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REVIEW

Pancreatic adenocarcinoma: imaging techniques for diagnosis and management

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Abstract

Pancreatic cancer is a leading cause of death from cancer but only a minority of patients with pancreatic ductal adenocarcinomas are eligible for curative resection. The increasing role of neoadjuvant therapy provides hope of improving outcomes. However, progress is also reliant on advances in imaging that can identify disease earlier and accurately assess treatment response. Computed tomography remains the cornerstone in evaluation of resectability, offering excellent spatial resolution. However, in high-risk patients, additional magnetic resonance imaging and positron emission tomography-computed tomography may further guide treatment decisions. Conventional computed tomography can be limited in its ability to determine disease response after neoadjuvant therapy. Dual-energy computed tomography and computed tomography or magnetic resonance imaging perfusion studies emerging as potentially better alternatives. Combined with pioneering advances in radiomic analysis, these modalities also show promise in analysing tumour heterogeneity and thereby more accurately predicting outcomes. This article reviews these imaging techniques.

Key words: Computed tomography; Computed tomography perfusion; Dual-energy computed tomography; Magnetic resonance imaging; Pancreatic cancer; Radiomics

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Introduction

Pancreatic cancer is the 12th most common malignancy worldwide with over 495 000 new cases annually (International Agency for Research on Cancer, 2020a), projected to increase 62% by 2040 (International Agency for Research on Cancer, 2020b). Pancreatic ductal adenocarcinoma accounts for 85–90% of cases (de la Santa et al, 2014). Surgical resection remains the only curative option, but pancreatic ductal adenocarcinoma has often progressed significantly by the time it is detectable. Consequently, only 10–20% of patients with pancreatic ductal adenocarcinomas are eligible for resection and, despite significant medical advances, the prognosis remains poor, with median survival ranging from 17–23 months for operable disease to 4–6 months for distant disease (Vincent et al, 2011). Neoadjuvant therapy shows promise in borderline resectable and locally advanced cases but earlier detection of pancreatic ductal adenocarcinoma remains the most significant consideration in improving outcomes (Varadhachary et al, 2006; Singhi et al, 2019). Therefore, progress is reliant on developments in imaging techniques such as dual-energy computed tomography, and magnetic resonance imaging or computed tomography perfusion, combined with advances in interpretation of imaging data to enhance the detection and monitoring of treatment response. This article describes imaging practices used in the management of pancreatic ductal adenocarcinoma and emerging techniques that can support current advances in treatment.

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Tumour detection

Ultrasound

Transabdominal ultrasound is a widely available, inexpensive tool for detecting pancreatic ductal adenocarcinoma but is operator-dependent with variable sensitivity and specificity (Tokar and Walia, 2013). Pancreatic ductal adenocarcinoma appears as a hypoechoic hypovascular lesion, sometimes with main duct and/or biliary dilatation. In contrast, endoscopic ultrasound has demonstrated equal-to-superior sensitivity and specificity

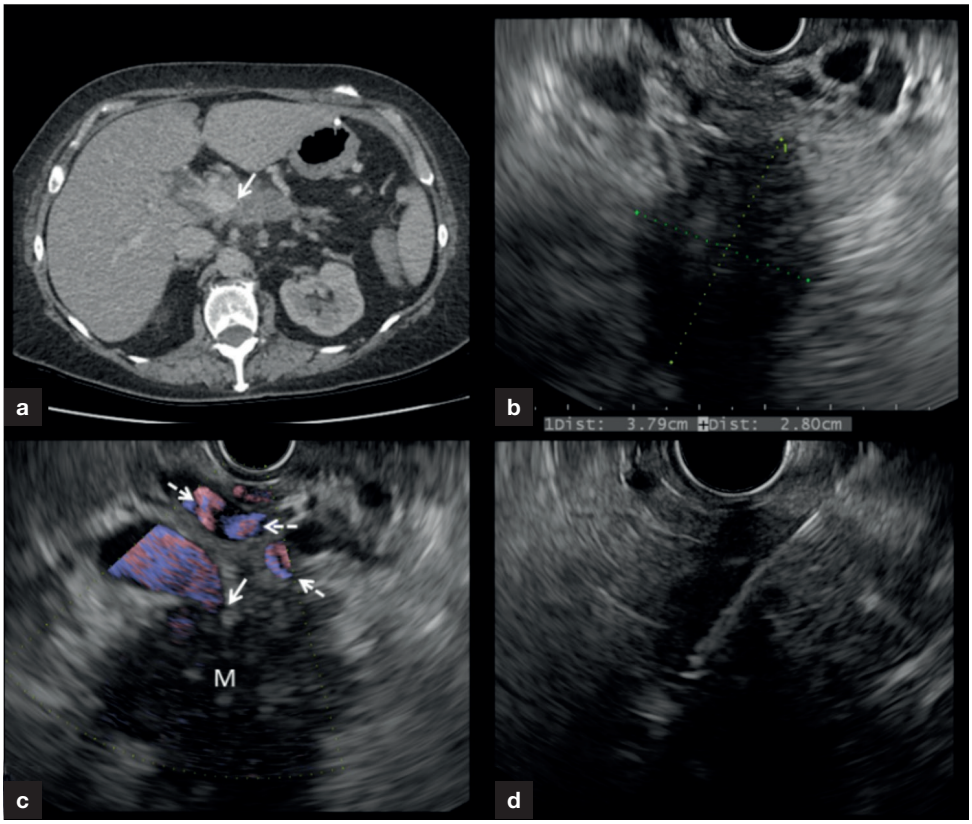

Figure 1. Locally advanced pancreatic ductal adenocarcinoma. a. Computed tomography image showing encasement and invasion of the portal vein (white arrow). b. Endoscopic ultrasound of the pancreatic ductal adenocarcinoma viewed from the gastric antrum. c. Doppler endoscopic ultrasound showing patency but truncation of the portal vein at the superior mesenteric vein/portal confluence (solid white arrow) as a result of local invasion by the pancreatic tumour (M), analogous to the appearance in (a). There is resultant collateral venous distension (dotted white arrows) secondary to occlusion at the portal confluence. d. 22G Echotip fine needle aspiration needle (Cook Medical) sampling the pancreatic ductal adenocarcinoma via the gastric pylorus.

to computed tomography for detecting pancreatic ductal adenocarcinoma, particularly when combined with fine needle aspiration (Săftoiu and Vilmann, 2009). However, the specificity of endoscopic ultrasound in detecting pancreatic ductal adenocarcinoma can be impaired when chronic pancreatitis is present, which can also appear as a hypoechoic focus. Endoscopic ultrasound can also provide details on tumour dimensions, local nodal disease and relationship to vessels (Figure 1) but needs to be combined with computed tomography to complete staging. Combined with being an invasive procedure, this negates its role as a first-line investigation in pancreatic ductal adenocarcinoma. Endoscopic ultrasound is therefore primarily used when histological confirmation is required.

Computed tomography

Post-contrast computed tomography remains the principal modality for staging pancreatic ductal adenocarcinoma as a result of its high spatial resolution and widespread availability. Computed tomography performed with a pancreatic protocol is recommended for pancreatic ductal adenocarcinoma (National Comprehensive Cancer Network, 2021). This protocol first acquires images in the late arterial phase at 35–50 seconds after contrast administration where tumour conspicuity is optimal and lesions usually appear low-attenuating. A portal-venous phase is also performed 60–90 seconds after contrast injection to better depict the tumour's relationship to the porto-mesenteric veins and detect metastases, especially within the liver. Computed tomography has well-validated sensitivity of around 89% and specificity of 90% for detection of pancreatic ductal adenocarcinoma (Treadwell et al, 2016). However, tumour conspicuity can be compromised with small lesions or with isoattenuating lesions. Diagnosis can also be confounded by concurrent autoimmune pancreatitis or diffuse

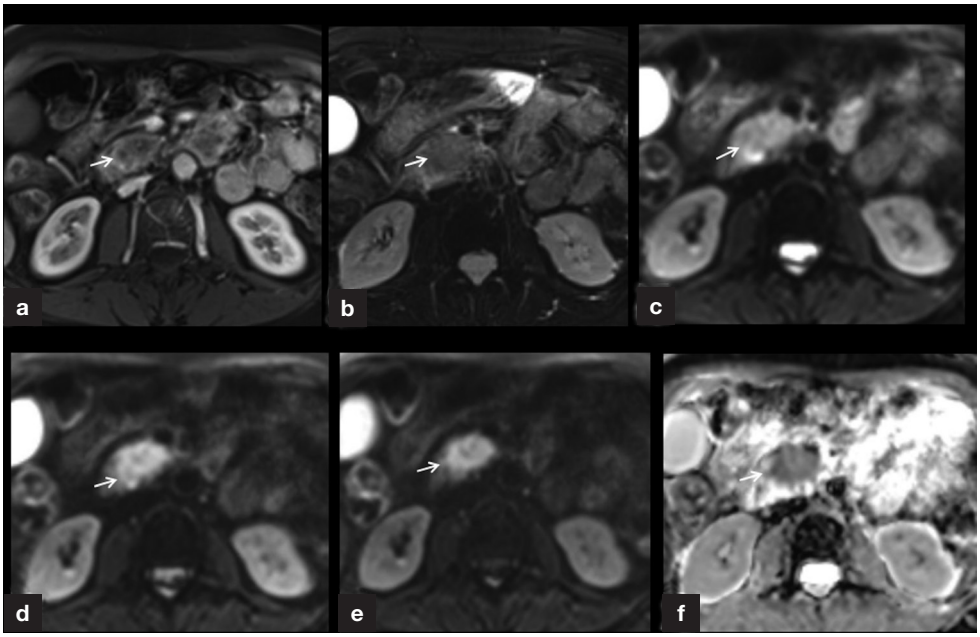

Figure 2. Magnetic resonance imaging of resectable pancreatic adenocarcinoma. a. T1-weighted fat-saturated post-contrast axial image in arterial phase shows a hypointense mass (arrow). b. T2-weighted fat-saturated image shows an intermediate signal lesion. c. Diffusion-weighted imaging with low b-value (b50) shows the lesion, which is mildly hyperintense. d and e. Diffusion-weighted imaging with higher b-values (b400 and b800) show progressive increase in signal in the lesion indicating restriction of diffusion. f. Apparent diffusion coefficient map shows low signal within the lesion signifying restriction of diffusion.

glandular subtype of pancreatic ductal adenocarcinoma. These scenarios rely on ancillary features such as main duct dilatation or interruption, alterations in the morphology of the gland and soft tissue vascular encasement with vessel narrowing. Consequently, other modalities such as magnetic resonance imaging and dual-energy computed tomography may help improve diagnostic confidence in these settings.

Magnetic resonance imaging

Magnetic resonance imaging is equivalent to computed tomography in the detection of pancreatic ductal adenocarcinoma with sensitivities of 84–93% (Treadwell et al, 2016). Some studies have demonstrated superior depiction of small or isoattenuating pancreatic ductal adenocarcinomas compared to computed tomography as a result of the inherent superior tissue characterisation of magnetic resonance imaging (Irie et al, 1997; Treadwell et al, 2016). Tumours are best appreciated on fat-suppressed T1-weighted imaging, appearing as a hypointense lesion, and on the subsequent post-contrast arterial phase as a hypo-enhancing area compared to background pancreas. When intravenous contrast is contraindicated, magnetic resonance imaging can still provide high tumour conspicuity using diffusion-weighted imaging (Figure 2) as most pancreatic ductal adenocarcinomas show restricted diffusion (Wang et al, 2011). However, in the presence of concomitant acute pancreatitis, specificity for pancreatic ductal adenocarcinoma on diffusion-weighted imaging can be significantly impaired. The sequence also lacks the spatial resolution to assess resectability independently.

Dual-energy computed tomography

Dual-energy computed tomography exploits differential X-ray absorption of body composition by imaging at low energy (80–100 keV kVp (kilovoltage peak in kiloelectronvolts)) and compensating the image degradation from increased noise-to-signal ratio by scanning almost simultaneously at higher energy (140 keV kVp). Using reconstruction algorithms, comparable image quality to conventional computed tomography can be achieved without significantly increased radiation exposure. The low energy portion of dual-energy computed tomography displays higher attenuation differences between pancreatic ductal adenocarcinoma and

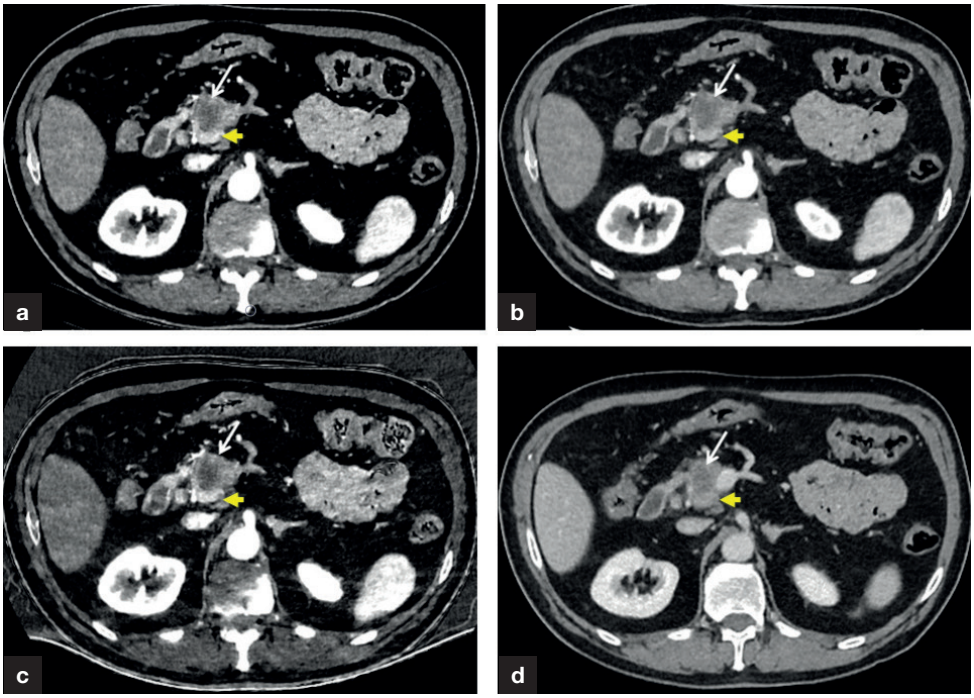

Figure 3. Dual-energy computed tomography images of ductal adenocarcinoma of the pancreatic head. a. Arterial phase axial computed tomography 50 keV and (b) 70 keV post-processed images. There is greater contrast between the tumour (white arrows) and normal adjacent pancreatic parenchyma (yellow arrows) on the lower 50 keV image, which is closer to the k-edge of iodine, but the image produced is noisier. c. Iodine-perfusion map showing similar increased conspicuity of the tumour compared to (d) the more conventional portal venous phase computed tomography image.

normal parenchyma compared to conventional computed tomography (Figure 3), thereby increasing tumour conspicuity (Quiney et al, 2015). In this context, dual-energy computed tomography offers a highly reproducible alternative to conventional computed tomography that could improve detection of early pancreatic ductal adenocarcinoma, although application is currently limited by a lack of widespread availability.

Positron emission tomography-computed tomography

On positron emission tomography-computed tomography, pancreatic ductal adenocarcinoma normally appears as a fluorodeoxyglucose-avid mass. Some studies demonstrate comparable tumour detection to pancreatic computed tomography with sensitivity of 73–96% and specificity of 60–94% (Wang et al, 2014). However, in the presence of mass-forming or autoimmune pancreatitis, specificity can be reduced as overlap in fluorodeoxyglucose uptake can render inflammation and malignancy indistinguishable (Kato et al, 2013). Owing to a lack of widespread availability combined with cost, positron emission tomography-computed tomography is not a first-line investigation for detecting pancreatic ductal adenocarcinoma and is primarily used in certain patients to improve the detection of metastasis (National Comprehensive Cancer Network, 2021).

Local staging

Surgical resection remains the only curative option for pancreatic ductal adenocarcinoma but still only achieves a 5-year survival of 20–25% for adenocarcinoma of the pancreatic head (Vincent et al, 2011). Non-metastatic pancreatic cancer is classified into resectable, borderline resectable or locally advanced/unresectable, with vascular involvement being the most significant determining factor. Arterial invasion of the common hepatic artery, coeliac axis or superior mesenteric artery is widely considered absolute contraindications to operability although some specialist centres have proceeded successfully using novel vascular reconstruction techniques (Cannella et al, 2019). There is greater variance in the

extent of portal vein and superior mesenteric vein tumour involvement deemed resectable and borderline resectable (Table 1), with some centres considering greater than 180° involvement of the superior mesenteric vein/portal vein confluence operable (Varadhachary

Table 1. Classifications of pancreatic ductal adenocarcinoma tumour characteristics that determine resectability

Resectability status		Classification		
		National Comprehensive Cancer Network (2021)	**The University of Texas MD Anderson Cancer Center (2021)**	**Society of Surgical Oncology (Callery et al, 2009)**
Resectable	Arterial	No involvement	No involvement	No involvement
	Venous	≤180° superior mesenteric vein or portal vein contact with no vein contour irregularity	Patent superior mesenteric vein-portal vein confluence	No superior mesenteric vein or portal vein abutment, distortion or tumour thrombus
Borderline resectable	Arterial	Head or uncinate: ■ Superior mesenteric artery abutment ≤180° ■ Common hepatic artery contact without extension to coeliac axis or hepatic artery bifurcation Body or tail: ■ Coeliac axis abutment ≤180° ■ Coeliac axis encasement >180° without gastroduodenal artery or aortic involvement*	■ Superior mesenteric artery or coeliac axis abutment ≤180° ■ Short-segment common hepatic artery or gastroduodenal artery encasement/abutment	■ Superior mesenteric artery abutment ≤180° ■ Gastroduodenal artery encasement up to the hepatic artery with short segment encasement or abutment of the hepatic artery, without extension to the coeliac axis
	Venous	■ >180° superior mesenteric vein or portal vein contact without vein contour irregularity (or ≤180° superior mesenteric vein or portal vein contact with contour irregularity or thrombosis) with patent vessel proximally and distally ■ Involvement of the inferior vena cava	■ Short-segment occlusion of superior mesenteric vein or superior mesenteric vein-portal vein confluence with patent vessel proximally and distally	■ Superior mesenteric vein or portal vein tumour abutment ± vein impingement or narrowing ■ Superior mesenteric vein or portal vein encasement without arterial encasement ■ Short-segment occlusion from tumour thrombus or encasement with suitable vessel proximal and distally
Unresectable	Arterial	Head or uncinate: ■ Superior mesenteric artery or coeliac axis encasement >180° Body or tail: ■ Superior mesenteric artery or coeliac axis encasement >180°* ■ Coeliac axis contact with aortic involvement	■ Superior mesenteric artery or coeliac axis encasement >180° ■ Aortic involvement	■ Superior mesenteric artery encasement >180° ■ Coeliac axis or common hepatic artery encasement with no reconstructive option
	Venous	Unreconstructible superior mesenteric vein or portal vein as a result of tumour involvement or occlusion	Unresectable venous occlusion	Superior mesenteric vein or portal vein occluded with no reconstructive option

**Coeliac axis encasement >180° may be defined as borderline resectable (by permitting a modified Appleby procedure) or unresectable under National Comprehensive Cancer Network (2021) guidelines for tumours involving the pancreatic body or tail*

et al, 2006; Callery et al, 2009). Regardless, vascular involvement predisposes to higher mortality and risk of a positive resection margin (Varadhachary et al, 2006). Precise imaging delineation of tumour involvement with adjacent vasculature is therefore critical to predicting outcomes.

Computed tomography

Computed tomography with a pancreatic protocol is the recommended modality for local staging and resectability assessment (National Comprehensive Cancer Network, 2021), providing good opacification of the vessels while maintaining tumour visualisation (Figure 4). Determining the likelihood of a clear resection margin on imaging is based on delineation of a preserved fat plane with adjacent vessels (superior mesenteric artery, superior mesenteric vein, portal vein, coeliac axis or common hepatic artery). Encasement, considered to be greater than 180° tumour contact or tumour-culpable vessel occlusion, is a strong predictor of vessel invasion (Figures 5 and 6), shown to have 84% sensitivity and 98% specificity for unresectable disease (Lu et al, 1997).

Magnetic resonance imaging

Magnetic resonance imaging, in particular fat-suppressed T2 and T1 sequences, combined with magnetic resonance angiography, provides an excellent alternative to computed tomography with comparable sensitivity and specificity for the diagnosis of vascular invasion in pancreatic ductal adenocarcinoma (Chen et al, 2016). The primary benefit is a superior ability to identify abdominal metastasis, with Kim et al (2019) showing that magnetic resonance imaging altered the decision on resectability in 14.4% of patients, mainly by identifying liver metastasis or vascular invasion not seen on computed tomography. Magnetic resonance imaging may also identify peritoneal deposits missed on computed tomography, particularly using diffusion-weighted imaging sequences (Chen et al, 2016; Kim et al, 2019).

Dual-energy computed tomography

Dual-energy computed tomography uses the photoelectric absorption of iodine during the low kVp component to accentuate the contrast and improve visibility of vascular structures compared to conventional computed tomography (Albrecht et al, 2016). This can provide better depiction of local vascular anatomy for surgical planning but appears inferior to

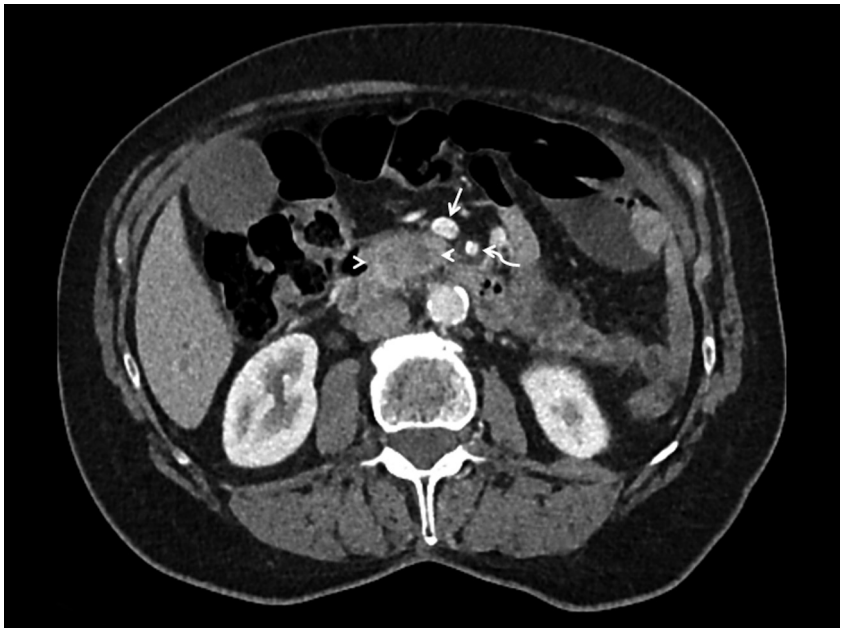

Figure 4. Resectable pancreatic adenocarcinoma on computed tomography. Hypodense mass in the head of the pancreas (arrow heads) confined to the pancreas. No evidence of contact with the distal superior mesenteric vein (straight arrow) or superior mesenteric artery (curved arrow).

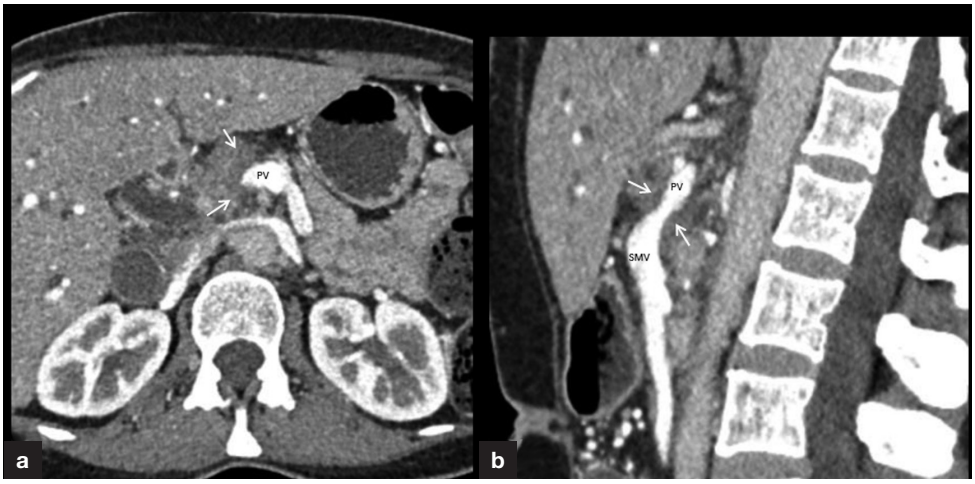

Figure 5. Pancreatic adenocarcinoma with venous abutment, borderline resectability. a. Axial post-contrast computed tomography shows 180° contact of tumour (arrows) with the portal vein (PV). There is focal deformity of the portal vein. b. Sagittal computed tomography image shows narrowing (arrows) of the formation of the portal vein (PV) at the level of the tumour. Below this, the superior mesenteric vein (SMV) is mildly distended.

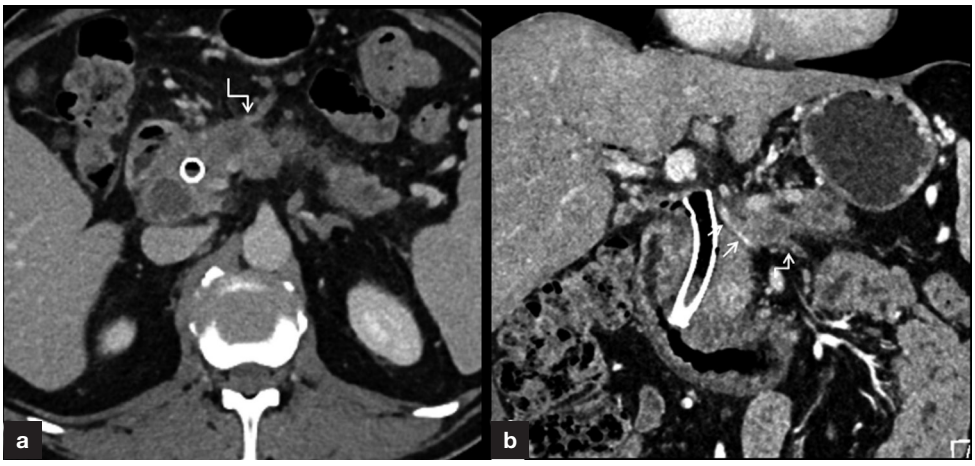

Figure 6. Pancreatic adenocarcinoma with unresectable venous encasement. Post-contrast computed tomography (a) axial and (b) coronal images show extensive venous encasement with partial obliteration of the main portal vein (straight arrows). The superior mesenteric vein is obliterated and not seen opacified. The tumour also involves the first jejunal branch of superior mesenteric vein (elbow arrows), precluding resection.

computed tomography for assessing local invasion and suitability for surgical resection (Bhosale et al, 2015). Dual-energy computed tomography can also isolate iodine distribution within imaged soft tissue to reduce metallic artefacts from surrounding surgical clips and biliary stents (Albrecht et al, 2016).

Positron emission tomography-computed tomography

Positron emission tomography-computed tomography is routinely performed without intravenous contrast, so has limited ability to assess local tumour vascular involvement. The main influence of positron emission tomography-computed tomography in assessing resectability is a superior ability to detect metastasis relative to computed tomography (Diederichs et al, 2000). However, the accuracy of positron emission tomography-computed tomography for sub-centimetre liver metastasis is below that of magnetic resonance imaging, which remains the best modality in this organ (Sahani et al, 2005). Nodal disease is considered a strong predictor of outcome in pancreatic ductal adenocarcinoma. Conventional use of nodal size of >1 cm in the short axis on computed tomography has poor sensitivity as low as 14% for nodal involvement (Roche et al, 2003). Positron emission tomography-computed tomography is better than magnetic resonance imaging and computed tomography

in identifying pathological nodes but still suffers from size restriction for nodes below 8 mm, limiting its sensitivity to around 21–38% (Wang et al, 2014).

Treatment response

The use of neoadjuvant therapy potentially broadens the scope of what is operable, with one meta-analysis showing approximately one-third of cases of borderline pancreatic ductal adenocarcinoma could be removed after neoadjuvant treatment and achieve comparable 5-year survival to the resectable subgroup (Assifi et al, 2011). Imaging techniques that can predict tumour characteristics and accurately monitor disease response are therefore essential to determining which cases benefit from neoadjuvant therapy.

Computed tomography

A reduction in tumour size on imaging can be a strong predictor of treatment response. One study showed partial regression, following neoadjuvant therapy, of contact with superior mesenteric vein or portal vein (Figure 7) on computed tomography. This resulted in 100% clear resection margin (R0) and achieved 91% R0 for similar changes related to the superior mesenteric artery, coeliac axis or common hepatic artery (Cassinotto et al, 2014). However, assessment of tumour response can be complicated by post-treatment inflammation, necrosis and fibrosis, leading to overestimations of the residual tumour burden. This was illustrated by Katz et al (2012) where only 0.8% of cases of pancreatic ductal adenocarcinoma showed a response on computed tomography following neoadjuvant therapy compatible with resectable disease, although intraoperatively this was contradicted with 66% found to be resectable. In these scenarios, other modalities such as functional and perfusion imaging may aid assessment.

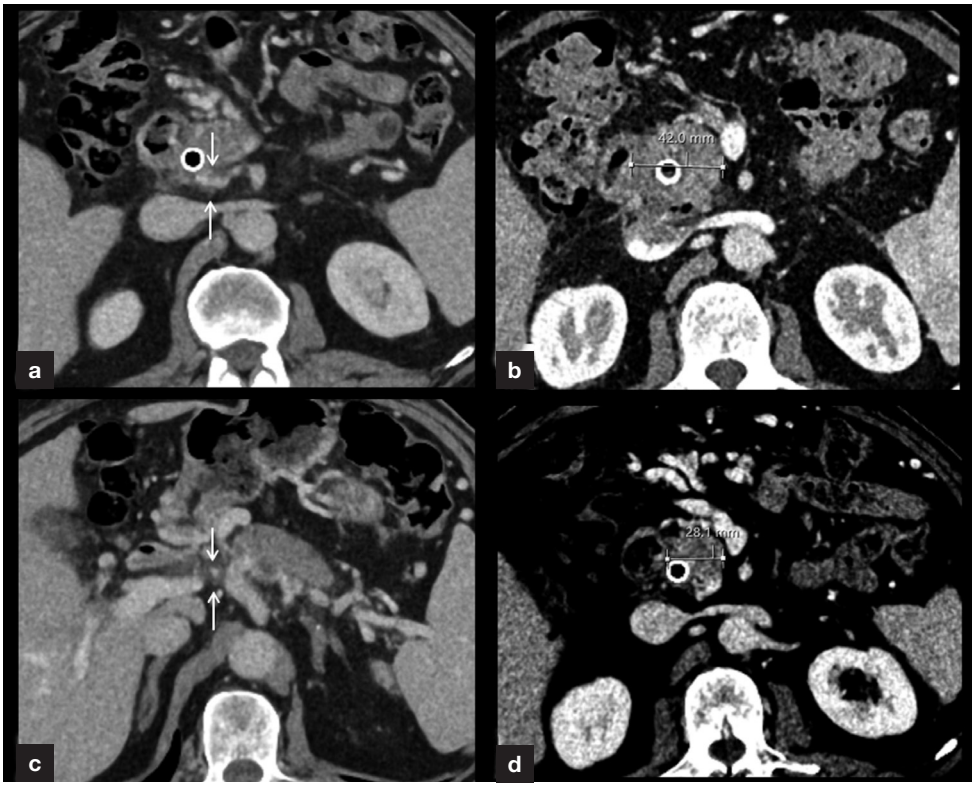

Figure 7. Pancreatic adenocarcinoma with arterial abutment of the common hepatic artery, pre- and post-neoadjuvant chemotherapy. a. Axial post-contrast computed tomography image shows tumour tissue surrounding the common hepatic artery (arrows). b. Axial image at a higher level shows a hypodense mass in the head of the pancreas around a metallic biliary stent. c. Post-treatment computed tomography shows persistent, but less, soft tissue around common hepatic artery (arrows); this was found to be fibrous tissue on trial resection. d. There is reduction in the size of tumour indicating response to treatment.

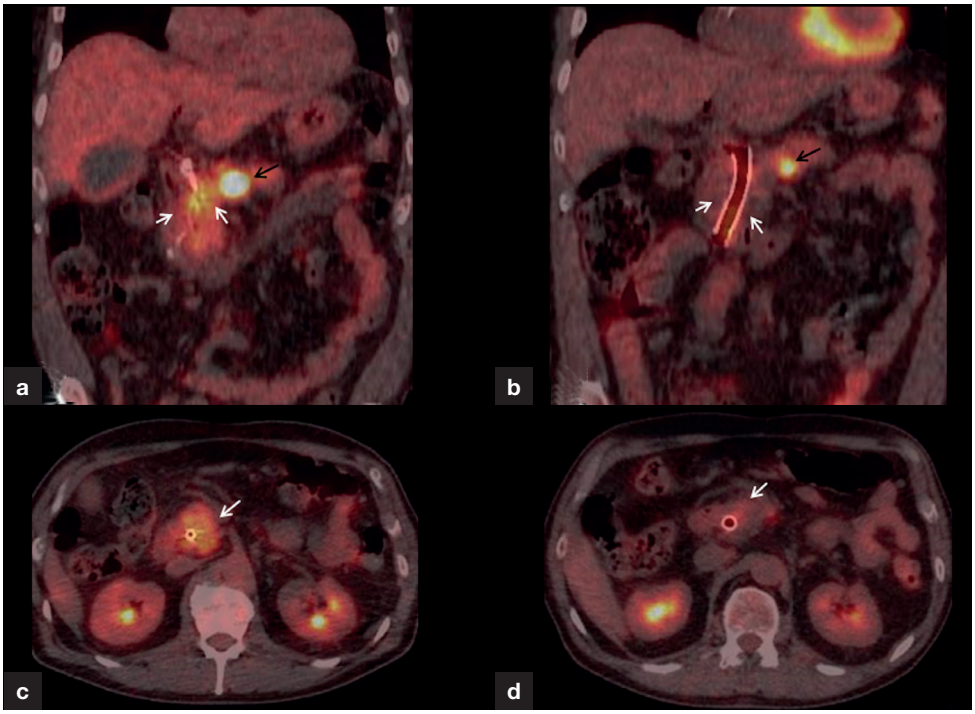

Figure 8. Combined positron emission tomography-computed tomography of pancreatic adenocarcinoma pre- and post-neoadjuvant chemotherapy. a. Pre-treatment coronal positron emission tomography-computed tomography image shows a metabolically active tumour in the head of pancreas (white arrows). There is also a hypermetabolic peripancreatic node (black arrow). b. Post-treatment scan shows reduced activity and size of the primary and the node. Axial images of (c) pre- and (d) post-treatment positron emission tomography-computed tomography demonstrates reduced activity and size of the head of pancreas tumour (white arrows).

Functional imaging

Positron emission tomography-computed tomography results can predict outcome in patients with pancreatic ductal adenocarcinoma, with a higher standardised uptake value associated with worse outcomes (Schellenberg et al, 2010) (Figure 8). Assessment of disease response relies on a reduction in standardised uptake value but accuracy can be compromised in the presence of post-treatment inflammation. Consequently, positron emission tomography-computed tomography is normally performed 6–8 weeks after chemoradiotherapy to enable resolution of such changes but this can delay treatment decisions. Magnetic resonance imaging diffusion-weighted imaging offers an alternative method that can be performed at a shorter timeframe of 3–5 weeks. Lower apparent diffusion coefficient values on diffusion-weighted imaging have been correlated with poorly-differentiated pancreatic ductal adenocarcinoma, inferring worse outcomes, while a rise in apparent diffusion coefficient values after chemotherapy has been associated with treatment response and predictors of successful resectability (Nishiofuku et al, 2016). Nonetheless, the role of functional imaging remains contentious as study sample sizes have been relatively small and positron emission tomography-computed tomography and diffusion-weighted imaging both lack the spatial resolution to accurately assess perivascular tumour involvement.

Perfusion studies

Computed tomography and magnetic resonance imaging perfusion studies use alterations in enhancement profiles to depict areas of increased intra-tumoural fibrosis or necrosis, which are thought to infer disease response while also providing detail on resectability. Computed tomography perfusion studies may also be able to predict response to chemotherapy. Park et al (2009) demonstrated this in patients with pancreatic ductal adenocarcinoma, with higher pre-treatment K-trans (quantitative measure of capillary permeability) depicted as a significant predictor of a positive response to neoadjuvant therapy. Complementary data from a study using magnetic resonance imaging perfusion by Akisik et al (2010) in eleven patients with pancreatic ductal adenocarcinoma showed responders had a significant

decrease in tumour perfusion and K-trans after down-staging. However, these studies had small sample sizes and used different software packages. Furthermore, reproducibility is complicated by difficulties accurately replicating the region of interest as a result of the poorly enhancing small lesions encountered in patients with pancreatic ductal adenocarcinoma and imperfect breath holding degrading signal-to-noise ratio.

Radiomics

Radiomics is an emerging method that uses large volumes of imaging data to extract quantitative features and provide information on tumour characteristics not appreciable from conventional imaging. Parameters like entropy, which measures the degree of randomness or non-uniformity in the lesion, and textural analysis have been used in radiomic computed tomography to evaluate lesion composition. Using such features, radiomics is hypothesised to be capable of measuring tumour heterogeneity to predict treatment response and overall survival in certain malignancies. Yun et al (2018) used radiomic analysis to demonstrate that increased tumour homogeneity correlated with worse disease-free survival in patients with pancreatic ductal adenocarcinoma. Some studies have used radiomic analysis to predict advanced tumour characteristics including low stromal content and oncogenic gene alterations like SMAD4, which have been linked with worse outcomes in cases of pancreatic ductal adenocarcinoma (Attiyeh et al, 2019). Chu et al (2019) illustrated that radiomics can differentiate normal from abnormal pancreatic tissue on computed tomography, which may help in improving early detection. Nevertheless, larger-scale studies are required to better define its role in the imaging interpretation of pancreatic ductal adenocarcinoma.

Conclusions

Currently, the main imaging modality used to assess pancreatic ductal adenocarcinoma in the pre- and post-treatment setting is conventional computed tomography, with positron emission tomography-computed tomography used as part of the initial staging if curative treatment is a potential option. Magnetic resonance imaging also has a role, particularly to improve detection of liver metastasis. Most patients with pancreatic ductal adenocarcinomas present late, with surgical outcomes remaining relatively poor, emphasising the potential role for neoadjuvant therapy. Although conventional imaging techniques appear limited in their ability to support these advances, functional imaging with computed tomography-magnetic resonance imaging perfusion, positron emission tomography-computed tomography and magnetic resonance imaging may be able to better appreciate tumour heterogeneity and evaluate treatment response. Nonetheless, earlier detection remains the most important factor to improving outcomes, with dual-energy computed tomography showing early promise to improve reader confidence in diagnosing pancreatic ductal adenocarcinoma. Greater accessibility to dual-energy computed tomography, better standardisation of the methodology in radiomics and further research on functional imaging provide possible avenues to support therapeutic advances and improve outcomes for this disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Key points

- Pancreatic adenocarcinoma has a poor prognosis and is frequently unresectable at diagnosis.
- The increasing use of neoadjuvant therapy offers potential to broaden the scope of treatable disease and improve survival but relies on complementary advances in radiology.
- Imaging conventionally consists of computed tomography but positron emission tomography-computed tomography and magnetic resonance imaging are increasingly being used to improve staging and detection of metastasis in high-risk patients.
- Accurate assessment of treatment response remains a significant challenge but dual-energy computed tomography and computed tomography-magnetic resonance imaging perfusion may provide potential solutions.
- Combined with better data analysis using radiomics, these strategies offer hope of improving detection and outcomes in patients with pancreatic adenocarcinoma.

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