Original Article

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Pathology Section

Clinicopathological Spectrum and Distribution Pattern of Neuroendocrine Neoplasms of the Gastroenteropancreatic System: A Cross-sectional Study of 152 Cases

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ABSTRACT

Introduction: Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs) are a heterogeneous group of tumours with varying biological, functional and clinical characteristics. GEP-NENs develop from the diffuse neuroendocrine system of the gastroenteropancreatic tract.

Aim: To analyse the clinicopathological features and the distribution pattern of GEP-NENs.

Materials and Methods: In this cross-sectional observational study, all cases of primary Gastrointestinal (GI) and pancreatobiliary tract NENs diagnosed in the Department of Pathology, Regional Cancer Centre, Trivandrum, Thiruvananthapuram, Kerala, India, from 1st January 2015 to 31st December 2020 were included. Pathological features, including tumour grade and stage, were analysed. The distribution pattern of NENs in different parts of the gastroenteropancreatic tract was noted and compared with tumour grade.

Results: A total of 152 patients were included in the study. The age of patients ranged from 9 to 84 years. Gastrointestinal tract involvement was noted in 124 cases and pancreatic involvement in 28 cases. The most common site in the GI tract was the duodenum (25 cases), followed by the rectum (22 cases). There were 62 resection specimens and 90 endoscopic biopsies. The Well-Differentiated Neuroendocrine Tumour (WDNET) category accounted for 124 cases, of which the most common grade was G2 74 (48.7%). Grade 3 NET comprised 7.14% of GI tract (7 cases) and 26.9% of pancreatobiliary tract WDNETs. There were 28 cases of Neuroendocrine Carcinoma (NEC), of which 13 were Small Cell Neuroendocrine Carcinoma (SCNEC) and 15 were Large Cell NEC (LCNEC). The most common site of NEC involvement was the oesophagus. On Immunohistochemical (IHC) examination, synaptophysin positivity was noted in 96% of cases and chromogranin positivity in 76.11% of cases. A pathological Tumour (pT) stage was determined in 62 resection specimens and the most common stage was pT3 29 (46.77%). Among the 18 resection specimens of NET G1 tumours, three cases showed lymph node metastasis. Of the 32 cases of resected NET G2 tumours, seven showed lymph node metastasis and five showed liver metastasis.

Conclusion: Morphology and the proliferation index play a crucial role in differentiating NET from NEC. WDNETs have metastatic potential, especially to lymph nodes and the liver. The differentiation of NET G3 from NEC is important for treatment decisions.

Keywords: Gastrointestinal tract, Neuroendocrine carcinoma, Pancreatobiliary tract, Small cell carcinoma

INTRODUCTION

The GEP-NENs are epithelial tumours with morphological and immunohistochemical features of neuroendocrine differentiation and originate from the diffuse neuroendocrine system located in the gastrointestinal tract and in the pancreas [1,2]. These tumours present with a variety of clinical symptoms, varying morphology and immune profiles. All NENs have malignant potential. Fundamental biological and genomic differences result in clinical heterogeneity of NENs [3-6]. The increasing knowledge on pathogenesis and the molecular background of this heterogeneous group of neoplasms has resulted in a significant evolution of the classification of digestive NENs. The latest World Health Organisation (WHO) classification, published in 2019, integrates both morphological and proliferative features and classifies NENs into WDNET and Poorly-differentiated NEC (PDNEC) [1]. The 2019 WHO 5th edition introduced the diagnostic category of WDNET grade 3 (NET G3), which refers to morphologically well-differentiated tumours with a mitotic count >20 per 2 mm^2 and/or a Ki-67 proliferation index >20%. The same mitotic count and Ki-67 criteria apply to NEC. However, PDNEC is frequently associated with extensive tumour necrosis and typically a Ki-67 index >55%. The distinction of WDNET G3 from NEC is clinically significant since the two respond differently to chemotherapy [1,7,8]. NEC responds well to platinum-containing chemotherapy whereas the response is poor in NET G3.

The present study aimed to analyse the clinicopathological features and distribution pattern of GEP-NENs. The tumour morphology, along with immunohistochemical expression of neuroendocrine markers and the proliferation index, which are important for subclassification, were studied.

MATERIALS AND METHODS

The present is a cross-sectional observational study from the Department of Pathology, Regional Cancer Centre, Trivandrum, Thiruvananthapuram, Kerala, India. All cases of GEP-NENs presented to the institute from 1st January 2015 to 31st December 2020 (six years) were included. The study period was from 1st August 2021 to 31st July 2022. The study was approved by the Institutional Review Board (IRB No 06/2021/06).

Inclusion criteria: All cases that meet the microscopic and immunohistochemical criteria of primary GEP-NENs, such as organoid arrangement of cells, granular chromatin and immunohistochemical expression of synaptophysin and chromogranin, were included in the study.

Exclusion criteria: Cases with prior history of chemoradiation and metastatic Neuroendocrine Tumours (NETs) to the gastroenteropancreatic system were excluded.

Study Procedure

The demographic data and clinical details were retrieved from the medical records. Information about the site and size of the lesion, as well as the clinical staging, was collected. The Haematoxylin and Eosin (H&E) stained slides were retrieved and re-examined. Where necessary, new sections were cut from tissue blocks. Histomorphological features analysed included cell morphology, pattern of arrangement, mitotic count, presence or absence of necrosis, vascular invasion and perineural invasion. The extent of tumour invasion, tumour size and lymph node status were noted in resection specimens. Immunohistochemical studies with cytokeratin, synaptophysin, chromogranin and Ki-67 were analysed. The tumour grade and stage were determined using the WHO classification (2019) [1]. WDNETs were graded into G1, G2 and G3 tumours on the basis of the number of mitoses per 2 mm^2 and the Ki-67 proliferative index. Tumours with fewer than two mitoses per 2 mm^2 and a Ki-67 index of less than 3% were classified as NET G1 and tumours with 2-20 mitoses per 2 mm^2 or a Ki-67 index between 3% and 20% as NET G2. Well-differentiated tumours with mitoses >20/10 High-Power Field (HPF) or a Ki-67 index >20% were classified as NET G3 [1]. NEC was diagnosed based on poorly-differentiated morphology, a high proliferation index and positive staining for neuroendocrine markers. NEC was classified as SCNEC and LCNEC based on cell morphology. The frequency and distribution pattern of NEN were studied. Clinicopathologic features such as age, sex, tumour grade, pathological stage and site distribution in different categories of NEN were analysed.

STATISTICAL ANALYSIS

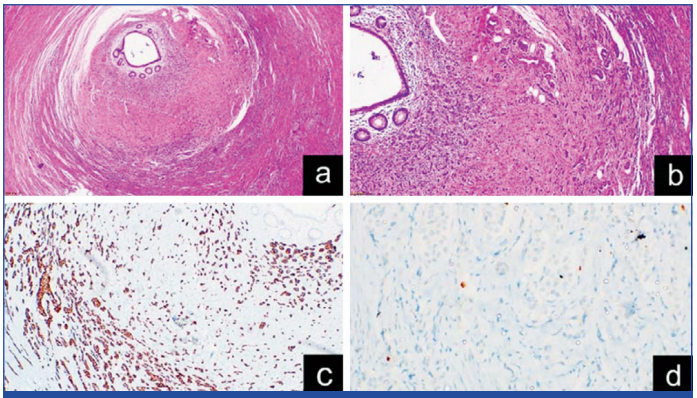
Categorical variables were summarised using counts and percentages. Continuous variables were presented using mean, median, standard deviation and interquartile range. Statistical significance was assessed using the t-test for continuous variables and the Chi-square test or Fisher's-exact test for categorical variables. All analyses were performed using Statistical Package for Social Sciences (SPSS) software (version 18.0).

RESULTS

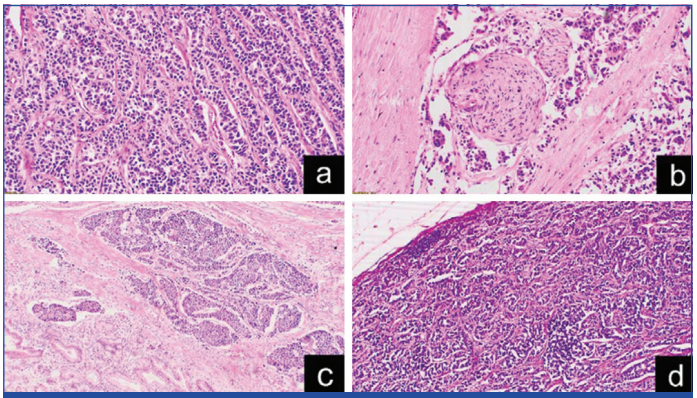
There were 152 cases of NEN diagnosed in the study period. The age range was nine to 84 years, with a mean age of 52 years. There were 96 male patients and 56 female patients. The diagnosis was made on endoscopic biopsies in 90 cases and resected surgical specimens in 62 cases. The majority of cases were GI tract NENs 124 (81.6%) cases and 28 cases involved the pancreaticobiliary tract (18.4%). The most common site in the GI tract was the duodenum {25 (16.45%) cases of total}, followed by the rectum 22 (14.47%) cases, appendix 21 (13.8%) cases, stomach 15 (9.87%) cases, oesophagus 12 (7.9%) cases, colon 11 (7.2%) cases, ileum 9 (5.92%) cases, periampullary region 7 (4.6%) cases and jejunum 2 (1.3%) cases.

Morphologically, WDNETs displayed characteristic organoid architectural patterns including nests, cords, ribbons and rosette formation. A monomorphic population of cells with round to oval nuclei, coarse or stippled (salt-and-pepper-like) chromatin with granular cytoplasm led to the morphological diagnosis of NET [Table/Fig-1-3]. NEC had a more diffuse growth pattern, poorly-differentiated cell morphology, brisk mitosis and foci of necrosis [Table/Fig-4-5].

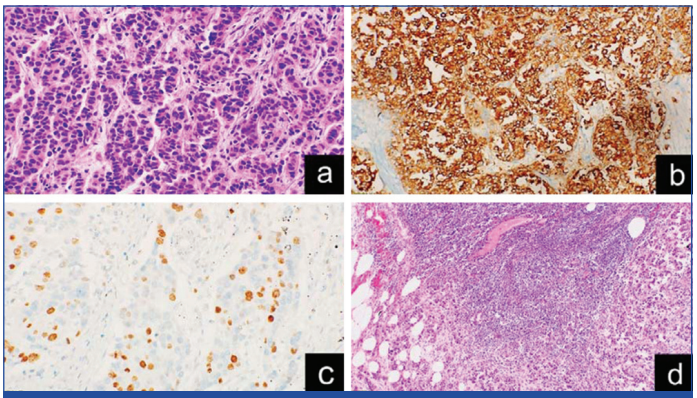
The IHC was performed with synaptophysin in 148 cases, chromogranin in 134 cases and pancytokeratin in 73 cases. Ki-67 staining was performed in all cases. Synaptophysin was positive in 142 of 148 cases (96%) and chromogranin was positive in 102 of 134 cases (76.11%). There was a statistically significant difference in the proliferation index among the different categories of NEN. Lymphovascular tumour emboli were seen in 21 cases and perineural invasion in nine cases.



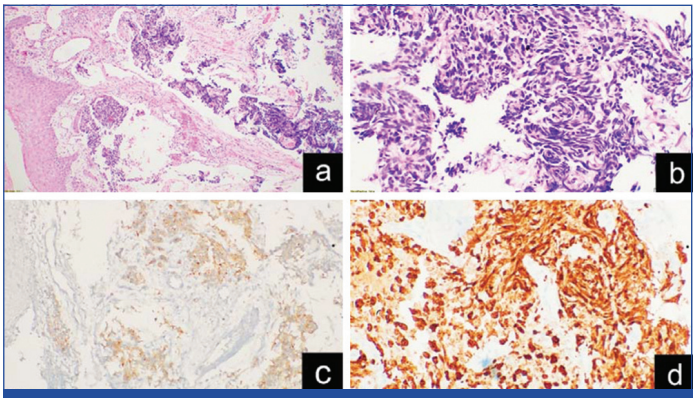
[Table/Fig-1]: a,b) Neuroendocrine Tumour (NET) grade 1 appendix infiltrating muscularis propria (H&E, X40), (H&E, X200); c) Tumour cells showing chromogranin positivity (IHC, X200), d) Low MIB 1 labelling index (IHC, X400).



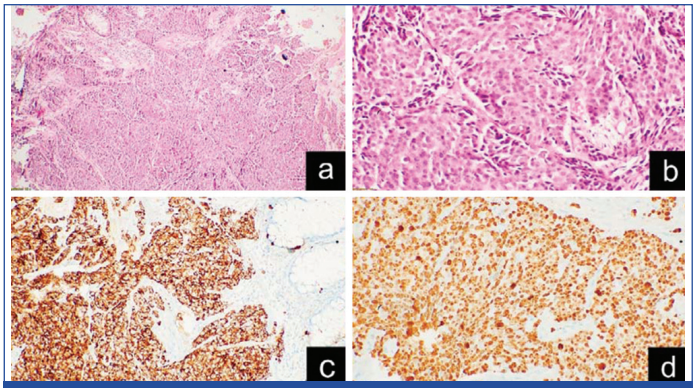
[Table/Fig-2]: a) Neuroendocrine Tumour (NET) grade 2 pancreas (H&E, X100); b) Perineural tumour infiltration (H&E, X200); c) Lymphovascular tumour emboli (H&E, X100); d) Lymph node metastasis (H&E, X40).



[Table/Fig-3]: a) Neuroendocrine Tumour (NET) grade 3 periampullary region (H&E, X200); b) Synaptophysin positivity (H&E, X200); c) MIB 1 labelling index (IHC, X400); d) Lymph node metastasis with extracapsular tumour extension (H&E, X40).



[Table/Fig-4]: a,b) Small cell carcinoma oesophagus (H&E, X40), (H&E, 400), Chromogranin positivity (IHC X400); d) High MIB 1 labelling index (IHC X400).



[Table/Fig-5]: a,b) Large Cell Neuroendocrine Carcinoma (LCNEC) rectum (H&E, X10), (H&E, 200); c) Chromogranin positivity (IHC X400); d) High MIB 1 labelling index (IHC X400).

Grading was done according to the 2019 WHO criteria [1]. WDNETs constituted 124 cases and the most common grade was G2 (n=74, 48.68% of NEN). A total of 36 cases of NET G1 (23.6% of NEN) and 14 cases of NET G3 (9% of NEN) were noted. There were 28 cases (18% of NEN) of PDNEC, of which 13 were SCNEC and 15 were LCNEC [Table/Fig-6-8]. The most common site of NET G1 was the duodenum (14 cases), followed by the appendix and rectum. The pancreas was the predominant site for NET G2 (18 cases), followed by the rectum, appendix and stomach. The most common site for NET G3 was the pancreas, followed by the rectum, colon, periampullary region and duodenum. Diagnosis was made on biopsy specimens in 90 cases and on resection specimens in 62 cases. Among the resection specimens, the most common pathological stage was pT3 29 (46.77%), followed by pT2 26 (41.93%) and pT1 7 (11.29%). Lymph node metastasis was noted in 12 cases and liver metastasis in eight cases. Of the 18 resected cases of NET G1, three cases showed lymph node metastasis. One case showed perineural tumour infiltration. Among the 32 resected cases of NET G2, seven cases showed lymph node metastasis, five cases showed liver metastasis and four showed perineural tumour infiltration. Of the four resected cases of NET G3, one case showed lymph node metastasis and one case showed liver metastasis.

Clinicopathological characteristics	WDNET (n=124)	PDNEC (n=28)	p-value
Gender			
Male	78	18	1.000*
Female	46	10	
Age groups (in years)			
Less than 30	8	0	0.148**
30-59	50	8	
More than 60	66	20	
Ki-67 (%)	8.99±10.67	71.79±20.60	<0.001***
Tumour site			
Gastrointestinal tract	98	26	0.151****
Pancreatobiliary tract	26	2	

[Table/Fig-6]: Association of clinicopathological characteristics with the type of Neuroendocrine Neoplasm (NEN).
*Chi-square test **Fisher's-exact test; ***Independent sample t-test ****Chi-square continuity correction

Clinicopathological characteristics	Grade 1 (n=36)	Grade 2 (n=74)	Grade 3 (n=14)	p-value
Gender				
Male	35	56	7	<0.592*
Female	1	18	7	
Ki-67 index (%)	1.39±0.494	7.89±5.003	34.36±8.811	<0.001**
Age groups (in years)				
Less than 30	5	3	0	0.210***
30-59	11	34	5	
More than 60	20	37	9	
Tumour sites				
Gastrointestinal tract (n=98)	35	56	7	<0.001***
Pancreatobiliary tract (n=26)	1	18	7	

[Table/Fig-7]: Association of clinicopathological characteristics of well-differentiated Neuroendocrine Tumours (NET) with the tumour grade (N=124).
*Chi-square test **One-way ANOVA: Analysis of variance;***Fisher's-exact test

Clinicopathological significance	Grade 3 WDNET (n=14)	PDNEC (n=28)	p-value
Gender			
Male	9	18	1.000*
Female	5	10	
Age groups (in years)			
Less than 30			0.637*
30-59	5	8	
More than 60	9	20	
Ki-67 (%)	34.36±8.811	71.79±20.60	<0.001**
Tumour site			
Gastrointestinal tract	7	26	0.005***
Pancreatobiliary tract	7	2	

[Table/Fig-8]: Comparison of grade 3 Well-Differentiated Neuroendocrine Tumours (WDNET) and poorly-differentiated NECs with respect to clinicopathological characteristics.
*Chi-square test **Independent sample t-test; ***Chi-square continuity correction

DISCUSSION

Neuroendocrine Neoplasms (NENs) can arise in almost all organ systems of the body and can exhibit a diverse range of clinical, morphological and genomic features with varied outcomes. They can be functional or non functional. GEP-NENs range from indolent well-differentiated NETs to aggressive PDNEC [1-4,6]. The system of classification and terminology of NENs was updated in 2017 by American Joint Committee on Cancer (AJCC) and in 2019 by WHO. A major change in the latest WHO classification is the separation of WDNET G3 from NEC [1]. NETs are well-differentiated epithelial neoplasms with neuroendocrine differentiation and typically show organoid architecture, uniform nuclei and coarse granular chromatin. All NETs are considered malignant neoplasms. Early-stage NETs have a low risk of metastasis if they are entirely removed. Tumours with well-differentiated morphology but with high proliferation, i.e., more than 20 mitoses per 2 mm^2 or a Ki-67 index of more than 20%, were classified as NECs under the previous WHO classification. According to the latest WHO classification, tumours retaining the morphological features of WDNETs (organoid histological patterns with nests, cords, trabeculae, ribbons and rosette formation) but with more than 20 mitoses per 2 mm^2 or a Ki-67 index of more than 20% are classified as NET G3. Poorly-differentiated tumours with high proliferation indices are classified as NEC. The introduction of NET G3 was based on the differences in the pathogenesis of WDNETs and PDNECs, which impact treatment and clinical outcomes [1,9,10]. Genomic data provide evidence that NETs and NECs are distinct entities. Mutations in MEN1, DAXX and ATRX are characteristic for NETs and are not seen in NECs. NECs have mutations in TP53, RB1 and other carcinoma-associated genes [1,8-10]. G3 NETs retain the mutation profile of well-differentiated neoplasms, thus differing at the genomic level from NECs. NECs respond well to platinum-containing chemotherapy, whereas WDNETs, including G3 NETs, often fail to respond to this regimen and paradoxically may be associated with longer survival. Many studies have shown that differentiation status is the most important prognostic factor in determining the clinical course of NENs, regardless of primary site or stage [1,6,11,12].

In the present study, Grade 2 NETs were the most common type of GEP-NENs (74 cases, 48.68% of total NEN), followed by Grade 1 NETs (36 cases, 23.6%). There were 14 cases (9%) of NET G3. This is in contrast to a study by Koseci T et al., in the Turkish population. In their study, NET grade 1 tumours formed the majority of GEP-NET cases (61.8%), followed by NET grade 2 (18.8%) and NET grade 3 (19.4%), which included both NET G3 and NEC cases [13]. Rafique Z. et al., studied 87 cases of NET and found the majority were NET G1 tumours, constituting 62% of cases [14].

Of the 124 WDNET cases in the present study, 14 were grade 3 WDNET (NET G3). Literature searches show the pancreatobiliary tract as the most common site of grade 3 WDNET; the current study likewise noted that grade 3 WDNETs were more common in the pancreas. In our series, NET G3 cases were associated with an older mean age than NET G1 and NET G2, similar to other studies [13-17]. PDNECs had a higher proliferative index and mean age than grade 3 WDNETs.

The NECs are poorly-differentiated epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation. By definition, these are high-grade neoplasms and include small cell carcinoma and large cell neuroendocrine carcinoma [1,6,8,17].

Literature searches show WDNETs are far more frequent than PDNECs [3,13,14,16,18]. In this study, the majority 124 (81.6%) cases were WDNETs, whereas there were 28 cases (18.4%) of PDNECs.

Of the 62 cases that underwent resection, pT3 was the most common category with 29 cases (46.77%), followed by pT2 26 (41.94%) cases and pT1 7 (11.29%) cases. A study by Rafique Z et al., also showed the predominant stage as pT3 (36.1%), followed by pT2 (25.5%) [11]. In the study by AkınTelli T., the most common stage at diagnosis was stage 4 (40.9%) [3].

Oesophagus: Endocrine cells in the oesophagus are relatively rare. NETs of the oesophagus are particularly uncommon and reports are limited to individual cases and small case series. In a large series by Modlin IM and Sandor A, consisting of 8,305 carcinoid tumours from the SEER database and two NCI archives, only three arose in the oesophagus, constituting 0.05% of all GI NET cases [19]. Of the four cases reported by Hoang MP et al., two were associated with Barrett oesophagus, which contained endocrine cell hyperplasia [20,21].

In the current series, 12 cases involved the oesophagus. All cases were PDNECs, including 10 cases of small cell carcinoma and two cases of large cell carcinoma. Secondary involvement from other organs, especially the lungs, was excluded by clinical and radiological correlation as well as by immunohistochemical evaluation.

Stomach: Unlike the rest of the GI tract, the etiology of many stomach NETs is known. Although some recent studies describe the stomach as the most frequently involved site, in the present study only 15 cases (9.9% of the total) involved the stomach [13,22]. The most common subtype was NET G2 with 11 cases. There were three cases of LCNEC involving the stomach.

Small intestine: NETs are common in the small bowel. In the present study, the most common site of NET was the duodenum with 25 cases. There were nine cases involving the ileum. Ampullary NETs tend to have a more aggressive phenotype, with generally higher-grade tumours and poorer outcomes [21]. The authors had seven cases involving the periampullary region, which included G1 NET, G2 NET and LCNEC.

Midgut NETs are those most associated with the classic carcinoid syndrome of diarrhea, flushing and right-sided heart fibrosis/damage, most likely because even small tumours have a stronger tendency to metastasise to local lymph nodes and to the liver, compared with other GI NETs. Even with nodal or distant metastases, survival is often still several years, as these NETs are rather indolent. NETs respond poorly to most chemotherapies [21].

Appendix: Despite frequent infiltrative growth into the muscularis propria and the subserosa, lymph node metastases are rare. In the present study, of the 21 appendiceal NENs, 10 were G1 NET and 11 were G2 NET. Appendiceal NENs constituted 13.8% of the total cases. Patients were younger and had excellent outcomes after appendectomy.

Colorectum: The distal colon and rectum are derived from the foetal hindgut. Outside of the caecum and proximal colon, which are midgut areas, most colonic NETs are found in the rectum. In the present study, 22 cases involved the rectum and 11 involved the colon.

Pancreas: The current WHO classification is very useful for stratifying patients with pancreatic NENs (panNENs) into different prognostic categories and its use is strongly recommended. The category of G3 NET was first described and extensively studied in pancreatic NENs. While pNECs grow rapidly and have a poor prognosis, the survival rate for slow-growing pNETs is better. A study by Uppin MS et al., showed the majority of NENs in the pancreas were grade 1 (81.81%) and the rest grade 2 (18.18%) [16]. Goodell PP et al., found that 57.77% of cases belonged to grade 2, followed by G1 and G3 [15]. In this study, NET G1 was rare in the pancreas. Most pancreatic NETs were NET G2. There were 14 cases of NET G3 involving the GI tract and pancreas (GI tract: 7 cases; pancreas: 7 cases). NET G3 constituted 7% of GI NENs and 27% of pancreaticobiliary NENs.

Ileum and appendix have been reported as among the most common sites for NET in earlier studies [5,14]. The present study demonstrates that the most common location in the GI tract is the duodenum, followed by the rectum and appendix. Similar findings were noted by Uppin MS et al., [16], in which the duodenum and periampullary regions were the most involved [16]. This is in contrast to the study by Amarapurkar DN et al., where the stomach (30.2%) was found to be the most common site [22]. In the study by Akın Telli T, the most common site of the tumour was the stomach (36.7%) [3]. Koseci T et al., also noted the stomach as the most common site of NET in their series of 149 cases [13]. Samanta ST et al., in their study on 100 cases of GEP-NENs, reported the most common primary site as the pancreas followed by the small intestine [18].

Limitation(s)

The sample size was limited in the present study. A larger sample size and longer follow-up will provide more reliable insights into the biological behaviour of these heterogeneous groups of neoplasms.

CONCLUSION(S)

The NENs are heterogeneous in terms of disease origin and pathogenesis. In the present study, the most common site of NEN in the GI tract was the duodenum. NET G2 was the most common subtype of gastroenteropancreatic NEN. The oesophagus was the commonest site of NEC. In the present study, grade 3 WDNETs were more common in the pancreatobiliary tract than in the GI tract. Moreover, grade 3 WDNETs were associated with an older mean age than low-grade WDNETs. Morphology and proliferation index play crucial roles in differentiating NET and NEC. WDNETs have metastatic potential, especially to lymph nodes and liver.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 14, 2025
- Manual Googling: Jul 18, 2025
- iThenticate Software: Jul 21, 2025 (25%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

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- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

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