

Gastrointestinal and pancreatic neuroendocrine tumours and carcinomas; a review of rare tumour type

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Abstract

Neuroendocrine tumours are a rare tumour type involving neuroendodermal cells. They are also termed carcinoids. Gastroenteropancreatic system is most commonly involved. They are classified as low, intermediate or high grade depending upon mitotic index and Ki-67 index. Their diagnosis involves measurement of chromogranin A levels. Ultrasound is the initial imaging modality for their evaluation. Endoscopic ultrasound allows close evaluation of the tumour. Staging is commonly undertaken by computed tomography scan. These tumours typically show hyper-enhancement on arterial phase. Their metastasis to the liver also shows arterial enhancement. Small bowel carcinoids tend to have hepatic and mesenteric spread. Mesenteric spread of disease gives a characteristic spoke wheel appearance. On magnetic resonance imaging, these tumours typically appear as hypointense on T1 weighted image, hyperintense on T2 weighted image and show avid enhancement on post-contrast scan. Surgical resection is appropriate treatment with follow-up at 6-month intervals during the first year. The current review was planned to cover the aetiology, diagnosis, staging, imaging techniques, imaging features and treatment of these rare tumours that need prompt diagnosis.

Keywords: Neuroendocrine tumours, Carcinoid tumour, Carcinoid.

Introduction

Neuroendocrine tumours (NETs) are a rare presentation of tumours that involve neuroendodermal cells.^{1,2} These tumours are usually characterised by hormonal activity. Gastroenteropancreatic system, being the prime location, contributes almost 70% of all NETs,² broadly categorised into pancreatic neuroendocrine tumours (pNET) and enteric (extra-pancreatic) neuroendocrine tumours (eNET).¹ Other primary sites usually include bronchopulmonary segments, thyroid, adrenals, parasympathetic and sympathetic systems.² Genitourinary

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system is uncommonly involved.³

A recent increase of approximately 20% has been observed in worldwide prevalence of NET primarily because of early detection with cross-sectional imaging and endoscopic ultrasound (EUS).⁴⁻⁶ Pancreatic NETs comprise 1-2% of all pancreatic neoplasms with incidence of 1 in 100,000 persons.^{6,7} Pancreatic NETs have predilection for vascular invasion resulting in tumour thrombosis, with portal vein being most commonly involved.⁸ In the gastrointestinal (GI) tract, ileum is commonly involved in 30% cases^{9,10} followed by rectum and appendix. Less commonly, stomach, duodenum and jejunum are involved.¹⁰ Among regional trends, recently there was an increase observed in the diagnosis of NETs in India with the pancreas being the most common site of involvement.¹¹ Bukhari et al. reports that 22.8% of tumours in Pakistan are NETs with adrenal being the most common site involved.¹² NETs are classified into low, intermediate and high grade according to their mitotic index and Ki-67 index.⁴ Low and intermediate are categorised into well-differentiated tumours and high grade as neuroendocrine carcinomas.^{4,6,7} This review covers the aetiology, diagnosis, staging, imaging techniques, imaging features and treatment of these rare tumours that need prompt diagnosis.

Aetiology

Most of the NETs have a sporadic presentation. However, association of these tumours with multiple endocrine neoplasia type I (MEN-I) and "familial clustering" has also been reported. A diagnosis of pancreatic NET can be seen with heavy smoking.¹³ However, conditions such as diabetes mellitus (DM), raised gastrin levels and ulcerative colitis have traditionally been associated with NETs.¹⁴ Other complex phakomatoses such as von Hippel Lindau disease, tuberous sclerosis and neurofibromatosis type I have also been associated with this condition.^{15,16} Gastrointestinal NETs are common in African-American population whereas Caucasians are affected usually by bronchial carcinoids.¹⁷

Diagnosis

Tumour location and clinical presentation are important for the diagnosis of gastroenteropancreatic NETs (GEP-NETs). Patients presenting with signs and symptoms of increased hormonal secretion need evaluation by laboratory assays. Specific hormonal assay need to be carried out for specific NET.^{15,18,19} Chromogranin A is a serum marker used commonly for NETs, as its elevated levels are found in approximately 60% to 80% cases.²⁰ Histopathology is required for final diagnosis.

Histopathological Diagnosis

Exact histological features of NETs depend upon the location and cells of origin, but certain features are common. Macroscopically, these tumours have solid looking nodular or polypoidal appearance with whitish to grayish colour.²¹ Microscopically, the tumour is composed of cells of round or oval nuclei having salt and pepper chromatin along with eosinophilic granular cytoplasm. Tumour nests are arranged in a sheet-like pattern.²¹

Neuroendocrine carcinomas are classified as small or large cell carcinomas with small cell carcinomas having spindle shaped tumour cells with scanty cytoplasm and large cell carcinomas having medium to large tumour cells with atypical nuclei.²¹

Role of Immunohistochemistry

The histopathological diagnosis of NET is confirmed by demonstration of immunohistochemical (IHC) neuroendocrine markers. Different known IHC markers include chromogranin, protein cell product 9.5, neural cell adhesion molecule, synaptophysin, neuron specific enolase and Leu.⁷ To confirm the endocrine nature of the cells, chromogranin A and synaptophysin are commonly employed. Chromogranin A is found in the secretory granules of neuroendocrine cells.²² Synaptophysin is the most sensitive and chromogranin A is the most specific marker.²³

When there is a presence of metastatic NET with an unknown primary, then use of IHC staining panel with homeobox protein CDX2, pancreatic and duodenal homeobox 1 (PDX1), insulin gene enhancer protein ISL-1 and thyroid transcription factor 1 (TTF1) can aid in identification of the primary origin of metastatic NET.²⁴

Staging

American Joint Commission on Cancer (AJCC) adopted a tumour, node, metastases (TNM) based staging system for all anatomic sites that is parallel to the TNM system established by European Neuroendocrine Tumour Society (ENETS).²⁵ Staging depends upon the size of tumour (T stage), extent of tumour invasion and tumour relation to other nearby anatomical locations.

World Health Organisation (WHO) has classified NET according to their mitotic index and Ki-67 index. Tumours categorised as low grade have Ki-67 index of less than 3% and a mitotic rate <2/10 HPF. Tumours categorised as high grade have a Ki-67 index of greater than 20% and a mitotic rate of >20/10 HPF. Intermediate grade tumours have a Ki-67 index ranging from 3% to 20% and a mitotic rate 2-20/10 HPF.⁴

Imaging modalities

Ultrasound provides the baseline modality for the evaluation of solid abdominal organs. However, cross-sectional parameters, such as computed tomography (CT) and magnetic resonance imaging (MRI), play an imperative role in the accurate diagnosis and management of GEP-NETs. The details provided by these modalities help provide options for better surgical planning, further characterisation of disease extent and presence of metastasis.

Ultrasound

The overall sensitivity of trans-abdominal ultrasonography (TUS) ranges 13-27% in diagnosing GEP-NET.²⁶ Bowel gas shadows limit the TUS evaluation of pancreatic body and tail. However, evaluation of liver metastasis by TUS has a high specificity, approximately ranging 92-100%.^{26,27}

Endoscopic ultrasound (EUS) has an advantage of using high probe frequency of 7.5-12 MHz and also close evaluation of the region of interest.²⁸ The reported rate of detection is 45-60% for enteric NETs and 80-100% for pancreatic NET.²⁹ However, it is operator-dependent and carries a narrow field of view.

Multidetector Computed Tomography

Multi-detector CT (MDCT) has a high spatial and temporal resolution and considered an initial imaging technique in suspected cases of abdominal pathology.⁹ With its features of rapid speed, thin collimation and multi-planar reconstruction, it assists in surgical planning and further

management. The use of focussed examination protocols makes it easier in getting fine anatomical details.^{28,30}

Calcification and haemorrhages are better appreciated in unenhanced phases followed by intravenous (IV) contrast administration. A multiphasic dynamic approach is feasible as NETs have metastasis that are hyper-vascular and show characteristic enhancement on early arterial phase of dynamic imaging.

Magnetic Resonance Imaging

MRI has superseded CT in terms of organ imaging and also for evaluation of metastasis. MRI has an overall sensitivity of 74-94% and specificity of 78-100%.^{31,32} Dynamic contrast enhanced imaging along with fat-suppressed contrast-enhanced T1-weighted (T1W FAT-SAT) is advisable for a high accuracy.³¹ Diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping serve as additional tool for non-hyper-vascular tumours. MR uses no ionising radiation and has better tolerability of contrast agents. MRI is particularly beneficial in patients with equivocal/negative findings CT/US. It may also be used as surveillance in younger patients at risk of developing the disease.

Somatostatin Receptor Scintigraphy/Octreotide Scan

An increased expression of somatostatin receptor (SSTR) at cell membrane is manifested by NETs, mostly by well-differentiated tumours.³³ Therefore, functional imaging targeting the receptors can be performed. Among the five subtypes of SSTR, SSTR-2 is expressed commonly.³³ Somatostatin analogues have a high affinity for tissues expressing SSTR and somatostatin receptor scintigraphy (SRS) commonly makes use of this property. Octreotide is a commonly used somatostatin analogue and labelled with indium 111 to diagnose the lesions that are receptor-positive by the help of scintigraphy and is considered the reference standard.²⁸ In one study, SRS had a greater sensitivity than any other conventional imaging technique for NET diagnosis.³⁴

Gallium Scan and Role of Positron Emission Tomography

Gallium-68 is a radioisotope that is produced from a ⁶⁸Ge/⁶⁸Ga generator. It is a positron emission tomography (PET) radioisotope. ⁶⁸Ga-DOTATATE, ⁶⁸Ga-DOTANOC and ⁶⁸Ga-DOTATOC are the radiopharmaceuticals that are

currently in use for imaging of neuroendocrine tumours overexpressing various SSTR subtypes.

⁶⁸Ga-DOTATOC PET has a sensitivity of 97%, specificity of 92% and a diagnostic accuracy of 96%.³⁴ ⁶⁸Ga-DOTATOC PET is also superior to ¹¹¹In-DTPA-octreotide SPECT in the detection of NET.³⁵

⁶⁸Ga-DOTANOC has also affinity for SSTR. ⁶⁸Ga-DOTATOC is more specific for SSTR-2, however, ⁶⁸Ga-DOTANOC has a selectivity for SSTR2, 3 and 5.³⁶ ⁶⁸Ga-DOTANOC also has a favourable dose profile.³⁷ ⁶⁸Ga-DOTANOC has high sensitivity in identification of small lesions, particularly found in liver, lymph nodes or bones.^{38,39}

⁶⁸Ga-DOTATOC and ⁶⁸Ga-DOTATATE are specific for SSTR-2, however, the affinity of ⁶⁸Ga-DOTATATE for SSTR-2 is almost 10 times higher. A study comparing ⁶⁸Ga-DOTATOC with ⁶⁸Ga-DOTATATE concluded that both the radiotracers are comparable in diagnostic accuracy and higher affinity of ⁶⁸Ga-DOTATATE for SSTR-2 is not relevant clinically.⁴⁰

Imaging Features for Tumour Detection Pancreatic Neuroendocrine Tumours

The characteristic appearance of pancreatic neuroendocrine tumours (pNETs) on ultrasound is that of a hypoechoic lesion with a hyperechoic halo around it.²⁸

On dynamic contrast-enhanced CT or MRI, they appear

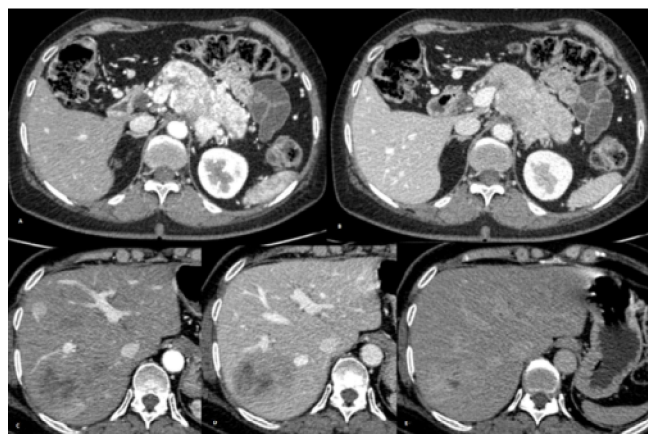


Figure-1: Contrast enhanced CT scan abdomen of a 54-year-old female with vague upper abdomen pain. (A) Arterial phase and (B) venous phase show a heterogeneously enhancing lesion involving neck, body and tail of pancreas. (C) Late arterial phase demonstrates a large enhancing lesion with areas of necrosis in segment VII of liver, another enhancing lesion is identified in segment VIII of liver. (D) Venous phase shows liver lesion in segment VII as more conspicuous and (E) shows fill in on delayed phase. It was proven as pancreatic neuroendocrine tumour with hepatic metastasis.



Figure-2: Contrast enhanced CT scan abdomen of a 69-year-old male with history of progressive jaundice. (A) axial and (B) coronal section show an enhancing mass in the periampullary region causing obstruction resulting in dilatation of pancreatobiliary system. (C) Coronal reconstruction shows dilated common bile duct as well as intrahepatic biliary ducts. Endoscopic ultrasound guided biopsy was performed and lesion was proven as neuroendocrine carcinoma. Liver lesions were labelled as cholangitic abscesses with a less likely possibility of metastases.

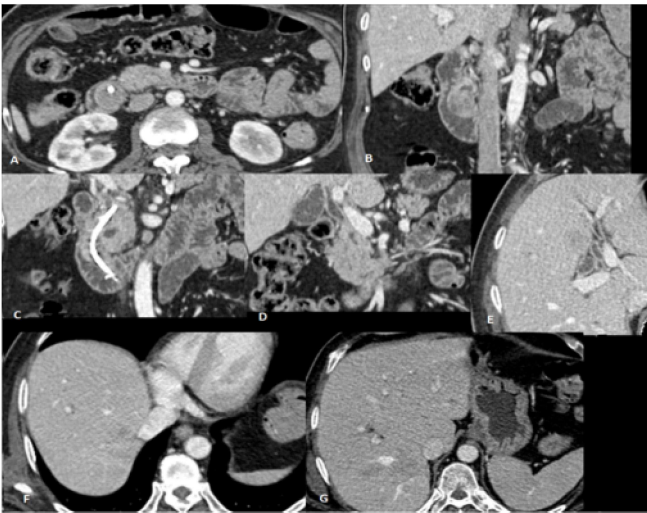


Figure-3: Follow up CT scan of patient in figure 2, patient underwent ERCP and stenting. CT scan was performed after ERCP and stent. (A) and (B) show interval progression in the size of periampullary lesion. (C) Coronal reconstruction showing the placed stent. (D) Coronal and (E) axial image show reduction in dilatation of common bile duct, there is enhancement of walls of common bile duct likely secondary to inflammation. (F) and (G) are axial images showing significant reduction in intrahepatic biliary duct dilatation as well as interval improvement in peripherally enhancing liver lesions suggesting them to be cholangitic abscesses.

as solid tumours that show avid enhancement, typically on arterial phase (Figure 1). This enhancement indicates the rich capillary network of these tumours.^{41,42} Smaller tumours usually appear homogeneous.

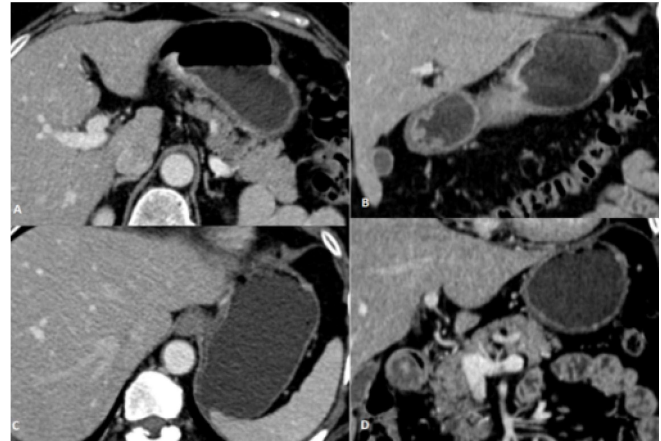


Figure-4: Contrast enhanced CT abdomen of a 48-year-old female presenting with abdominal pain and diarrhea. Axial sections (A) and (B) and coronal sections (C) and (D) show small, well-defined, enhancing areas along the wall of stomach. There is no perigastric fat stranding or lymphadenopathy seen. The patient underwent upper gastrointestinal endoscopy, it showed gastric polyps. Biopsy was performed and histopathology proved it to be neuroendocrine tumour.

Larger tumours may appear heterogeneous and show areas of non-enhancement, indicating necrosis. Cystic degeneration, fibrosis and calcification may also be evident.^{41,42}

Pancreatic neuroendocrine carcinomas carry a poor prognosis and usually have an infiltrative appearance. Vascular invasion may be present. Metastases are usually also hyper-vascular and show hyper-enhancement. NET in peri-ampullary region usually present with pancreato-biliary obstruction (Figures 2-3).

Extra-pancreatic/Enteric Neuroendocrine Tumours

NETs of enteric origin approximately form around 67% of the cases.¹⁰

Gastric NETs originate from enterochromaffin cells. They are an incidental finding on endoscopy and seen as multiple, small less than 1-2 cm sized polyps usually located in gastric fundus and body.¹⁰ On multiphasic dynamic contrast-enhanced CT, extra-pancreatic / enteric neuroendocrine tumours (eNETs) are usually identified as sub-mucosal enhancing lesions (Figure 4).^{10,43} Raised gastrin levels are common findings.⁴³ Endoscopic evaluation is advisable to localise the lesion and for histopathological evaluation, while CT and MR are used for the staging of disease.²⁹

Duodenal NETs are rare and account for approximately 2-3% of the cases.^{9,10} They are usually an incidental finding

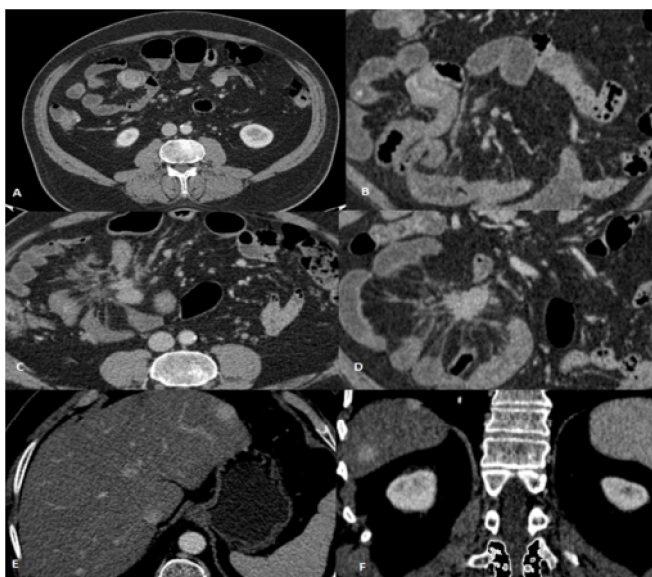


Figure-5: Contrast enhanced CT abdomen of a 57-year-old male with history of abdominal pain and vomiting. (A) axial and (B) coronal images show a homogeneously enhancing lesion in ileum, (C) Axial and (D) coronal images show enhancing soft tissue mass in the root of mesentery with spiculated margins, there is adjacent desmoplastic reaction noted with spicules radiating from it giving spoke wheel appearance. (E) and (F) show enhancing lesions in the liver. Histopathology showed carcinoid tumor of the ileum with involvement of mesentery and hepatic metastasis.

on oesophago-gastro-duodenoscopy and are commonly located in the upper third of duodenum. Due to their intaluminal/intramural location and small size, these tumours are difficult to be demonstrated on CT and MRI.¹⁰ When large, they usually manifest as hyper-vascular lesions which may be intaluminal polypoidal mass or intramural lesions. Endoscopy and biopsy is recommended for definitive diagnosis.

Ileal NETs are responsible for about 26-30% of the cases, are usually sporadic and may be multiple.⁴⁴ Disease may present with hepatic metastases at the time of presentation.¹⁰ On multiphasic dynamic contrast-enhanced CT, the main lesion may appear polyp-like or plaque-like. They usually show avid enhancement (Figure 5).⁴⁵ The primary lesion may contain calcification.⁴⁶

Mesenteric metastases are common with small bowel carcinoids and appear as spiculated / well-defined on CT. There is surrounding stranding fibrosis and radiating spicules representing desmoplastic reaction. This gives a characteristic "spoke wheel" appearance.⁴⁵ In the liver, metastases show avid enhancement on arterial phase and become isodense to liver parenchyma in the delayed phase.

Colonic NET are rare. They resemble adenocarcinoma and appear as poorly differentiated masses. Contrast-enhanced CT is essential for staging and typically shows a hyper-attenuating lesion. EUS better evaluates the adjacent rectal wall invasion.

On dynamic contrast-enhanced MRI, NETs usually appear hyper-intense on T2WI and appear hypo-intense on T1WI. Post-contrast scan shows avid enhancement and variable heterogeneity in terms of necrotic / cystic component in poorly differentiated/aggressive tumours.²⁸

Differential Diagnosis:

Pancreatic NETs

- ☞ Pancreatic ductal adenocarcinoma (typically hypo-vascular tumours, rarely show areas of calcification, usually encases / infiltrates superior mesenteric artery and coeliac trunk, involves common bile duct).
- ☞ Metastasis.
- ☞ Paraganglioma.

Gastric NETs

- ☞ Oat cell carcinoma.
- ☞ Sclerosing mesenteritis.
- ☞ Desmoplastic carcinoma.
- ☞ Lymphoma.

Treatment

Regardless of the site of origin of tumour, complete surgical resection is the first line of treatment and is potentially curative.⁴⁷ Surgical approach is influenced by tumour size, location, stage, and symptoms of the patient. Limited resection is considered in cases of non-invasive and small lesions that are usually less than 2cm. Surgery with lymph nodal resection is recommended for small-bowel NETs. Surgery can be curative in the presence of liver metastases with a five-year survival rate of about 60-80%.⁴⁸ In the presence of focal liver lesion, partial hepatic resection can be performed with the primary tumour resection. However, resection of liver is not considered in the presence of multifocal liver disease.⁴⁸

Oncological Management

If surgery is not possible due to aggressive local disease or extensive metastatic spread of disease, then medical management is mandatory to relieve the symptoms and regress tumour spread and growth.⁴⁹

When metastatic liver lesions are present, then complete

metastatectomy has been suggested, if feasible.⁵⁰ Procedures targeting the liver lesions such as trans-arterial chemo embolization, ablative therapies or internal radiation with yttrium-90 microspheres has also been advocated.⁵¹

Peptide receptor radionuclide therapy (PRRT) was developed because many receptors are visualised via the radiotracers, therefore, use of radio-isotopes for therapeutic purpose could provide an effective means for treatment of NET with distant spread. PRRT is available in Europe under local guidelines.⁵² ¹⁷⁷Lu-[DOTA0,Tyr3] octreotate therapy is one such treatment for disseminated NET and provides benefit in overall survival with few adverse effects and response rate comparable to other alternative treatment options.⁵³ A recent trial has shown that use of PRRT leads to an increase in progression-free survival.⁵⁴

Somatostatin receptor analogues (SSAs) such as octreotide or lanreotide also have an impact on progression-free survival and are used as first-line in low grade NETs.⁵⁵

Trials of interferon alpha and molecular agents such as everolimus, sunitinib and bevacizumab have also been undertaken for the treatment of NETs that have metastatic spread or extensive local spread of disease.⁵⁶⁻⁵⁹

Follow-up

A multidisciplinary approach is mandatory for follow-up of NETs. This includes biochemical (chromogranin A levels, hormonal assays and vasoactive amines), radiological, and histological evaluation.⁶⁰ Dynamic contrast-enhanced CT or MR imaging plays a central role in long-term assessment after surgery. The follow-up protocol usually includes imaging at every 6 months for the first year and then annually, if negative. For intermediate and high grade tumours, a shorter 3-month follow-up is indicated. Three-month follow-up is also recommended for patients undergoing treatment.⁶⁰

Conclusion

The review covered the aetiology, diagnosis, staging, imaging techniques, imaging features and treatment of these rare tumours that need a prompt diagnosis.

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