Review Article on Multimodality Advanced Imaging and Intervention in Gland Disease

New advances in CT imaging of pancreas diseases: a narrative review

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Abstract: Computed tomography (CT) plays a pivotal role as a diagnostic tool in many diagnostic and diffuse pancreatic diseases. One of the major limits of CT is related to the radiation exposure of young patients undergoing repeated examinations. Besides the standard CT protocol, the most recent technological advances, such as low-voltage acquisitions with high performance X-ray tubes and iterative reconstructions, allow for significant optimization of the protocol with dose reduction. The variety of CT tools are further expanded by the introduction of dual energy: the production of energy-selective images (i.e., virtual monochromatic images) improves the image contrast and lesion detection while the material-selective images (e.g., iodine maps or virtual unenhanced images) are valuable for lesion detection and dose reduction. The perfusion techniques provide diagnostic and prognostic information lesion and parenchymal vascularization and interstitium. Both dual energy and perfusion CT have the potential for pushing the limits of conventional CT from morphological evaluation to quantitative imaging applied to inflammatory and oncological diseases. Advances in post-processing of CT images, such as pancreatic volumetry, texture analysis and radiomics provide relevant information for pancreatic function but also for the diagnosis, management and prognosis of pancreatic neoplasms. Artificial intelligence is promising for optimization of the workflow in qualitative and quantitative analyses. Finally, basic concepts on the role of imaging on screening of pancreatic diseases will be provided.

Keywords: Pancreas; dual energy CT; perfusion CT; CT quantitative; texture analysis

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Introduction

Modern multidetector computed tomography (MDCT) scanners acquire the entire abdominal volume and provide high-resolution images within seconds. CT is widespread, relatively cheap, and allows for panoramic examinations with high diagnostic performance. For these reasons, CT plays a central role in the evaluation of pancreatic diseases and their complications, from the evaluation of pancreatitis, trauma, and for the management of disease with different degree of malignancy [(e.g., neuroendocrine tumors (NET)

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and pancreatic ductal adenocarcinoma (PDAC)] (1-7).

Conversely, magnetic resonance imaging (MRI) with MR-cholangiopancreatography is considered the imaging modality of choice, and a problem-solving tool for the evaluation of pancreatic diseases, thanks to the optimal contrast resolution of soft tissues, biliary and pancreatic ducts, as well as for the differentiation of pancreatic lesions to fibrosis after chemoradiation therapy, all in absence of radiation exposure (8,9). At the same time, CT demonstrates its drawbacks with lower accuracy in the detection of small lesions and cystic lesions, in the differentiation of residual PDAC from fibrosis after chemotherapy or radiotherapy, in the differentiation of PDAC, and in detection chronic pancreatitis and of ductal injuries (2,4,10-12). Moreover, the radiation exposure still represents a significant issue in young patients requiring serial examinations in follow-up (13-15).

However, the most recent advances in CT technology, such as Dual-Energy CT (DECT), perfusion CT (PCT), and the application of Radiomics and Artificial Intelligence (AI) are promising techniques for improving the diagnostic performances by moving the limits of CT from qualitative to quantitative imaging (16).

In this paper, an overview on the recent advances in pancreatic CT with the main clinical applications will be provided. After a brief summary on the current CT technique, the main applications of DECT, PCT, Texture Analysis, Radiomics and AI will be discussed. Finally, basic concepts on the role of imaging in the screening of pancreatic diseases will be provided. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/gs-20-551).

Research strategy

The research strategy involved the online databases "PubMed" (https://pubmed.ncbi.nlm.nih.gov/) and "Scopus" (https://www.scopus.com/). The searching strategy included the following keywords: Pancreas, CT, Protocol, Dual Energy, Perfusion, Radiomics, Radiogenomics, Artificial Intelligence, Screening. Papers in English published between January 1980 and May 2020 were included for review. Proceedings' abstracts were excluded from this review.

The CT study of the pancreas: the standard protocol

The CT evaluation of the pancreatic lesions requires the administration of intravenous contrast material and a biphasic acquisition during the late arterial—pancreatic phase, and during the portal venous phase (17). The pancreas has a conspicuous arterial supply: the highest contrast enhancement between 35 and 45 s after the injection of the contrast bolus and the peak is at nearly 40 s (18). For these reasons, the early arterial phase is not routinely indicated in pancreatic studies, with the exception of angiographic studies (17,19). Thus, the best contrast-to-noise ratio (CNR) between hypoattenuating lesions, pancreatic parenchyma and peripancreatic vessels is achieved in the pancreatic phase (35–40 s after the injection of the bolus) (18,20). Conversely, the best CNR for hypoattenuating liver metastases and the best visualization of venous structures without artifacts is achieved during the portal venous phase, after 55–60 s since the bolus injection (20,21).

The standard CT protocol can be optimized in several ways. First, while the suggested injection rate of contrast material is 3–5 mL/s, higher fluxes (up to 8 mL/s) allow for earlier and better contrast enhancement of pancreatic parenchyma (22). Similarly, high-concentration contrast materials and doses tailored on body weight significantly improve the contrast enhancement of pancreatic parenchyma (23,24). Finally, the use of bolus tracking techniques allows for further optimization of the contrast enhancement (22).

The split-bolus technique consists in the acquisition of only one post-contrast phase after the administration of two boluses separated by a nearly 35 seconds interval, in order to obtain the pancreatic and portal venous phase in the same image with consequent reduction of radiation exposure (25).

Some authors suggested the additional administration of oral contrast agent to provide adequate gastric and duodenal distention. Rather than iodine, neutral oral contrast agent such as water is preferred (22,24).

Recent advances in pancreatic CT: acquisitions at low voltages and iterative reconstructions

The acquisitions at low voltages have two aims: the improvement of contrast enhancement and CNR, together with dose reduction (17).

The low voltages in CT aim to provide X-ray spectra with an energy the closest as possible to the k-edge of iodine, which is 33.2 keV, with significant increase of photoelectric absorption and iodine attenuation. However, by lowering the voltage, the contrast increases together with the noise. To compensate the increased noise, a higher tube current is necessary (26). Indeed, the spreading of low-

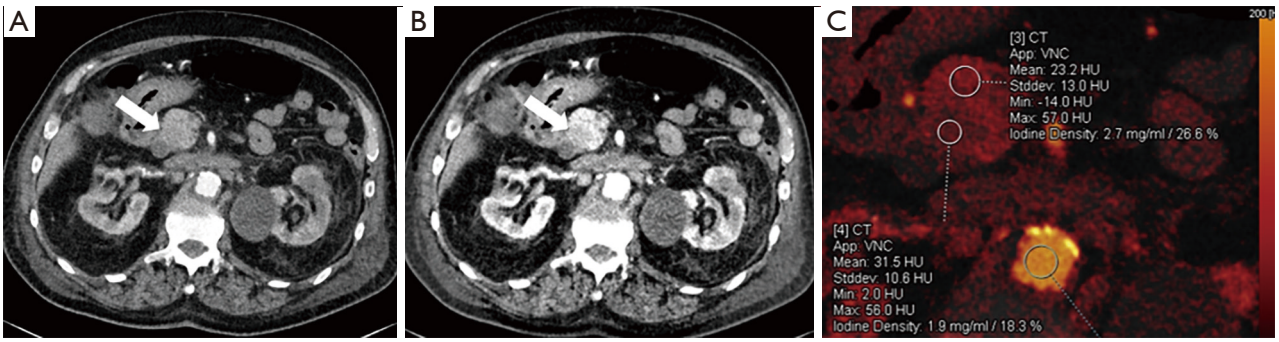

Figure 1 CT of pancreatic ductal adenocarcinoma (PDAC); male, 78 y.o. Dual energy acquisition, 100/150 Sn kV, pancreatic phase (Somatom Force, Siemens Healthineers, Forcheim). (A) Mixed image 0.7. (B) monochromatic plus 45 keV. (C) iodine map. The arrows point the hypo-attenuating lesion on the pancreatic head. Note the improved contrast resolution of the lesion on the monochromatic image at 45 keV (B). The iodine map shows lower iodine uptake of the pancreatic lesion compared to the remnant pancreatic parenchyma (C).

voltage acquisitions is related the newer generation, high-performance X-ray tubes, capable to deliver high current (up to 1,200 mA) at low voltages (down to 70 kV); the automatic current modulation can be adopted to further decrease the radiation dose (27,28).

The low-voltage acquisition protocols have demonstrated promising results in pancreatic imaging. Several studies recorded both improved contrast enhancement and conspicuity of PDCA, with acceptable image quality, when the low-voltage acquisition protocols are used (29-31).

The optimization of low-dose protocols strongly relies on iterative reconstructions (IR). These algorithms have different architecture: the shared aim is the selective suppression of image noise with improvement of image quality and contrast (32). The application of IR showed promising results in depiction of pancreatic duct (33,34). However, some authors raised concerns related to the altered image texture when the IR algorithms are applied, with potential issues in the so-called low contrast recognition tasks (35,36).

Together with improvement in contrast enhancement and lesion conspicuity, the low-voltage acquisitions allow for reduction of radiation exposure. When compared to standard 120 kVp, the low-dose acquisitions reduce the radiation exposure by nearly 25%, further decreased by the IR (37,38). The selective noise suppression achieves acceptable image quality and lesion conspicuity at reduced doses (30,39); however, some issues remain in obese patients (17).

Dual energy CT: qualitative and quantitative evaluations

After the introduction of the first dual energy (DECT) scanner in 2006, several different technologies have been developed, relying on tube technology (Dual Source, Fast kV Switching, and Split Filter) or on detectors (Dual Layer) (40). The photon counting technology belongs to the second group, but still not commercially available (41).

The DECT consists in acquisitions of the same volume at two different voltages (40,42). The theoretical bases of DECT assume that any material can be detected and quantified if its spectral curve is known and observed at least from two points of view (i.e., the different acquisition voltages). Once the material is detected, it can be quantified or selectively subtracted (material-selective images, e.g., iodine maps and virtual unenhanced, VUE). Moreover, a virtual monochromatic X-ray beam can be simulated to irradiate the known material with the known spectral curve and quantity, the so-called energy-selective images (e.g., virtual monochromatic images) (40).

The monochromatic images are one of the main applications of DECT in pancreatic imaging: a virtual beam close to the k-edge of iodine significantly improves the contrast enhancement (40). In pancreatic CT, the monochromatic images at low keV (<65 keV) improved lesion detection and conspicuity of PDAC, in particular when compared to standard 120 kVp images (*Figure 1*) (43-45). Similarly low-voltage acquisitions, the visualization of pancreatic duct is improved with monochromatic images at low keV (*Figure 2*); this is valuable in chronic pancreatitis (46). Another application of monochromatic images at low keV is the optimization of contrast enhancement, with the possibility of post-processing in case of inadequate contrast bolus injection or with the aim of contrast dose reduction in patients with impaired renal function (47,48). A relatively

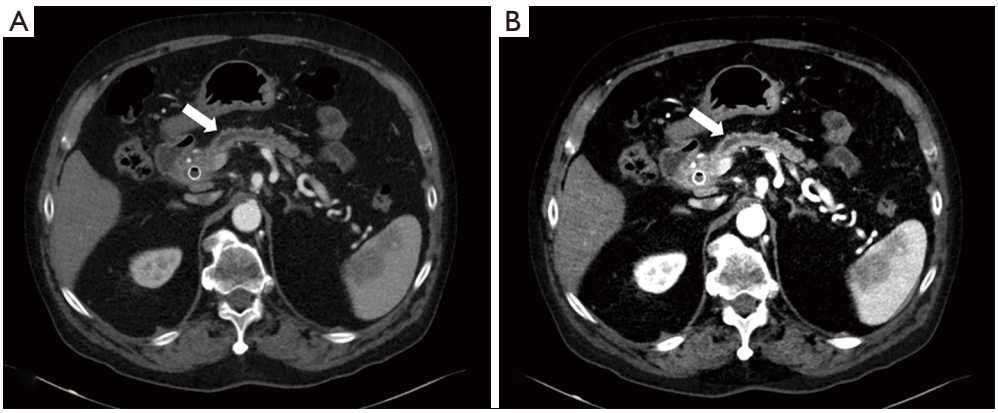

Figure 2 CT of pancreatic ductal adenocarcinoma (PDAC) in presence of biliary stent; male, 75 y.o. Dual energy acquisition, 100/150 Sn kV, pancreatic phase (Somatom Force, Siemens Healthineers, Forcheim). (A) Monoenergetic plus at 70 keV. (B) Monoenergetic plus at 45 keV. Image shows the better depiction of pancreatic duct at low keV in B (white arrows).

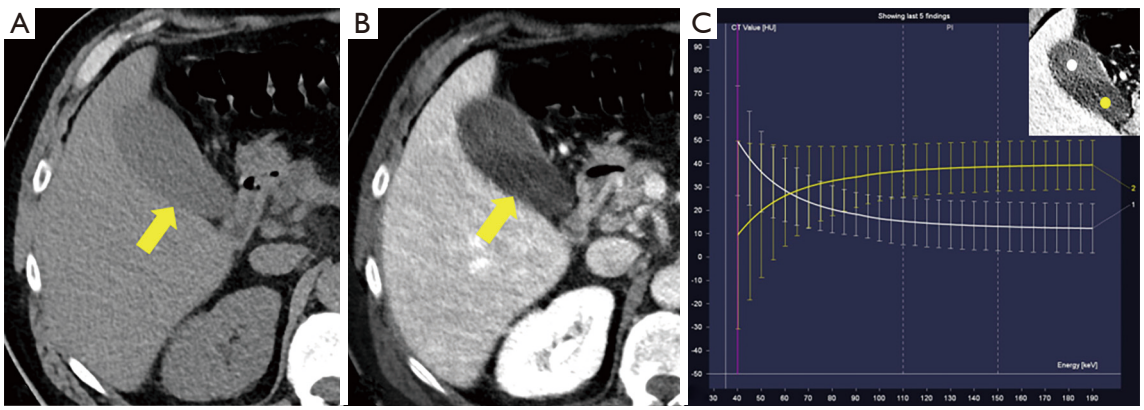

Figure 3 Biliary hypo-attenuating microlithiasis of the galldbladder; male, 48 y.o. Dual energy CT, basal acquisition at 120 kV and portal venous phase at 100/150 Sn kV (Somatom Force, siemens Healthineers, Forcheim). (A) basal acquisition at 120 kV. (B) monoenergetic plus at 40 keV, portal venous phase. (C) spectral curves of the gallstones (yellow) and bile (i.e., water, white). The hypoattenuating gallstones are not clearly detected at 120 kV (A) while they are depicted as hypodense at 40 keV (B) (yellow arrows); the attenuation profile of gallstones is confirmed by the yellow spectral curve in c.

interesting application of energy-selective images is the spectral analysis of the biliary content of gallbladder. The spectral curve of hypo-attenuating gallstones, poorly detectable on CT, presents a slope typically opposite to water at low-keV: this may be relevant in patient with acute biliary pancreatitis (*Figure 3*) (49). Conversely, the monochromatic images at high keV may be helpful in the management of streaking artifacts in patients with biliary prostheses (12). The monochromatic images also improve the detection of liver metastases, both hypervascular and hypovascular, while staging the PDAC in CT (50,51). A drawback of monochromatic images in previous generation Dual Source scanners was the increased noise at low keV, significantly affecting the image quality and lesion detection when compared to low-voltage acquisitions (52). This issue was overcome with the introduction of noise-optimized monochromatic images (53): the advantage on the low-voltage acquisition is the relatively low influence of patient's size on image quality of monochromatic images (54).

In pancreatic CT, the iodine maps and VUE reconstructions are the most-used, material-selective images (17,55). The qualitative and quantitative evaluation of iodine maps are useful for parenchymal evaluation, lesions detection and characterization, with potential use for the

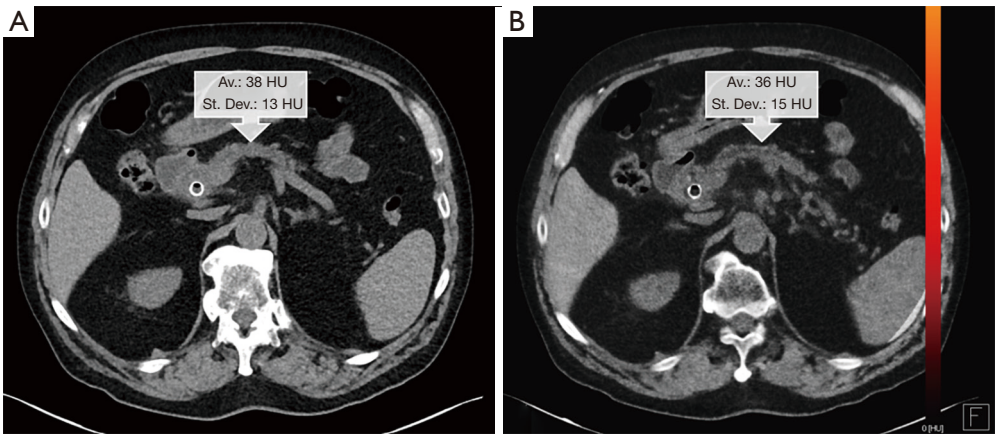

Figure 4 CT of pancreatic ductal adenocarcinoma (PDAC) in presence of biliary stent; same patient of *Figure 2*. Dual energy acquisition, 100/150 Sn kV, pancreatic phase (Somatom Force, Siemens Healthineers, Forcheim). (A) Basal acquisitition at 120 kV. (B) Virtual Unenhanced Image. The Virtual Unenhanced Images (B) are of acceptable image quality with similar attenuation values when compared to the standard, basal acquisition (A). Av., average attenuation in HU. St. Dev., standard deviation.

evaluation of treatment response to systemic treatments of PDAC. The iodine maps can be helpful in the differentiation of hyper-attenuating debris or hemorrhage from the residual parenchyma in acute pancreatitis or trauma (56). Regarding the lesion detection, the iodine maps have shown promising results in reader's confidence for tumor detection and vascular involvement (*Figure 1*) (45). The iodine quantification has shown high sensitivity (up to 93.3%) and specificity (up to 89.5%) in discrimination of PDAC from mass-forming pancreatitis (57). Regarding hypoattenuating lesions, the demonstration of iodine uptake (e.g., >1 mg/mL) is helpful for the differentiation between solid and cystic lesions; among cystic lesions, the iodine quantification provides useful information about signs of malignant transformation, such as the presence of solid nodules (58). Moreover, the discrimination of an intrapancreatic accessory spleen may represent a diagnostic challenge: the iodine maps are helpful in highlighting the different contrast enhancement of hypervascular pancreatic lesions (17). Finally, variations of iodine uptakes showed promising results in the evaluation of treatment response of PDAC (59).

The VUE images are other material-selective images used in pancreatic imaging. The selective subtraction of iodine from post-contrast acquisitions has the potential for reduction of radiation exposure by avoiding the basal acquisition (40). The VUE have provided acceptable image quality in several studies with good correlation between the attenuation values of VUE and the reference basal acquisitions (*Figure 4*) (60-62). Thus, using VUE as an acceptable substitute of basal acquisitions, a minimum dose reduction of 21% is possible (62). Some authors found a partial subtraction of calcifications in gallstones in VUE; the diagnostic performance for pancreatic calcifications requires further validation (63).

It has to be pointed that in pancreatic imaging, the use of DECT and what phase should be acquired with this technique, is still under debate (64). However, since the latest generation of DECT scanners are almost dose-neutral, dual energy acquisitions are advised for pancreatic CT (48,65).

Quantitative CT: perfusion

The perfusion study consists in multiple, post-contrast acquisitions with high temporal resolution (12,17). Perfusion studies require the administration of a relatively small bolus of contrast material (12–18 g of iodine) with a high injection rate (≥4 mL/s) and a medium-to-high concentration (>300 mg/mL). The CT acquisition can be divided in two phases: the first pass requires the entire volume to be scanned with a temporal resolution ≤2 s for 45 s; the interstitial phase requires a temporal resolution of 5–15 s (the duration and temporal resolution of the interstitial phase depends on the kinetic model applied for post-processing) (66).

The post-processing of the sequential acquisitions allows for the extrapolation of quantitative parameters such as the blood volume (BV), the blood flow (BF), the time to

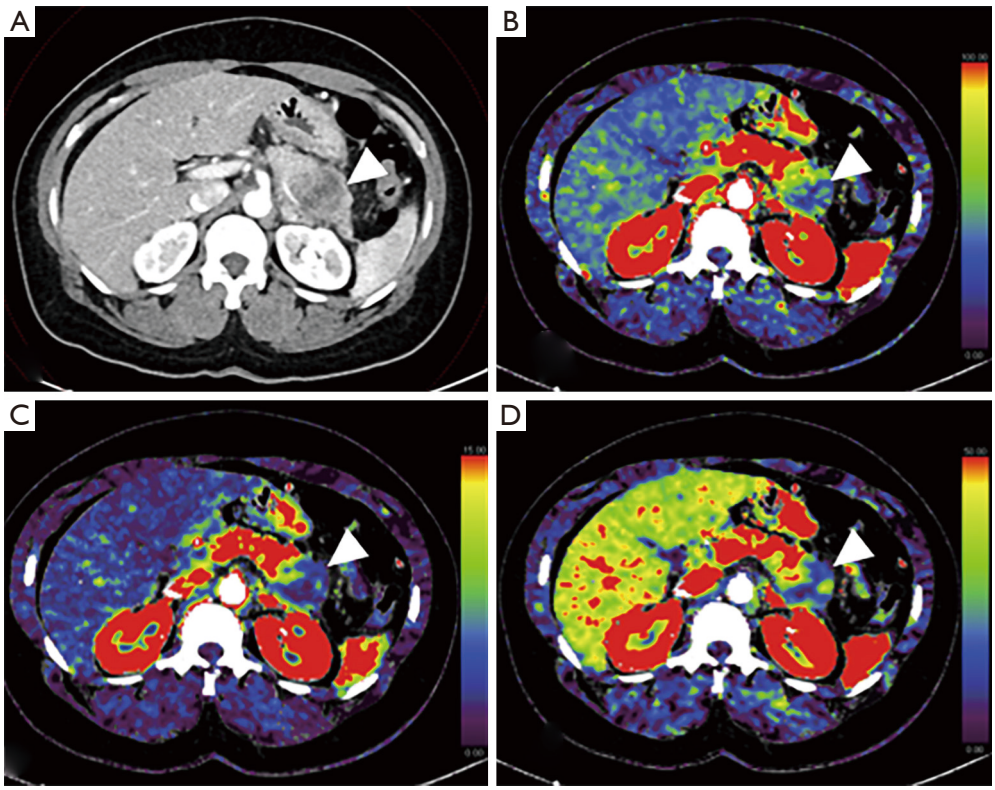

Figure 5 Volume Perfusion CT of mucinous cystadenocarcinoma in the pancreatic body (arrowheads); female, 74 y.o. (A) Dual energy acquisition, 100/150 Sn kV, mixed image 0.8, pancreatic phase (Somatom Force, Siemens Healthineers, Forcheim). (B,C,D) Volume perfusion CT, 70 kV, color maps. (B) Blood Flow. (C) Blood Volume. (D) Flow Extraction Product. The colored maps provide quantitative evaluation on vascularity and interstitium of the different solid components of the pancreatic lesion.

peak (TTP) and time-attenuation curves (TAC). These parameters estimate the characteristic and abnormal changes of microvascularity and interstitium, both in inflammatory and oncological diseases, also with relevant information on the functional status of the pancreas (12,17,67-69).

The pancreatic parenchyma has an arterial vascularization with rapid enhancement and washout (69); the variations of the perfusion quantitative parameters provided promising initial results on pancreatic diseases. In patients with acute pancreatitis, lower BF and BV in early stage of the disease are able to predict the development of ischemic and necrotic complications (70,71). As opposite to normal parenchyma, in chronic pancreatitis the contrast enhancement is more gradual, with longer TTP and lower BV and BF. This trend is more pronounced in case of exocrine insufficiency where the perfusion decreases, and the enhancement is even more delayed (72). The differentiation of PDAC from chronic, mass-forming pancreatitis, presents several challenges in CT: perfusion studies may be helpful since the reduction on BV and BF are more pronounced in PDAC than in chronic pancreatitis (73,74).

Perfusion CT parameters provide valuable diagnostic and prognostic information about neoangiogenesis and interstitium of PDAC and NET (*Figure 5*). Higher values of BF and BV are associated with better response of PDAC to chemotherapy (75,76), while a higher BF is correlated to lower replication index, benign behavior, and no microvascular involvement in NET (77).

Nowadays, perfusion CT has a prominent role in research mainly due to the high radiation exposure. However, the latest technological advances in 4D perfusion and low-voltage acquisitions for dose reduction have the potential for bringing the perfusion studies in clinical routine (78).

Quantitative CT: pancreatic volumetry and attenuation

The pancreatic volume can be calculated with several

techniques: the most widely used are the manual segmentation, where the radiologist manually outlines the pancreatic contours, and the semiautomatic segmentation, where the software calculates the tridimensional volume-of-interest (VOI) starting form references manually placed (79,80). The pancreatic volume is related to anthropometric data (e.g., gender, age and body mass index, BMI) but it is also related to exocrine and endocrine function (81).

Regarding the insulinotropic activity, the pancreatic volume is lower in patients with diabetes mellitus (DM) (82). In patients with Type 1 DM, the pancreatic volume is lower than in Type 2 DM, and the volumetric reduction of the pancreas becomes more relevant during the course of the disease (83). Moreover, in recently diagnosed type 1 DM, the pancreatic volume is lower than normal population; this may suggest that the reduction of pancreatic volume may occur earlier than the disease onset and that it may have a role as an early indicator of DM (84).

The reduction of the acinar cell mass, due to parenchyma atrophy in chronic pancreatitis or for surgical resection, has been related to exocrine deficiency that may lead to non-alcoholic fatty liver disease (NAFLD); changes in pancreatic volume before and after surgical resection allowed for prediction of DM and NAFLD after surgical resection (85,86).

The analysis of pancreatic attenuation is used to evaluate the fat content of pancreatic parenchyma: the rationale is the theoretical decrease of pancreatic density in presence of visceral fat. The pancreatic attenuation is usually evaluated by placing a Region-of-Interest (ROI) over the pancreatic parenchyma on unenhanced CT and may be normalized by considering the splenic density. A more sophisticated evaluation involves the histogram analysis to extract and quantify the percentage of fat (<–30 Hounsfield Units, HU) (17). The decrease of pancreatic attenuation and the presence of parenchymal fat are predictive of occurrence of pancreatic fistula after pancreaticoduodenectomy (87).

Texture analysis, radiomics and radiogenomics

The texture analysis quantifies the tissue heterogeneity; the different algorithms use the gray-level values of the pixels together with the relationships among the pixels to extract numerical parameters that can unlikely be evaluated by the human's eye (17,88). The definition "Radiomics" includes the amount of quantitative data that can be obtained from medical images for clinical decision support, and not routinely available on the radiological report. When the radiomic data are combined with the genomic data, a radiogenomic analysis is performed. The radiomics data can be classified in semantic and agnostic: the semantic data are the information provided in the radiological report, that can be extracted with computer assistance (e.g., shape, contour); conversely, the agnostic data are derived with mathematical analysis such as texture analysis (17).

The radiomic and texture analysis are being increasingly used in oncological imaging, with diagnostic and prognostic intent for several diseases, but also for the evaluation of treatment response (89). When applied to pancreatic CT, texture analysis showed promising results in the preoperative prediction of pathological grade of NET (90). A significant challenge in pancreatic CT is the evaluation of response to chemoradiation therapy of PDAC: the radiomic analysis has the potential for overcoming the limitations of dimensional criteria (91). The extraction of CT texture parameters also prognostic information: texture parameters are able to predict aggressiveness and pathological grade of PDAC but also correlate with patients' survival (92,93).

However, despite the promising results of radiomics, the texture analysis is still not included in clinical routine and further research is necessary for adequate correlation between genetic profile of PDAC and texture parameters (17,48,65).

Artificial intelligence and machine learning

The development of machine learning algorithms opened new fields of research in medical imaging and represents one of the major challenges in the near future (94). The machine learning algorithms use Bayesian statistics and random forest classifiers to analyze radiomic data while deep learning algorithms use artificial neural networks to learn a composition of parameters that reflect the analyzed data (95). The typical tasks the machine learning algorithms are trained for include the segmentation, detection or classification of tumor lesions (17,48,65). Potential applications for pancreatic imaging are the organ segmentation with automated volumetry, but also the classification of pancreatic lesions and the discrimination between fibrosis and residual tumor after treatment (17).

Screening for pancreatic cancer

Several screening protocols have been recommended for subjects at high risk of pancreatic cancer, particularly in

individuals with familiarity, with Peutz-Jeghers syndrome, BRCA2 mutations, Lynch syndrome (96).

In this setting, usually MRI or endoscopic ultrasound are the preferred techniques because of the absent radiation exposure (97). However, low-dose acquisitions and DECT may improve the conspicuity and the detection of incidentally discovered pancreatic lesions during abdominal examinations (17,48,65).

Conclusion

CT represents a fundamental diagnostic tool for the evaluation of pancreatic diseases. The new CT techniques, such as DECT or perfusion CT, as well as new post-processing tools, such as radiomics and texture analysis, will extend the information provided by CT, moving the limit from morphological evaluation to quantitative and functional evaluation of pancreatic diseases.

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Footnote

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