

How new technologies could impact on radiology diagnosis and assessment of pancreatic lesions: Future perspectives

Andrea Laghi, Marta Zerunian, Damiano Caruso

Department of Radiological Sciences, Oncology and Pathology, Sant'Andrea Hospital, Sapienza-University of Rome, Rome, Italy

INTRODUCTION

Advances in cross-sectional imaging technology have made a detailed assessment of pancreatic gland possible, despite the deep anatomical location. Although many focal solid lesions are incidentally detected during an abdominal ultrasound, their characterization is still an important diagnostic issue. In fact, despite the availability of computed tomography (CT), magnetic resonance (MR), and positron emission tomography (PET), differential diagnosis between benign, precancerous, or cancerous lesions still has some degree of uncertainty. According to a recent Cochrane meta-analysis, none of these modalities has significantly higher sensitivity and specificity than the others.^[1] Thus, for correct characterization, patients are often referred to EUS with fine-needle aspiration, which, unfortunately, is not widely available.

Another diagnostic problem, recently come to the attention of radiologists, is the evaluation of the response to neoadjuvant therapy of pancreatic ductal adenocarcinoma (PDAC). It has been recently

demonstrated that CT diagnostic performance to predict R0 resectability decreases from 83% to 58% after neoadjuvant therapy, underlining the limitations of a simple morphologic analysis.^[2]

Those are the two main areas of pancreatic imaging where improvement is necessary and where technological innovations may help radiologists to obtain better diagnostic performances. The key is the shift from morphologic to functional imaging and from qualitative to quantitative analysis. In this area, perfusion and diffusion imaging are at the moment the best available options and those closest to be used in clinical practice. In this brief review, we will discuss current evidence of perfusion and diffusion in pancreatic imaging, and we will touch on the future perspective of quantitative imaging, namely, radiomics.


CURRENT TECHNICAL INNOVATIONS

Magnetic resonance imaging perfusion

The assessment of tumor perfusion by MR includes different techniques. In particular, for

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Address for correspondence

Prof. Andrea Laghi, Department of Radiological Sciences, Oncology and Pathology, Sant'Andrea Hospital, Sapienza-University of Rome, Via Di Grottarossa 1035, 00189, Rome, Italy. E-mail: andrea.laghi@uniroma1.it

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abdominal imaging, dynamic contrast-enhanced MR imaging (DCE-MRI) has been widely studied.^[3] DCE-MRI evaluates tissue changes on T1 signal at specific times after dynamic intravenous injection of gadolinium chelate.^[3] A simple time-intensity curve is derived from the acquired data, and semi-quantitative or quantitative (perfusion) analysis is subsequently performed. Perfusion analysis generates quantitative parameters which reflect different aspects of tissue vascularity. In particular, K^{trans} measures the volume transfer constant from arterial blood to extravascular extracellular space, and it is a reliable method to assess vessel permeability.^[3] K^{trans} is becoming relevant in the assessment of tumor response to therapy, in particular following antiangiogenic drugs. Akisik *et al.* showed, in a small cohort of patients, how K^{trans} can predict response to combined chemotherapy and antiangiogenic therapy in pancreatic tumors with a reduction of perfusion parameters after successful treatment.^[4] DCE-MRI can also improve the early diagnosis of PDAC, as shown by Yang *et al.* in a small population of 33 patients.^[5] So far, no data regarding pancreatic lesions characterization are available, and thus, further studies are needed.

Computed tomography perfusion

CT perfusion is another method to assess tissue vascularity. Despite radiation exposure, CT perfusion has the main advantage of the linear relationship between Hounsfield Units and tissue iodine concentration, making calculation of perfusion parameters easier than with MR.^[3] Among quantitative perfusion parameters, the ones most commonly used to characterize pancreatic lesions and to evaluate the response after chemoradiotherapy are K^{trans} (see the previous paragraph), blood flow (BF), and blood volume (BV). BF expresses the BF rate through the tissue vasculature, whereas BV indicates the volume of blood flowing within the functioning tissue vasculature.^[6]

Yadav *et al.* assessed perfusion CT parameters in patients affected by PDAC in comparison to those with mass-forming chronic pancreatitis (MFCP), which have similar CT features on morphologic analysis.^[7] CT perfusion can help to discriminate different pancreatic masses by exploiting their perfusion characteristics, not assessable by conventional multiphase CT which provides only tissue density information. Results showed a significant difference between PDAC and MFCP in parameters such as BF and BV. In particular, PDAC showed 45.3% lower BF and 43.6% lower BV compared to MFCP. In addition, to differentiate PDAC

from MFCP, cutoff values of 19.1 ml/100 g/min for BF and 5 ml/100 g for BV were identified, with respective sensitivities and specificities of 100% and 73.8% for BF and 92.3% and 67.9% for BV. Thus, CT perfusion is able to help in the differential diagnosis of pancreatic solid masses although further studies will be necessary to make this technique more robust and applicable on a larger scale.

Dual-energy computed tomography perfusion

Dual-energy CT (DECT) is a technique that allows to acquire datasets at two different photon spectra and permits to distinguish different materials and to extract iodine maps with material decomposition algorithms.^[8] The use of DECT has potential clinical implications for pancreatic imaging.

Yin *et al.* performed a single-center study on 35 patients and showed that DECT is able to differentiate MFCP from PDAC through normalized iodine concentrations both on arterial and pancreatic parenchymal phases.^[9] In addition, significant differences were observed in the value of the slope K of the spectrum curve. Regarding the assessment of PDAC after chemoradiotherapy, a preliminary study was performed by Kawamoto *et al.* suggesting the possible role of DECT for posttherapy assessment through tumor iodine uptake quantification.^[8] Advantages of DECT over CT perfusion are in the easier technical approach (DECT perfusion data can be derived from any DECT acquisition protocol without the need for an additional dedicated scan) and in lower patient radiation exposure. However, more data are needed to confirm these preliminary observations.

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is a sophisticated MR technique whose signal originates from the Brownian motion of water molecules at the cellular level. DWI allows to evaluate vascular and microstructural changes in a tissue, without radiation exposure or intravenous injection of contrast medium.^[10] Tissue cellularity and cell membrane status are main determinants of tissue signal which is able to discriminate different entities such as neoplastic lesions, cytotoxic edema, and abscess.

Despite initial enthusiasms, due to the fact that many studies reported a clear difference in signal intensity at DWI between PDAC and the normal

pancreatic gland,^[11] more recent data report that up to 47% of pathologically confirmed PDAC are not clearly distinguishable from surrounding pancreatic parenchyma, due to the concomitant tumor-associated acute pancreatitis.^[12] Thus, DWI does not improve PDAC detection compared with conventional MR techniques.

For lesion characterization, no data are available for DWI in the differential diagnosis between PDAC and MFPC. However, DWI improves characterization between benign and malignant intraductal papillary mucinous neoplasms as demonstrated by Jang *et al.*^[13]

A more sophisticated and quantitative approach with DWI is represented by intravoxel incoherent motion (IVIM)-derived perfusion-related parameters. In conventional DWI, microscopic microcirculation (perfusion) and diffusion are merged in the single measurement named apparent diffusion coefficient (ADC). On the contrary, IVIM is a model that separates capillary microcirculation from molecular diffusion using multiple b-values.^[3] The most extensively studied IVIM-derived parameters are true diffusion (D), pseudo-diffusion coefficient (D*), and perfusion fraction (f). Interesting data regarding pancreatic lesion characterization are reported by Hecht *et al.* who observed a moderate correlation between histopathology and DWI in the assessment of fibrosis in PDAC;^[14] in particular, DWI negatively correlates with fibrosis, with a positive trend correlation with f, suggesting both perfusion and diffusion effects contribute to stromal desmoplasia. Moreover, ADC was significantly lower in tumors with dense fibrosis and may be used as a biomarker of characterization of PDAC internal architecture in the case of fibrotic content.

An important issue potentially assessable by DWI and derived IVIM parameters might be the assessment of the response to chemoradiotherapy. In fact, due to apoptosis and necrosis, tumor cell density decreases and water content increases with consequent higher ADC and lower DWI values; these changes might be observed in responding tumors earlier than volumetric changes [Figure 1a-d]. Promising data were observed in other abdominal studies, while few data are available for pancreatic tumors.^[15,16]

Positron emission tomography-computed tomography
PET/CT represents a hybrid imaging technique combining functional and morphologic imaging. Glucose

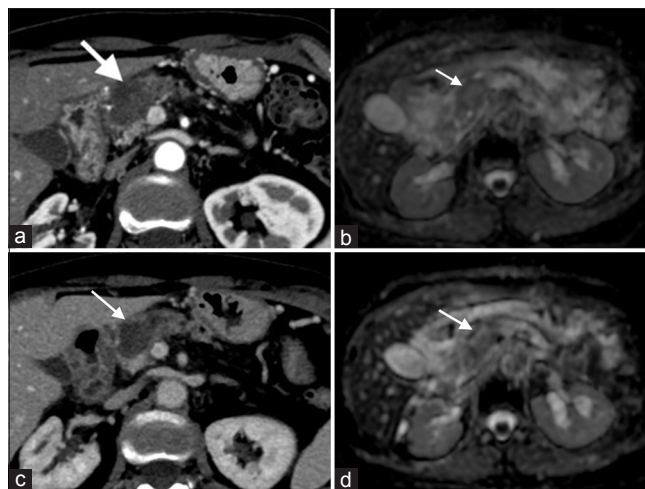


Figure 1. (a) Contrast-enhanced computed tomography scan at the time of the diagnosis. A large pancreatic ductal adenocarcinoma was detected in the pancreatic head (arrow). (b) Magnetic resonance imaging: apparent diffusion coefficient map showing relative diffusion restriction indicating viable tumor (arrow). (c) Contrast-enhanced computed tomography scan following radiotherapy. Pancreatic ductal adenocarcinoma did not show significant size reduction (arrow). (d) Magnetic resonance imaging: apparent diffusion coefficient map following radiotherapy showed a slight increase in signal intensity indicating a response to therapy (arrow)

analog ¹⁸F-fluorodeoxyglucose as metabolic tracer enables to recognize active metabolic areas such as in tumors or in infections.^[17]

The most common quantitative parameter analyzed is the maximum standardized uptake value, which quantifies the glucose metabolic uptake of tumoral cells.

PET/CT is extensively used in diagnosing, staging, and post-therapy follow-up of PDAC.^[16,17] A recent meta-analysis performed by Zhu *et al.* emerges the role of PET/CT as a prognostic factor to predict overall survival and event-free survival in PDAC.^[17] However, large heterogeneity of the studies decreases the statistical power of the analysis, and the authors concluded that larger and multicenter studies are necessary to strengthen the results and clinical applications.

FUTURE PERSPECTIVES

New frontier of imaging is not only to explore deeply microscopic structure of a lesion, as with perfusion and diffusion, but also to shift from qualitative to quantitative data analysis, as it is achieved with radiomics. Radiomics consists in the conversion of digital medical images (derived from US, CT, MR, and PET) into mineable high-dimensional data. Among

different radiomics methods, texture analysis is an example of analysis that measures tumor heterogeneity and reveals quantitative information expressed as mathematical parameters. Kurtosis, entropy, and skewness, the parameters most largely investigated, have been shown to correlate with lesion perfusion, hypoxia, and other biological features.^[18] The next step is to merge radiomics data with molecular analysis and generate radiogenomics analysis, with the ultimate goal to improve personalized medicine.

An important contribution in this novel analysis, to assess pancreatic lesions, was achieved by Canellas *et al.*, showing the predictive role of entropy as texture parameter in the discrimination of aggressiveness and early disease progression of pancreatic neuroendocrine tumors on CT scan.^[19] Furthermore, a variation of texture parameters reflects corresponding tissue changes after chemoradiotherapy as described by Chen *et al.*^[20]

CONCLUSIONS

Advances in technology have the potential to address the most relevant diagnostic questions related to pancreatic imaging, *i.e.*, accurate lesion characterization and early assessment of response to treatment of PDAC. However, before those new technologies can be used in clinical practice, further prospective and controlled studies are advisable. In particular, for radiomics development, collection of large and standardized, high-quality data, will be necessary. The ultimate goal of these efforts is to move forward to personalized imaging, which is one of the pillars of personalized medicine.

Conflicts of interest

There are no conflicts of interest.

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