

# Clinicopathological Spectrum of Gastroenteropancreatic Neuroendocrine Tumours- A Series of Ten Cases

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## ABSTRACT

Neuroendocrine neoplasms are unique, as many of them are associated with secretory properties and specific syndromes of uncontrolled hormone hypersecretion. Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs) represent the second most common digestive tract malignancy. Epithelial neuroendocrine neoplasms of the gastroenteropancreatic system are divided into Neuroendocrine Tumours (NETs) and Neuroendocrine Carcinomas (NECs). NETs are classified as G1, G2 and G3 based on their proliferative activity. NECs are further classified into Large Cell NEC (LCNEC) and Small Cell NEC (SCNEC) based on the morphology of the tumour cells. The present case series was aimed to present the histopathological spectrum of NETs of the GEP system with respect to clinical and imaging findings, as well as, the associated role of Immunohistochemistry (IHC) as a supplement to histopathological diagnosis. It consists of 10 cases collected over a two-year period from January 2022 to December 2023 at the State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India. All cases of neuroendocrine neoplasms of the GEP system were included. There were seven resection cases and three biopsy cases. A total of (4/10) 40% of the cases belonged to the 40-50 years age group. A total of 5/10 (50%) cases were of the oesophagus, 2/10 (20%) were of the pancreas, and 20% (2/10) were of the rectum, while 1/10 (10%) was of the stomach. A total of 5/10 (50%) cases were SCNEC, 3 (30%) cases were mixed neuroendocrine non neuroendocrine neoplasms, and 2 (20%) cases were NETs (G1 and G3). GEP neuroendocrine neoplasms are sporadic, but they can be multiple and part of a familial syndrome. Assessment of the location and extent of GEP neuroendocrine neoplasms is crucial for management. Treatment consists of surgery, chemotherapy and somatostatin analogues. Challenges for the future include individualisation of treatment based on clinical and/or biological features and the evaluation of innovative therapies, including immunotherapy.

**Keywords:** Histopathology, Immunohistochemistry, Neuroendocrine carcinoma, Oesophagus

## INTRODUCTION

The Neuroendocrine Tumours (NETs) are unique, as many of them are associated with secretory properties and specific syndromes of uncontrolled hormone hypersecretion. Any organ in the body has the potential to develop this tumour [1,2]. There has been a steady increase in the incidence of NETs. In a series of 64,971 NETs reported to the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute (NCI), the reported annual age-adjusted incidence rate grew from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012 [3]. In the digestive tract, GEP-NETs represent the second most common cancer [4]. The most common sites of primary NETs in the digestive tract are the small intestine (30.8%), rectum (26.3%), colon (17.6%), pancreas (12.1%) and appendix (5.7%) [5]. Epithelial neuroendocrine neoplasms of the GEP system are divided into NETs and Neuroendocrine Carcinomas (NECs). NETs are classified as G1, G2, and G3 based on their proliferative activity. The World Health Organisation (WHO) Classification 2022 proposes a three-tiered grading system for Neuroendocrine Neoplasms (NEN) of the gastrointestinal and pancreatobiliary tract. Necrosis has no role in the diagnostic criteria of NENs in the GEP system [4].

Well-differentiated NETs are composed of uniform, round to polygonal cells with a low nucleocytoplasmic ratio, abundant cytoplasm and 'salt-and-pepper' chromatin with few mitoses arranged in nests, ribbons, acini and trabeculae with delicate vasculature. NECs are further classified as Large Cell Neuroendocrine Carcinoma (LCNEC) and Small Cell Neuroendocrine Carcinoma (SCNEC) based on the morphology of the tumour cells. SCNECs are composed of sheets

or nests of small cells with a high nuclear-to-cytoplasmic ratio, scant cytoplasm, nuclear molding, hyperchromatic nuclei, finely granular chromatin and inconspicuous nucleoli. Large cell NECs are composed of round to polygonal cells with a moderate amount of cytoplasm, round nuclei, vesicular chromatin and prominent nucleoli [6-8].

Synaptophysin, chromogranin and Insulinoma-associated protein 1 (INSM1) are the immunohistochemical stains used for the accurate characterisation of neuroendocrine neoplasms, with p53 and Retinoblastoma Protein (RB) aiding in the diagnosis when there are overlapping morphological features of G3 NET and NEC. In G3 NETs, there is wild-type p53 and retained RB, while NECs exhibit diffuse positive or null staining for p53 and loss of staining for RB [1]. In GEP-NENs, the antigen Ki-67 (Ki-67) proliferative index has a well-documented and accepted diagnostic and prognostic role, and its evaluation is mandatory in their diagnostic work-up [9]. The classification of GEP-NENs, along with the diagnostic criteria, is illustrated in [Table/Fig-1] [1].

Mixed Neuroendocrine Non Neuroendocrine Tumours (MiNEN) are tumours that consist of both a neuroendocrine component and a non neuroendocrine component, which may include squamous cell carcinoma, adenocarcinoma, etc., with each component comprising at least 30% of the resection specimen [10]. Both components must be established separately in different groups of cells using IHC. They pose a diagnostic challenge, especially in biopsy. The prognosis of these tumours depends on the grade of the more aggressive component [11].

Neuroendocrine neoplasm	Classification	Diagnostic criteria
Well-differentiated Neuroendocrine Tumour (NET)	NET, grade 1	<2 mitoses/2 mm <sup>2</sup> and/or Ki67 <3%
	NET, grade 2	2-20 mitoses/2 mm <sup>2</sup> and/or Ki67 3-20%
	NET, grade 3	>20 mitoses/2 mm <sup>2</sup> and/or Ki67 >20%
Poorly differentiated Neuroendocrine Carcinoma (NEC)	Small Cell NEC (SCNEC)	>20 mitoses/2 mm <sup>2</sup> and/or Ki67 >20% (often >70%), and Small cell cytomorphology
	Large cell NEC (LCNEC)	>20 mitoses/2 mm <sup>2</sup> and/or Ki67 >20% (often >70%) and large cell cytomorphology

**[Table/Fig-1]:** Classification of GEP-NEN along with the diagnostic criteria [1].  
\*NET: p53 wild type and RB retained; NEC: p53 diffuse/null and RB lost

The present study was aimed to explore the histopathological spectrum of NETs of the GEP system in relation to clinical and imaging findings, as well as, the associated role of IHC as a supplement to histopathological diagnosis. This is a rare series, one of its kind, shedding light on the pathological and immunohistochemical spectrum of NETs of the GEP occurring at the State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India, which is a state-of-the-art tertiary cancer care centre in the northeastern region of India.

## CASE SERIES

This case series consists of 10 cases diagnosed over two years, from January 2022 to December 2023, in the Department of Oncopathology, State Cancer Institute, Gauhati Medical College, Guwahati. Ethical clearance was obtained from the Institutional Ethics Committee, No. SCI/GMC/ECR/2020/139.

**Inclusion criteria:** All cases of NEN of the GEP system.

**Exclusion criteria:** i) NEN of other systems; ii) Non-NEN of the GEP system.

The demographic data, clinical profiles and radiological findings were retrieved from patient records. The selected cases were routinely processed using the automated tissue processor Thermo Fisher Scientific, STP120, and stained with haematoxylin and eosin using the automated stainer Thermo Fisher Scientific, Gemini AS model and examined, while IHC was performed in the automated IHC stainer Leica Bond Max, as required. The various antibodies used were obtained from BioGenex: Pancytokeratin (panCK) (AMA46), synaptophysin (AM363), chromogranin (AM126), and Ki67 (AM410). The slides were examined, data were entered into an Excel sheet, a master chart was prepared, and statistical analysis was conducted.

Results are presented in the form of demographic analysis (age, gender, organ-related), clinical analysis (symptoms presented and imaging findings), pathological analysis (tumour size, lymphovascular invasion, morphological subtypes, perineural invasion, tumour regression grade, immunohistochemical profile), and finally, the follow-up management, including details of cases lost to follow-up. A detailed evaluation of all 10 cases is provided in [Table/Fig-2,3], respectively.

**Demographic analysis:** The prevalence of GEP-NEN in the study Institute for the two-year period from 2022 to 2023 was 0.17% (10/5747), with MiNEN constituting 3/10 (30%) cases. The series consisted of 10 patients, 7 (70%) males and 3 (30%) females; there were seven resection cases and three biopsy cases. The highest number of cases, i.e., 4/10 (40%), belonged to the 40-50 years age group. [Table/Fig-4] is a bar diagram showing the age-wise frequency distribution of all the cases. [Table/Fig-5] is a pie-chart showing the organ-wise percentage distribution of cases. Out of 10, 5 (50%) cases were of the oesophagus, 2 (20%) each were of the pancreas and rectum, and 1 (10%) was of the stomach, as illustrated in the pie-chart labelled [Table/Fig-6]. [Table/Fig-7] is a pie-chart showing that 5 (50%) cases were SCNEC, 3 (30%) cases were MiNEN, and 2 (20%) cases were NET (G1 and G3).

**Clinical analysis:** Three cases of oesophageal tumours presented with dysphagia and haematemesis, while two presented with

only difficulty in swallowing. The single case of a stomach tumour presented with abdominal distention; both cases of rectal tumours presented with bleeding per rectum, and one pancreatic tumour presented with jaundice, vomiting and abdominal distention, while the other presented with only jaundice. Imaging findings in cases of oesophageal, stomach and rectal tumours showed circumferential wall thickening; the pancreatic tumour showed a well-defined mass lesion. Functional imaging was not performed in any of the cases due to the non availability of facilities during the study period.

**Pathological analysis:** The average size of the NET was 4.31 cm, with sizes ranging from 2-10 cm. Lymphovascular invasion was seen in a single case of mixed squamous cell carcinoma NEC (oesophagus), and perineural invasion was observed in a residual SCNEC case (rectum). Two out of the 10 cases received Neoadjuvant Chemoradiotherapy (NACRT) to reduce tumour burden followed by surgery. Residual tumours were present in two cases of SCNEC: one in the rectum with a tumour regression grade of 3 and the other in the oesophagus with a tumour regression grade of 2. Regional lymph nodal metastases were found in three of the 10 cases: Mixed Adenocarcinoma Neuroendocrine Carcinoma (MANEC) in the stomach (9 out of 16), residual SCNEC in the oesophagus (4 out of 13), and Mixed Squamous Cell Carcinoma NEC in the oesophagus (1 out of 30). Omental metastasis was found in a single case of MANEC in the stomach. [Table/Fig-8] shows a case of NET grade 3 in pancreas, [Table/Fig-9] shows a case of mixed squamous cell carcinoma neuroendocrine carcinoma with lymphovascular invasion in esophagus, [Table/Fig-10] shows a case of SCNEC in rectum with perineural invasion, [Table/Fig-11] shows a case of SCNEC in oesophagus and [Table/Fig-12] shows a case of MANEC in stomach.

The immunohistochemical study of the cases for synaptophysin, chromogranin and Ki67 showed that 9 (90%) were positive for Synaptophysin and 6 (60%) were positive for chromogranin. The highest Ki67 was found to be 90%. Pancytokeratin and CK7 were found to be membranous positive in the adenocarcinoma component of mixed adenocarcinoma NEC in the stomach. [Table/Fig-2,3] provides an elaborative pathological evaluation and follow-up of the seven resection and three biopsy cases, respectively.

**Follow-up of patients:** The patients were followed-up until June 2024 (4-23 months). Seven of the ten patients are doing well, one patient was lost to follow-up, one expired after one week of surgery due to postoperative complications, and another after four months of surgery. Two patients underwent NACRT followed by surgery, two received adjuvant chemotherapy and radiotherapy following surgery, three were operated only, one received only chemotherapy and radiotherapy as treatment, and one received palliative treatment. Additionally, one patient was lost to follow-up after diagnosis via biopsy.

## DISCUSSION

The present case series is an attempt to achieve a detailed understanding of the pathological spectrum of GEP epithelial NENs with the available resources. IHC for Ki67 is essential in the work-up of pancreatic NETs, as tumour grade represents the cornerstone for the prognostic evaluation of patients [9]. In the study conducted by Xie J et al., over a 12-year period across 11 hospitals in China, 405 cases of gastric NETs were collected, with 53.83% (218/405) NEC cases and 46.17% (187/405) being Mixed Adenoneuroendocrine Carcinoma (MANEC) cases. Lymphovascular invasion was noted in 41.48% (168/405) of cases, perineural invasion in 31.36% (127/405) of cases, and Ki67 ≥60% in 61.97% (251/405) of cases [12].

The results of the present series are similar to those of Xie J et al., with 50% (5/10) of cases being Small Cell Neuroendocrine Carcinoma (SCNEC) and 3 (30%) being Mixed Neuroendocrine Non Neuroendocrine Neoplasm (MiNEN) [12]. However, there is a striking difference in the rates of lymphovascular and perineural invasion, which were only 10%, and only 20% of the cases showed Ki67 >60%.

Case	Age (years)	Gender	Site	Imaging	Tumour size (cm)	Diagnosis	Stage	Lympho-vascular invasion	Perineural invasion	Synapto-physin	Chro-mogranin	Pancy-tokeratin	Ki67 (%)	Regional lymph nodes	Neo adjuvant tx	Adjuvant tx	Follow-up	TRG
1	43	M	Oesophagus	CT: Circumferential wall thickening involving mid and lower thoracic oesophagus	3.5x2.5x1	MINEN (Mixed SCC NEC)	T2N1	Present	Absent	Positive	Positive	Positive	25	1 of 30	-	RT+5 cycles of CT (Paclitaxel, Carboplatin)	23 months	-
2	78	F	Rectum	MRI: Circumferential polypoidal nodular wall thickening in rectum, proximal and middle third, mass 1.8 cm proximal to anal verge	4x2x2	MINEN (MANEC)	T3N0	Absent	Absent	Positive	Positive	Positive	30	0 of 12	-	-	Patient expired after 4 months of operation	-
3	47	M	Rectum	MRI: Circumferential polypoidal wall thickening in rectum, middle third	2x1.5x1.2	Residual SCNEC	ypT3N1c	Absent	Absent	Positive	Positive	Positive	40	0 of 7	6 cycles of NACT (Cetuximab, Bevacizumab, Folfox)	-	11 months	3
4	44	M	Stomach	UGIE: UPG at antrum and pylorus, USG-wall thickening in antrum pyloric region causing luminal narrowing and distended stomach	10x8x0.8	MINEN (MANEC)	pT4aN3aM1	Absent	Absent	Positive	Negative	Positive	30	9 of 16	-	5 cycles of NACT (Capecitabine +Oxaliplatin)	8 months	-
5	66	M	Pancreas	CECT: Mass lesion in head and uncinate process of pancreas	3.2x3.1x2.9	G1NET	T2N0	Absent	Absent	Positive	Positive	Positive	2	0 of 7	-	-	Expired after 1 week of surgery due to postoperative complications	-
6	67	M	Pancreas	CT: Heterogenous exophytic mass lesion in tail of pancreas m 4.2x3x3.8 mm	5x3x2.5	G3NET	T3N0	Absent	Absent	Positive	Negative	Positive	22	0 of 14	-	-	13 months	-
7	35	F	Oesophagus	CECT: mild thickening of mid thoracic oesophagus 3 cm in length 6 mm in thickness	2.5x2x0.3	Residual SCNEC	ypT1bN2Mx	Absent	Present	Negative	Positive	Positive	80	4 of 13	NART+3 cycles of NACT (Carboplatin+ Paclitaxel)	-	10 months	2

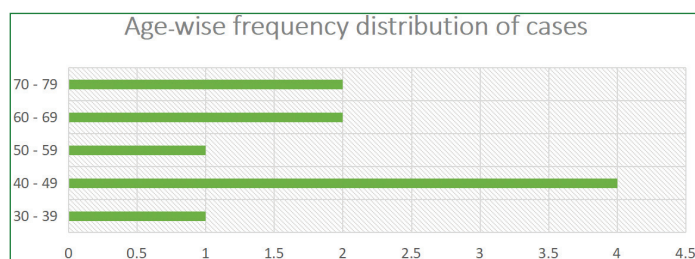
**Table/Fig-2j:** Detailed pathological parameters of the 7 resection specimens.

M: Male; F: Female; Ki67: Proliferative index; GEJ: Gastro-oesophageal junction; NACT: Neoadjuvant chemotherapy; NART: Neoadjuvant radiotherapy; UGIE: Upper gastrointestinal endoscopy; USG: Ultrasonography; CECT: Contrast enhanced computed tomography; SCNEC: Small cell neuroendocrine carcinoma; G3NET: Grade 3 neuroendocrine tumour; MINEN: Mixed neuroendocrine non neuroendocrine neoplasm; SCC: Squamous cell carcinoma; MANEC: Mixed adenocarcinoma neuroendocrine carcinoma; TRG: Tumour regression grade

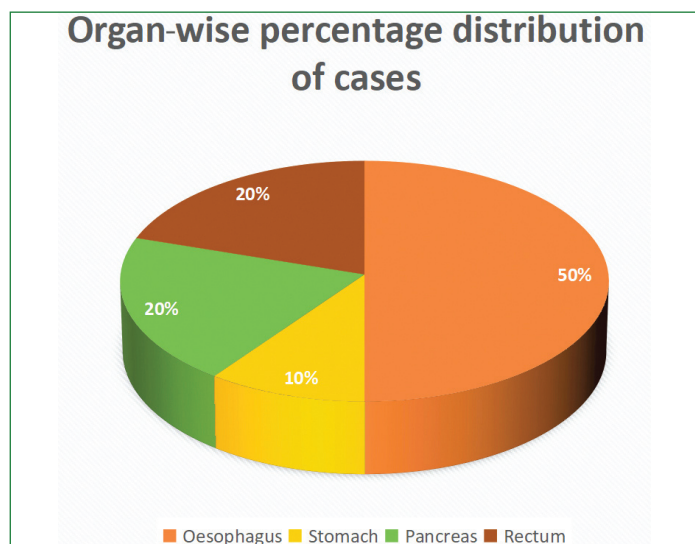
Case	Age (years)	Sex	Site	Imaging	Diagnosis	Synapto-physin	Chro-mogranin	Pancy-tokeratin	Ki67 (%)	Treatment	Follow-up
8	47	F	Oesophagus	CT: Circumferential wall thickening involving lower thoracic oesophagus extending to GEJ	SCNEC	Positive	Negative	Positive	90	-	Lost to follow-up
9	71	M	Oesophagus	UGIE: UPG from 25-35 cm of esophagus	SCNEC	Positive	Negative	Positive	45	26 cycles of RT and CT (carboplatin and paclitaxel)	12 months
10	54	M	Oesophagus	CT: Circumferential wall thickening involving mid thoracic oesophagus and metastatic lesions in the liver, adrenals, kidneys and lungs	SCNEC	Positive	Positive	Positive	35	Palliative treatment	14 months

[Table/Fig-3]: Detailed parameters of the three biopsy cases.

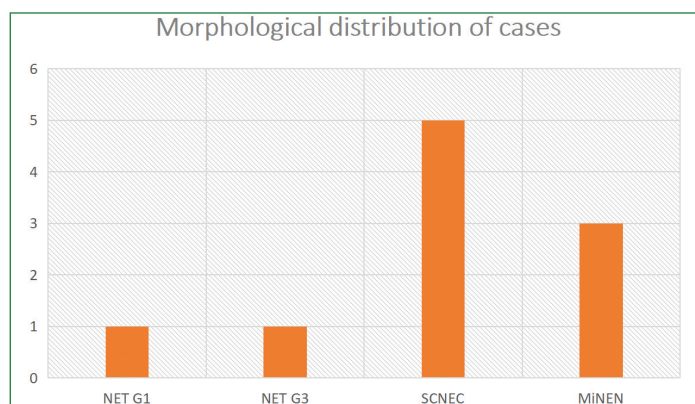
M: Male; F: Female; Ki67: Proliferative index; GEJ: Gastro-oesophageal junction; UGIE: Upper gastrointestinal endoscopy; SCNEC: Small cell neuroendocrine carcinoma



[Table/Fig-4]: Bar diagram showing age-wise frequency distribution of gastroenteropancreatic neuroendocrine neoplasms.

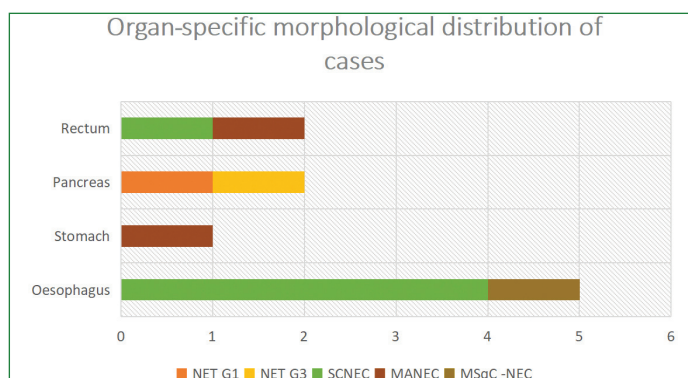


[Table/Fig-5]: Pie chart showing the organ-wise percentage distribution of gastroenteropancreatic neuroendocrine neoplasms.

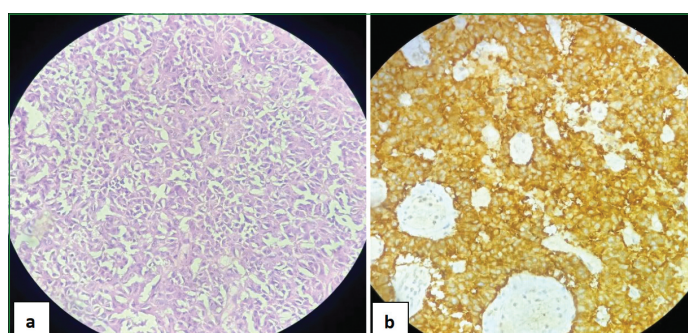


[Table/Fig-6]: Bar diagram showing the morphological distribution of gastroenteropancreatic (GEP) neuroendocrine neoplasms.

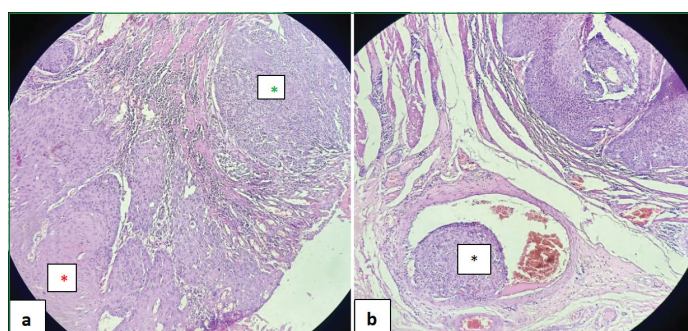
Various studies with Ki67 percentages has been presented in [Table/ Fig-13] [13-24]. The present series showed that the highest number of cases, specifically 90%, demonstrated proliferative activity >20%, which sharply contrasts with the studies presented in [Table/Fig-13] [13-24]. This could indicate a greater incidence of higher-grade tumours in this particular geographical area, emphasising the need



[Table/Fig-7]: Bar diagram showing organ-wise distribution of GEP-NEN according to WHO classification of Neuroendocrine tumours (NET) 2022.



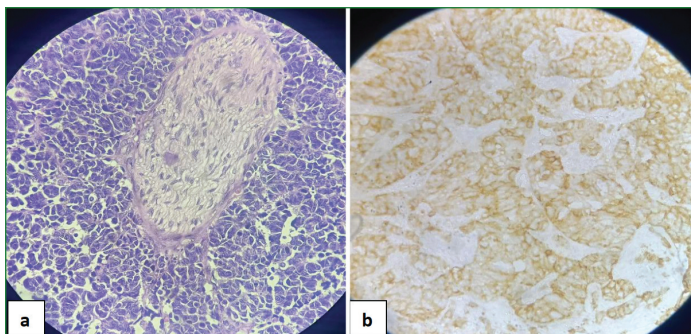
[Table/Fig-8]: Neuroendocrine Tumour (NET) grade 3 in pancreas: a) Tumour cells arranged in sheets and nests with Mitotic count >20/2 mm<sup>2</sup> (H&E, 400x); b) Stain for synaptophysin showing diffuse strong membranous and cytoplasmic positivity in tumour cells of G3 Neuroendocrine Tumour (NET), pancreas (IHC, 400x).



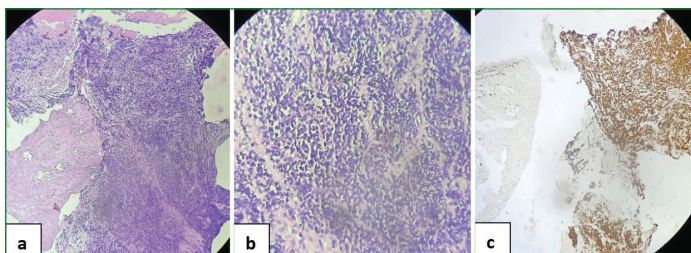
[Table/Fig-9]: Mixed squamous cell carcinoma Neuroendocrine Carcinoma (NEC) in oesophagus: a) Showing both the neuroendocrine component (green asterisk) and squamous cell carcinoma component (red asterisk) (H&E, 100x); b) Showing lymphovascular invasion (black asterisk) (H&E, 100x).

to conduct an in-depth and elaborative study of GEP-NENs with a considerable follow-up period.

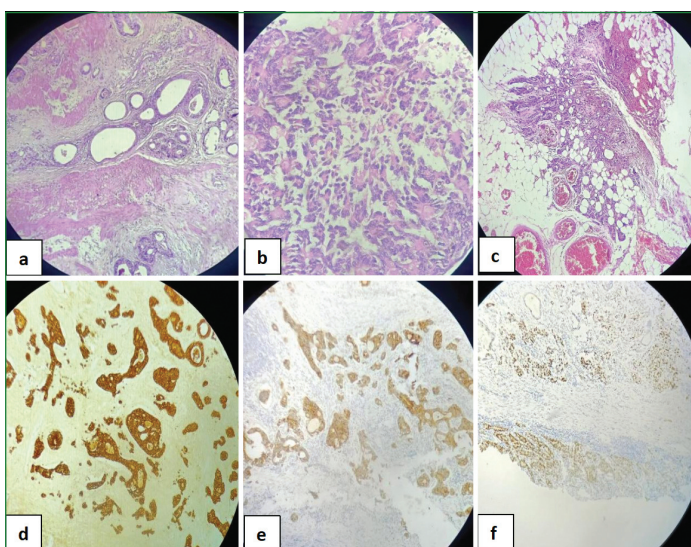
Management of NETs consists of appropriate surgery with adequate negative margins, even in metastatic disease, to prevent obstruction in bowel tumours [25,26]. There is hardly any role for chemotherapy. Somatostatin analogues, like octreotide, are recommended with precautionary measures of their associated adverse effects, like nausea, vomiting, diarrhoea and cholelithiasis [27,28]. In peptide receptor



**[Table/Fig-10]:** Small Cell Neuroendocrine Carcinoma (SCNEC) in rectum: a) Showing perineural invasion. Tumour cells have high nucleocytoplasmic ratio with hyperchromatic nuclei, granular chromatin, nuclear molding and scant eosinophilic cytoplasm (H&E, 400x); b) Stain for chromogranin showing diffuse cytoplasmic positivity in tumour cells (IHC, 400x).



**[Table/Fig-11]:** Small Cell Neuroendocrine Carcinoma (SCNEC) in oesophagus: a) Showing sheets of small cells alongside squamous epithelium and foci of necrosis (H&E, 100x); b) Showing the morphology of cells, cells are small having increased nucleocytoplasmic ratio, scant cytoplasm, hyperchromatic nuclei with inconspicuous nucleoli and nuclear molding (H&E, 400x); c) Stain for Ki67 showing 90% proliferative activity (IHC, 100x).



**[Table/Fig-12]:** Mixed adenocarcinoma Neuroendocrine Carcinoma (NEC) in stomach: a) Showing the glands corresponding to adenocarcinoma component (H&E, 100x); b) Showing small tumour cells with stippled chromatin and scant cytoplasm arranged in nests corresponding to neuroendocrine component (H&E, 400x); c) Showing metastasis in omentum (H&E, 100x); d) Stain for PanCK showing strong diffuse cytoplasmic and membranous positivity in the glandular component; e) Stain for synaptophysin showing diffuse moderate cytoplasmic positivity in the neuroendocrine component (IHC, 100x); f) Stain for Ki67 showing the area of highest proliferation (IHC, 100x).

radionuclide therapy, administered intravenously every eight weeks for four doses, a therapeutic radio label of <sup>177</sup>Lutetium is attached to a somatostatin analogue, which concentrates in neuroendocrine tissue. This label delivers local cytotoxic radiation to the NET [29]. Molecular biologic therapies, like sunitinib and everolimus, have also been utilised, showing good progression-free survival in some trials [30,31]. Currently, there are no guidelines for adjuvant or neoadjuvant treatment for MiNEN. Tumours driven by NEC are typically treated with etoposide and cisplatin-based regimens, while adenocarcinoma-driven tumours are treated with a 5-fluorouracil backbone. However, treatment options vary depending on the tumour's site, and therapies align with those for adenocarcinoma of that specific site [32-35].

S. No.	Study	Pathologic type of NET	Year	No. of cases with ki 67% <3	No. of cases with ki 67% 3 to 20	No. of cases with ki 67% >20
1	Arnold CN et al., [13]	GEP-NET	2007	9	7	3
2	Pape UF et al., [14]	Foregut NET	2008	44	85	29
3	Scarpa A et al., [15]	Pancreatic NET	2010	130	85	22
4	Garcia-Carbonero R et al., [16]	GEP-NEN	2010	126	109	53
5	Norlén O et al., [17]	Small intestinal NET	2012	203	89	7
6	Martin-Perez E et al., [18]	Pancreatic NEN	2013	71	93	20
7	Boyar Cetinkaya R et al., [19]	Pancreatic NET	2014	34	45	-
8	Sohn B et al., [20]	Rectal NET	2017	47	8	7
9	Benetatos N et al., [21]	Pancreatic NET	2018	46	41	4
10	Komaç Ö et al., [22]	GEP-NEN	2019	43	30	20
11	Fujimori N et al., [23]	Pancreatic NEN	2020	145	72	20
12	Gonulal B et al., [24]	GI-NET	2022	7	10	5
13	Present series	GEP-NEN	2024	1	0	9

**[Table/Fig-13]:** Different studies with Ki67% [13-24].

## CONCLUSION(S)

The GEP-NENs are sporadic, but they can be multiple and may be a component of a familial syndrome. Assessment of the location and extent of GEP-NENs is crucial for management. Treatment consists of surgery, chemotherapy and somatostatin analogues, although alternative options are emerging in this scenario. Hence, a better understanding of this unique group of tumours would facilitate a multidisciplinary approach and improve the quality of life. Challenges for the future include the individualisation of treatment based on clinical and/or biological features and the evaluation of innovative therapies, including immunotherapy.

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