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Imaging of pancreatic ductal adenocarcinoma – An update for all stages of patient management

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HIGHLIGHTS

- Imaging is crucial for patient management in pancreatic ductal adenocarcinoma.
- Contrast-enhanced CT is preferred for diagnosis and staging; MRI for hepatic staging.
- Imaging performs poorly for lymph node staging and response to neoadjuvant therapy.
- Anatomic findings and disease biology should both be considered for patient staging.
- A multidisciplinary team is essential for obtaining the best patient outcomes.

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is a common and lethal cancer. From diagnosis to disease staging, response to neoadjuvant therapy assessment and patient surveillance after resection, imaging plays a central role, guiding the multidisciplinary team in decision-planning.
Review aims and findings: This review discusses the most up-to-date imaging recommendations, typical and atypical findings, and issues related to each step of patient management. Example cases for each relevant condition are presented, and a structured report for disease staging is suggested.
Conclusion: Despite current issues in PDAC imaging at different stages of patient management, the radiologist is essential in the multidisciplinary team, as the conveyor of relevant imaging findings crucial for patient care.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related death in the modern world, with dismal survival rates [1]. Resection remains the only potentially curative option and, combined with systemic chemotherapy, provides the best therapeutic intervention for improving survival [2–4]. However, tumor resectability relies on an early diagnosis, which is often not possible, due to patients presenting with advanced disease and also diagnostic imaging challenges to detect subclinical disease [5]. Furthermore, defining which patients are best suited for surgery, and which patients should be offered neoadjuvant or palliative therapy is not a simple task. Several staging systems have been developed, with different resectability criteria, and are used in different institutions; the National Cancer Comprehensive Network (NCCN) is the most widely used classification [6–8]. Lastly, there are unresolved issues and difficulties when evaluating patients in the post-neoadjuvant therapy, and post-surgical follow-up periods [9–12]. Imaging plays a central role in all stages of patient management, and the radiologist's assessment is the cornerstone of surgical and medical decision-planning. This review aims to present and discuss the

Abbreviations: ADC, apparent diffusion coefficient; CT, celiac trunk; DWI, diffusion-weighted imaging; EUS, endoscopic ultrasound; HA, hepatic artery; LGA, left gastric artery; MIP, maximum-intensity projection; MPR, multiplanar reformation; MRCP, magnetic resonance cholangiopancreatography; NCCN, National Comprehensive Cancer Network; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; PV, portal vein; SA, splenic artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SV, splenic vein.

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Table 1
CT protocol used in our Institution for pancreatic ductal adenocarcinoma diagnosis and staging.

Oral contrast	Neutral (water, 500 mL ingested over 10 min)	
Intravenous contrast	300 mg/mL; 1.5 mL/kg @ 3-5 mL/s; followed by 20 mL saline flush	
Acquisition phases	Without contrast	Useful for detection of calcifications
	Pancreatic	35-50 s Pancreatic tumor detection; Arterial staging
	Portal venous	70-80 s Metastases detection; Venous staging
	Delayed	3-5 min Isoattenuating tumor detection
Acquisition	Volumetric (isotropic)	Thin slices ($\leq$ 1 mm) Monoenergetic (40 keV)* MPR (tumor-organ relations) MIP (tumor-vascular relations)

* CT equipment with new-generation spectral / dual-energy / photon-counting technology for improved image contrast is recommended. MPR: multiplanar reformation; MIP: maximum intensity projection.

most up-to-date imaging issues on pancreatic cancer diagnosis, staging, response to neoadjuvant therapy and patient follow-up.

2. Diagnosis of pancreatic ductal adenocarcinoma

2.1. *Imaging technique and typical findings*

CT is the preferred technique for PDAC diagnosis, due to its wide availability and high diagnostic accuracy, with a reported 89–97% sensitivity [9,13]. CT equipments with dual-energy / spectral technology further improve lesion conspicuity and detection, and the newer photon-counting CT equipments have also been reported to do so [14–16]. Lower energy-level (usually 40–50 keV) monoenergetic images provide greater attenuation by iodine contrast material, leading to improved image contrast between the hypovascular PDAC and highly vascularized pancreatic parenchyma. Transabdominal ultrasound maintains some relevancy, as it is the most accessible and least expensive imaging technique, and many pancreatic tumors are first identified on abdominal ultrasound scans [17]. However, due to its low sensitivity and operator dependence, CT should still be performed as a first-line imaging test when PDAC is suspected, or for diagnostic confirmation and tumor staging when a tumor has been identified in ultrasound. MRI is currently a second-line diagnostic technique due to its higher cost and lower availability, with a similar sensitivity to CT for diagnosing PDAC: 83–93.5% [18]. Its use is mainly reserved for diagnostic problem-solving. PET-CT has an estimated 90% sensitivity in detecting pancreatic cancer, but it does not offer clear benefits over CT or MRI for this purpose [19]. Finally, endoscopic ultrasound (EUS) has a reported 91–100% sensitivity for PDAC detection, while also allowing the collection of pancreatic tissue with fine-needle biopsy for histological diagnosis [20,21]. Due to its lower accessibility when compared with other imaging alternatives, EUS is usually reserved for tissue collection for histological analysis.

For PDAC diagnosis, an adequate CT protocol is of paramount importance, including pancreatic, portal venous and delayed phases (Table 1, Fig. 1). Sufficient iodine contrast dose and rate of injection, as well as a saline flush, are necessary to provide adequate lesion conspicuity in dedicated pancreatic multi-phase acquisitions [22,23]. The use of bolus-tracking technique allows acquisition timing to be individualised to each patient circulatory dynamics, ensuring optimal post-contrast phases, and is therefore recommended [22]. When using MRI, an adequate protocol is equally important (Table 2). Typical PDAC diagnostic findings include: (1) pancreatic hypovascular mass with dilation of the upstream main pancreatic duct; (2) simultaneous dilation of the common bile duct and main pancreatic duct if the tumor is located

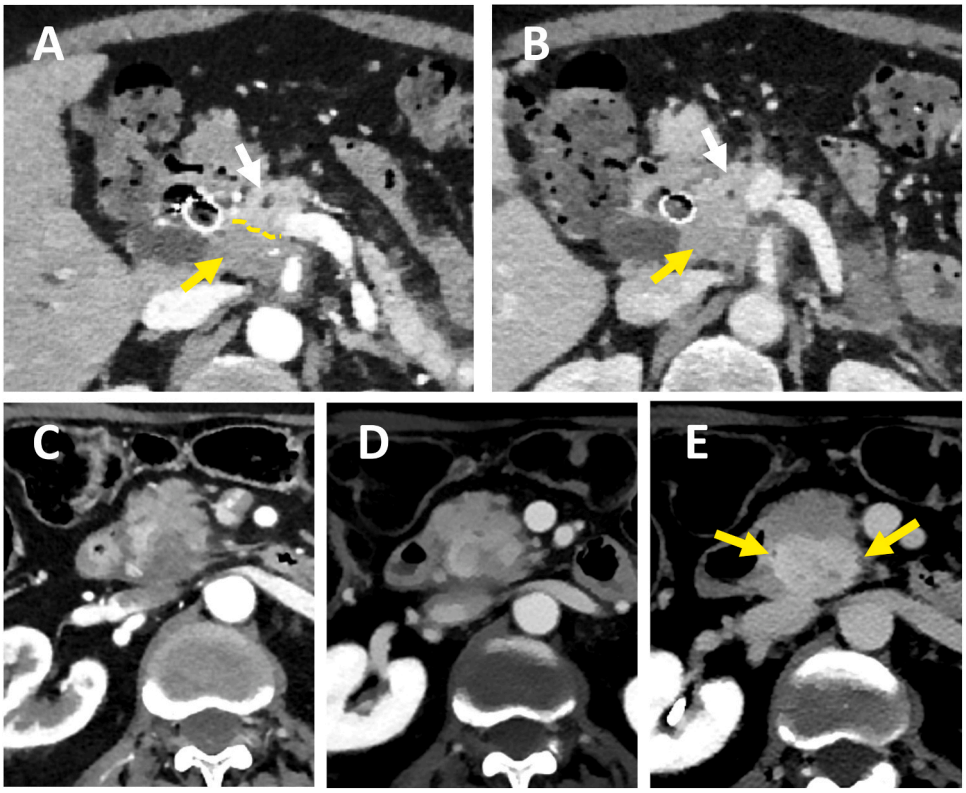

Fig. 1. Importance of the pancreatic and delayed phases for tumor detection. In the pancreatic phase (A), there is a clear distinction (dashed line) between tumoral tissue (yellow arrow) and pancreatic parenchyma (white arrow). In the portal venous phase (B), the distinction between tumor and normal pancreas is not clear. (C - E) depicts another case, where a pancreatic tumor is ill-defined on the pancreatic (C) and portal venous (D) phases, but well-defined on the delayed phase (E, arrows).

Table 2
MRI protocol used in our Institution for pancreatic ductal adenocarcinoma diagnosis and staging.

Acquisitions		T2 TSE	Axial and coronal
		T1 GRE	In- and opposed-phase
		DWI*	b = 10 s/mm^2
		DWI	b ≥ 800 s/mm^2; ADC map
		MRCP	3D or 2D thick slab
Intravenous contrast	THRIVE (fat-saturated T1 GRE)	Without contrast	-
		Pancreatic	35-50 s
		Portal venous	70-80 s
		Delayed	3-5 min

* Fat-suppressed T2 TSE can be acquired as an alternative depending on local preference and MR equipment perfomance. ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; GRE: gradient recalled echo; MRCP: magnetic resonance cholangiopancreatography; THRIVE: T1-weighted High Resolution Isotropic Volume Examination; TSE: turbo spin-echo.

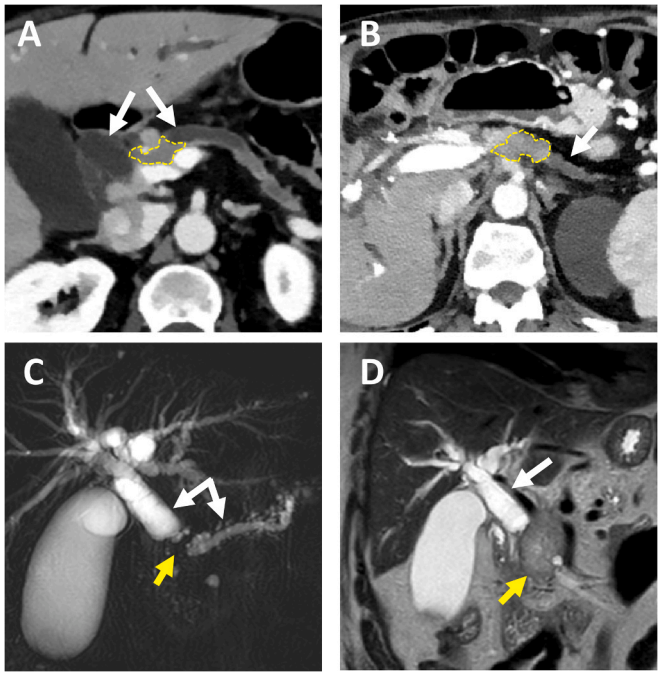

Fig. 2. Typical findings of PDAC. (A) depicts a double duct sign, where both the main pancreatic duct and the biliary tree are dilated (arrows) due to an obstructing tumor in the pancreatic head (dashed line). In (B) there is parenchymal atrophy of the pancreatic tail (arrow), due to an obstructing tumor in the pancreatic body (dashed line). (C) shows a double duct sign in MRCP (white arrows), caused by a presumed obstructing lesion (yellow arrow). (D) reveals an obstructing (white arrow) pancreatic head tumor in a T2-weighted image (yellow arrow).

in the head – also known as "double duct sign"; (3) main pancreatic duct stenosis with signs of chronic pancreatitis in the upstream pancreas (Fig. 2). Imaging staging should be performed before a biliary stent is placed, so ductal anatomy is clearly defined and inflammatory changes do not overlap with tumoral tissue.

Notably, new developments in artificial intelligence applications may provide new opportunities for PDAC diagnosis, such as risk assessment using clinical records and accurate detection using only non-contrast-enhanced CT, as demonstrated in a large multicentric study [24,25].

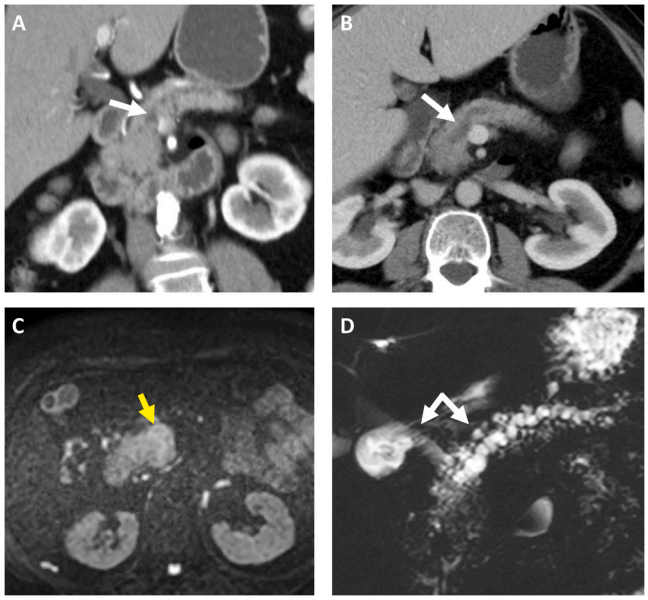

Fig. 3. Isodense PDAC. This patient presented with dilated main pancreatic duct (A and B, white arrows) and slightly dilated biliary tree, but a pancreatic tumor was not clearly seen on CT on both pancreatic (A) and portal venous (B) phases. MRI clearly identifies the obstructing tumor in the pancreatic head, as observed on DWI (C, yellow arrow) and a double duct sign on MRCP (D, white arrows).

2.2. Small and isoattenuating tumors

In 5.4–11% of cases, and most commonly with < 20 mm tumors, PDAC is isoattenuating: it does not stand out from the pancreatic parenchyma in the pancreatic or portal venous phases [26–29]. These tumors have been reported as a frequent cause of missed diagnosis for early PDAC, especially when found incidentally in imaging studies [5]. Indirect signs such as main pancreatic duct dilation upstream of an abrupt stenosis, a double duct sign, segmental pancreatic atrophy or faint enhancement are key to the diagnosis and should prompt further investigation [5,30]. This is also where a delayed acquisition can be very useful, as it has been shown to improve sensitivity for these lesions, which often enhance in delayed scans [29]. MRI is also helpful for detecting small and isoattenuating tumors (Fig. 3), with a reported sensitivity of 79.2% [28]. A reduced field-of-view DWI acquisition and MR perfusion techniques have been reported to improve image quality and pancreatic focal lesion characterization, and could therefore be useful in this context [31,32]. Another useful imaging technique for characterizing small and indeterminate tumors on CT is EUS, with a reported sensitivity of 87.3%, which can be improved with the use of contrast enhancement [20,33,34].

2.3. Diffuse tumoral infiltration and mass-forming pancreatitis

An uncommon diagnostic challenge is the diffuse neoplastic infiltration, mainly in the tail of the pancreas, without dilation of the main pancreatic duct [35]. The main differential diagnosis is autoimmune pancreatitis, which presents similar imaging findings. Likewise, mass-forming pancreatitis can mimic a neoplastic lesion and be impossible to differentiate from PDAC on CT. In both cases, magnetic resonance cholangiopancreatography (MRCP) may be useful, showing the "duct penetrating sign" - characteristic of benign lesions and enhanced with secretin administration [36,37]. Also, MRI can show multi-organ involvement in cases of autoimmune pancreatitis, often in the kidneys in the context of IgG4-related disease, facilitating this diagnosis (Fig. 4) [38,39]. Additional useful findings favoring auto-immune pancreatitis instead of PDAC include the typical diffuse enlargement with loss of

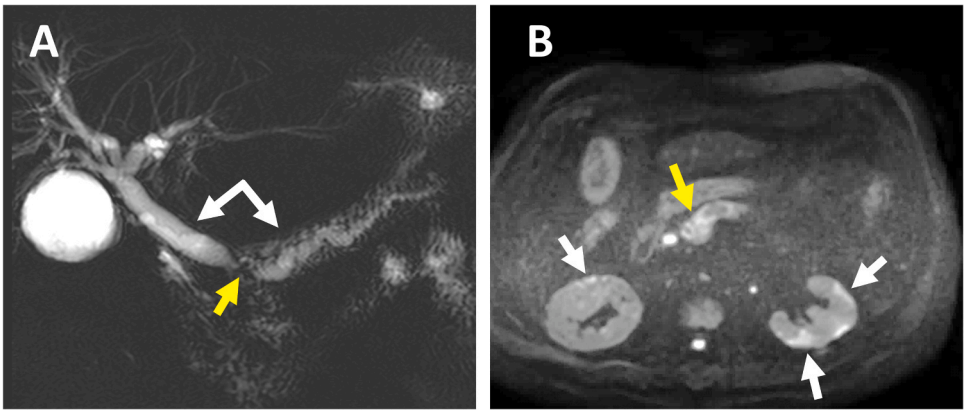

Fig. 4. Diagnostic problem-solving with MRI. This patient presented with dilated main pancreatic duct and biliary tree (A, white arrows), highly suspicious for a pancreatic head tumor (yellow arrow). However, DWI revealed not only a restricting pancreatic head (B, yellow arrow), but also areas of restriction in both kidneys (B, white arrows). These findings prompted the diagnosis of auto-immune pancreatitis, which was confirmed after a 2-week steroid trial.

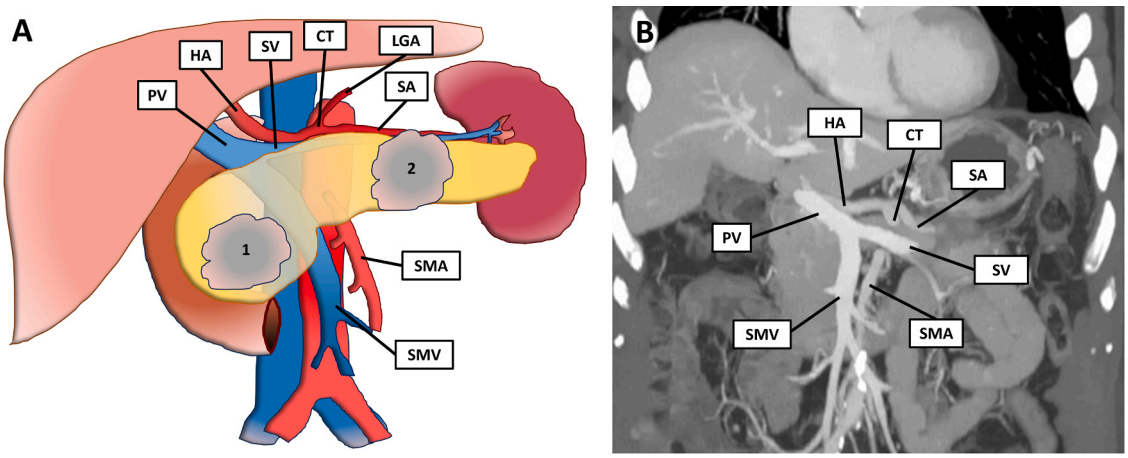

Fig. 5. (A) is a schematic representation of relevant anatomical structures for PDAC staging. If a tumor is located on the pancreatic head (1), a cephalic duodenopancreatectomy is performed, and if the tumor is located on the pancreatic body and/or tail (2), then a distal pancreatectomy is performed. More extensive tumors might require a total pancreatectomy. (B) is a coronal MIP displaying the relevant blood vessels for PDAC staging, an extremely useful tool for showcasing findings in multidisciplinary team meetings. CT: celiac trunk; HA: hepatic artery (comprises both common hepatic and hepatic proper); LGA: left gastric artery; PV: portal vein; SA: splenic artery; SMA: superior mesenteric artery; SMV: superior mesenteric vein; SV: splenic vein.

lobulation of pancreatic parenchyma (sausage-shape), homogeneous enhancement, absence of upstream main pancreatic duct dilatation, capsulelike rim and absence of vascular invasion[39,40].

3. Staging of PDAC

When deciding what treatment to offer a patient with PDAC, either resection, neoadjuvant therapy or palliative care, imaging plays the most central role. Patients' disease is initially staged as resectable, borderline resectable, locally advanced, or metastatic. This review will focus on the latest NCCN PDAC staging criteria, as it is the most widely used classification [6]. The goal is to obtain an R0 resection, which provides the best chance for patient survival, and the surgical procedure is dependent on tumor location, vascular and adjacent organ involvement.

3.1. Local and vascular staging

Vascular involvement is the major resectability determinant in PDAC and is best assessed with contrast-enhanced CT (Fig. 5). Multiplanar reformations (MPR) and maximum intensity projections (MIP) are extremely useful, both for diagnosis and for showcasing findings to the surgeon. The terms "abutment" and "encasement" refer to $\leq 180^{o}$ and $> 180^{o}$ tumoral contact with a blood vessel, respectively, the latter predicting the presence of vascular invasion [41–43]. Blood vessel deformity and the "teardrop sign", as well as occlusion, are also highly predictive of vascular invasion (Figs. 6 and 7) [44].

As summarized in Table 3, resectable tumors have no arterial contact, and no / limited venous contact (abutment). Patients in this category can be proposed for upfront surgery. Borderline resectable tumors include tumors with limited vascular involvement, or vascular involvement that can be surgically repaired. Patients with borderline resectable disease are offered neoadjuvant therapy; surgical resection can be later performed, depending on response to neoadjuvant therapy and local surgical expertise. Patients with locally advanced disease have extensive vascular involvement. These patients are offered systemic chemotherapy, chemoradiation, or inclusion in clinical trials. Depending on response assessment and performance status, resection surgery can still be performed after neoadjuvant therapy [3,6]. If disease progression is evident with vascular involvement precluding surgery or metastatic disease, then the best palliative care or inclusion in clinical trials are the remaining options.

Since being first introduced in 1997, the criteria for borderline resectable staging category have been updated over the years, reflecting accumulating evidence and international consensus [8,45]. These patients have limited vascular involvement and surgical resection is

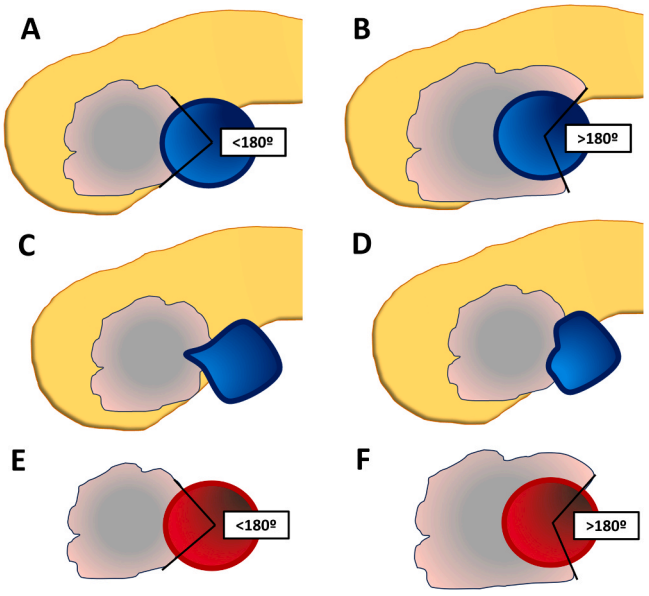

Fig. 6. Schematic representation of blood vessel involvement in PDAC staging. (A) tumor-vein contact ≤ 180º (abutment); (B) tumor-vein contact > 180º (encasement); (C) teardrop sign; (D) vessel contour deformity; (E) and (F) arterial abutment and encasement (≤ and > 180º), respectively.

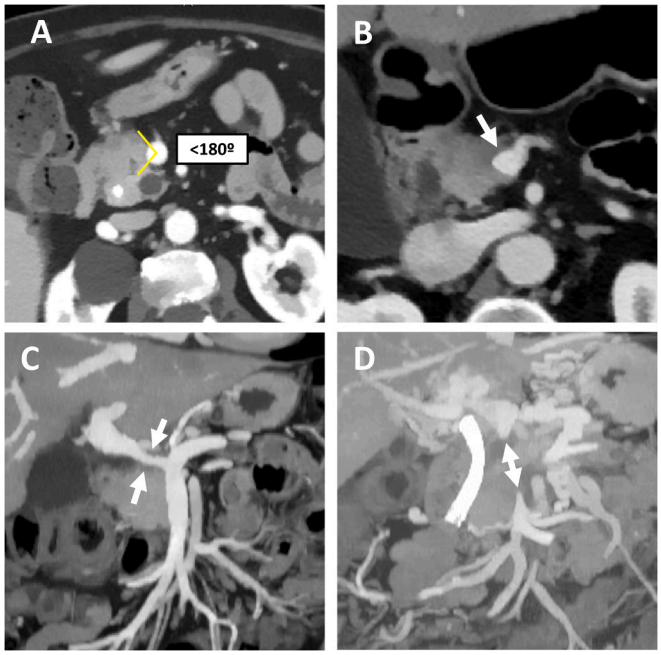

Fig. 7. Venous involvement in PDAC. (A) Tumor-superior mesenteric vein contact < 180º (abutment). (B) Teardrop sign of the superior mesenteric vein (arrow). (D) Portal vein stenosis and deformity (arrows). (D) Superior mesenteric vein occlusion (arrows).

possible, but a margin-free resection is unlikely, therefore benefiting clearly from neoadjuvant therapy. The definition of vascular involvement with objective criteria (vessel circumference involvement and contour irregularity) has contributed to a more standardized classification. More recently, the involvement of proximal jejunal branches was categorized as unresectable disease in 2017, but this involvement is not included in the latest versions [6,46]. This led to a reported improved accuracy in disease staging and better patient stratification [47]. It is important to be aware of the evolving nature of these staging criteria,

Table 3
NCCN V2.2023 resectability criteria adapted from [6].

Resectable	Arteries	No tumoral contact
	Veins	No tumoral contact / ≤ 180º PV or SMV contact without deformity
Borderline	Arteries	≤ 180º SMA or CT contact Limited CHA contact (not extending to its bifurcation nor the CT) Anatomical variant with arterial involvement allowing for surgical management
	Veins	≤ 180º PV or SMV contact with deformity > 180º PV or SMV contact but surgically repairable Tumoral contact with IVC
Unresectable	Arteries	> 180º SMA or CT contact; extensive HA involvement
	Veins	> 180º PV or SMV contact non-surgically repairable

CHA: common hepatic artery; CT: celiac trunk; IVC: inferior vena cava; HA: hepatic artery; NCCN: National Comprehensive Cancer Network; PV: portal vein; SMA: superior mesenteric artery; SMV: superior mesenteric vein. Abutment and encasement are considered synonyms with < 180º and > 180º tumoral contact, respectively.

with consequences both for clinical practice over time and for the validity of reported data, when comparing with current guidelines.

Vascular anatomical variants are common and can have surgical implications for PDAC [43,48–50]. Not only should replaced or accessory hepatic arteries be identified to avoid surgical complications, these variants can also provide surgical opportunities, when providing an alternative hepatic arterial supply without tumoral involvement (Fig. 8). Anatomical variants can also preclude surgery or determine a hepatic resection, especially if a replaced hepatic artery is involved by tumor and there is no collateral arterial inflow.

Celiac trunk stenosis, either due to atherosclerosis or arcuate ligament syndrome, can predispose patients to hepatic ischemia, as the collateral arterial flow to the liver is disrupted during surgery (Fig. 9) [51–53]. CT is the preferred method for diagnosing this condition, allowing preventive surgical procedures, such as arcuate ligament release and celiac artery stenting [43,54].

Besides the vascular staging, involvement of adjacent organs should be identified, most often the duodenum, stomach, left adrenal, left kidney, spleen and colon, as these will have to be resected during surgery if involved by the tumor [55]. Also, tumoral extension to the mesocolon, most often the transverse mesocolon, should be identified at this stage for surgical planning, possibly determining a colon resection.

Of mention, EUS has been reported to improve staging accuracy, especially when compared with older CT technology, identifying 14% unresectable patients previously staged as resectable on CT [56–58]. However, newer CT technology has improved diagnostic and staging accuracy, and comparative studies with EUS are not yet available.

3.2. Hepatic, peritoneal, and pulmonary staging

Liver metastases can be detected by CT, however with a relatively low sensitivity: 69% [59,60]. MRI is superior for this purpose, especially when performed with gadoxetic acid, with a reported sensitivity of 85% [60]. Furthermore, DWI has been reported to detect undiagnosed liver metastases on CT in 10–12.9% of patients and prevent futile surgeries in metastatic patients [61–63]. As such, it is recommended that liver staging is performed using MRI (Fig. 10). PET-CT has a reported 93% sensitivity in the detection of liver metastases for lesions > 1 cm, which is reduced to 70% when considering all lesion sizes [64].

There is no evidence determining the best timing for liver staging MRI (with or without gadoxetic acid) in the case of biliary obstruction, if before or after stent placement. Performing MRI before stent placement, will avoid artifacts in the case of metallic stents and allow better biliary anatomy depiction. Also, biliary stent placement may be associated with cholangitis, which may cause liver perfusion changes and course with small hepatic abscesses [65,66]. For these reasons, we perform hepatic

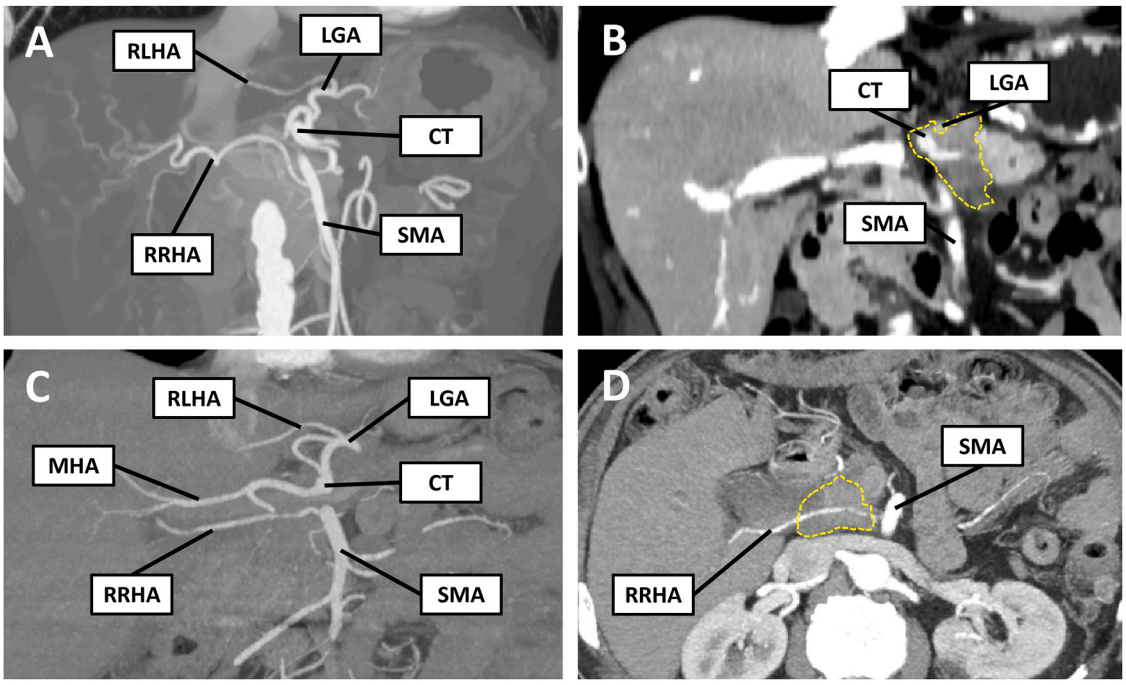

Fig. 8. Arterial variants with surgical implications. (A) depicts the anatomy of a patient with a replaced right hepatic artery (RRHA) originating from the superior mesenteric artery (SMA) and a replaced left hepatic artery (RLHA) originating from the left gastric artery (LGA). The celiac trunk (CT) was encased by the tumor, as represented in (B, dashed line). As arterial collaterals were present between both replaced hepatic arteries, a celiac trunk resection along with tumor resection were performed, and the patient maintained a preserved liver vascularization. (C) represents another patient with the following anatomy: RLHA from LGA, middle hepatic artery (MHA) from CT, and RRHA from SMA. The RRHA was encased by tumor, as shown in (D, dashed line). This allowed tumor resection along with the RRHA, after an embolization procedure for facilitating the development of collaterals.

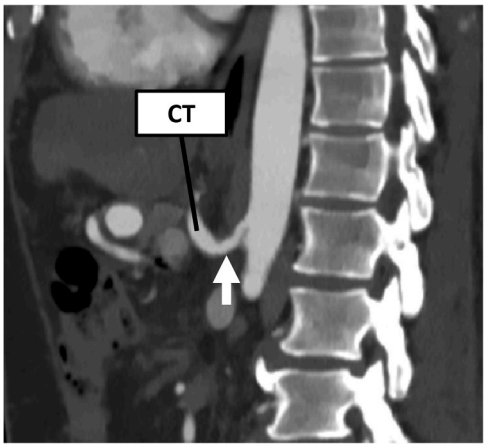

Fig. 9. Arcuate ligament syndrome. Proximal celiac trunk (CT) stenosis with a hooked appearance (arrow), with pos-stenotic dilatation.

staging MRI as soon as possible.

Finally, differentiating small hepatic abscesses from metastases can be a difficult task. Contrast-enhanced CT findings have been reported to help in this regard, favoring the diagnosis of abscesses: patchy parenchymal enhancement, perilesional hyperemia and, especially, arterial rim enhancement persistent through portal venous phase [67]. Dual-energy CT may improve on the technique's ability to distinguish both lesions [68]. DWI may also be helpful, as hepatic metastases tend to present lower ADC values at their periphery, when compared with abscesses [69].

Peritoneal metastases usually manifest as nodular lesions, detectable by both CT and MRI (Fig. 11). However, early peritoneal disease can be hard to identify, and evidence is lacking into imaging effectiveness for its diagnosis [70,71]. Staging laparoscopy can be performed for this purpose, and has been shown to be more sensitive than CT, but its usefulness has been debated due to poor cost-effectiveness when staging MRI is performed [72,73]. Nevertheless, recent data reporting high rates of positive staging laparoscopies has prompted some authors to advocate its use in the majority of patients prior to resection [74].

PDAC can also metastasize to the lung, but the usefulness of including chest CT in tumoral staging and follow-up has been debated [75,76]. Nevertheless, we include a chest CT in our staging protocol, which may serve as a baseline for comparison in future studies, should indeterminate or suspicious lung nodules be identified.

3.3. *Lymph node staging*

Lymph node staging is still poorly performed by imaging. CT has a reported sensitivity of only 14–44% for diagnosing nodal tumor infiltration when 10 mm short-axis is used as diagnostic criterion [77,78]. Combining size criteria with contour irregularity, heterogeneous signal intensity and/or density and increased number of visible nodes has been reported to improve sensitivity [78]. EUS has been reported to be superior in identifying suspicious lymph nodes in loco-regional and para-aortic locations, and is currently regarded as the most sensitive imaging technique for this purpose [57,58]. Nevertheless, it is not routinely included in lymph node staging recommendations [6]. Gallium-68-labeled fibroblast activation protein inhibitor PET-CT was reported to improve detection of pathologic lymph nodes in a preliminary study, but more data is needed before recommending its use [79]. A promising artificial intelligence model outperformed radiologists in lymph node staging using CT, while also providing prognostic information for patients [80]. Enlarged lymph nodes should be mentioned in the radiological CT or MRI report, especially when outside of loco-regional location, but this low diagnostic performance with current imaging methods must be kept in mind [81].

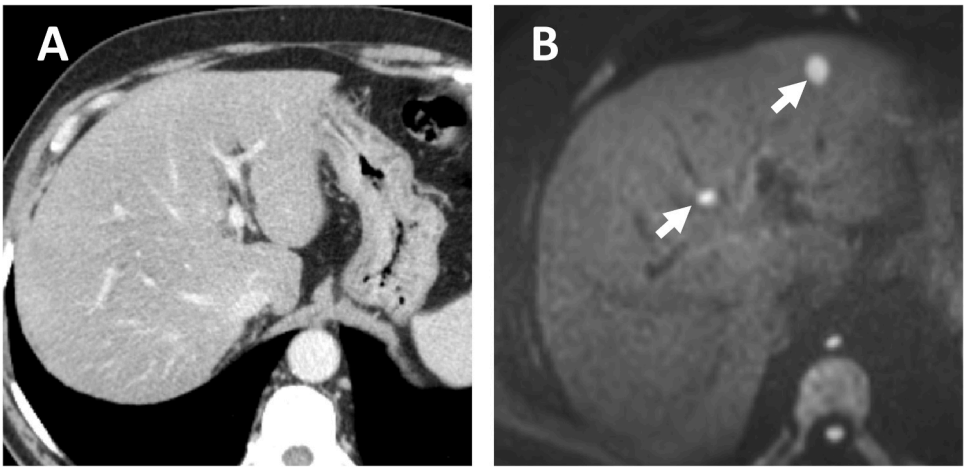

Fig. 10. Importance of MRI for hepatic staging. In a contrast-enhanced CT for PDAC staging (A), no liver lesions were found. The staging MRI clearly revealed hepatic metastases (arrows) with restricted diffusion on DWI (B).

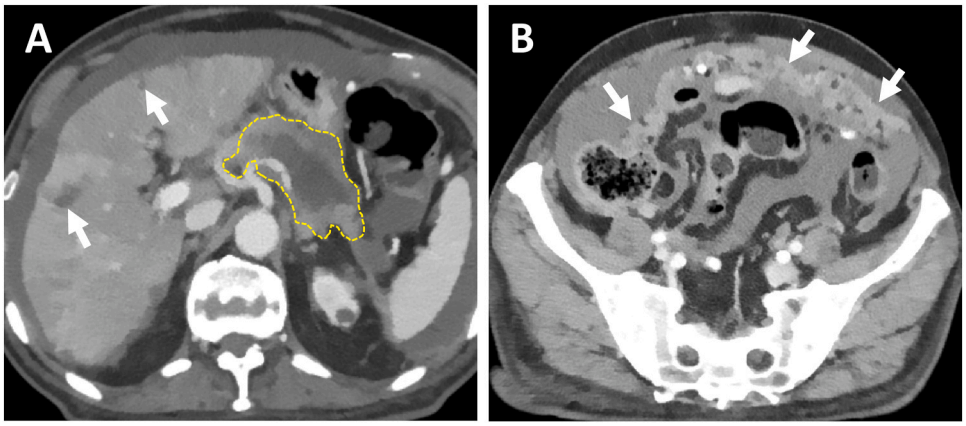

Fig. 11. Metastatic PDAC with peritoneal metastases. (A) reveals a bulky PDAC of the body and tail (dashed line), with hepatic metastases (arrows). There are also peritoneal metastases, as observed with an "omental cake" appearance in the pelvis (B, arrows).

3.4. Radiological structured report

The use of a radiological structured report is recommended, to provide a clear and standardized communication of imaging findings to surgeons and oncologists [6,55]. This also ensures that no relevant structures for tumor staging are forgotten or overlooked in the report. An example structured reporting template is suggested in Table 4, adapted from [55]. The reporting template should be tailored in each center to provide the multidisciplinary team with the information needed in an easily accessible way. Note that extensive descriptions of vascular involvement in patients with metastatic disease are usually not necessary, unless there is a specific motive for it, such as inclusion in a clinical trial.

3.5. Current issues with PDAC staging

Some aspects of the current widely used NCCN staging classification for PDAC have been debated [82]. Mainly, the dependence on strict anatomic criteria for defining treatment strategies for patients with PDAC, directed at surgical feasibility, often fails to consider disease biology.

Starting with anatomic staging issues, the 180º threshold can be insufficient for vascular staging, as the longitudinal extension of vessel involvement also determines surgical technique and has been shown to predict survival: patients with more than 20 mm of vascular involvement have a worse prognosis and may be candidates for neoadjuvant therapy [83]. Another issue is the involvement of the splenic artery which may fit in the resectable category, while the involvement of the celiac trunk, hepatic artery or superior mesenteric artery determine borderline resectable or locally advanced disease [82]. Patients may therefore be proposed for upfront surgery with a resectable although aggressive disease, missing potential survival benefits from neoadjuvant therapy. Finally, large tumor size, which is not category-defining for resectability, has also been associated with poor prognosis, and should be considered when deciding which treatment to offer a patient [84,85].

The presence of para-aortic lymph node metastases, which may easily be missed on imaging as previously discussed, is another predictor of poor prognosis [82,86–88]. Despite these diagnostic difficulties and the fact that they are not routinely removed on surgery, these nodes are considered metastatic disease, and adjuvant chemotherapy has been recommended for improving outcomes in these patients [89,90].

Surgical resection is not recommended for metastatic patients according to current guidelines; however, it is performed after neoadjuvant therapy in some institutions, for selected patients with oligometastatic disease. This has been reported to improve survival, but more evidence is needed before widespread acceptance [91–93].

Recurrence risk is also not sufficiently addressed in the anatomic classification. In a large series evaluating early recurrence, pre-operative risk factors were identified, including: CA 19–9 $>$ 210 U/mL, Charlson age-comorbidity index $\geq$ 4, tumor size $>$ 3 cm; post-operative risk

Table 4
Structured reporting template.

Pancreatic tumor	Location	*Head / Neck / Body / Tail*
	Size	*Largest axis; approximate measurement if ill-defined*
	MPD and biliary tree	*Dilated / Not dilated*
	Adjacent organ involvement	*NA / Describe involvement (stomach, adrenal, colon, etc.)*
Arteries	CT	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)* *Mention stenosis or atherosclerosis*
	CHA	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)* *Extension to CT or bifurcation*
	SA	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)*
	SMA	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)*
	SMA branches	*Free* *Mention involved branches (extension in mm)*
	Variant anatomy	*NA / Replaced CHA / Accessory RHA / Replaced RHA / Accessory LHA / Replaced LHA / Other**
	Variant involvement	*NA / Free / ≤ 180° / > 180° / Deformity / Occlusion**
Veins	PV	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)*
	SMV	*Free* *≤ 180° / > 180° / Deformity / Occlusion (extension in mm)*
	Collaterals	*NA / pancreatic head / hepatic hilum / mesenteric / LUQ*
Metastases	Liver	*Absent / Present / Indeterminate*
	Peritoneum	*Absent / Present / Indeterminate* *Ascites Absent / Present*
	Lung	*Absent / Present / Indeterminate*
Lymph nodes	If suspicious, mention location(s)	*NA / Peri-pancreatic / Hepatic hilum / Celiac / Aortocaval / Para-aortic / Splenic*
Other findings		*Free writing*

One or more options presented in *italics* should be chosen in each field according to imaging findings, and longitudinal extension of vessel involvement provided in millimeters. *Further description can be added at the end of the report, when variant anatomy or involvement cannot be adequately described in the template. CHA: common hepatic artery; CT: celiac trunk; LHA: left hepatic artery; LUQ: left upper quadrant; MPD: main pancreatic duct; NA: non-applicable; PV: portal vein; RHA: right hepatic artery; SA: splenic artery; SMA: superior mesenteric artery; SMV: superior mesenteric vein.

factors were also identified, including: poor tumor differentiation, microscopic lymphovascular invasion, lymph node ratio > 0.2, and CA 19–9 > 37 U/mL [94]. None of these are considered in the anatomic resection criteria. Furthermore, the inclusion of neoadjuvant therapy based on risk factors for early recurrence was shown to improve survival [95]. Local recurrence has additionally been associated with high rates of post-venous reconstruction thrombosis, rather than anatomic or technical factors, further demonstrating the relevance of disease biology in determining patient outcomes [96].

Management of patients with PDAC with resectable disease is also currently being discussed. Neoadjuvant therapy has been proposed in purely resectable patients, showing some improvement in disease-free survival in a small number of trials [97]. However, conflicting evidence showed no clear improvement in survival, and more data on this issue is needed before issuing favorable recommendations for clinical practice [98,99]. More recently, a randomised clinical trial found no survival benefit from the use of neoadjuvant therapy in resectable patients with PDAC, when compared to upfront resection, further disfavoring its use [100].

In summary, accumulating data tend to consider PDAC as a systemic disease and favor the use of neoadjuvant therapy even in selected high-risk resectable patients, while also selecting patients previously categorized as unresectable or even oligometastatic, as candidates for surgical resection with favorable outcomes. Patient management decisions should therefore be made in a multidisciplinary team setting, considering both the anatomic staging and additional prognostic factors.

3.6. Alternative staging classifications

Other staging classifications have been developed, including additional prognostic factors in the decision-making process. The MD Anderson Cancer Center developed a well-known classification incorporating anatomic criteria, tumor biology and patient performance status for patient categorization [101,102]. This type of classification has been used later in a consensus meeting to categorize borderline resectable and locally advanced patients in different types, according to anatomic, biological, and conditional factors [103]. Here, in addition to the anatomic classification (resectable, borderline resectable and locally advanced), biological factors (serum CA 19–9 >500 IU/mL and/or positive regional lymph node metastases) and conditional factors (performance status) were added for an integrative patient stratification.

Additionally, other classifications were developed based on anatomic criteria, but without such widespread use as the NCCN classification. These include the American Society of Clinical Oncology, Intergroup Alliance, and Americas Hepato-Pancreato-Biliary Association / Society of Surgical Oncology / Society for Surgery of the

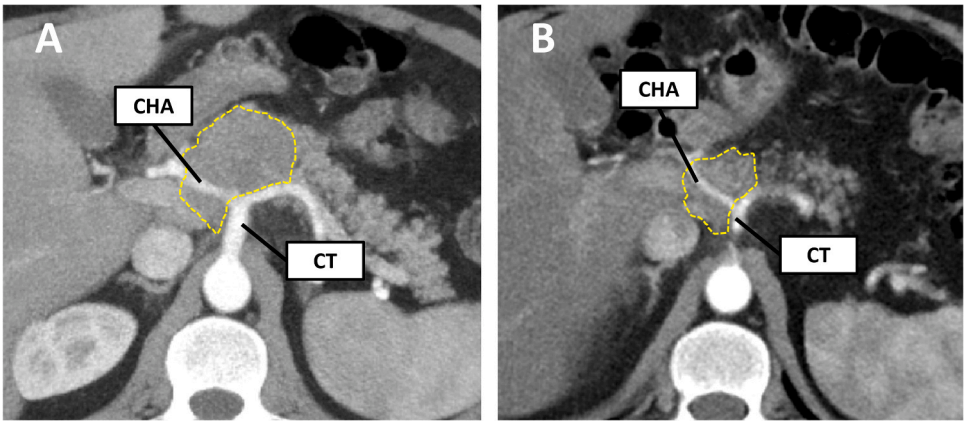

Fig. 12. Response to neoadjuvant therapy. (A) reveals a locally advanced PDAC (dashed line) with common hepatic artery (CHA) encasement up to the celiac trunk bifurcation (CT). After the completion of neoadjuvant chemotherapy, the tumor had reduced in size (B, dashed line), but maintained a long encasement of the CHA. The patient underwent surgery, with an R0 resection.

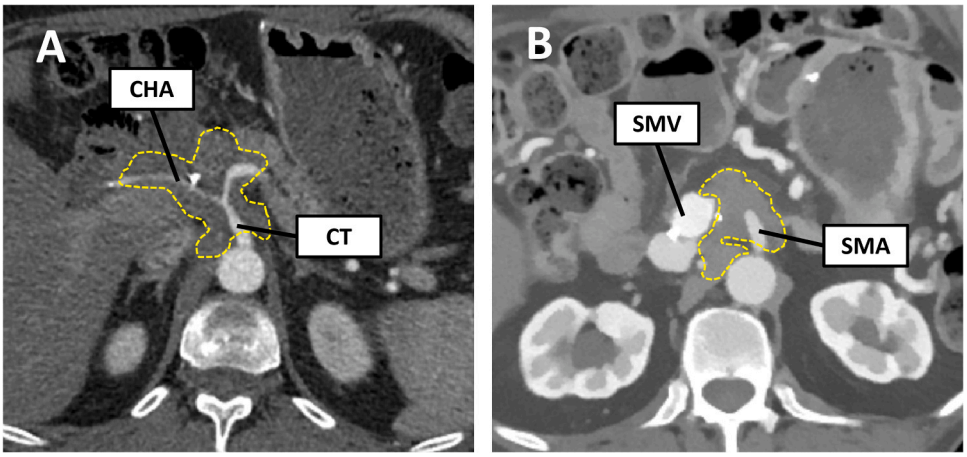

Fig. 13. Recurrence of PDAC. Two cases of local recurrence of PDAC (dashed lines), in (A) encasing the celiac trunk (CT) and common hepatic artery (CHA), and in (B) encasing the superior mesenteric artery (SMA) and invading the superior mesenteric vein (SMV) with a teardrop sign.

Alimentary Tract [7,104,105]. These classifications also use the resectable, borderline resectable and unresectable / locally advanced categories, but with different criteria, which were highlighted in a consensus meeting [103].

4. Response to neoadjuvant therapy

Assessing response to neoadjuvant therapy for PDAC is a difficult task in clinical practice. Tumor size criteria are not useful for this purpose, as the fibrotic tumoral stroma remains, even when a response has occurred in cancer cells [106–108]. The current methods for evaluating response to neoadjuvant therapy reside on tumoral markers evolution (serum CA19–9 concentration) and the absence of disease progression as evidenced by imaging studies [3,9,109]. If progression is not apparent – the pancreatic tumor is stable or has reduced in size, and tumor markers have not increased – then a response is presumed and the patient can be proposed for surgery, in the case of initial borderline or even locally advanced disease (Fig. 12). Also, standard criteria for vascular resectability based on the amount of tumor-vessel contact are not useful post-neoadjuvant therapy, and an improvement of tumor-vascular involvement is highly predictive of an R0 resection, even if partial [109]. Furthermore, the presence of tumor regression after neoadjuvant therapy was not correlated with survival, in a cohort of patients with R0 resections [110]. Disease extension as observed on CT should not just be disregarded, however. Smaller tumor size and reduction of arterial contact, as well as imaging scores based on arterial involvement and resectability status, performed both before and after neoadjuvant therapy, were correlated with probability of R0 resection [111,112].

Some studies have evaluated the role of DWI for response assessment, reporting a correlation of apparent diffusion coefficient (ADC) with histopathological response, but others have not found it useful [113–117]. The value of DWI in this context remains undetermined, and further studies are needed to provide recommendations for clinical practice [118].

The role of FDG-PET for neoadjuvant therapy response assessment has also been evaluated. Both CT and MRI FDG-PET's metabolic response has been reported to be associated with pathologic response, being superior than CA19–9 for this purpose [119,120]. FDG-PET MRI added to contrast-enhanced CT showed improved accuracy for determining resectability status when compared with contras-enhanced CT alone, in a retrospective study [121]. A recent systematic review reported FDG-PET's potential for predicting and assessing response to neoadjuvant therapy; however, the small numbers of patients enrolled in each study and methodological heterogeneity prompt the need for well-designed prospective trials [122].

Recent developments in molecular imaging provided potential biomarkers for response to neoadjuvant therapy evaluation, as well as improving diagnostic and staging accuracy, with encouraging results [123]. However, these require validation and thus cannot yet be recommended for clinical practice.

Considering current limited tools for response assessment, the therapeutic decision after neoadjuvant therapy should always be made by a multidisciplinary team, taking into account imaging, biochemical and patient fitness data. The surgical decision is heavily dependent on the surgical team expertise, especially in cases of initially advanced disease or extensive vascular involvement [3,6].

5. Patient surveillance after resection

First, some important issues regarding pathologic assessment of PDAC resection margin should be discussed. The R0 definition for PDAC resection has been debated, and controversy regarding microscopic margin involvement has contributed to variability in reported R1 rates [124–126]. Although UICC's classification considers R0 as absence of tumor cells at the resection margin, a free resection margin of ≥ 1 mm defining R0 is also frequently used, and was associated with better survival when compared with < 1 mm [127,128]. Despite this, in the presence of lymph node positive disease, recurrence patterns were reportedly similar for both R0 and R1 patients [129]. Also, free margins larger than 1.5 mm have been reported to correlate with survival, as explained by the dispersed growth pattern of PDAC [125,130]. Other issues including challenges in specimen grossing and sampling, and the variable R0 definitions used in published literature, have been considered as important factors undermining the data quality of reported clinical outcomes of PDAC resection [125].

Evidence for recommending specific surveillance methods after PDAC resection is lacking, and the value of surveillance has been debated [131,132]. Nevertheless, patients undergoing post-resection surveillance have been reported to have improved detection of disease recurrence at asymptomatic stages, were more likely to receive treatment for the recurrence and presented longer overall survival [133,134]. A tumoral recurrence is usually found in the surgical bed, in the mesenteric root or the pancreatic remnant (Fig. 13). Local perivascular densification is common post-resection; however, a perivascular densification increasing in size in serial imaging or leading to a *de novo* change in the caliber or regularity of the vessel should be considered suspicious for local recurrence [135]. Distant recurrence is most commonly found in the liver or lungs [136]. A surveillance scheme including serum CA19–9 and CT (chest, abdomen and pelvis) every 3–6 months for 2 years after surgical resection has been recommended, and is followed in our institution [6]. MRI is usually not included in a surveillance setting but can be used for disease staging if a recurrence is

suspected.

6. Conclusion

Imaging plays a central role in all stages of patient management for PDAC: diagnosis, staging, response to neoadjuvant therapy and post-surgical surveillance. Diagnostic and staging performance of current imaging modalities is high; however, there are unresolved issues when staging patients and assessing response to neoadjuvant therapy, and evidence is lacking for dedicated patient surveillance protocols. Nevertheless, an experienced radiologist remains essential in the multidisciplinary team caring for patients with PDAC.

CRediT authorship contribution statement

Matos Celso: Writing – review & editing, Methodology, Conceptualization. **Marques Rui Mateus:** Writing – review & editing, Methodology. **Santiago Inês:** Writing – review & editing. **Andrade Luísa:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Bilreiro Carlos:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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