The borderline resectable/locally advanced pancreatic ductal adenocarcinoma staging with computed tomography/magnetic resonance imaging

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly fatal malignancy, and the high mortality is in large part due to the advanced stage of disease most commonly observed at the time of diagnosis.[1-3] The prognosis and treatment depend on tumor resectability, which is directly related to a timely diagnosis.[4] Surgical resection is possible only in nonmetastatic, technically resectable tumors. Unfortunately, >50% of patients have distant metastases at diagnosis. Thus, only a small percentage of patients have potentially resectable disease and may undergo surgery resection.[5-7] Moreover, 15%–30% of patients with a resectable tumor on preoperative imaging are found to be unresectable at surgical exploration.[5,8,9] This implies that a timely diagnosis and an accurate staging before surgery are crucial.[10-13] Imaging has a pivotal role in tumor detection, characterization, and staging; as such, the decision-making process for patients with PDAC is based on imaging.[14] This paper reviews the capabilities of different imaging modalities in the staging of PDAC.

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IMAGING METHODS

Imaging must provide a reliable PDAC detection, characterization, and staging. A correct timing and protocol could improve patient management.

In European and in Asian countries, ultrasound (US) is often the first noninvasive imaging method for the evaluation of the pancreatic gland, for both symptomatic and asymptomatic patients.[15] Each pancreatic solid mass detected by US has a high probability of being an adenocarcinoma, even if not all solid masses detected by US are ductal adenocarcinoma.[16] The intravenous administration of contrast media may be useful and could aid in characterizing this tumor immediately after detection.[17,18] A solid pancreatic mass with hypoechoic

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appearance on B-mode US and a hypoenhancing aspect on contrast-enhanced ultrasound (CEUS) should be considered a PDAC until otherwise proven.[15,19] Moreover, US and CEUS may be helpful if direct tumor visualization on computed tomography (CT) or magnetic resonance imaging (MRI) is hampered by the lack of typical radiological signs.[15,20-23]

Computed tomography

Multidetector computed tomography is the gold standard for ductal adenocarcinoma identification, characterization, and local staging, owing to a high spatial resolution. On CT, PDAC usually appears hypoenhancing, hypodense solid mass after contrast media administration.[16] Small pancreatic adenocarcinoma can be isodense on CT, and thus barely detectable; a false negative on CT, after US detection, would be catastrophic in the management of the patient;[21,22] nevertheless, PDACs – even if small – are frequently well detected by US/CEUS, and therefore, the addition of US/CEUS to CT can increase the accuracy in tumor detection.

The optimal CT examination protocol consists of four phases (unenhanced, pancreatic/late arterial phase, portal/venous phase, and late phase). The late phase could be useful in the detection of isodense small pancreatic adenocarcinoma.[24]

Magnetic resonance imaging

MRI may be used for the detection of PDAC, nevertheless with a lower spatial resolution than CT. On MRI, PDAC is usually hypointense on T1-weighted images, due to its high fibrotic component and marked desmoplasia;[25,26] while on T2-weighted images, it has a variable signal intensity, but it is mainly slightly hypointense with respect to the surrounding pancreatic parenchyma. MRI has a lower spatial resolution compared with CT; nevertheless, literature data suggest that local staging using MRI can achieve the same results of CT. There are no statistically significant differences between CT and MRI in detection, characterization, and local staging of PDAC.[27,28] However, MRI seems to be more accurate than CT in the evaluation of small liver PDAC metastases.[29] Diffusion-weighted imaging (DWI) is a relatively new MRI technique that enables the identification of random diffusivity of water molecules within biological tissues, owing the ability in differentiating between normal pancreatic parenchyma and solid tumors in 92% of cases[30] due to the hyperintensity signal from the pancreatic adenocarcinoma in the diffusion images with low values in apparent diffusion coefficient maps. Thus, DWI can improve PDAC detection. In addition, this sequence can help detect metastases in the liver and in other organs. MRI is more accurate than CT in the detection of small pancreatic adenocarcinoma and in liver staging.[29,31]

IMAGING STANDARDS AND ACCURACY

The National Comprehensive Cancer Network (NCCN)[32] has proposed a staging system for PDAC based on tumor extension, along with the recommendations for treatment according to tumor stage. The NCCN criteria define resectability status based on the Americas Hepato-Pancreatico-Biliary Association consensus report.[10,11,33-35]

In the absence of distant metastases, PDAC is classified into three main categories: resectable, borderline resectable, and locally advanced or un-resectable. Although theoretically the distinction between borderline resectable and locally advanced disease can be conceptually simple,[29,36] the precise definition has been variable and may be based on the imaging or clinical criteria. The final definition of borderline resectable pancreatic cancer as reported is more than an anatomical concept.[37] Biologically defined borderline-resectable tumors are those that, despite technical resectability, are likely to have an unfavorable biology. Technically defined borderline tumors, instead, are those involving peripancreatic vessels to a limited extent, for which surgical resection would likely to be compromised by a positive resection margin (R1 or R2).[38] For locally advanced PDAC, it has been demonstrated that neoadjuvant combined chemotherapy and radiation therapy allows downstaging in approximately 30% of patients,[39,40] being able to achieve R0 surgical resections in some cases.[41] As a consequence, it is very important to assess correct staging in terms of vessel involvement and the presence of distant metastases, both before and neoadjuvant therapy. The positive predictive value of CT in determining the unresectability of PDAC is very high (89%–100%), but it is lower for predicting resectability (45%–79%),[10,11] especially after neoadjuvant therapy, mainly due to small liver or peritoneal metastases. In the scientific literature, some studies have shown that up to 20% of patients classified as having resectable disease before surgery actually have CT-occult metastatic disease found at laparoscopy or laparotomy.[42-45] Regarding vessel infiltration, CT may be useful in the estimation

of the length and the circumferential extension of vascular infiltration, but it is not so accurate in the detection of focal vessel infiltration. To overcome this limitation, in local staging, US could be very useful due to its high spatial resolution. In particular, endoscopic US provides the highest accuracy for the evaluation of tumor-vessel relationships. When compared to peripancreatic vessels, the US conspicuity of PDACs is very high. On normal condition, the vessel lumen is anechoic; when vascular infiltration is present, tumor detectability is improved, and PDAC can be seen as solid echoic tissue interrupting the vessel wall.

The second issue in determining tumor resectability is to rule out the presence of distance metastases. MRI has high accuracy in detecting liver metastases, even if of small dimensions, with a sensitivity of up to 100%, compared with up to 80% sensitivity of CT.[41,46] Moreover, Teadwell *et al.*[47] suggested that MRI and CT are equivalent for the assessment of vascular invasion and infiltration. Furthermore, MRI has demonstrated significantly greater tumor conspicuity of small PDAC, which may be isodense in respect to the adjacent parenchyma at CT studies, obtaining good performance in the preoperative evaluation of these tumors.[28,41,48]

Despite the fact that CT is more widespread, cheaper, and more tolerated by patients than MRI, the latter is recognized by the NCCN as an important tool, in particular, as a second-line study added to CT in high-risk patients in which CT shows negative findings for metastatic disease, while the clinical suspicion is very high, or in patients with small or doubtful liver lesions on CT.[33,41]

PREOPERATIVE IMAGING STUDY

In a personal retrospective series of about 300 surgical procedures for PDAC, 149 were studied with CT and MRI. The accuracy of CT and MRI were similar regarding tumor resectability. Regarding detection of liver metastases, the only statistical significant values, due to numerosity, were found in MRI studies, which showed a sensitivity, positive predictive value, and accuracy of 93.75%, 95.07%, and 89.68%, respectively. When MR results were compared to intraoperative findings, concordance in metastases detection was found to be linked to the timing of scanning. In particular, concordant examinations were performed 17.83 ± 1.33 days before surgery, whereas discordant examinations were conducted 27.71 ± 4.23 days before surgery [Table 1].

Table 1. Mean time between exams and surgery

Days before surgery (metastasis)	MRI
Unpaired *t*-test	
P	0.0166
t; df	2.423; 154
Mean±SEM of C	17.83±1.328, *n*=139
Mean±SEM of D	27.71±4.277, *n*=17
Difference between means	9.879±4.077
95% CI	1.824-17.93

MRI: Magnetic resonance imaging, SEM: Standard error of mean, C: Concordance, D: Discordance, CI: Confidence interval

CONCLUSIONS

The final definition of borderline resectable pancreatic cancer is more than an anatomical concept, being related to both clinical and imaging findings. Technically, borderline tumors are those tumors that involve vessels to a limited extent considering that vein involvement has a less effect on the results of resection compared to arterial vessels. CT and MRI are equivalent for local staging. The exclusion of liver metastases is an indispensable condition for defining borderline resectable pancreatic cancer. MRI is superior to CT in detecting liver metastases, especially when performed strictly before surgery.

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