is often observed at the gastrojejunostomy or duodenojejunostomy.

How can we overcome these? Follow-up images are essential to distinguish perivascular cuffing from local recurrence. The use of multiplanar reconstructions may help to clarify the level of anastomoses. Reactive adenopathy is expected to regress at follow-up imaging. The same applies for oedema that is often observed at the anastomosis site. What is of paramount importance is that the Radiologist reviewing these images should be familiar with the different types of pancreatectomies and the vascular reconstructions and should always have all the necessary clinical information from the referring team. i.e. surgical procedure followed/ adjuvant chemotherapy regimen.

In a recent study designed to assess the agreement between initial and second subspecialised-opinion interpretations of imaging after pancreatic cancer resection regarding the diagnosis of recurrence, a 32% disagreement was observed. Second-opinion interpretations had a higher sensitivity and specificity on recurrence compared to the initial interpretations, while additional imaging studies were recommended less frequently during the second opinion review [19].

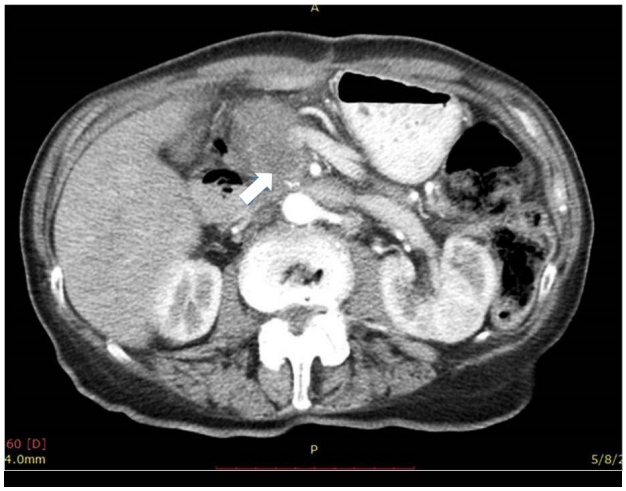

Fig. 8. *Extensive local tumour recurrence infiltrating the portal vein (arrow) is seen on this contrast enhanced CT image.*

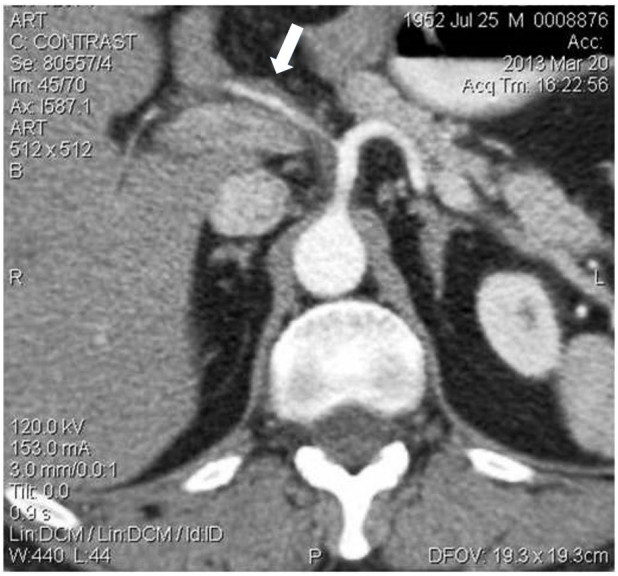

Fig. 9. *Fibrotic tissue is seen on contrast enhanced CT extending along the hepatic artery (arrow), a normal postoperative finding after Whipple operation.*

Is MDCT always enough?

Post-surgery pancreatic cancer patients should be assessed with a multiphase MDCT examination of the abdomen and pelvis. This should include an unenhanced scan to identify hyperdense foci due to presence of clips, stents or blood products, followed by a late arterial phase (bolus tracking, 200 HU threshold, 15 s delay) and a venous phase (60 s delay after the threshold has been reached) as proposed in a recent study [20]. Patients are to receive 1.5 ml/kg of high-concentration, nonionic contrast material, at a rate of 3–4 ml/s, followed by a 50-ml saline bolus. CT may show tumour recurrence, liver and lymph nodes metastases **(Fig. 10)**.

Magnetic resonance imaging (MRI) on the other hand may be used as an alternative imaging modality to CT, when renal insufficiency or contrast sensitivity prevent the use of iodinated intravenous contrast material [21].

In a study comparing contrast enhanced cross sectional morphological imaging (CT/MRI) and fluodeoxyglucose positron emission tomography (FDG-PET) scan findings in patients presenting with pancreatic cancer recurrence, FDG-PET reliably detected local recurrences, in addition to being more advantageous for the detection of non locoregional and extra-abdominal recurrences, whereas CT/MRI was more sensitive for the detection of hepatic metastases [22].

Node metastases can only be suggested by a progressive increase in lymph node diameter and/or the presence of recurrent tumour. In such patients, PET can be extremely useful in differentiating post-operative changes and reactive adenopathy from local tumour relapse or lymph node metastasis. Fused PET/CT may improve the specificity of nodal characterisation compared to CT alone, helping to identify metastatic deposits in lymph nodes that demonstrate nonspecific or borderline enlargement at CT. Abnormal FDG uptake in the surgical bed three months after surgery is usually indicative of recurrence. However, as

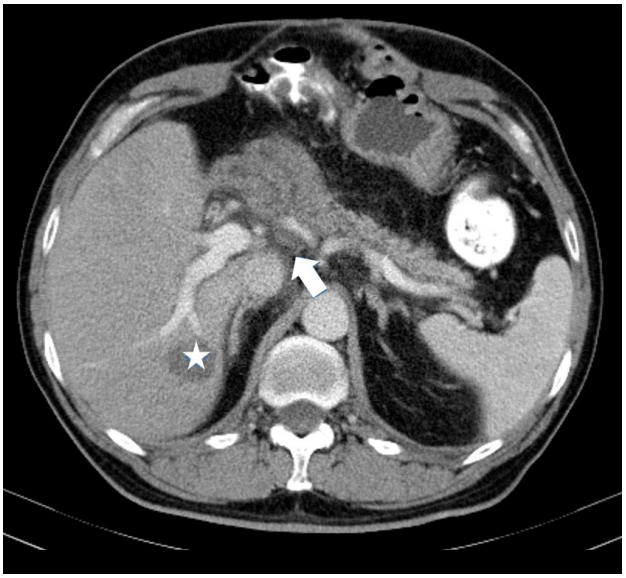

Fig. 10. *Contrast enhanced CT shows liver metastasis in segment VI (asterisk) and local recurrence around the hepatic artery (arrow).*

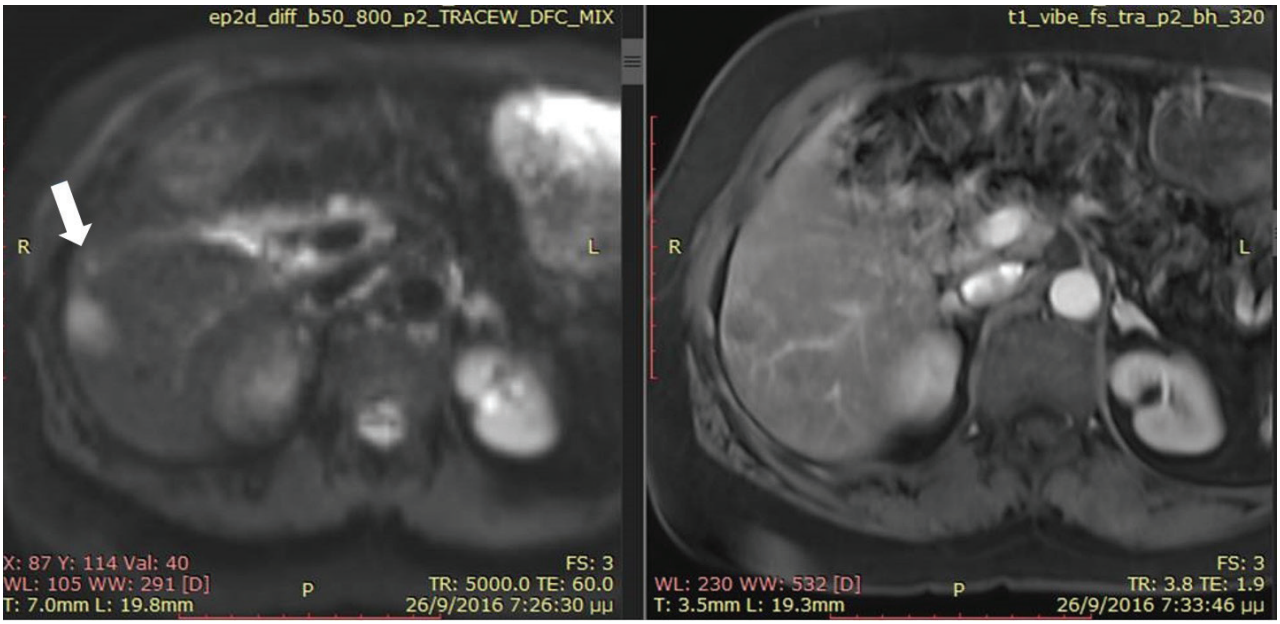

Fig. 11. *Correlation between axial b800 DWI MR image (left) and fat suppressed contrast - enhanced T1W MR image (right): on DWI a second small liver metastasis is clearly depicted (arrow).*

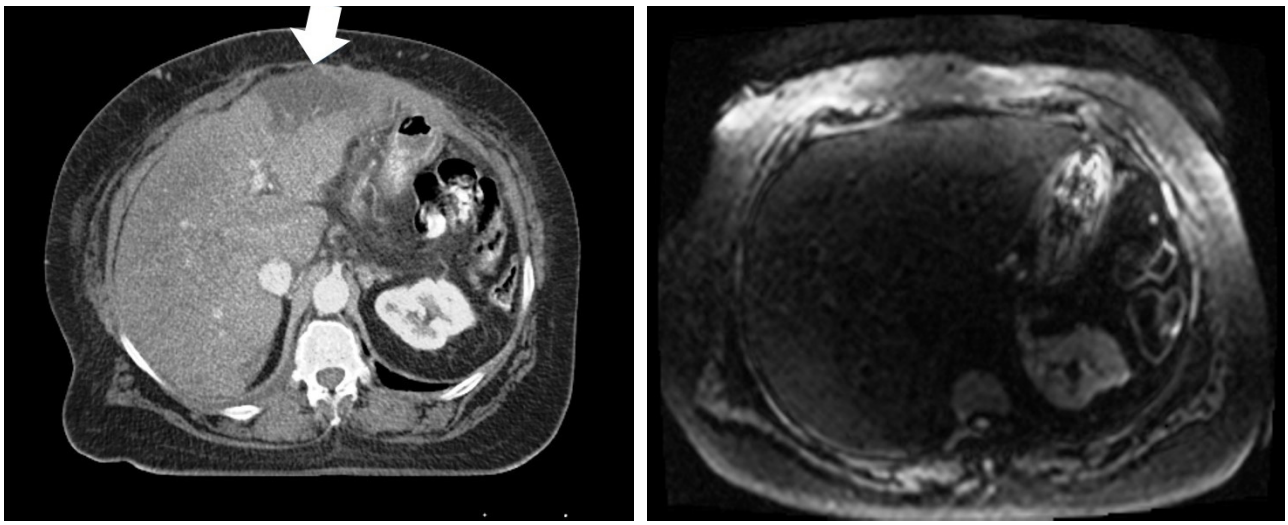

Fig. 12. *Correlation between contrast - enhanced CT (left) and b 800 DWI (right) image: hypoenhanced areas in the liver on CT (arrow) do not correlate with presence of liver metastases on DWI.*

postoperative inflammatory changes in the pancreas may also cause some FDG uptake, it is recommended that follow-up PET or PET/CT is performed at least six weeks after surgery to minimise these false-positive results [23].

Regarding depiction of liver metastases, studies performed in potentially resectable pancreatic cancer patients have shown that diffusion-weighted MR imaging (DWI) is superior in the detection of liver metastases when compared to MDCT **(Fig. 11)**. In one of the earlier studies performed in 31 consecutive patients with newly diagnosed, potentially resectable pancreatic cancer, a respiratory-triggered single-shot echo-planar imaging DWI sequence (b values: 0, 300, and 600 s/mm^2 was acquired, which allowed for 86.7% and 97.5% sensitivity and specificity in detecting liver metastases compared to 53.3% and 77.8% for MDCT, changing the therapeutic management

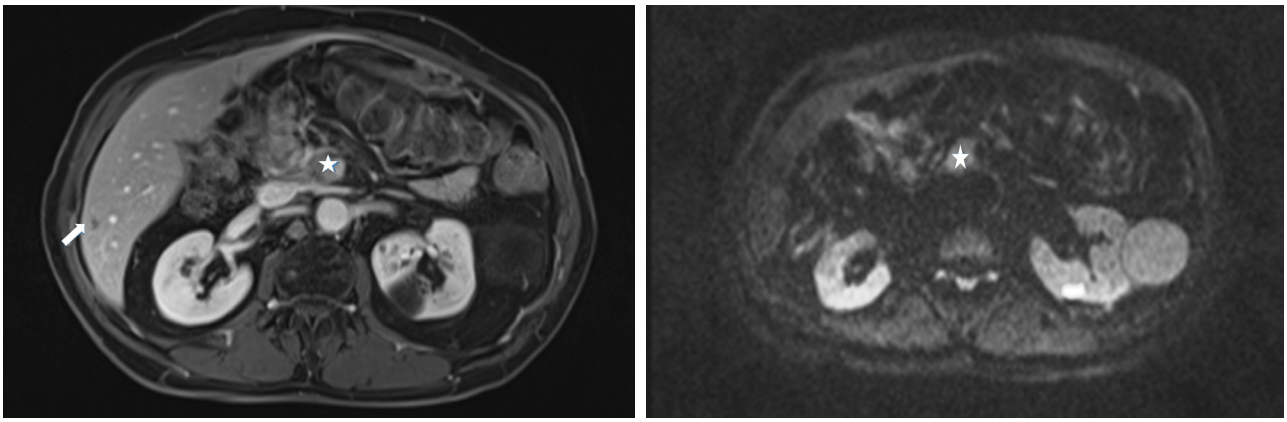

Fig. 13. *Fat suppressed contrast enhanced T1W MRI (left) shows tumour relapse in the perivascular area (asterisk) and a small lesion in liver segment VI (arrow). DWI (right) viewed on b 800 images, demonstrate tumour relapse (asterisk) and characterise better the liver lesion as a benign one.*

in 13% [24]. MRI should be used when there are equivocal imaging findings on CT, to prove or to rule out liver metastasis, while it seems to be equal to CT in the detection of local recurrence **(Figs. 12, 13)**.

According to a recent meta-analysis on diagnostic performance of CT versus FDG PET-CT for the detection of recurrent pancreatic cancer, post-operative CT has a moderate diagnostic accuracy in the detection of recurrent disease. FDG PET-CT imaging could be of additional value when disease recurrence is suspected despite negative or equivocal CT findings [25].

Conclusion

Accurate recognition of pancreatic cancer recurrence is essential for the best systemic treatment selection, local complications treatment and increase of the overall survival of these patients. Post-operative imaging is most challenging in differentiating surgical alterations and late complications from actual cancer recurrence and should be reviewed by Radiologists subspecialised in hepatopancreaticobiliary imaging. In the follow up evaluation, MDCT remains the method of choice although MRI including DWI is more sensitive for the detection of hepatic metastases. FDG-PET is advantageous for the detection of non locoregional and extra-abdominal recurrences. R

Conflict of interest

The authors declared no conflicts of interest.

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