Section: Surgery

Case Report

MULTIPLE NEUROENDOCRINE TUMORS OF DUODENUM …ENDOSCOPIC SURPRISE AND SURGICAL DILEMMA

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ABSTRACT

Background: The manifold population of neuroendocrine neoplasms (NENs) arising in the duodenal mucosa and ampullary region has been investigated in several papers, leading to the characterization of various tumor entities according to histological structure, hormonal expression, clinical profile, genetic background, and/or patient outcome [1-3) The duodenal NETs are mainly located in the second part of the duodenum and are usually Single. Even though it is reported in various case series, Multiple neuroendocrine tumour of the first, second and Third part of duodenum is extremely rare and very difficult for a pre op diagnosis and planning. This case is presented to highlight the endoscopic features and therapeutic challenge in the unusual presentation.

Clinical Presentation: A 65/M patient was admitted with vague upper abdominal pain and dyspepsia and Vomiting. On OGD he was found to have Unusual multiple umbilicated lesions involving the first, second part of duodenum. Endoscopic diagnosis was Lymphoma / Duodenal carcinoma. The endoscopy biopsy was suggested it to be duodenal carcinoma with neuroendocrine differentiation.

In view of existing CKD Patient was investigated with MRI scan and MRI showed multiple polypoidal lesion duodenum first and second part. Patient was worked up and had planned Whipple resection and Histopathology revealed it as neuroendocrine tumour with low grade differentiation. The case is discussed with the stress on unusual endoscopic appearance and rarity of multiplicity.

Results: This entity of NETs of duodenum are rare tumours predominantly seen on the second part and single tumour and endoscopic appearance was very unusual. Most were low-grade tumors, ranging from reportedly self-limiting gangliocytic paragangliomas (GPs) to a variety of well-differentiated epithelial neuroendocrine tumors (NETs). This latter category comprised clinically silent or endocrinally active (such as gastrinomas) neoplasms of the duodenum as well as nonfunctioning, somatostatin cell tumors (often called ‘somatostatinomas’ despite their usual lack of clinically relevant signs of endocrine hyperfunction), commonly localized in the ampullary region and often causing biliary or pancreatic duct obstruction and regional lymph node (LN) metastases. A minority of tumors arose in a genetic background, such as gastrinomas in multiple endocrine neoplasia type 1 (MEN1) syndrome and somatostatin cell tumors in type 1 neurofibromatosis [4–6]. In addition to these differentiated, grade 1 or 2, NETs, a few high-grade (grade 3) neuroendocrine carcinomas (NECs) have also been reported [7,8, 9].

Conclusion: Duodenal neuroendocrine tumours are relatively very rare mesenchymal tumour with a unique histological appearance, and it needs to be distinguished from GIST and other gastrointestinal mesenchymal tumours. But

this paper highlights an unusual presentation in view of its endoscopic appearance and Multiplicity.
Keywords: Duodenal Neuroendocrine Tumors , Low garde, NET multiple.

INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms that arise from the peripheral neuroendocrine system dispersed in various organs.[1] Gastrointestinal neuroendocrine tumors (GI-NETs), like all NETs, are being increasingly reported in recent times.[1,2] This increase in the incidence of GI-NETs reflects the widespread use of endoscopy, and an increased awareness of GI-NETs among clinicians and pathologists. The manifold population of neuroendocrine neoplasms (NENs) arising in the duodenal mucosa and ampullary region has been investigated in several papers, leading to the characterization of various tumor entities according to histological structure, hormonal expression, clinical profile, genetic background, and/or patient outcome.[1-3] Neuroendocrine tumors (NET) form <1% in all malignant tumors. Gastrointestinal NET is a rare type of low-grade malignant tumor, comprising 0.4% to 1.8% of all GI malignancies out of which duodenal neuroendocrine tumor (d-NET) only accounts for 2% to 3% of GI NETs. D-NETs are mostly non-functional and often discovered incidentally during a routine upper gastrointestinal endoscopy for other indications.[5] Although primary d-NETs are rare, slow growing neoplasms with indolent clinical behavior, they can be potentially malignant.[6] These tumors tend to spread to the submusosal layer even during the early stages of the disease, so the treatment of choice for localized disease is still debated. The duodenal NETs are mainly located in the second part of the duodenum and are usually Single. According to the secretory activity, they can be functional or non-functional. In 90% of cases these tumors are non-functional and are often discovered incidentally during upper endoscopy that is being carried out for other reasons.[5] D-NETs may occur sporadically, but in 20% of patients they occur within the syndrome of multiple endocrine neoplasia type 1 (MEN 1).[9] Approximately 10% of d-NETs are functional, most often presenting with clinical picture of Zollinger Ellison syndrome (95% of all functional D-NETs) and with carcinoid syndrome (5% of all functional D-NETs).[10] D-NETs mostly present as solitary lesions confined to the mucosa and submucosa layer within diameter less than 2 cm. D-NETs are usually multiple in patients with MEN-1 syndrome. Even though it is reported in various case series, Multiple neuroendocrine tumour of the first, second and Third part of duodenum is extremely rare and very difficult for a pre op diagnosis and planning. This case is presented to highlight the endoscopic features and therapeutic challenge in the unusual presentation.

CASE REPORT

A 65-year-old male presented with vague upper abdominal pain and dyspepsia for a period of 1 year. He consulted a local physician who prescribed analgesics and PPIs, but symptoms were persisting and gradually progressive. Over the past 6 months he developed delayed vomiting ~2hrs after food intake, vomitus containing semi-digested food particles, suggestive of gastric outlet obstruction. Over 6 months he complained of significant weight loss and loss of appetite. He was also a known case of Chronic Kidney Disease on medications. The patient was admitted for evaluation.

On general examination, patient vitals were stable and he was moderately built and nourished with BMI ~ 20. He was having mild pallor. There was no icterus or generalised lymphadenopathy.

On local examination, his abdomen was soft, with no local rise of temperature or tenderness in any quadrant. There was no mass palpable, no organomegaly, no ascites. Hernial orifices were normal. No palpable inguinal lymph nodes. No palpable mass in scrotum. Per rectal examination was within normal limits. No palpable supraclavicular lymph nodes.

Other systems examinations were within normal limits.

Patient was taken up for an Upper GI Endoscopy. On OGD he was found to have Unusual multiple umbilicated lesions measuring approximately 1-2cm in size, involving the first and second part of duodenum, with circumferential involvement causing narrowing of the lumen and hence the cause for gastric outlet obstruction, but the scope could be negotiated with slight difficulty. Ampulla was visualised and it was free from the lesions. Multiple,[8] biopsies were taken from the lesions circumferentially. Endoscopic diagnosis was Lymphoma / Duodenal carcinoma. The endoscopy biopsy report came to be duodenal carcinoma with neuroendocrine differentiation.

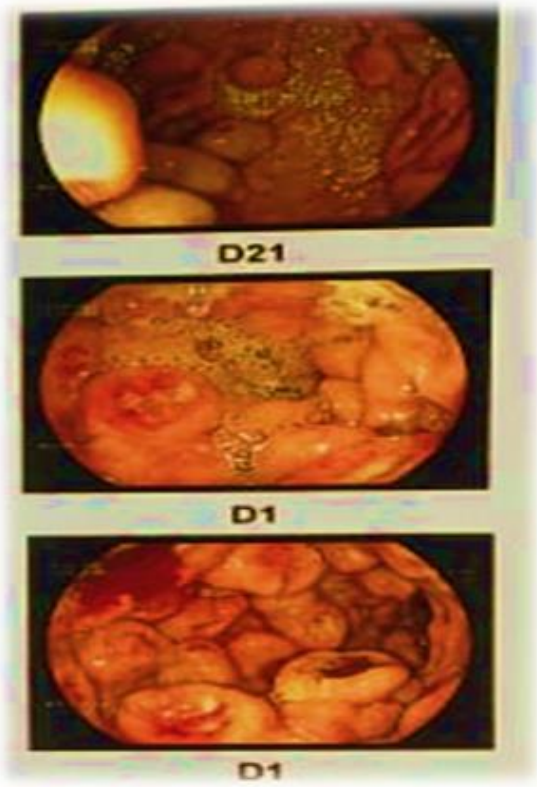
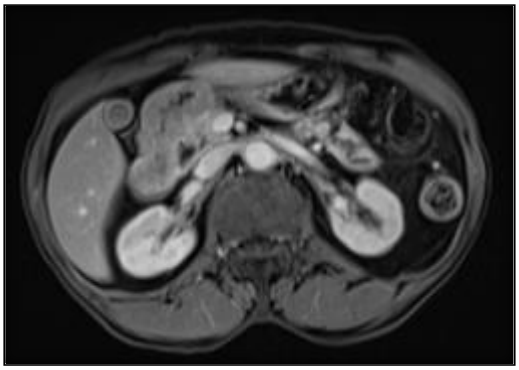
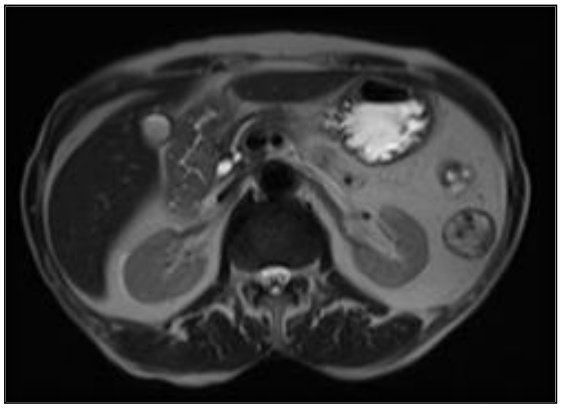


Figure 1: An unusual UGI Endoscopic Appearance

Serum Chromogranin levels were checked and found to be elevated- 115.90 (Normal = < 76.30)
Serum gastrin levels were normal.
In view of existing CKD, Patient was investigated with a MRI scan. MRI showed multiple polypoidal lesions involving the first and second part of the duodenum for a length of ~6.8cm and maximum thickness 14mm. Wall of the duodenum was thickened as compared to the stomach and there was slow passing of the contrast. There were no visible lymph nodes.



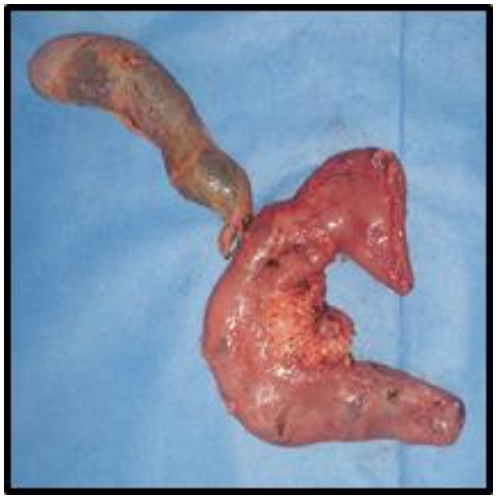
POST CONTRAST T1W IMAGE



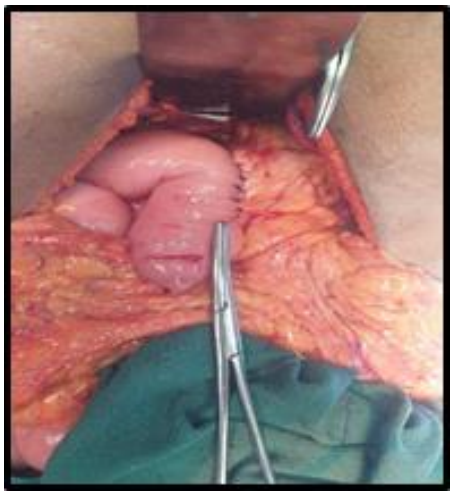
T2W IMAGE

Figure 2: MRI scan images of the tumor

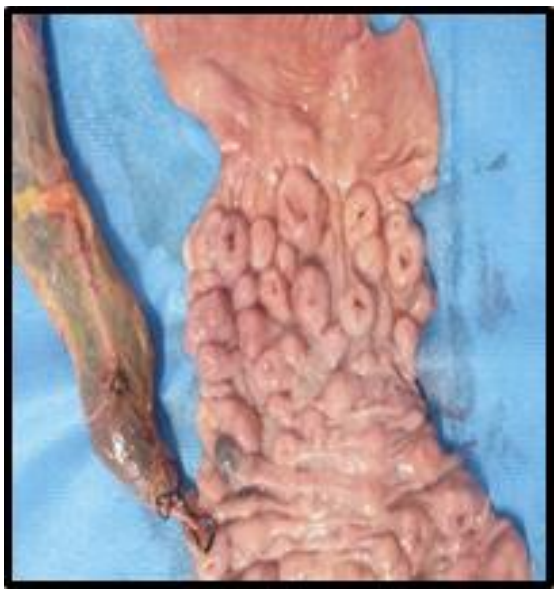
A decision to proceed with Classical Whipple Resection was made in view of the extensive morphology of the disease. The patient of preoperatively optimised with adequate hydration and strict monitoring of urine output, anaemia correction, antibiotics, ppis, incentive spirometry, and then taken up for elective surgery. On table, no gross mass lesion/ascites/lymph nodes were noted. Classical Whipple's was performed and the specimen cut open for examination-



WHIPPLE'S RESECTION SPECIMEN



PANCREATICO-JEJUNOSTOMY



CUT OPEN SPECIMEN

Figure 3: Whipple's Resection with Cut Open Specimen

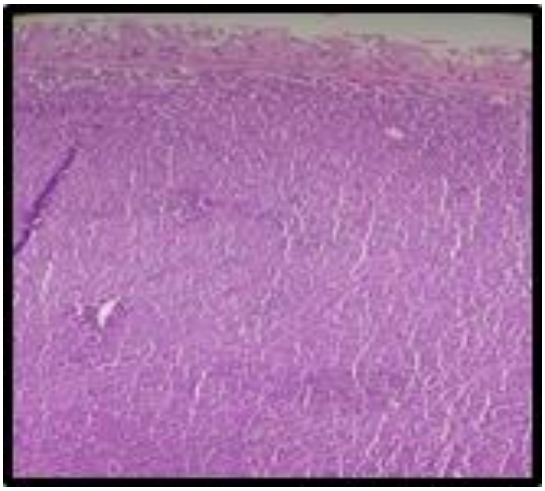
Specimen was sent for histopathological examination Histopathology revealed it as neuroendocrine tumour with low grade differentiation (T2N1Mx) -

Macroscopy

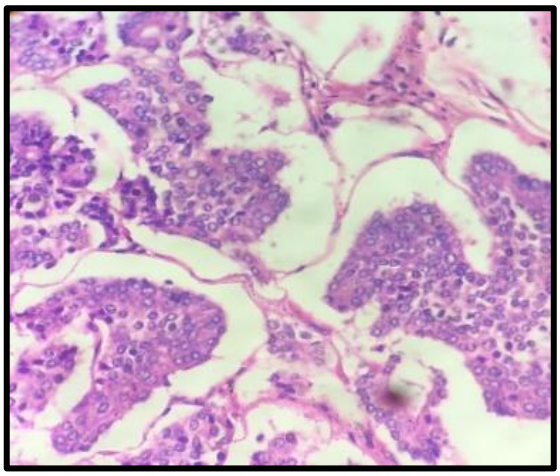
- Largest tumor nodule 2x1.5x1cm
- Tumor invades submucosa
- LN Positivity – Levels 8, 13, 17

Microscopy

- Monotonous cells arranged in nests, trabeculae, cords and tubules. Individual cells are uniform cells with moderate cytoplasm, oval nuclei, with salt and pepper chromatin.
- Mitotic Index 0-1/10hpf
- No necrosis, No Lymphovascular Invasion.
- Ampulla involved by neoplasm
- Proximal margin 3.5cm clearance
- Distal margin 1cm clearance
- Gall bladder, Common Bile Duct, Pancreas free of neoplasm



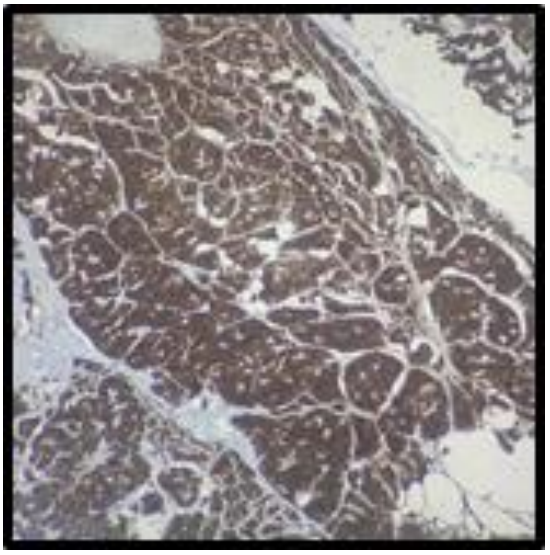
Monotonous cells in nests and trabeculae



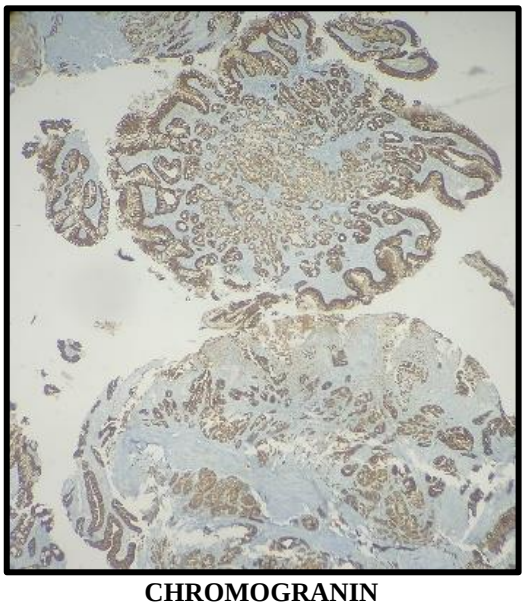
Salt and Pepper Chromatin

Figure 4: Microscopic Appearance of Tumor

Immunohistochemistry was performed which showed positivity for synaptophysin and chromogranin. Ki 67 <3%.



SYNAPTOPHYSIN



CHROMOGRANIN

Figure 5: Immunohistochemistry

Post operatively patient was given ICU care for 3 days. Orals started on POD 6. Discharged on POD 8.

DISCUSSION

D-NETs are usually non-functional, sporadic and well-differentiated slow-growing tumors [13]. Nonfunctional d-NETs are mostly incidentally discovered during an upper gastrointestinal endoscopy. The most common symptoms that lead to diagnostic work-up are abdominal pain (37%), upper gastrointestinal bleeding (21%), anemia (21%) and jaundice (18%).[14] Functioning NETs are characterized by the presence of clinical symptoms due to excess hormone secretion by the tumor. The most common functional d-NET is gastrinoma. One fourth of gastrinomas are related to MEN 1 syndrome.[16] While sporadic usually result from single lesion, in MEN 1 represent like multiple lesions.[16] The second most common functional tumors are duodenal somatostatinomas which are rare NETs. The pancreas is the most common site of somatostatinoma (68%), followed by the duodenum (19%), ampulla of Vater (3%), and small intestine (3%).[18] Duodenal somatostatinomas are more often associated with nonspecific symptoms and neurofibromatosis, but less often with somatostatinoma syndrome or metastasis. Although typical somatostatinomas are large, solitary, malignant tumors that are often discovered with lymph node or liver metastases at the time of diagnosis, duodenal somatostatinomas are mostly well-differentiated tumours.[20] Periampulary tumors are more aggressive tumors regardless of their histology and grade. Tumor size doesn't correlate with the depth of invasion, the presence of metastases and overall survival.[23] Carcinoid syndrome is generally rare in patients with d-NETs. Even in patients with serotonin-producing d-NETs, carcinoid syndrome becomes clinically evident in patients with liver metastasis, when secreted serotonin enters the systemic circulation escaping hepatic degradation.[25]
Classification and prognosis of NETs In 2010, the World Health Organization (WHO) updated its classification of NETs based on the histopathology of the tumor and the assessment of proliferation fraction and/or mitotic count. Classical histological features and positive immunostaining for two neuroendocrine markers, usually chromogranin A and synaptophysin, are mandatory to establish the diagnosis of NET regardless of the primary tumor site. The proliferative rate of the neoplasm is the most important feature used for grading (G).[26] It is assessed as the percentage of neoplastic cells showing positive immunostaining for the proliferation marker Ki-67 and by counting mitotic figures At least 500 tumor cells are needed and it is evaluated in areas of highest mitotic density. Mitoses are counted on 50 high-power microscopic fields (HPFs)and are assigned as count per 10 HPF. Tumors with higher Ki-67 expression are associated with worse prognosis. Childs et al. concluded that response to chemotherapy increases with Ki-67 index but Ki-67 alone is not reliable parameter to select patients for this form of treatment.[27]

Table 1: WHO Classification of Neuroendocrine Neoplasms

Terminology	Differentiation	Grade	Mitotic rate*, mitoses/2 mm²	Ki-67 index*, %
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type	Poorly differentiated	High	>20	>20
NEC, large cell type	Poorly differentiated	High	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)	Well or poorly differentiated	Variable	Variable	Variable

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma. * Final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher category.

The World Health Organization (WHO) classification places NETs into three main categories, which emphasize the tumor grade rather than the anatomical origin (Table 1). The classification categorizes NETs as either well-differentiated (grade 1 and 2) neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas (grade 3). Grading system correlates well with the pathological classification. For instance, approximately 85% of patients with G1 and G2 tumors are well-differentiated.[28] Most recently, G3 NETs presenting with a well-differentiated morphology have been suggested to be classified separately as well-differentiated grade 3 NETs.[29] Patients with well-differentiated d-NETSs (G1) have a 5-year survival rate of 80 to 85% while patients with well-differentiated NEC (G2) have a 5-year survival rate of 72%.[30]
Primary work up for diagnosis of NETs can be done with the help of biochemical markers. Due to NETs ability to synthesize and release peptide hormones and the monoamine neurotransmitters, sensitive assays for the measurement of these substances have been developed. Biochemical markers may have important diagnostic, predictive and prognostic value.
Serum CgA is elevated in 56-100% of d-NETs and positively correlates with metastatic disease and overall tumor burden.[34] Excessive secretion of CgA is mediated by IGF-1 receptor activation of the Arf 1 protein from the Golgy apparatus.[35] Sensitivity and specificity of CgA for the detection of NETs is 68% and 86%, respectively.[36] However, falsely elevated CgA levels are associated with several clinical conditions: liver, heart and renal failure, chronic inflammatory diseases, arterial hypertension and the use of proton pumps inhibitor. Hence serum CgA was not of much importance in this case as the patient was a known case of CKD.
5-HIAA is an important tumor marker and is mandatory to make the diagnosis of carcinoid

syndrome. A 24-hour urine sample is preferred for the 5-HIAA test. Measurement of 5-HIAA has a sensitivity of 64% and a specificity of 98% in diagnosis of NETs.[39] There is a good correlation between tumor mass and urinary 5-HIAA levels, both in functional and non-functional tumors.[39]

Imaging studies include Upper gastrointestinal endoscopy with biopsies that represent the gold standard in the diagnosis of d-NETs. The pathologic diagnosis is therefore established according to histological morphology and architectural pattern of NETs, as well as immunohistochemical staining, as described previously in the text. Endoscopic ultrasonography (EUS) has an important role in assessing the depth of tumor invasion and lymph node assessment. EUS can detect tumors located in the submucosa that ca not be seen during upper endoscopy. The ability to perform ultrasound guided fine-needle aspiration (FNA) for d-NETs in deeper layers is another advantage of EUS. The majority of d-NETs have a well-defined hypoechoic and relatively homogeneous pattern on EUS.[51,52]

Computed tomography (CT) and magnetic resonance imaging (MRI) have an important role in monitoring patients with advanced GEP-NETs. These methods can detect tumors less than 1 cm in diameter in 15% of cases, 1 to 3 cm in diameter in 20-50% of cases and larger than 3 cm in 95% of cases.[53] CT scans are often the initial imaging study for a patient presenting with signs or symptoms suggestive of a NET. There are no studies comparing the effectiveness of CT and MRI in detecting primary d-NETs and liver metastases. However, according to European Neuroendocrine Tumor Society (ENETS) guidelines, MRI is considered superior for the detection and follow-up of both primary tumors and liver metastases when compared to CT.[54] The main advantage of MRI is the use of diffusion - weighted sequences, which have very high sensitivity and low specificity. Therefore, MRI with diffusion-weighted sequences should be used in patients with d-NETs.

Due to unpredictable behaviour and low incidence of d-NETs, treatment strategies remain uncertain. D-NETs are mostly presented as solitary lesions confined to the mucosa and submucosa and therefore are available for endoscopic treatment. Initial biopsy is needed to provide the diagnosis of these tumors before starting with treatment. According to current recommendations, endoscopic resection is used for treatment of well differentiated non-functional dNETs (G1) smaller than 10 mm in diameter, which are confined to mucosa or submucosa.[51] Endoscopic methods available in treatment of d-NETs are: endoscopic polipectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Depending on the technique applied, EMR can be subdivided into EMR with ligation, EMR with circumferential precutting and EMR with a cap.[51] There is a consensus that tumors larger than 20 mm in diameter and all sporadic gastrinomas must be treated surgically.[51] Additional surgical interventions are recommended after endoscopic methods in the case of G1 or G2 d-NETs with positive margins, G2-G3 histological grading and invasion into muscular layer or vessel infiltration of tumor cells.[62] Although there is a lack of randomised trials about the role of laparoscopy for d-NETs, there is some evidence to show that laparoscopy provides certain advantages; for example reduced risk of external contamination compared with open surgery, reduced risk of post-operative infection and shorter length of hospital stay. Moreover, laparoscopy is a safe and beneficial method for exact localizing the tumor which earlier imaging methods failed to detect.[70] Tsujimoto et al. described endoscopic full-thickness resection of the duodenum under laparoscopic observation as a safe surgical procedure for small d-NETs, which may be complementary to endoscopic resection.[71] Recent case study showed that laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy (LAEFR) may be a minimally invasive and effective treatment for non-periampullary duodenal lesions.[72]

A radical resection should be considered for tumors > 2 cm.[70] Most commonly used surgical approaches include duodenopancreatectomy or Whipple procedure, pylorus-preserving duodenopancreatectomy and segmental distal duodenectomy. Recent studies showed that specialised centers can perform a duodenopancreatectomy laparoscopically with low surgical mortality (5%) and acceptable morbidity (20-30%).[70] However, even after the complete surgical resection, tumors larger than 2 cm in diameter often recur.[66]

Non-ampullary dNETs and ampullary dNETs differ in clinical features and consequently in treatment approach. For non-ampullary dNETs smaller than 1 cm in diameter, transduodenal resection is favorable to endoscopic resection. Ampullary dNETs are more aggressive tumors and their tumor size doesn't correlate with the depth of invasion, the presence of metastatic disease and overall survival.[75] It is considered that the Kausch-Whipple procedure or pylorus-preserving pancreaticoduodenectomy is the treatment of choice for all ampullary dNETs.[75] Although surgical resection is the mainstay of treatment, to date no studies have been done to establish optimal management of these tumors.

Due to the rarity of this disease, data on systemic therapy options that deal specifically with d-NETs are scarce or non-existent. Patients with well differentiated metastatic d-NETs that exhibit expression of somatostatin analogs on somatostatin-receptor-scintigraphy (SRS), especially if they have significant tumor burden or progressive disease, should receive therapy with somatostatin analogs (SSA) for control of carcinoid syndrome,[86] and possibly, for antiproliferative effect on tumor growth.[87] Available SSAs are octreotide and lanreotide. For patients with advanced NETs usually after failure of SSA treatment, as a second line therapy due to its less-favorable toxic profile, use of

interferon-alpha can be considered. For patients with advanced unresectable or metastatic disease, that show presence of somatostatin receptors on SRS, peptide receptor radionuclide therapy (PRRT) should be considered. For patients with G3, i.e. neuroendocrine carcinoma (NEC), either with progressive advanced (inoperable), or progressive metastatic disease, or symptomatic metastatic disease in need of quick relief of the symptoms, combination chemotherapy using cisplatine and etoposide is recommended first line therapeutic option regardless of the origin of the primary tumor.[114] For patients with well or moderately differentiated NETs (G1/G2) with progressive, advanced or metastatic disease, various combinations of streptozotocin, 5-fluorouracil, and doxorubicin are recommended chemotherapy options.[115]

CONCLUSION

- d-NETs most commonly occur in the 6th decade with male predominance
- 90% of cases these tumors are non-functional and are often discovered incidentally during upper endoscopy – ATYICAL appearance here
- Commonly single, multiple NETs being mostly associated with genetic syndromes such as MEN-1
- Usually from 2nd part of Duodenum, involving ampulla – All 3 parts circumferentially involved here.
- Due to unpredictable behavior and low incidence of d-NETs, treatment strategies remain uncertain.
- While small single lesions can be endoscopically resected, larger/ampullary/multiple lesions demands a radical surgery such as WHIPPLE'S RESECTION.

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