72283_Auto_EditedC.docx

WORD COUNT 5199
TIME SUBMITTED 11-FEB-2022 12:02PM
PAPER ID 82442266

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 72283

Manuscript Type: REVIEW

Advances in the imaging of gastroenteropancreatic neuroendocrine neoplasms

Ramachandran A *et al*. Imaging advances in neuroendocrine tumors

Anupama Ramachandran, Kumble Seetharama Madhusudhan

Abstract

Gastroenteropancreatic neuroendocrine neoplasms comprise a very heterogeneous group of tumors which differ in their pathogenesis, hormonal syndromes produced, biological behaviour and consequently, in their requirement for and/or response to specific chemotherapeutic agents and molecular targeted therapies. Various imaging techniques are available for functional and morphologic evaluation of these neoplasms and the selection of investigations performed in each patient should be customised to the clinical question. Also, with the increased availability of cross sectional imaging, these neoplasms are increasingly being detected incidentally in routine radiology practice. This article is a review of the various imaging modalities currently used in the evaluation of neuroendocrine neoplasms along with a discussion of the role of advanced imaging techniques and a peek into the newer imaging horizons, mostly in the research stage.

Key Words: Neuroendocrine tumor; Gastroenteropancreatic; Intravoxel incoherent motion; Diffusion weighted imaging; Perfusion imaging; Dual energy computed tomography

Ramachandran A, Madhusudhan KS. Advances in the imaging of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol* 2022; In press

Core Tip: The prognosis of gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) depends on the stage of the disease and tumor grade. Traditional imaging techniques like multiphase contrast enhanced computed tomography perform well at disease staging. For tumor grading, histopathological examination, with determination of number of mitoses and Ki-67 index is considered optimal. Advances in imaging techniques have enabled detection of smaller neuroendocrine neoplasms (< 2 cm). By analysing functional information like diffusion, perfusion and tumor heterogeneity, quantitative imaging is currently focussed on non-invasive prediction of the grade of GEPNENs preoperatively.

INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) are a rare and heterogeneous group of tumors which originate from the gastrointestinal and pancreatic neuroendocrine cells[1,2]. They may be benign or malignant and may or may not secrete hormones. Use of the previous terminology - 'carcinoid' tumor - is no longer encouraged. The gastrointestinal tract (GIT), having the highest density of neuroendocrine cells in the body, is the most common site of involvement of NENs, comprising nearly 60% of all NENs[3]. Pancreatic NENs account for about 7% of all GEPNENs[4]. Majority of the pancreatic NENs are sporadic. However, association with 4 familial syndromes (in up to 25%) is well described- multiple endocrine neoplasia type I, von Hippel Lindau syndrome, neurofibromatosis type I and tuberous sclerosis[5,6]. Classification based on histologic differentiation and grade is desirable as it provides insight into tumor biology, clinical course and helps in planning management. In 2019, the 5th edition of the World Health Organization (WHO) classification of tumors series published the latest NEN classification (Table 1)[7].

The latest WHO classification recognizes that well-differentiated NENs may be high grade, but they are distinct from the poorly differentiated neuroendocrine carcinomas (NECs). A vast majority of GEPNENs are well-differentiated and slowly growing. The Grade 3 NENs are most common in the pancreas, but can occur throughout the GIT[7]. Given the differences in prognosis, tumor grade is the most important factor determining the treatment of GEPNENs. The treatment of GEPNENs depends on grade, differentiation, site of origin, stage of tumor and the opinion about the best treatment strategy is evolving. Surgical resection remains the cornerstone and is the only curative treatment. For patients with small (< 2 cm), low grade NETs, decisions on surgery *vs* active surveillance need to be individualised based on tumor size, morphology (homogeneous, well circumscribed tumor < 1 cm correlate with low malignant potential) and patient characteristics like age and presence of comorbidities[8].

The commonly used imaging modalities include ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission

tomography (PET)-CT. Imaging is primarily aimed at accurate detection, characterizing and staging of these neoplasms and also in assessing response to treatment. Sensitivity of common imaging modalities used in the evaluation of GEPNENs are summarised in Table 2.

Improvements and advances in the imaging techniques have mainly focussed on the non-invasive prediction of the grade of the NENs. The European Neuroendocrine Tumor Society (ENETS) has also recommended that pre-operative assessment of the grade of the NENs is essential for prognosis prediction and management planning[9]. In addition, with the improvements in the imaging technologies, the detection rates of small NENs have significantly improved, with many often being detected incidentally.

US

Transabdominal ultrasonography (USG) often is the commonest initial modality used for patients with gastrointestinal symptoms. It has a great value in detection of liver metastases (sensitivity reaching 85%-90%). Pancreatic NENs in general appear as hypoechoic masses with a hyperechoic halo on USG[10].

However, transabdominal USG has limitations. Trans abdominal USG has a poor sensitivity (13%-27%) for detection of GEP NENs[11]. The technique is dependent on the experience of the operator. Presence of bowel gas and increased subcutaneous fat can obscure adequate visualization.

The advent of harmonic imaging, pulse inversion sequence, low mechanical index techniques and ultrasound contrast agents (UCAs) has enabled routine application of contrast enhanced ultrasonography (CEUS), which has overcome the limitations of conventional B mode USG. The inherent advantage of CEUS is its ability to assess tumor enhancement patterns in real time during transabdominal USG[12]. The enhancement patterns are described during arterial, portal venous and late phases. UCAs are gas microbubbles stabilized by a shell, the composition of which varies depending on the type of contrast agent. UCAs are blood pool agents and increase the back scatter of US, enhancing the echogenicity of flowing blood[12]. Harmonic imaging

detects harmonic signals from the microbubbles and CEUS specific US modes filter signals from the background tissue, thereby showing even very slow blood flow without Doppler related artifacts. UCAs unlike CT and MRI contrast agents are excreted by transpulmonary route and hence can be used safely in patients with deranged renal function.

The differential perfusion on CEUS has been shown to identify and diagnose pancreatic tumors. Pancreatic adenocarcinomas are in general hypovascular, while NENs are hypervascular. Takeda *et al*[13] found three patterns of hyperenhancement of PNENs and found that CEUS was useful in differentiation of PNETs and pancreatic adenocarcinomas. Malagò *et al*[14] also showed that enhancement patterns of non-functioning PNENs on CEUS (hyper, iso or hypovascular) correlated well with Ki-67 index and CEUS improved the detection of hepatic metastases. Hypervascular lesions had lower Ki-67 index. Another study showed that enhancement patterns of NENs on CEUS correlated significantly with CT enhancement pattern and histological Ki-67 index and CEUS was a good predictor of response of tumors to somatostatin analogues[15].

ELASTOGRAPHY

Elastography is an advancement in USG which enables real time measurement of tissue stiffness along with display in colors superimposed on the grey scale images.[16] In general, elastography helps in differentiation of benign and malignant lesions based on stiffness, as malignant lesions are usually hard. There are limited studies reporting the usefulness of transabdominal shear wave elastography (SWE) in the evaluation of pancreatic tumors in the literature. Park *et al*[17] showed that elastography can differentiate benign and malignant solid pancreatic lesions based on the difference in the shearwave velocity values (relative stiffness) between the tumor and the normal parenchyma. An early study by Uchida *et al*[18] found that NENs were homogeneous and soft on elastography, comparable to the normal pancreas. They also reported that a combination of elastography with B mode USG, improved the diagnostic accuracy to

90%, from 70%-80 % when B mode USG was used alone. However, if the visualization on the baseline B mode USG is suboptimal, the results of CEUS and elastography are also often unsatisfactory. These limitations have been overcome by the use of endoscopic ultrasound (EUS).

EUS

EUS is considered the most accurate test for diagnosis of pancreatic masses[19]. EUS uses higher frequency (7.5-12 MHz) probes, placed in proximity to the area of interest and hence performs better at detection of tumors smaller than 2 cm for which CT and MRI have poor sensitivity[20]. Overall, EUS has a sensitivity of 82% to 93% and a specificity of 92% to 95% for localizing PNENs[20]. EUS is particularly useful in the detection of benign insulinomas that lack somatostatin receptors and consequently are not detected on somatostatin receptor scintigraphy/single photon emission computed tomography (SPECT)/PET. EUS also plays an important role in the detection of functional pancreatic and extrapancreatic (duodenal) gastrinomas, both of which generally have a small size (average 1 cm) at diagnosis. The additional benefit of EUS is its ability to guide accurate tissue sampling *via* fine needle aspiration and core biopsy.[24] CEUS can also be performed through EUS with the use of second generation UCAs (eg. Sonovue), which produce harmonic signals at low acoustic powers.. A recent study showed that the time intensity curve analysis during CEUS showed high diagnostic accuracy in grading PNENs, and could differentiate grade 1/2 tumors from grade 3 / carcinomas.[25]

EUS elastography

EUS elastography of pancreas has been shown to be a promising imaging technique in several studies[26-28]. However, a prospective study by Hirche *et al*[29] including 70 patients with undifferentiated pancreatic masses showed an overall lower sensitivity (41%), specificity (53%) and accuracy (45%) for detection of malignancy. One of the early studies evaluating conventional strain elastography for pancreatic lesions showed significant strain difference between benign and malignant lesions[30]. The major utility

of EUS elastography is in increasing the yield of sampling by aiding better tumor targeting, especially in the background of pancreatic parenchymal fibrosis[31]. SWE EUS is a recent development and studies evaluating its utility in pancreas are just emerging[32,33]. A recent comparative study suggested that conventional strain elastography was superior to SWE in the characterization of pancreatic lesions[34].

CT

CT scan is the cornerstone and the most commonly performed imaging modality for the diagnosis and preoperative staging of GEPNEN. Standard CT scan has low sensitivity (about 60%) in the detection of GIT NENs[35]. Dynamic dual-phase protocol, which includes the arterial and portal venous phases, is recommended in patients with suspected NEN[36,37] (Figure 1). For pancreatic NEN, the late arterial phase acquired at 40-45 s (pancreatic phase) suits best. For detection of small bowel NENs, CT enterography (oral administration of neutral contrast agent like mannitol for bowel distension) or CT enteroclysis (administration of neutral contrast *via* nasojejunal tube) is required. CT enteroclysis combines the advantages of enteroclysis with imaging capabilities of multidetector computed tomography (MDCT). Study by Kamaoui *et al*[38] showed that CT enteroclysis has 100% sensitivity and 96.2% specificity in detection of small bowel neuroendocrine tumors. A comparative study from Mayo Clinic found that CT enterography is better than capsule endoscopy in detecting small bowel tumors with a sensitivity of up to 93%[39]. This ability of chronic traumatic encephalopathy to detect small bowel tumors remains high (sensitivity of 88%) even in the presence of gastrointestinal bleeding[40].

The characteristic imaging feature on CT scan suggesting the diagnosis of NENs is their intense enhancement in the late arterial phase, owing to the hypervascular nature of the tumor. The arterial phase also helps in outlining the relationship of the tumor with the adjacent arteries. Using the maximum intensity projection technique, virtual angiographic images can be obtained. Volume rendering techniques applied to the arterial phase provide easily explainable images to the surgeon. Portal venous phase

helps to draw the relationship of tumor with major veins, especially splenic vein and superior mesenteric vein for pancreatic NENs (PNENs). Dual phase imaging is also crucial for evaluation of hepatic metastases. The classic liver metastases from NEN, being hypervascular, are most evident on the arterial phase images. About 6%-15% of NET liver metastases are appreciated only in the arterial phase[41,42]. However up to 16% are hypovascular and show delayed enhancement[41].

One of the early studies suggested that the size of the tumor is an important prognostic factor, with tumors < 1 cm showing lesser incidence of liver metastasis (20%-30%) compared to those with > 1 cm (> 40% risk)[43]. Studies have shown that up to 42% of PNENs may not show arterial phase hyperenhancement[44,45]. Such arterial phase hypoenhancing tumors were associated with a significantly lower 5 year survival (54%) compared to lesions which were iso-enhancing (89%) or hyperenhancing (93%)[46]. Rodallec *et al*[47] found that tumor enhancement on CT scan correlated with microvascular density (MVD) evaluated on histology and that hypo-enhancing pancreatic NENs correlated with poorly differentiated tumors and a decrease in overall survival rate. These studies show that the CT enhancement characteristics of NENs have a prognostic value. Gallotti *et al*[6] found that incidentally detected pancreatic NENs, size > 3 cm, complex enhancement pattern and, presence of calcification, vascular invasion, main pancreatic duct dilatation, and peripancreatic lymph nodes were associated with non-benign tumors and require more aggressive course of management.

The role of various CT quantitative parameters based on enhancement of the NEN in the arterial or pancreatic and the venous phases has been evaluated in the prediction of tumor grade. Kim *et al*[48] found that portal enhancement ratio (HU value of the tumour divided by the HU value of pancreatic parenchyma on portal phase images) had the best odds ratio (49.6) and a cut-off value of < 1.1 had a sensitivity of 92% and specificity of 81% in differentiating grade 3 PNENs from grade ½. This high sensitivity and specificity of portal enhancement ratio in differentiating neuroendocrine carcinomas from well differentiated NENs was also confirmed by another study[49]. Yamada *et al*[50]

showed that corrected true enhancement values in the pancreatic phase had a sensitivity of 92%, specificity of 84% and area under the curve of 0.897 in differentiation grade 1 from grade 2 PNENs. D'Onofrio *et al*[51] showed that various tumor enhancement parameters (tumor permeability ratios, tumor parenchyma ratios, tumor arterial ratio and tumor venous ratio) were significantly different between grade 1 and grade 3 and between grade 2 and grade 3 PNENs. However, these values could not differentiate grade 1 from grade 2 tumors.

Dual energy CT

Dual energy CT (DECT) is advancement in CT, which allows acquisition of images at two energy levels, with lower energy being 80-100 kVp and higher being 140 kVp. Using DECT, material decomposition of images and generation of iodine maps, virtual non contrast images, and monochromatic images at different energy levels is possible (Figures 2 and 3). Monoenergetic images at low keV (55keV) in the pancreatic phase of DECT show improved image contrast for evaluation of pancreatic masses[52]. Monochromatic spectral images improve the sensitivity of detection of NENs like insulinomas, particularly the hypovascular and iso-attenuating tumors and the sensitivity is comparable to MRI[53]. One study showed that iodine uptake obtained from DECT is useful in the differentiation of hepatocellular carcinoma from liver metastases arising from NENs, with the former showing significantly higher iodine uptake (3.8 ± 1.2 *vs* 2.3 ± 0.6)[54]. This iodine uptake parameter on DECT may also be used in assessing response to treatment of NENs.

Perfusion CT

Perfusion CT is a technique which measures the dynamic changes in the attenuation of the tissues after contrast administration. It allows quantitative measurement of tissue perfusion, thereby assisting in the assessment of tumor viability and biologic behaviour[55]. The commonly used quantitative parameters of perfusion CT in oncoimaging are blood flow, blood volume, vascular permeability-surface area product

and mean transit time (Figures 4 and 5). These parameters serve as imaging biomarkers of tumor angiogenesis, which is ideally assessed histologically by calculating the MVD[56]. NENs are among the tumors with significant angiogenesis. Unlike majority of the cancers, where increased tumor vascularity is associated with aggressive behaviour, higher microvascular density in NENs is associated with a low tumor grade[55]. Low MVD was found to be an unfavourable prognostic factor for PNENs in several studies despite the presence of other favourable conventional histoprognostic factors, and call for a more aggressive treatment approach[57-59]. A study by d'Assignies *et al*[60] on 36 patients with PNENs found a significant correlation between MVD and blood flow assessed by using perfusion CT. In their study, the authors found that tumors that are small (< 2 cm), benign (grade 1), with a proliferation index of ≤ 2%, and without histologic signs of microvascular involvement had a significantly higher blood flow. Volume perfusion CT has been shown to improve the detection of pancreatic insulinomas, particularly the ones which have transient hyperenhancement (comprising 30% cases)[61,62]. A recent study demonstrated that addition of low dose perfusion CT to contrast enhanced CT improved the detection rate of PNENs from 83.6% to 89.1% and found that blood flow parameters were significantly different between grade 1 and grade 2 tumors[63].

Perfusion CT has also been shown to have a role in monitoring response to treatment with antiangiogenic drugs. Few studies have shown that the perfusion parameters of PNENs and liver metastases decrease as early as 48 h after treatment with anti-angiogenic drugs and perfusion CT offers a significant role in an early non-invasive assessment[64,65]. A major limitation of perfusion CT is the higher radiation dose, resulting in an additional dose of approximately 7 mSv[66].

MRI

MRI is best performed as a problem solving tool when CT scan findings are equivocal or negative, and is aimed at acquiring images of the lesion and organ with better soft tissue contrast. For instance, MRI has shown better sensitivity for detection of liver

metastases compared to CT and somatostatin receptor scintigraphy[67]. The absence of exposure to ionizing radiation makes MRI the apt modality for screening young individuals suspected of having NEN and those with syndromic association who require multiple follow up imaging[68]. Most NENs are hypointense on T1-weighted and hyperintense on T2-weighted images[10]. Contrast enhancement pattern and morphologic appearances are similar to that seen in CT scan (Figure 6). For detection of PNENs, the sensitivity of MRI ranges from 85%-100% and specificity from 75%-100%[69].

Diffusion weighted imaging

Diffusion weighted imaging (DWI) is a widely used technique in clinical imaging as it reflects the microscopic environment of neoplasm including tumor cellularity and extracellular matrix. The application of DWI oncology is mainly in tumor detection and assessing response to chemotherapy and radiotherapy. Wang *et al*[70] demonstrated that the apparent diffusion coefficient (ADC) values of pancreatic neuroendocrine tumors correlated well with Ki-67 Labelling index, thus indicating that DWI has a prognostic value (Figure 6). Another study showed that the ADC values were significantly different between benign and non-benign PNENs (1.48×10^{-3} mm^2/s *vs* 1.04×10^{-3} mm^2/s, respectively)[71]. Lotfalizadeh *et al*[72] showed that DWI has the additional value in identification of high grade tumors (grade 3) and can accurately differentiate grade 3 from grade 1/2 tumors (AUROC-0.96). The ADC values showed an inverse relation with the grade of the tumor.

Another major utility of DWI MRI is in the detection and characterization of liver metastases. Several studies have shown that DWI is more sensitive for detection of liver metastases than T2-weighted and multiphase gadolinium enhanced MRI, especially for the detection of smaller lesions[73–75]. Besa *et al*[76] showed that ADC of liver metastases from NEN weakly and significantly correlated negatively with tumor grade and Ki-67 and that mean ADC and minimum ADC values were significantly different between the three grades (1.6, 1.35 and 0.9×10^{-3} mm^2/s and 0.84, 0.5 and 0.27×10^{-3} mm^2/s for

grades 1, 2 and 3 respectively). DWI is hence recommended in routine MRI abdomen protocol for detection of liver metastases from NEN.

Histogram analysis of the ADC of the whole tumor has also been shown to predict tumor grade and aggressiveness. Pereira *et al*[77] found that whole tumor histogram analysis of the ADC, including the skewness and kurtosis can reliably differentiate grade 1 from grade 2/3 tumors. Another study also showed that this histogram analysis of ADC was useful in predicting tumor grade, vascular invasion and metastasis (node, liver) in PNENs and that $ADC_{entropy}$ and $ADC_{kurtosis}$ were the best markers in identifying tumor aggressiveness[78].

DWI is also useful in predicting and assessing response to various medical treatments for NENs. A recent study by Ingenerf *et al* showed that the change in the ADC values of liver metastases from NENs after transarterial radioembolization was significantly different between the partial response and progressive disease groups, thus concluding that ADC can be used as an additional marker for treatment response evaluation[79].

While DWI investigates diffusion of water molecules in tissues, it does not detect perfusion of blood. Intravoxel incoherent motion (IVIM) DWI detects translational motion of water molecules in a voxel and can simultaneously quantify their diffusion and microcirculation in tissue capillary network[80]. IVIM images are quantified by ADC, which integrates the effects of both diffusion and perfusion. IVIM therefore enables evaluation of tissue perfusion without the requirement of a contrast agent. The quantitative parameters in IVIM include the pure diffusion coefficient (D_{slow}), which reflects the diffusion of water molecules, the pseudo-diffusion coefficient (D_{fast}), which reflects the diffusion movement of capillary microcirculation perfusion, and the perfusion fraction (f), which represents the volume ratio between the perfusion effect of local microcirculation and the overall molecular diffusion (Figures 7 and 8). IVIM-DWI is a useful method to assess true tumor cellularity of PNEN, represented by tissue diffusion, as increased microcirculation of hypervascular PNENs may cause the pseudodiffusion effect and thus leads to the overestimation of ADC values[80]. Hwang *et al*[81] observed that IVIM DWI can differentiate grade 1 PNENs from grade 2 or 3

PNETs. They found that pure diffusion coefficient is a better marker of tumor cellularity than ADC, and was significantly higher in grade 1 PNENs, thereby enabling prediction of tumor grade on imaging. A recent study showed that D_{slow} and D_{fast} parameters help in the differentiation of high grade PNENs from pancreatic adenocarcinoma with high diagnostic accuracy (0.460 *vs* 0.579 × 10^{-3} mm^2/s and 13.361 *vs* 4.985 × 10^{-3} mm^2/s, respectively[82].

Diffusion kurtosis imaging

26

Diffusion kurtosis imaging (DKI) is a new rapidly advancing MRI technique based on the concept that water molecules in biological environment have non Gaussian properties. This is in contrast to standard DWI which calculates ADC using monoexponential analysis, assuming that diffusion of water in tissues follows Gaussian behaviour[83]. At higher b values (> 1000 s/mm^2), due to the barriers encountered by water molecules in tissues, there is deviation from Gaussian distribution. The deviation when quantified, in fact represents the tissue microenvironment. Two quantitative parameters-Diffusion coefficient (D) and Kurtosis (K), representing deviation from Gaussian distribution can be extracted from DKI. DKI thus provides a more accurate model of diffusion and quantifies tissue heterogeneity, irregularity of cellular microstructure by capturing non Gaussian diffusion parameters (Figure 9)[83,84]. A drawback which hampers the use in routine practice is the long acquisition time due to scan acquisition at multiple b values. There are studies showing application of DKI for assessment of pancreas[85,86]. Shi *et al*[84] found that radiomics model of DKI and T2 weighted imaging could improve the diagnostic accuracy for PNENs.

MR elastography

MR elastography (MRE) is a phase contrast based MRI technique for evaluation of mechanical tissue properties *e.g.* tissue stiffness, non-invasively. MRE of pancreas is at a relatively early stage. Recent studies have used MRE to differentiate healthy from pathologic pancreatic tissue[87]. The normal pancreatic stiffness in adults measured by

MRE is 1.1-1.21 kPa[87]. Shi *et al*[88] used MRE for characterization of solid pancreatic masses. They found that malignant masses had significantly higher stiffness (3.27 kPa) than benign masses (1.96 kPa). PNENs had a median stiffness of 2.32 kPa. They also suggested that stiffness ratio (ratio of stiffness of mass to normal parenchyma) may perform better in the differentiation of benign from malignant pancreatic masses.

MRI perfusion

MRI perfusion techniques for assessment of tumor perfusion have the major advantage that they lack adverse effects of radiation compared to the radiation intensive CT perfusion. T1 weighted dynamic contrast enhanced (DCE) MRI is the technique applied in the evaluation of tumors in the abdomen[89]. This provides both semiquantitative and quantitative information on the microvascular perfusion of the tissue. The semiquantitative analysis is based on the time-signal intensity curve and the quantitative analysis is based on the Tofts two-compartment pharmacokinetic model (intravascular and extravascular-extracellular compartments) with the parameters evaluated being Ktrans (volume transfer constant, wash in), Kep (reverse efflux rate constant, wash out) and Ve (extravascular extracellular space volume fraction)[90]. This technique has shown promising results in the evaluation of PNENs. The study by Donati *et al*[91] showed that Ktrans and Kep values were higher in NENs (2.709 min^{-1} ± 0.110; 5.957 min^{-1} ± 0.371) compared to other focal lesions and healthy pancreatic parenchyma. This in fact reflects the wash in (Ktrans) and wash out (Kep) of contrast from the hypervascular NENs. Also, well differentiated and poorly differentiated NENs showed different perfusion characteristics. In the study by Kim *et al*[92], Ktrans value of NENs were significantly higher than that of neuroendocrine carcinomas (0.339 min^{-1} ± 0.187 *vs* 0.077 min^{-1} ± 0.036). Ductal adenocarcinomas being hypovascular, show significantly lower average values of Ktrans and Kep[91-93]. The role of DCE MRI in the evaluation of response to systemic chemotherapy and targeted molecular therapy by assessing the changes in the values of MRI perfusion parameters reflecting good or poor response to treatment is a direction for future studies.

POSITRON EMISSION TOMOGRAPHY CT AND MRI

Hybrid anatomic and functional imaging using PET/CT is a valuable tool in the current practice of grading and management of NENs. In general, in dual tracer PET/CT (somatostatin receptor imaging with Ga^{68} DOTATATE/TOC/NOC PET/CT and glucose metabolism with FDG PET/CT), low grade tumors, which express somatostatin receptors, bind to somatostatin analogue, but not to FDG[94]. In contrast, poorly differentiated GEPNENs with high Ki-67 index would be negative on somatostatin PET/CT but FDG avid[95]. Zhang *et al*[96] suggested that dual tracer PET /CT may be used as an alternative to tissue sampling, as it reflects both cellular somatostatin receptor expression and glucose metabolism. The authors also found a positive correlation between SUVmax (standardized uptake value) and Ki-67 index with respect to FDG PET/CT and negative correlation with respect to Ga^{68} DOTATATE PET/CT. However, low grade insulinomas show low expression of somatostatin receptors in contrast to other secreting and non-secreting NENs and are frequently not detected on Ga^{68} DOTATATE PET/CT[97]. Since virtually all benign insulinomas express glucagon-like peptide 1 (GLP-1) receptors (incretin receptors), these receptors can be targeted by PET/CT for preoperative localisation of occult benign insulinomas. GLP-1R PET/CT had higher sensitivity than MRI and SPECT/CT for localisation of benign insulinomas in a study by Antwi *et al*[98], glucose dependent insulinotropic polypeptide receptor (GIPR) is another incretin receptor overexpressed in GEPNENs. It is a potential target for imaging the small percentage (~10%) of GEPNENs which do not express SSTR and GLP1R, as confirmed by studies in animal models[99].

With technical advances, simultaneous PET and MRI acquisition in an integrated scanner is now possible. The first study in 2013 by Beiderwellen *et al*[100] showed that every lesion detected on PET/CT was identified on PET/MRI. Hope *et al*[101] evaluated hepatic lesions in patients with NENs using Ga^{68} DOTATOC PET/CT and PET/MRI and found that there was strong correlation between SUV max obtained in PET/CT and PET/MRI. However, due to the high cost, the routine use of PET/MRI is limited.

RADIOMICS, TEXTURE ANALYSIS AND MACHINE LEARNING

Radiomics is the process of conversion of digital biomedical images to mineable data and the subsequent analysis of this data[102]. Texture analysis is an imaging technique under the wider arena of radiomics, that extracts, analyzes and interprets quantitative imaging features, and enables objective assessment of tumor heterogeneity beyond what is possible to human eyes[103]. In statistical- based model of texture analysis, from each voxel in an region of interest, various first order (*e.g.* First order entropy, kurtosis, skewness, standard deviation, mean intensity) and second order (*e.g.* Contrast, uniformity, second order entropy, *etc.*), or higher order features are extracted and analyzed using post processing softwares. As mentioned previously, tumor grade is an important prognostic factor of NENs and their prediction non-invasively is valuable.

CT radiomics is increasingly finding its place in the grading of NENs. Canellas *et al*[104], evaluating PNENs on CT scan, found that tumors with high entropy (a texture parameter reflecting tissue heterogeneity) values had 3.7 times higher odds of being aggressive (grades 2 and 3). In this study, entropy was a better predictor of tumor grade than the size of the lesion. Choi *et al*[105] found that lower kurtosis, lower sphericity and higher skewness correlated to grade 2 or 3 PNENs. A study on 3D texture analysis of PNENs in 100 patients showed that kurtosis was significantly different between all the three grades and entropy could differentiate grade 1 from grade 3 and grade 2 from grade 3, but not grade 1 from grade 2[51]. These results of CT texture analysis were confirmed in other recent studies[106,107] thus emphasizing its role in prediction of tumor grade.

MRI radiomics also help in characterising PNENs. MRI texture analysis was found useful in differentiating non-functioning PNEN from solid pseudopapillary neoplasm in a study by Li *et al*[108], Non-linear discriminant analysis was found to have the lowest misclassification rate of all the types of analyses performed in their study. Shindo *et al*[109] studied ADC histogram for differentiation of pancreatic adenocarcinoma from PNENs. In their study, ADC entropy had the highest area under the curve (AUC) for differentiating adenocarcinoma from NEN. De Robertis *et al*[78] found that ADC

histogram analysis of diffusion weighted MRI, using radiomics, could predict aggressiveness of pancreatic NENs. They found high ADC kurtosis values in tumors with vascular invasion (AUC of 0.763 for a cut off value of 4.13) and distant metastases (AUC of 0.820 for a cut off of 3.642)[78]. The future prospects of radiomics is in the direction of development of a robust predictive model combining qualitative and quantitative imaging parameters.

Machine learning is increasingly being used in medicine and has various applications including detection of disease, classification of images, identifying treatment and monitoring adherence to therapy[110,111]. The standard radiomics analysis on CT or MRI requires marking of the tumor margins for analysis. However, deep learning using convolutional neural network (CNN) performs analysis automatically and provides better results[112]. A few recent preliminary studies have shown the promising role of deep learning using CNN in the prediction of grade of PNEN and survival using contrast enhanced CT[113-115]. Clinical trials for translation of these imaging techniques into clinical practice and validation for routine use are ongoing.

In short, the quantitative parameters derived from imaging, relevant for prognostication of GEPNENs include tumor size, enhancement ratios derived from HU values, iodine uptake on DECT, entropy on CT texture analysis, tumor blood flow, tumor blood volume, and mean transit time on perfusion CT, ADC and ADC histogram analysis of DWI, true and pseudo-diffusion coefficients and perfusion fraction on IVIM DWI, Ktrans and Kep on perfusion MRI and SUVmax on dual tracC

CONCLUSION

With the recent advances in CT, MRI, USG and hybrid imaging techniques like PET/CT and PET/MRI using dual tracers, small pancreatic and bowel NENs are now being increasingly detected and staged. In addition to tumor detection and staging, their non-invasive grading, prognostication and monitoring response to treatment are shown to be feasible and reliable with the emerging studies using quantitative imaging techniques like CT and MR perfusion studies, DWI, IVIM and texture analysis with

radiomics. Standardization of these techniques with more large scale studies would be an important future prospect. These advances in imaging will help in making the right treatment choice, contributing to an overall improvement in patient outcome.

72283_Auto_EditedC.docx

ORIGINALITY REPORT

15%
SIMILARITY INDEX

PRIMARY SOURCES

1	Mohammed Saleh, Priya R. Bhosale, Motoyo Yano, Malak Itani et al. "New frontiers in imaging including radiomics updates for pancreatic neuroendocrine neoplasms", Abdominal Radiology, 2020 Crossref	116 words — 2%
2	www.ncbi.nlm.nih.gov Internet	85 words — 2%
3	www.science.gov Internet	51 words — 1%
4	Eui Jin Hwang, Jeong Min Lee, Jeong Hee Yoon, Jung Hoon Kim et al. "Intravoxel Incoherent Motion Diffusion-Weighted Imaging of Pancreatic Neuroendocrine Tumors", Investigative Radiology, 2014 Crossref	50 words — 1%
5	"Endoscopic Ultrasound", Springer Science and Business Media LLC, 2010 Crossref	38 words — 1%
6	Yun Bian, Jing Li, Kai Cao, Xu Fang, Hui Jiang, Chao Ma, Gang Jin, Jianping Lu, Li Wang. "Magnetic resonance imaging radiomic analysis can preoperatively predict G1 and G2/3 grades in patients with NF-pNETs", Abdominal Radiology, 2020 Crossref	38 words — 1%

7	www.wjgnet.com Internet	37 words — 1%
8	Francescamaria Donati, Piero Boraschi, Rosa Cervelli, Federica Pacciardi et al. "3 T MR perfusion of solid pancreatic lesions using dynamic contrast-enhanced DISCO sequence: Usefulness of qualitative and quantitative analyses in a pilot study", Magnetic Resonance Imaging, 2019 Crossref	31 words — 1%
9	epdf.pub Internet	30 words — 1%
10	"ECR 2020 Book of Abstracts", Insights into Imaging, 2020 Crossref	29 words — 1%
11	"Contrast-Enhanced Ultrasound in Pediatric Imaging", Springer Science and Business Media LLC, 2021 Crossref	22 words — < 1%
12	Brian Morse, Taymeyah Al-Toubah, Jaime Montilla-Soler. "Anatomic and Functional Imaging of Neuroendocrine Tumors", Current Treatment Options in Oncology, 2020 Crossref	22 words — < 1%
13	Katharina Detjen, Linda Hammerich, Burcin Özdirik, Muenevver Demir et al. "Models of gastroenteropancreatic neuroendocrine neoplasms – Current status and future directions", Neuroendocrinology, 2020 Crossref	21 words — < 1%
14	Ming-ming Xu, Amrita Sethi. "Imaging of the Pancreas", Gastroenterology Clinics of North America, 2016	19 words — < 1%

Crossref

15	Sunil Amin, Michelle Kang Kim. "Islet Cell Tumors of the Pancreas", Gastroenterology Clinics of North America, 2016 Crossref	18 words — < 1%
16	worldwidescience.org Internet	18 words — < 1%
17	Terufumi Kawamoto, Tsunekazu Hishima, Kiminori Kimura. "Calcified liver metastases from a non-functioning pancreatic neuroendocrine tumor", Clinical Journal of Gastroenterology, 2014 Crossref	15 words — < 1%
18	crcp.tums.ac.ir Internet	15 words — < 1%
19	www.freepatentsonline.com Internet	15 words — < 1%
20	www.frontiersin.org Internet	14 words — < 1%
21	Ying Wu, Hongling Peng, Xia Zhao. "Diagnostic Performance of Contrast-Enhanced Ultrasound for Ovarian Cancer: A Meta-Analysis", Ultrasound in Medicine & Biology, 2015 Crossref	13 words — < 1%
22	diagnosticpathology.biomedcentral.com Internet	13 words — < 1%
23	pesquisa.bvsalud.org Internet	13 words — < 1%
24	academic.oup.com	

Internet

11 words — < 1%

25 T Albrecht. "Guidelines for the Use of Contrast Agents in Ultrasound - January 2004", Ultraschall in der Medizin, 08/2004
Crossref

10 words — < 1%

26 Poot, D.H.J., A.J. den Dekker, E. Achten, M. Verhoye, and J. Sijbers. "Optimal Experimental Design for Diffusion Kurtosis Imaging", IEEE Transactions on Medical Imaging, 2010.
Crossref

9 words — < 1%

27 core.ac.uk
Internet

9 words — < 1%

28 www.hindawi.com
Internet

9 words — < 1%

29 Bang-Bin Chen. "Artificial intelligence in pancreatic disease", Artificial Intelligence in Medical Imaging, 2020
Crossref

8 words — < 1%

30 Beiderwellen, Karsten J., Thorsten D. Poeppel, Verena Hartung-Knemeyer, Christian Buchbender, Hilmar Kuehl, Andreas Bockisch, and Thomas C. Lauenstein. "Simultaneous 68Ga-DOTATOC PET/MRI in Patients With Gastroenteropancreatic Neuroendocrine Tumors : Initial Results", Investigative Radiology, 2013.
Crossref

8 words — < 1%

31 Dushyant V. Sahani, Sanjeeva P. Kalva, Leena M. Hamberg, Peter F. Hahn et al. "Assessing Tumor Perfusion and Treatment Response in Rectal Cancer with Multisection CT: Initial Observations", Radiology, 2005
Crossref

8 words — < 1%

32	Marc Giovannini. "Contrast-Enhanced and 3-Dimensional Endoscopic Ultrasonography", Gastroenterology Clinics of North America, 2010 Crossref	8 words — < 1%
33	www.mdpi.com Internet	8 words — < 1%
34	D. Urbain, D. De Looze, I. Demedts, E. Louis, O. Dewit, E. Macken, A. Van Gossum. "Video Capsule Endoscopy in Small-bowel Malignancy: A Multicenter Belgian Study", Endoscopy, 2006 Crossref	7 words — < 1%
35	Michel Claudon, Christoph F. Dietrich, Byung Ihn Choi, David O. Cosgrove et al. "Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) in the Liver – Update 2012", Ultrasound in Medicine & Biology, 2013 Crossref	7 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE MATCHES	OFF
EXCLUDE BIBLIOGRAPHY	OFF		