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Pancreatic ductal adenocarcinoma staging: a narrative review of radiologic techniques and advances

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Abstract

Radiology plays an important role in the initial diagnosis and staging of patients with pancreatic ductal adenocarcinoma (PDAC). CT is the preferred modality over MRI due to wider availability, greater consistency in image quality, and lower cost. MRI and PET/CT are usually reserved as problem-solving tools in select patients. The National Comprehensive Cancer Network (NCCN) guidelines define resectability criteria based on tumor involvement of the arteries and veins and triage patients into resectable, borderline resectable, locally advanced, and metastatic categories. Patients with resectable disease are eligible for upfront surgical resection, while patients with high-stage disease are treated with neoadjuvant chemotherapy and/or radiation therapy with hopes of downstaging the disease. The accuracy of staging critically depends on the imaging technique and the experience of the radiologists. Several challenges in accurate preoperative staging include prediction of lymph node metastases, detection of subtle liver and peritoneal metastases, and disease restaging following neoadjuvant therapy. Artificial intelligence (AI) has the potential to function as 'second readers' to improve upon the radiologists' detection of small early-stage tumors, which can shift more patients toward surgical resection of potentially curable cancer. AI may also provide imaging biomarkers that can predict disease recurrence and patient survival after pancreatic resection and assist in the selection of patients most likely to benefit from surgery, thus improving patient outcomes.

Keywords: artificial intelligence, cinematic rendering, computed tomography, magnetic resonance imaging, pancreatic cancer, radiology, radiomics

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer mortality worldwide based on GLOBOCAN 2020 estimates, and over 466 000 patients with pancreatic cancer succumbed to the disease in 2020[1]. The age-standardized incidence of PDAC is fourfold to fivefold higher in countries with a high development index, with the greatest incidence in Europe, North America, Australia, and New Zealand[1]. Therefore, PDAC is expected to surpass breast cancer as the third leading cause of cancer death in the United States and Europe[1]. Despite therapeutic advances, the 5-year survival rate of patients with PDAC remains ~10% since most patients are diagnosed at an advanced stage of disease[2]. Surgical resection remains the only curative therapy for patients with PDAC, and radiology plays a pivotal role in disease staging and patient management. The purpose of this article is to review the current role of radiology and emerging technologies in treating PDAC.

HIGHLIGHTS

- Radiology plays an important role in the initial diagnosis and staging of pancreatic cancer.
- CT is the preferred modality over MRI due to wider availability, greater consistency in image quality, and lower cost.
- Patients can be triaged into resectable, borderline resectable, and locally advanced based on tumor involvement of arteries and veins.
- Accuracy of diagnosis and staging critically depends on the imaging technique and experience of the radiologists.
- Artificial intelligence has the potential to function as 'second readers' to improve the detection of small early-stage tumors and provide imaging biomarkers to predict patient prognosis.

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Role of radiology in cancer detection

Radiology plays a critical role in the initial diagnosis, staging, and evaluation of treatment response for patients with PDAC. Both computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used for the detection and staging of suspected PDAC. Both CT and MRI provide similar sensitivity in tumor detection, ranging from 76 to 96% for CT and 83 to 94% for MRI[3]. At most institutions, CT is preferred over MRI due to wider availability, greater consistency in image quality, better patient tolerance, and lower cost[4]. MRI is typically used as a second-line modality in patients with contraindications to CT, such as renal insufficiency or severe iodinated contrast allergy. Positron emission tomography/computed tomography (PET/CT) and positron emission tomography/magnetic resonance imaging (PET/MRI) are not routinely used in the staging of patients with PDAC, but may play a role in select patients[5].

PDACs classically present as hypoenhancing masses with associated pancreatic duct dilatation and glandular atrophy of the body and tail. Pancreatic head tumors can cause common bile duct dilatation in addition to pancreatic duct dilatation, also known as the 'double duct sign'[3]. Up to 20% of PDACs enhance to the same degree as the background pancreas, and this isoattenuating pattern is more commonly found with smaller ($\leq$20 mm) tumors[6,7]. These small isoattenuating tumors can be difficult to detect on CT; therefore, radiologists often rely on secondary signs of the pancreatic duct or common bile duct dilatation for tumor detection. MRI and PET/CT have reported sensitivities of 79.2 and 73.7% in the detection of isoattenuating tumors, respectively[7], and may aid in detecting suspected pancreatic tumors that are occult on CT[4] (Figs 1, 2). Endoscopic ultrasound is crucial in confirming tissue diagnosis of suspected pancreatic malignancy. It is also an important second-line modality in detecting suspected pancreatic tumors that are occult on CT or MRI[3].

Imaging protocols

The accuracy of tumor detection and staging critically depends on image quality and the experience of the radiologists. The Society of Abdominal Radiology and the American Pancreatic Association endorse a dual-phase CT protocol for the detection and staging of PDAC[8]. The CT examination should be performed with intravenous contrast (>300 mg I/ml) at an injection rate of 3–5 ml/s with scans obtained at the pancreatic parenchyma phase (40–50 s) and portal venous phase (65–70 s). A neutral or low-Hounsfield unit oral agent should be administered. CT imaging should be obtained with submillimeter slice thickness, reconstructed into 0.75–3 mm axial slices. Multiplanar and three-dimensional reconstruction can help assess vascular involvement[8].

The MRI protocol should include T2-weighted single-shot fast spin echo, T1-weighted in and opposed phase gradient echo, T2-weighted fat-suppressed fast spin echo, diffusion-weighted imaging, T2-weighted magnetic resonance cholangiopancreatography (MRCP), and 3D T1-weighted fat-suppressed gradient echo sequences before and after intravenous gadolinium contrast administration[4].

Staging criteria

The American Joint Committee on Cancer (AJCC) stages PDAC based on the TNM staging system[9]. T stage is mainly based on tumor size (T1 <2 cm; T2 between 2 and 4 cm; T3 >4 cm), and T4 is defined as a tumor with vascular involvement regardless of size. N staging is based on absence (N0) and number of regional lymph node involvement (N1 between 1 and 3 lymph nodes, N2 greater than 4 lymph nodes). M staging is based on absence (M0) or presence (M1) of distant metastatic disease[9]. The primary goal of the AJCC system is to provide prognostic information instead of driving management decisions. From a management perspective, tumors are staged into resectable, borderline resectable, locally advanced, and metastatic disease. Patients with resectable disease are eligible for upfront surgical resection or surgical resection following neoadjuvant chemotherapy, and patients with higher-stage disease are treated with chemotherapy and/or radiation therapy[4]. There are subtle variations in resectability criteria among organizations[4,10–13].

Both arterial and venous involvement are pivotal in determining resectability. Based on the National Comprehensive Cancer Network (NCCN) guidelines (Table 1), tumors without arterial tumor contact or superior mesenteric vein (SMV) or portal vein (PV) tumor contact are considered resectable (Fig. 3). Tumors with $\leq$180° contact with the SMV or PV without contour irregularity are also considered resectable. Arterial abutment of the celiac artery or superior mesenteric artery (SMA) (<180°) is considered borderline resectable (Fig. 4), whereas arterial encasement ($\geq$180°) is usually considered locally advanced (Fig. 5). Solid tumor contact with the common hepatic artery without extension to the celiac artery or hepatic artery bifurcation as well as solid tumor contact with variant arterial anatomy are also considered borderline resectable, and the presence and degree of tumor contact may affect surgical planning. Venous encasement (>180°) or venous abutment (180°) with contour irregularity or thrombosis are considered borderline resectable if the involved venous segment can be resected and reconstructed. Unreconstructible venous involvement is considered locally advanced[4] (Fig. 6). According to the Dutch Pancreatic Cancer Group criteria, resectable disease is defined by the absence of celiac artery, SMA, or common hepatic artery tumor contact, and SMV and/or portal vein tumor contact of $\leq$90° (as opposed to $\leq$180° in the NCCN guideline). Arterial tumor contact by $\leq$90° or venous tumor contact by >90 to 270° without venous occlusion is considered borderline resectable. Arterial tumor contact by >90° or venous tumor contact by >270° or venous occlusion is considered locally advanced[13].

Accuracy of PDAC staging

The reported accuracy in determining tumor resectability ranges from 73 to 87% for CT and 70 to 79% for MRI[3], although this may depend on radiologists' experience. CT offers superior spatial resolution and is less susceptible to artifacts compared to MRI. Also, CT allows for greater confidence in the assessment of tumor–vascular relationships. MRI is a critical problem-solving tool in the characterization of indeterminate liver lesions[4] (Figs 6, 7), which influences staging localized vs. metastatic disease. PET lacks the spatial resolution critical for the staging of locoregional involvement and is not used routinely in staging[4]. The primary benefit of PET/CT or PET/MRI over CT or MRI is

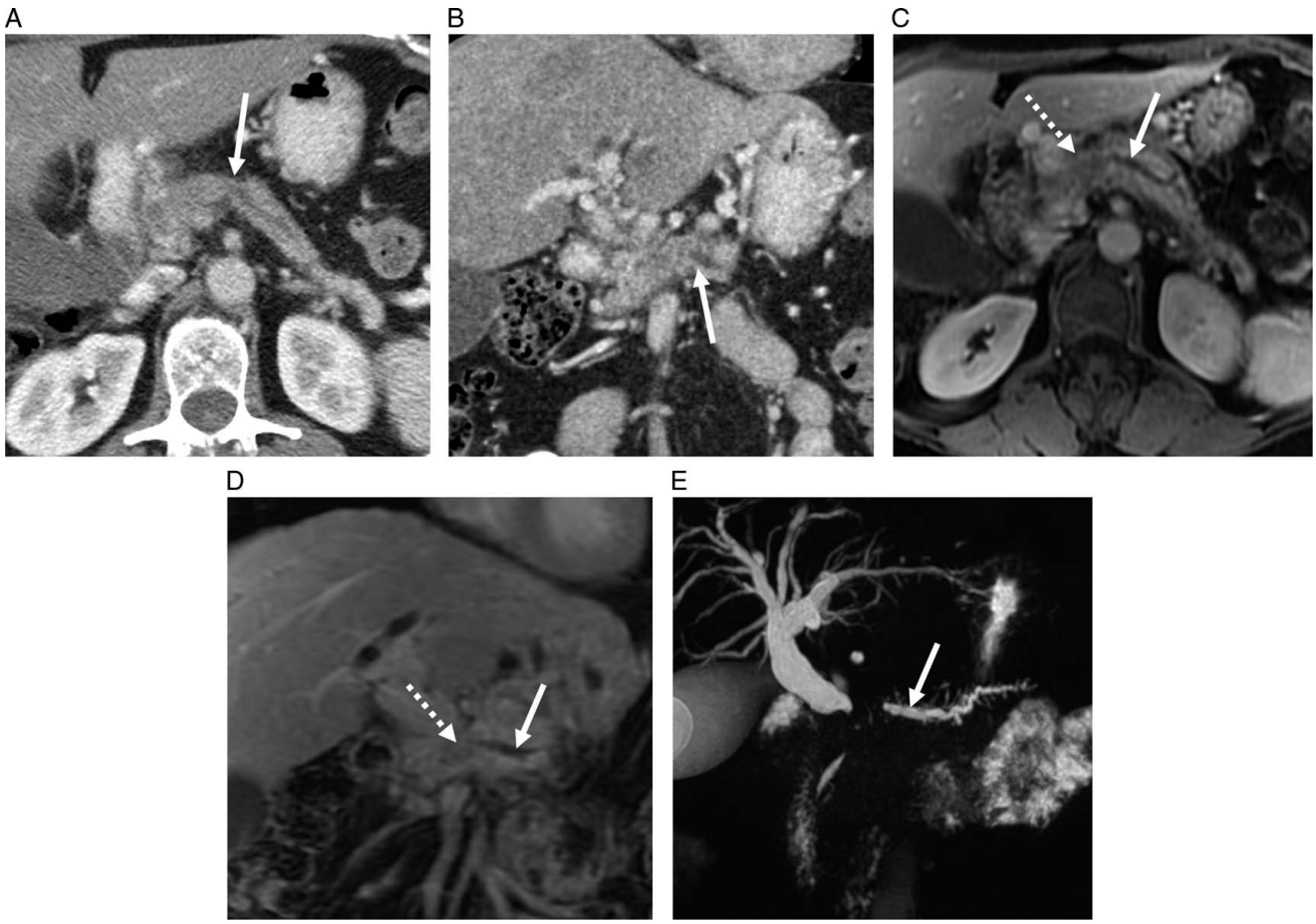

Figure 1. A 55-year-old woman who presented with lower abdominal pain. Axial (A) and coronal (B) intravenous (i.v.) contrast-enhanced computed tomography (CT) images in the portal venous phase obtained at outside institutions did not report any pancreatic abnormality. In retrospect, there was mild dilatation of the pancreatic duct (arrow) without discrete pancreatic mass. Two-month follow-up axial (C) and coronal (D) i.v. contrast-enhanced T1-weighted MR (magnetic resonance) images showed subtle hypoenhancing mass (dotted arrows) as the cause for the pancreatic duct dilatation (arrows). Coronal magnetic resonance cholangiopancreatography image (E) showed an abrupt cut-off of the dilated pancreatic duct, an important secondary sign in the diagnosis of PDAC (pancreatic ductal adenocarcinoma).

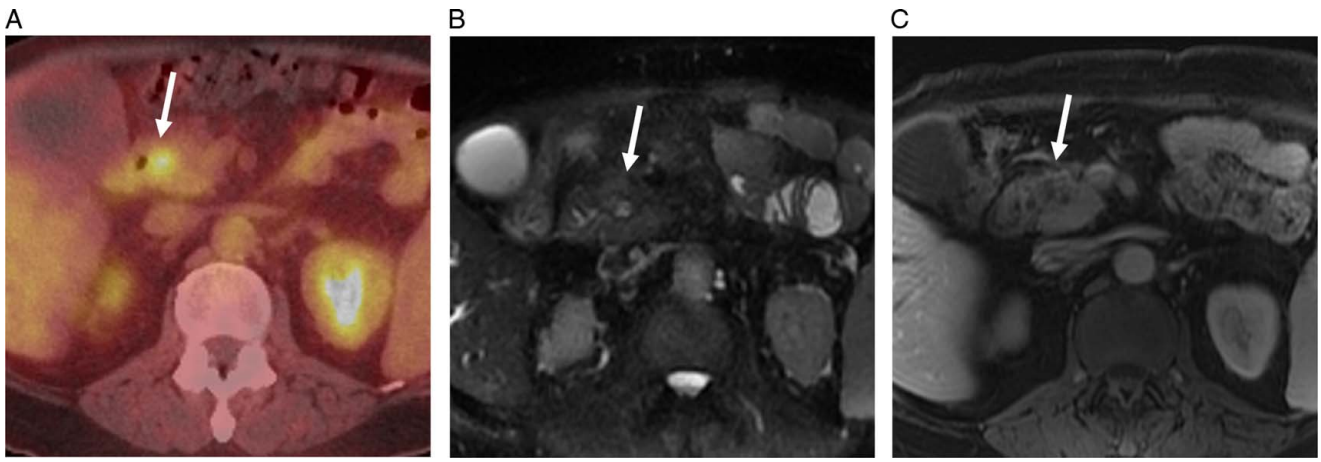

Figure 2. A 76-year-old man with a history of chronic lymphocytic leukemia who underwent positron emission tomography/computed tomography (PET/CT) for treatment surveillance. Axial-fused PET/CT (A) image showed an FDG (fluorodeoxyglucose) avid focus in the pancreatic head (arrow). Axial T2-weighted MR (magnetic resonance) image (B) showed a mildly T2 hyperintense mass in the pancreatic head (arrow). Axial intravenous (i.v.) contrast-enhanced T1-weighted MR image (C) showed heterogeneous enhancement within the pancreatic head mass (arrow). Biopsy confirmed diagnosis of PDAC (pancreatic ductal adenocarcinoma).

Table 1

Resectability criteria for pancreatic ductal adenocarcinoma[4,13].

	National Comprehensive Cancer Network		Dutch Pancreatic Cancer Group	
Resectability status	**Arterial**	**Venous**	**Arterial**	**Venous**
Resectable	No tumor contact with CA, SMA, or CHA	No tumor contact with SMV or PV ≤180° contact without vein contour irregularity	No tumor contact with CA, SMA, or CHA	≤90° SMV or PV contact
Borderline resectable	*Pancreatic head/uncinate process:* Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation Solid tumor contact with SMA ≤180° Solid tumor contact with variant arterial anatomy *Pancreatic body/tail:* Solid tumor contact with CA ≤180°	Solid tumor contact with SMV or PV >180° Solid tumor contact with SMV or PV ≤180° with contour irregularity of the vein or thrombosis, which can be resected with venous reconstruction Solid tumor contact with inferior vena cava	≤90° tumor contact with CA, SMA, or CHA	>90–270° SMV or PV contact without occlusion
Locally Advanced	*Pancreatic head/uncinate process:* Solid tumor contact >180° with SMA or CA *Pancreatic body/tail:* Solid tumor contact >180° with SMA or CA Solid tumor contact with CA and aorta	Unreconstructible SMV or PV due to tumor involvement or occlusion	>90° tumor contact with CA, SMA, or CHA	>270° contact or occlusion

CA, celiac artery; CHA, common hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

the capacity to detect distant metastatic disease, including liver, peritoneum, lung, and bone. PET/CT may also improve the detection of lymph node involvement due to the complementary functional and anatomic information it provides[14]. In patients at high risk of advanced disease[(e.g. large primary tumor, large regional lymph nodes, or markedly elevated cancer antigen 19-9 (CA 19-9)], PET/CT[4] or PET/MRI[5] may be performed to identify extra-pancreatic disease.

Challenges in staging

There are several limitations in radiologic studies for the initial staging of PDAC. Although preoperative assessment of lymph node status is a key prognostic factor, current radiologic criteria based on size and morphologic features yield limited sensitivity and specificity in detecting lymph node metastases. A meta-analysis showed that CT had a pooled sensitivity of 25% and a positive predictive value of 28% in predicting extra-regional lymph node metastases in pancreatic and periampullary cancer[15]. Preoperative identification of suspicious extra-regional lymph nodes is valuable in guiding lymph node sampling during surgery[16].

Subtle liver or peritoneal metastases can be occult on preoperative CTs in up to 30% of cases[17–20], and diagnostic laparoscopy may be useful for patients at high risk of advanced disease[19,20]. High-quality imaging is essential in the detection of subtle liver or peritoneal metastases. Small liver and peritoneal metastases may be obscured by image noise, thick image slices, or suboptimal contrast injection. Liver metastases from PDAC are typically hypoenhancing on the portal venous phase and can mimic the appearance of cysts or hemangiomas. On arterial phase images, these liver metastases may contain peripheral enhancing rims, and this targetoid appearance can significantly improve the diagnostic confidence of small liver metastases (Fig. 6). MRI has improved tissue characterization compared to CT and is valuable for characterizing small indeterminate liver lesions (Fig. 7).

It is worth emphasizing that PDAC staging accuracy can vary significantly based on radiologists' experience. In a retrospective study, Corrias *et al.*[21] showed that second opinion interpretations of PDAC staging exams by radiologists with subspecialization in oncologic imaging contributed to changes in cancer staging in 13.0–18.4% of patients and changes in patient management in 20.0–38.4% of patients. Pawlik *et al.*[22] similarly demonstrated that 18.7% of patients with suspected PDAC sent to a tertiary referral center who underwent a repeat CT experienced changes in their clinical stage, including detection of previously occult metastatic disease and change in locoregional staging. Therefore, decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center[4].

Disease restaging after neoadjuvant therapy

Disease restaging after neoadjuvant chemotherapy or chemotherapy and radiation therapy presents additional challenges for radiologists. Patients with borderline resectable, locally advanced disease, and select patients with resectable disease are treated with neoadjuvant therapy aimed at downstaging the tumor, improving the likelihood of R0 resection, and selecting patients with disease that is either stable or responsive to treatment[23]. However, it can be difficult to distinguish between viable tumor and treatment-induced fibrosis (Figs 8, 9)[24]. Katz *et al.*[25] showed that radiographic downstaging was rare after neoadjuvant therapy, and the response evaluation criteria in solid tumor (RECIST) response was not an effective treatment endpoint for patients with borderline resectable PDAC. The accuracy of CT in predicting R0 resection

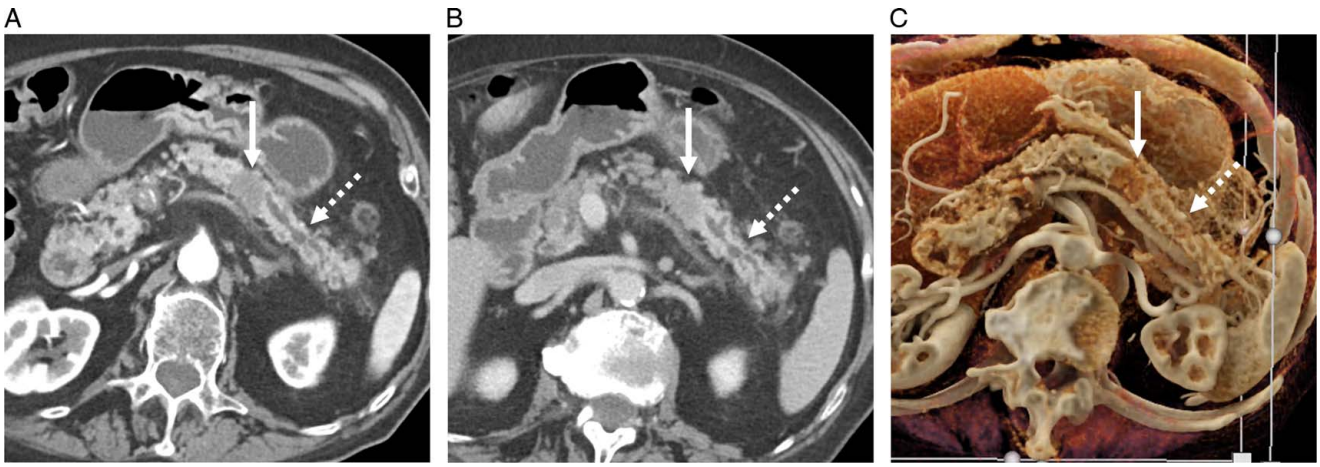

Figure 3. An 85-year-old woman with resectable pancreatic ductal adenocarcinoma. Axial intravenous (i.v.) contrast-enhanced computed tomography (CT) images in the arterial phase (A) and portal venous phase (B) demonstrated a subtle hypoenhancing mass arising from the body of the pancreas (arrows) with mild dilatation of the pancreatic duct in the body and tail (dotted arrows). (C) Cinematic rendering of the axial i.v. contrast-enhanced CT image accentuated the texture difference between the mass (arrow) and the background pancreatic parenchyma and improved lesion conspicuity. Mild dilatation of the pancreatic duct (dotted arrow) is visible. There was no evidence of vascular involvement, and the tumor was staged as resectable. The patient subsequently underwent a distal pancreatectomy.

decreased significantly after neoadjuvant therapy compared to upfront surgery[26,27]. Despite these challenges, several radiologic features have been associated with favorable treatment response, including partial regression of tumor contact with any peripancreatic vessel, replacement of solid tumor–vascular contact by a perivascular halo, reduction of tumor size, and increased tumor attenuation (Fig. 8)[16,24].

Structured reporting in PDAC staging

Structured radiology reports are generally recommended for preoperative staging of PDAC to ensure completeness of critical features in accurate staging[8,28–30] (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JS9/B459). However, there remains significant variability in the utilization of PDAC reporting templates even among academic radiologists due to concerns about interference with clinical workflow, lack of interest among radiologists, and complexity of existing reporting templates[31]. Potential solutions for improved implementation of PDAC structured reporting include simplifying reporting templates, creating new templates based on expert consensus, increasing educational efforts, and hosting libraries of shared templates[31].

Emerging technologies – advanced visualization

Three-dimensional (3D) volumetric CT images, including volume rendering and maximum intensity projection images, are considered standard of care in the pancreatic cancer CT imaging protocol[8]. These reconstructions allow for the full assessment of the circumferential and longitudinal vascular contact and reveal changes in vessel caliber or contour that may be difficult to detect on axial or two-dimensional (2D) coronal or sagittal images. Cinematic rendering, a recently described 3D rendering technique, uses a global illumination model that considers direct and indirect lighting to create images with photorealistic quality[32,33]. Cinematic rendering can accentuate subtle texture changes and improve tumor conspicuity (Figs 3–5)[34] relative to traditional 2D images, 3D volume rendering, or maximum intensity projection images. Cinematic rendering may be able to enhance the visualization of spatial relationships among the tumor and adjacent vasculature, differentiating true tumor infiltration from simple proximity to vessels (Figs 3–5). This can potentially improve the assessment of resectability and assist in determining optimal vascular reconstruction options[35,36]. Cinematic rendering vascular maps illustrate the major arteries and veins with exquisite detail and can highlight the presence of variant vascular anatomy that may increase the risk of complications, such as hemorrhage, ischemia, anastomotic leakage, or pseudoaneurysm formation[37]. At our institution, cinematic rendering has been routinely incorporated into the multidisciplinary PDAC clinic since 2018, and it has played an important role in tumor staging as well as patient management[35]. Moreover, cinematic rendering data can be imported into augmented reality headsets to provide an immersive experience for the surgeon for operative planning[38].

Also, 3D printing has been used to create accurate patient-specific models from medical imaging data that may enhance preoperative planning for complex vascular or oncologic surgery. A recent retrospective study by Song *et al.*[39] showed that 3D-printed models of pancreatic cancer helped improve the surgeons' understanding of pancreatic cancer anatomy and could assist in surgical planning. Implementation of these advanced visualization techniques varies across institutions depending on local resources (e.g. hardware, software) and technical expertise.

Emerging technologies – artificial intelligence

Artificial intelligence (AI) is poised to revolutionize medicine, and radiology is a natural gateway due to the inherent digital nature of radiology data. AI can be broadly defined as using computers to perform tasks typically associated with human intelligence. Machine learning, a branch of AI, enables the extraction of

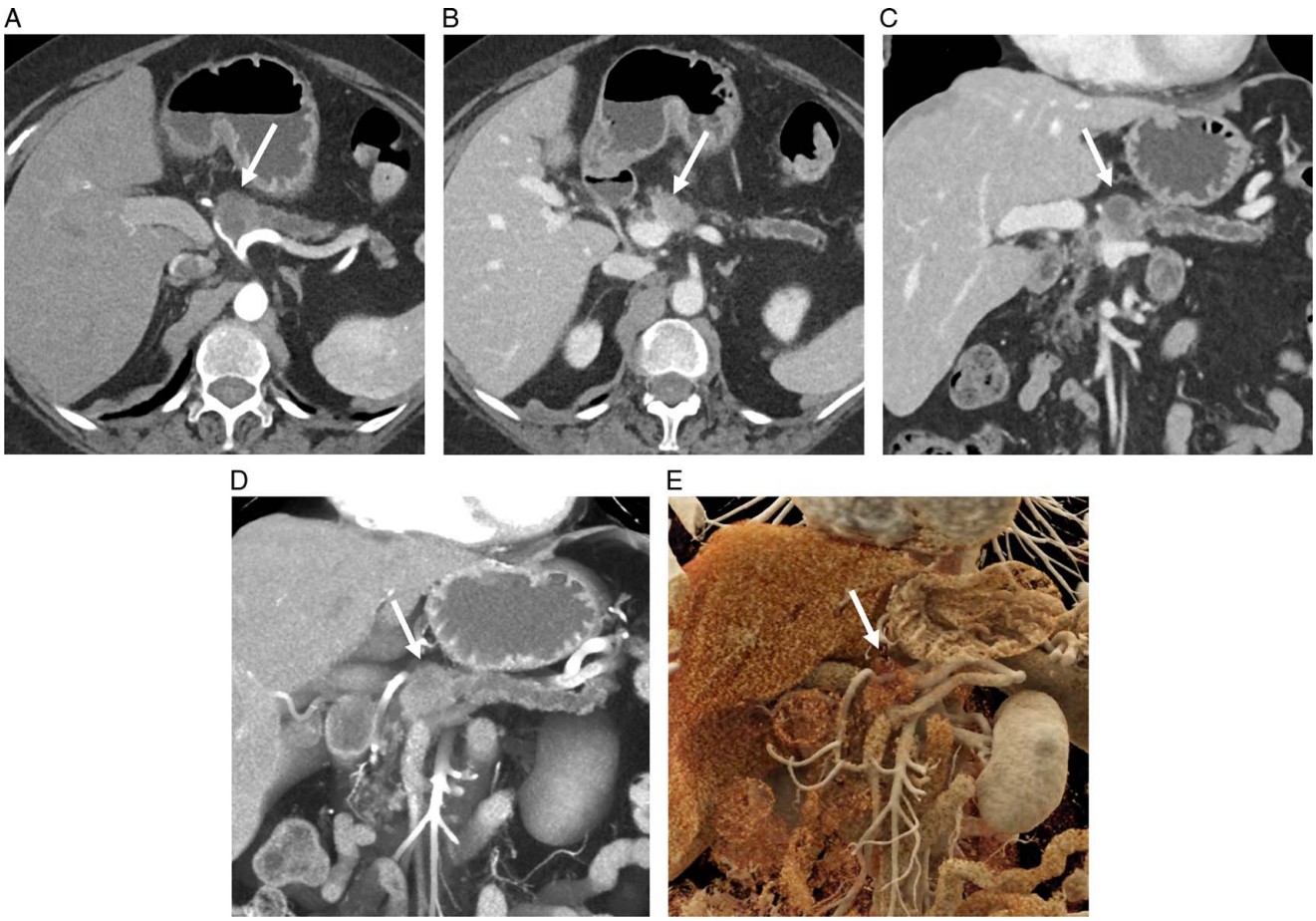

Figure 4. A 76-year-old woman with borderline resectable pancreatic ductal adenocarcinoma. Axial intravenous (i.v.) contrast-enhanced computed tomography (CT) images in the arterial phase (A) and portal venous phase (B), and a coronal i.v. contrast-enhanced CT image in the portal venous phase (C) demonstrated a hypoenhancing mass arising from the neck of the pancreas (arrows) with associated pancreatic duct dilatation and atrophy of the body and tail. The tumor abutted the common hepatic artery, splenic artery, portal vein, and superior mesenteric vein, and was staged as borderline resectable. Volume rendering (D) and cinematic rendering (E) of coronal i.v. contrast-enhanced CT images in the arterial phase may improve appreciation of tumor contact (arrow) with adjacent vessels. The patient underwent neoadjuvant chemotherapy and subsequent Whipple resection.

meaningful patterns from examples rather than through explicit programming. Deep learning (DL), a subfield of machine learning first developed in the 1950s, utilizes networks of interconnected nodes that process input data and adjust the network weights to minimize prediction errors[40]. Recent developments in powerful parallel computing hardware, the availability of large training data, and improved network architectures have notably enhanced the performance of deep learning, which has significant potential for clinical translation[40]. Radiomics converts imaging data into high-dimensional features that can be used to characterize spatial heterogeneity inherent in disease processes[41]. The features of radiomics can be classified into signal intensity, shape, and texture[41,42]. Signal intensity (first-order) features are derived from histograms of individual voxel signal intensities, providing measures of central tendency and shape of the distribution. Shape features are extracted from the three-dimensional surface of the region of interest. Texture features are calculated in three dimensions, considering the correlation of signal intensities of adjacent voxels. In addition, feature extraction may be performed after applying a secondary filter, such as a wavelet or Gaussian filter[41,42].

AI has multiple applications in radiology, including image segmentation, registration, detection, and classification. It can also facilitate information transfer through natural language processing[43]. The following sections summarize the potential role of AI in tumor detection, prediction of tumor resectability, and treatment response.

AI-assisted tumor detection

AI can theoretically function as 'second readers' to improve radiologists' sensitivity in the detection of small tumors, which potentially can be cured with surgical resection. A preliminary study by Liu *et al.*[44] showed promising results suggesting that DL could accurately differentiate CT scans of patients with PDAC from CT scans of healthy controls. More recently, Chen *et al.* developed a DL tool that differentiated CT scans of patients with PDAC vs. healthy controls with 89.9% sensitivity, 95.9% specificity, and 93.4% accuracy in the local test set. They validated this DL tool on a Taiwanese nationwide external validation set and achieved 89.7% sensitivity, 92.8% specificity, and 91.4% accuracy[45]. Also, Park *et al.* developed a different DL tool that

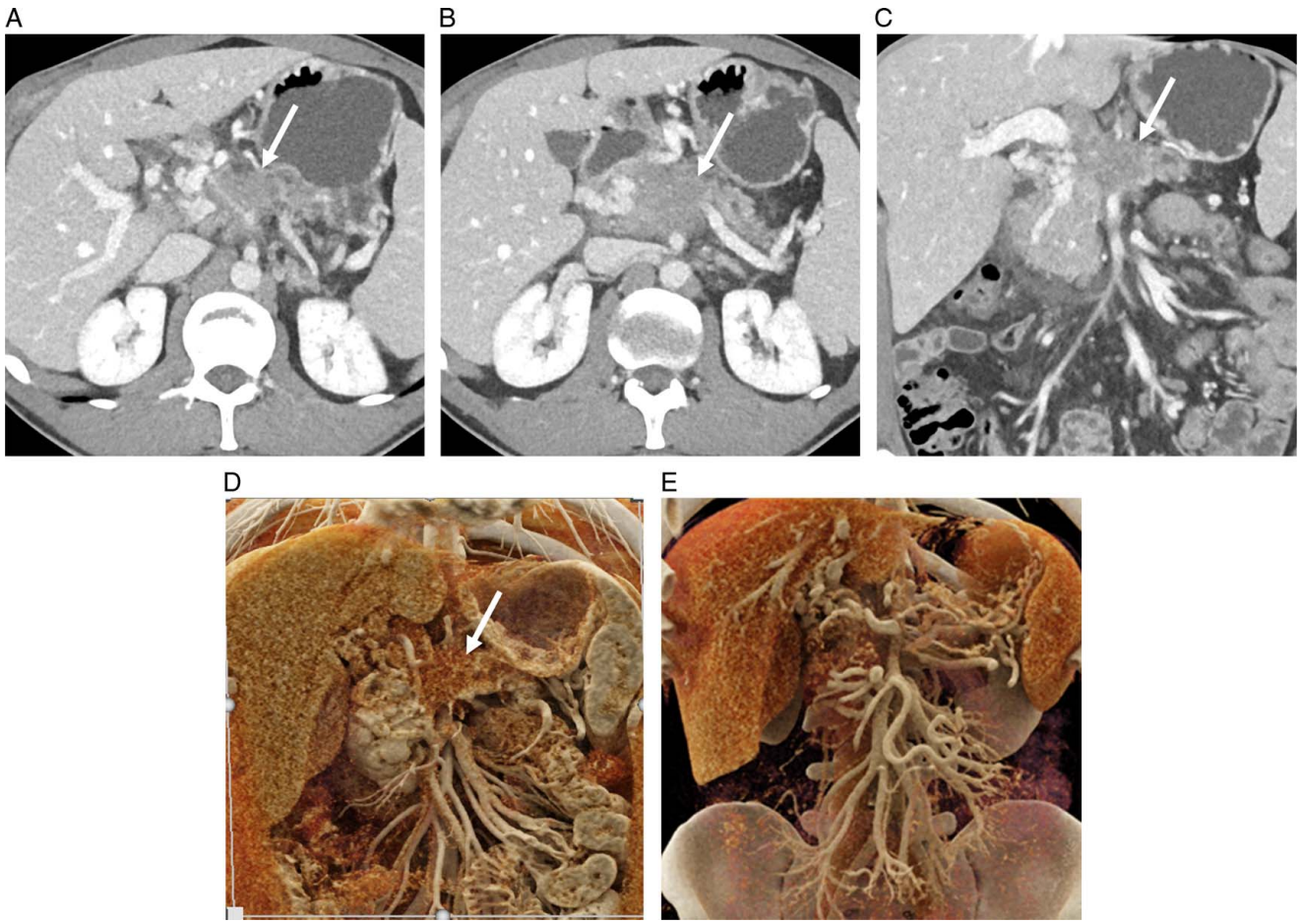

Figure 5. A 36-year-old man with locally advanced pancreatic ductal adenocarcinoma. Axial (A and B) and coronal (C) intravenous (i.v.) contrast-enhanced computed tomography (CT) images in the portal venous phase showed an infiltrative hypoenhancing mass arising from the pancreatic neck and proximal body (arrows) with encasement of the celiac artery, superior mesenteric artery, portal vein, and superior mesenteric vein, with chronic portal vein occlusion and prominent venous collaterals. Cinematic rendering of coronal i.v. contrast-enhanced CT images in the portal venous phase (D and E) again showed extensive tumor encasement with prominent vascular collaterals. The tumor was staged as locally advanced, and the patient was treated with systemic chemotherapy.

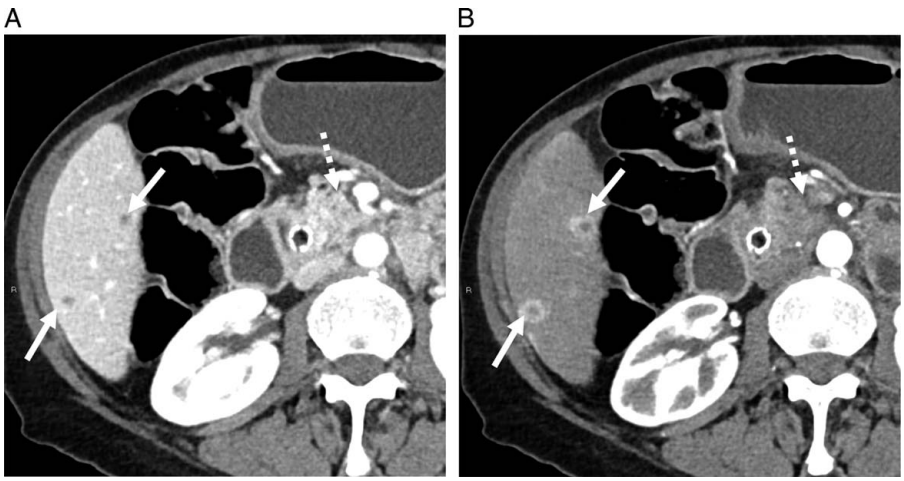

Figure 6. A 61-year-old woman with metastatic pancreatic adenosquamous carcinoma. (A) An axial intravenous (i.v.) contrast-enhanced computed tomography (CT) image in the portal venous phase showed small hypoenhancing liver lesions (arrows) and an ill-defined hypoenhancing pancreatic head mass (dotted arrow). These small lesions would be difficult to characterize based solely on venous phase imaging appearance. (B) An axial i.v. contrast-enhanced CT image in the arterial phase showed avid enhancement along the periphery of the liver lesions (arrows). The targetoid appearance significantly improved the diagnostic confidence of liver metastases. An ill-defined pancreatic head mass (arrowhead), compatible with pancreatic cancer, is visible.

achieved high sensitivity comparable to radiologists in the detection of not only pancreatic solid masses (98–100%) but also cystic masses 1.0 cm or larger (sensitivity 92–93%)[46], bringing us closer to a universal pancreatic neoplasm detector (Table 2).

Other studies have used radiomics to facilitate the detection of PDAC, demonstrating that radiomics signatures from PDAC were distinct from the background pancreas[45,53,54]. More impressively, radiomics signatures could identify subtle differences in prediagnostic CT scans obtained with a median of 386 days before PDAC diagnosis, with 95.5% sensitivity, 90.3% specificity, and 92% accuracy[55]. If these promising results are validated in future studies, radiologists will be able to diagnose patients significantly earlier at lower disease stages. In this scenario, a higher proportion of newly diagnosed patients will be eligible for curative surgical resection, which will have a significant positive impact on patient outcomes.

AI-assisted prediction of margin positivity

Researchers have also applied radiomics to predict the likelihood of R0 resection in several studies. As discussed earlier, there is substantial variability among radiologists in the accuracy of local staging[21,22], and this assessment becomes even more challenging after neoadjuvant therapy[16,24]. Bian *et al.*[47] extracted 1029 CT radiomics features from 181 patients with pancreatic head cancer, and the radiomics model achieved 64.8% sensitivity, 74.0% specificity, and 71.3% accuracy in the prediction of SMV margin positivity after resection. The radiomics model achieved superior performance compared to the assessment using the NCCN criteria, which achieved 38.9% sensitivity, 74.0% specificity, and 63.5% accuracy. Rigiroli *et al.* extracted 1695 CT radiomics features from the tumor and perivascular soft tissue surrounding the SMA from 194 patients with PDAC, and the radiomics model achieved 62% sensitivity, 77% specificity, and an AUC of 0.71 in predicting SMA margin positivity. In comparison, the multidisciplinary team assessment achieved 11% sensitivity, 97% specificity, and an AUC of 0.54[48]. These studies suggest that radiomics features may be predictive of R0 resection and may help select patients most likely to benefit from surgical resection (Table 2).

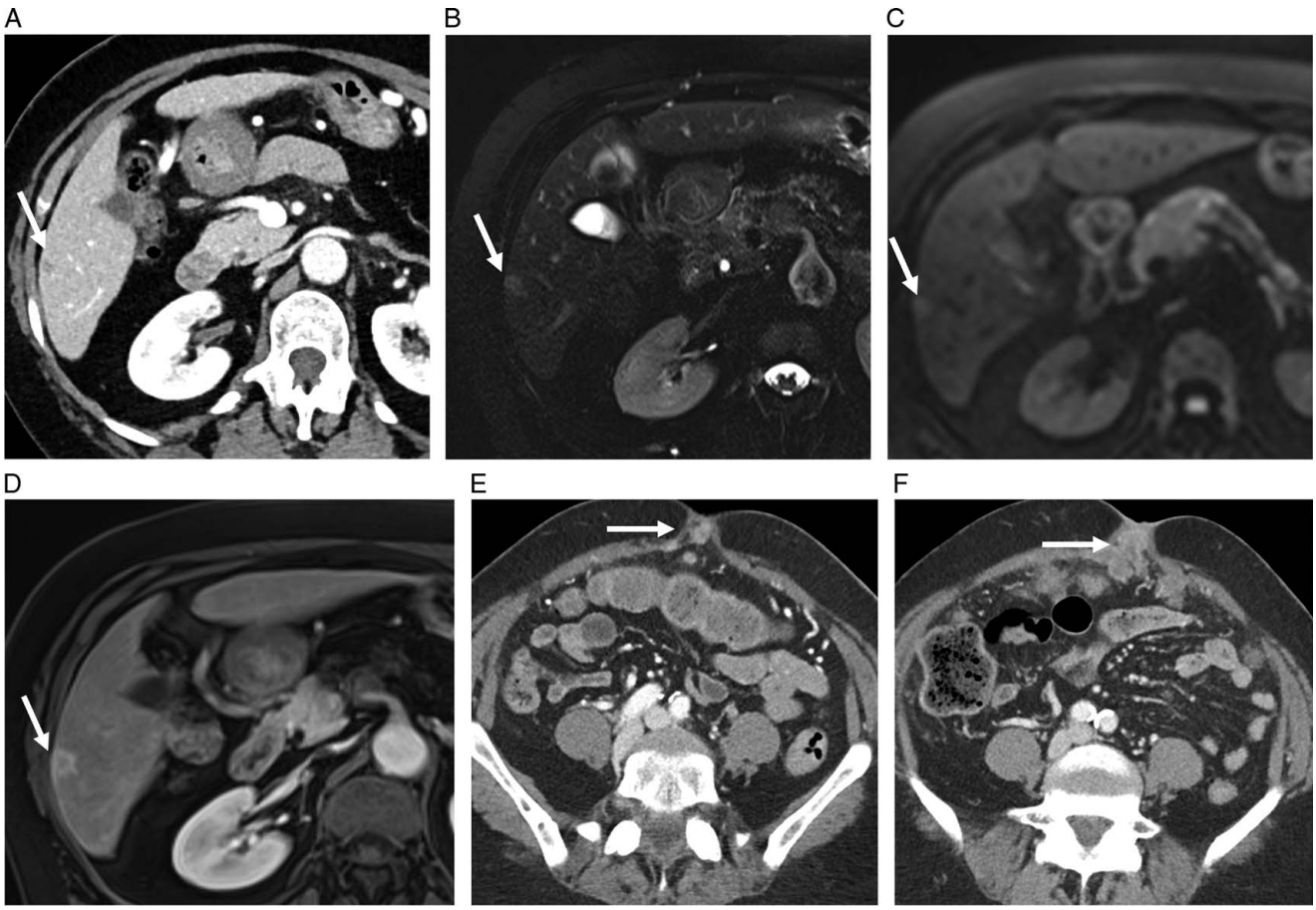

Figure 7. A 61-year-old woman with pancreatic ductal adenocarcinoma. (A) An axial intravenous (i.v.) contrast-enhanced computed tomography (CT) image in the portal venous phase showed a 5-mm indeterminate liver lesion (arrow). (B) An axial T2-weighted MR (magnetic resonance) image showed a subtle T2 hyperintense liver lesion (arrow). (C) An axial diffusion-weighted MR image showed mild diffuse restriction within the liver lesion (arrow). (D) An axial i.v. contrast-enhanced T1-weighted MR in the portal venous phase showed avid peripheral enhancement. MRI features were highly suspicious for liver metastases. Follow-up axial i.v. contrast-enhanced CT images in the portal venous phase obtained 5 months (E) and 7 months (F) later showed progressive enlargement of multiple enhancing peritoneal nodules (arrows), also known as Sister Mary Joseph nodules, compatible with peritoneal carcinomatosis.

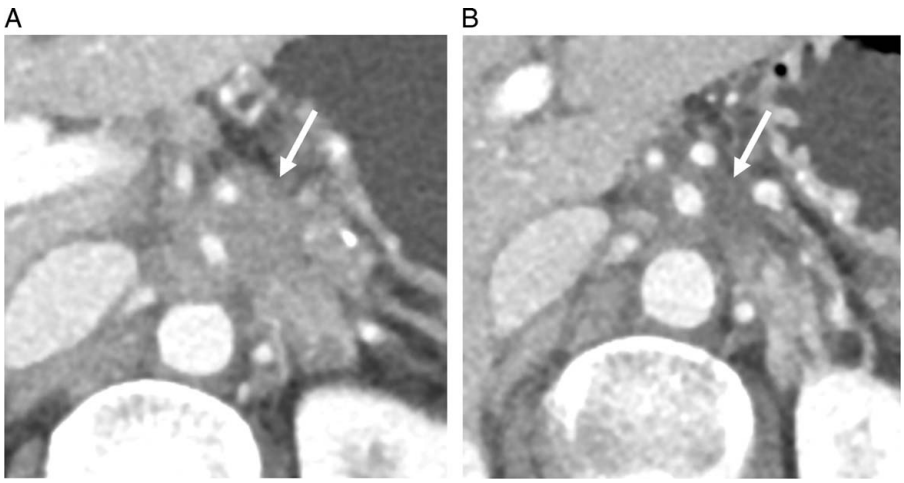

Figure 8. A 76-year-old woman with locally advanced pancreatic ductal carcinoma who underwent neoadjuvant chemotherapy. (A) Baseline axial intravenous (i.v.) contrast-enhanced computed tomography (CT) image in the portal venous phase showed a locally advanced tumor (arrow) with encasement of the celiac artery, common hepatic artery, and splenic artery. (B) Restaging CT after neoadjuvant therapy showed decreased tumor size and replacement of solid tumor contact with an ill-defined perivascular halo. The patient underwent distal pancreatectomy with a complete response on pathology examination.

AI-assisted prognostic prediction

In patients with resectable disease, accurate preoperative evaluation of lymph node status is imperative in triaging those most likely to benefit from neoadjuvant chemotherapy and proceeding to upfront surgery. As discussed earlier, current radiologic criteria based on size and morphologic features have limited sensitivity in detecting lymph node metastases. However, mounting evidence indicates that radiomics features extracted from PDAC tumor regions can help predict the presence or absence of lymph node metastases[56–59]. A recent systematic review of 14 articles using preoperative radiomics features to predict lymph node metastases in patients with PDAC revealed pooled sensitivity of 77.4%, pooled specificity of 72.4%, and an AUC of 0.79 in the validation datasets[49] (Table 2), which showed significant improvement compared to size and morphologic criteria[15]. Most existing studies required manual segmentation of the tumor boundaries, a laborious process that limited typical study sample sizes ($n < 300$). The subjectivity inherent in the segmentation of the infiltrative tumor boundaries in PDAC may also limit its reproducibility[60]. Recently, Bian *et al.*[50] developed an automated AI algorithm for the segmentation of the tumor and lymph nodes as well as the prediction of lymph node metastases in patients with PDAC. In the validation set, the AI model achieved the highest AUC (0.92) in predicting lymph node metastases, compared with CT criteria (0.65), the clinical model (0.77), and the radiomics model (0.68) (Table 2). This type of automated pipeline will improve the feasibility of future validation in large-scale prospective multicenter studies.

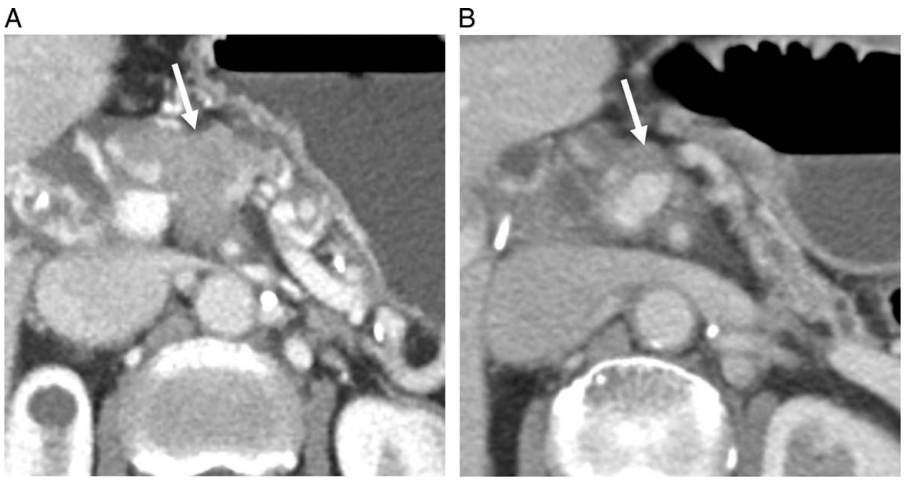

Figure 9. A 76-year-old woman with locally advanced pancreatic ductal adenocarcinoma who underwent neoadjuvant chemotherapy. (A) Baseline axial intravenous (i.v.) contrast-enhanced computed tomography (CT) image in the portal venous phase showed a locally advanced tumor (arrow) with encasement of the celiac artery, common hepatic artery, splenic artery, and portal vein. (B) Restaging CT after neoadjuvant therapy showed decreased tumor size and partial replacement of solid tumor contact with an ill-defined perivascular halo. The patient underwent distal pancreatectomy with poor to no response on pathology examination.

Table 2

Highlights of recent peer-reviewed studies of artificial intelligence in pancreatic imaging.

Clinical problem	Dataset	Imaging and machine learning technique	Model performance (AUC)	Reference
Detection of PDAC	752 PDAC 490 controls	CT; Deep learning	0.999	Liu *et al.*[44]
	1215 PDAC 1537 controls	CT; Deep learning	0.95–0.96	Chen *et al.*[45]
Detection of solid and cystic pancreatic neoplasms	377 PDAC 61 NEN 45 SPN 132 IPMN 20 MCN 46 SCN 69 Benign, unspecified 1294 controls	CT; Deep learning	0.87–0.91	Park *et al.*[46]
SMV margin positivity	181 PDAC	CT; Radiomics	0.75	Bian *et al.*[47]
SMA margin positivity	194 PDAC	CT; Radiomics	0.71	Rigiroli *et al.*[48]
Lymph Node Positivity	2453 PDAC (meta-analysis)	CT; Radiomics	0.79	Mirza-Aghazadeh-Attari *et al.*[49]
	734 PDAC	CT; Deep learning; Radiomics	0.92	Bian *et al.*[50]
Risk of liver metastases	688 PDAC	CT; Radiomics	0.71	Zambirinis *et al.*[51]
	204 PDAC	MRI, Radiomics	0.815	Huang *et al.*[52]

AUC, area under the curve; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NEN, neuroendocrine neoplasm; PDAC, pancreatic ductal adenocarcinoma; SCN, serous cystic neoplasm; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SPN, solid pseudopapillary neoplasm.

Researchers have also used radiomics features to predict the development of liver metastases after PDAC resection in multiple studies[51,52]. Zambirinis *et al.*[51] analyzed 254 radiomics features from the liver from preoperative CTs in 688 patients with resected PDAC and the radiomics model identified patients at risk for early (< 6 months) liver metastases with an AUC of 0.71. Huang *et al.*[52] extracted 3906 radiomics features from the pancreatic tumor from preoperative MRIs in 204 patients with resected PDAC, and the radiomics model achieved 75.0% sensitivity, 82.2% specificity, and an AUC of 0.815 in predicting the development of liver metastases (Table 2). We speculate that radiologic features from both the primary tumor and the liver parenchyma are important in predicting future liver metastases. Future studies should incorporate features from both the tumor and the liver, in combination with clinical features, to optimize the prediction of liver metastases.

Physicians have also used radiomics and deep learning to predict overall survival for patients with resected PDAC[61–63] to help select patients more likely to benefit from pancreatic resection. In a recent systematic review of 23 articles, 91.3% (21/23) of studies found that radiomics features were predictive of overall survival in patients with PDAC[64]. Entropy, a first-order feature and marker of tumor heterogeneity, was the most reported significant prognostic feature. However, these studies were characterized by a high risk of patient selection bias due to retrospective study designs, and few had performed external validation to ensure generalizability[64]. Disappointingly, a recent retrospective, international, multicenter study that trained the PDAC survival prediction model based on data from 352 patients from 5 Canadian hospitals and tested the model on 215 patients from 34 Irish hospitals showed poor generalizability with limited clinical utility on external validation[65]. Consequently, the promising results of these AI-assisted prognostic prediction studies should be interpreted with caution, and robust multicenter prospective validation studies are necessary before clinical translation. Current AI algorithms are narrow in scope, and hospital systems will need to deploy many algorithms concurrently. Therefore, a well-designed, vendor-neutral infrastructure based on collaboration among radiologists, data scientists, software developers, and information technology experts is critical for clinical deployment[66]. At present, there is no separate reimbursement to offset the cost of AI development and implementation. Future studies are needed to help institutions implement technologies that are cost-effective and clinically impactful.

Limitations

Preliminary studies using emerging technologies such as advanced visualization and AI have revealed the potential of these tools to improve the initial diagnosis and staging of patients with PDAC. However, there remain several limitations. Most of these studies have been single-center retrospective studies, and their promising results should be validated in future multicenter prospective studies. Secondly, one of the major criticisms of AI is its 'blackbox' nature, making it difficult for clinicians to decipher the rationale behind AI predictions. Explainable or 'glassbox' AI is an active area of research that aims to render AI models more easily understandable and may help improve their clinical acceptance. Thirdly, these tools should be integrated seamlessly into the workflow to ensure widespread clinical implementation.

Conclusion

Radiology plays a significant role in the initial diagnosis and staging of patients with PDAC, triaging patients with resectable disease, and determining treatment response to neoadjuvant chemotherapy and radiation. CT is the most used radiologic modality for PDAC staging, with MRI and PET/CT usually reserved as problem-solving tools. Current challenges in staging

include preoperative diagnosis of lymph node metastases, subtle liver and peritoneal metastases, and R0 resection following neoadjuvant therapy. Artificial intelligence offers the potential of earlier disease diagnosis at the localized disease stage and prognostic radiologic biomarkers to optimize patient management, which can help improve patient outcomes.

Ethical approval

This study has been approved by the institutional review board at Johns Hopkins University (IRB00243982).

Consent

The patients reported in the manuscript signed informed consent/authorization for participation in research that included the permission to use data collected in future research projects, including the images and figure legends used in this manuscript. Copies of the written consent are available for review by the Editor-in-Chief of this journal on request.

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Author contribution

L.C.: study design and manuscript writing; E.F.: study design and manuscript revision.

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There are no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

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Not applicable.

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