Original Research Article

Clinicopathological spectrum of neuroendocrine neoplasms; retrospective study at a tertiary care centre

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Abstract

Introduction: Neuroendocrine tumors are cancers that begin in specialized cells called neuroendocrine cells. Neuroendocrine cells have traits similar to those of nerve cells and hormone-producing cells. Neuroendocrine neoplasms (NENs) belong to a group of malignancies with poorly defined, confusing histology and nomenclature to match. Neuroendocrine cells (NE) are distributed throughout the body and hence NENs have been described in the central nervous system, respiratory tract, larynx, gastrointestinal (GI) tract, thyroid, skin, breast, and urogenital system. Among which gastrointestinal tract and lungs are the most common primary tumor sites.**Materials and Methods:** It was a retrospective cohort study conducted at the Department of General Surgery, JSS Hospitals, Mysuru from June 2014 to June 2019 (5 years). A series of 75 patients with NENs, data was collected through the administrative database, medical records, direct interview of patients. All those patients who were diagnosed to have neuroendocrine tumors incidentally detected/detected post-operatively through histopathological examination were included. All those patients diagnosed to have neuroendocrine tumors but deemed to be medically unfit for surgery were excluded from the study.

Results: There were 75 cases of NENs diagnosed in the study period which included 44 male and 31 female patients in the age range of 13 to 80 years (mean: 54 years) Majority of them (80%) were >45 years of age. The diagnosis was made on endoscopic biopsies in 41 cases and resected surgical specimens were available in 34 patients. Biopsy diagnosis was mostly made in NENs of GI tract whereas all the pancreatic, periampullary lesions, colon, appendix, breast were diagnosed on resected specimens.**Conclusion:** The duodenum followed by colorectal, stomach were found to be the most common sites of NENs. The majority of tumors are NET G1 and were classified based on WHO classification and most of the G3 tumors were not amenable to surgical clearance. 87% of the NENs were completely resectable, in our study. Still, limited available studies opine differently in most of the parameters pertaining to NENs. Hence, more studies with a large number of subjects, are required in this regard.

Keywords: Neuroendocrine tumors, periampullary lesions, colon, appendix, breast.

Introduction

Neuroendocrine tumors are cancers that begin in specialized cells called neuroendocrine cells. Neuroendocrine cells have traits similar to those of nerve cells and hormone-producing cells[1]. Neuroendocrine neoplasms (NENs) belong to a group of malignancies with poorly defined, confusing histology and nomenclature to match[2]. Neuroendocrine cells (NE) are distributed throughout the body and hence NENs have been described in the central nervous system, respiratory tract, the larynx, gastrointestinal (GI) tract, thyroid, skin, breast, and urogenital system[3]. Among which gastrointestinal tract and lungs are the most common primary tumor sites[4-6].The "neuro" property is based on the identification of dense-core granules (DCGs4) that are similar to DCGs present in serotonergic neurons, which store monoamines. Unlike neurons, however, NE cells do not contain synapses. The "endocrine" property refers to the synthesis and secretion of these monoamines[7].

The neuroendocrine (NE) system includes various endocrine glands, such as the pituitary, the parathyroids, and the NE adrenal, as well as endocrine islet tissue embedded within glandular tissue (thyroid or pancreatic) and scattered cells in the exocrine parenchyma, such as endocrine cells of the digestive and respiratory tracts, which belong to diffuse endocrine systems[8].Clasically, well-differentiated NENs were referred to as carcinoid tumors, a term that is very vague, which doesn't clearly demarcate between benign/malignancy, grading, severity. As there is a wide range of confusions regarding nomenclature, varied clinical presentation, histopathological findings, in this study we have focussed on the clinicopathological spectrum of NENs, in patients who presented to our Department of General Surgery and allied branches at our tertiary care hospital.

Materials and Methods

It was a retrospective cohort study conducted at the Department of General Surgery, JSS Hospitals, Mysuru from June 2014 to June 2019 (5 years). A series of 75 patients hospital medical records data was collected analyzed through an administrative database, medical records, direct interviews of patients.

Study design: Retrospective cohort study

Place of **study**: JSS Hospitals, Mysuru

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Source of data: Hospital medical records
Sample size: Series of 75 patients
Duration of study: 5 years (June 2014 to June 2019)
Methods of data collection: Through the administrative database, medical records, direct interview of patients.
Inclusion criteria:

- All those patients were diagnosed to have neuroendocrine tumors.
- Incidentally detected neuroendocrine tumors.
- Patients with neuroendocrine tumors detected post-operatively through histopathological examination.

Exclusion criteria
All those patients diagnosed to have neuroendocrine tumors but deemed to be medically unfit for surgery.

Results and Observations

Age and sex distribution

There were 75 cases of NENs diagnosed in the study period which included 44 male and 31 female patients in the age range of 13 to 80 years (mean: 54 years) Majority of them (80%) were >45 years of age. The diagnosis was made on endoscopic biopsies in 41 cases and resected surgical specimens were available in 34 patients. Biopsy diagnosis was mostly made in NETs of GI tract whereas all the pancreatic, periampullary lesions, colon, appendix, breast were diagnosed on resected specimens.

Table 1: Gender Distribution

	Frequency	Percent (%)
Male	44	58.66
Female	31	41.34
Total	75	100.0

Clinical features

The majority of cases were non-functional and 17 patients were asymptomatic, which were diagnosed on UGI endoscopy while evaluating for other diseases. The most common presentation was vomiting, followed by pain abdomen. 38% of the subjects had associated loss of weight/appetite. *Matthew H Kulke* reported vague abdominal symptoms as the most common presentation, in their study[9]. Only 1 patient presented with mass per abdomen, which on further evaluation and on Histopathological Examination (HPE), turned out to be a retroperitoneal NEN. None of the cases presented with carcinoid syndrome. All were sporadic cases of NENs. The clinical features are summarized in Fig 1**.**

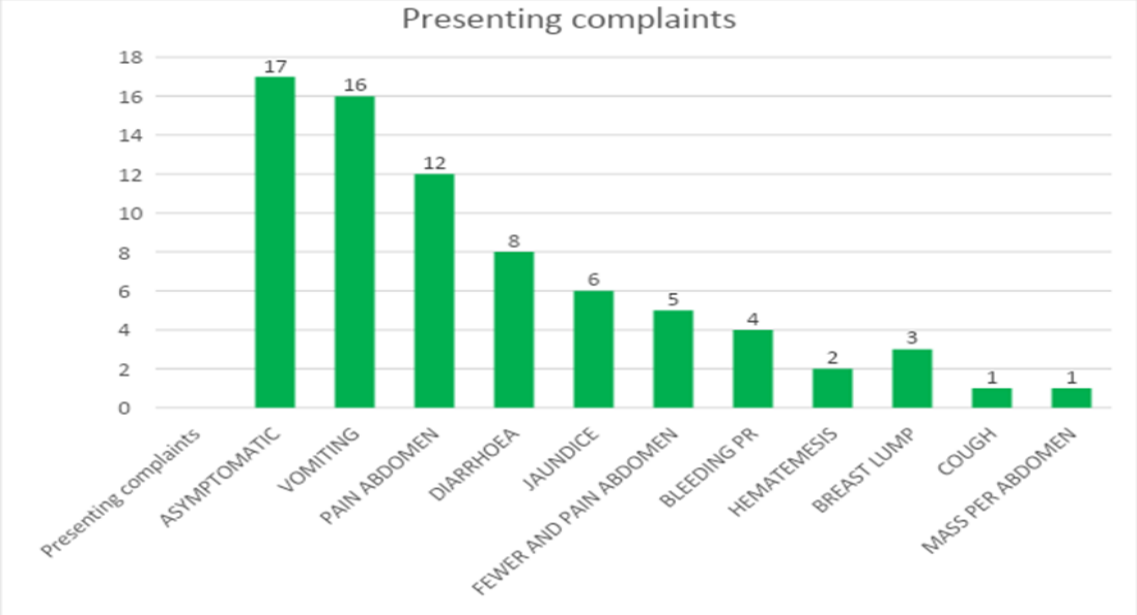

Fig 1: Presenting complaints

Location

Gastrointestinal (GI) NENs were found in 67 patients whereas 11 were spread in other parts of the body. In GIT, the commonest location was the small intestine, in which the 1st part of the duodenum (n=17) was most common followed by the 2nd part (n=7). In our study, the next common location was found to be the rectum(majority of them were in the form of asymptomatic rectal polyps), followed by stomach (11 cases), pancreas (8 cases), appendix (6 cases), 3 each in breast and colon. Only a single case of distal ileal, pituitary, lungs, gall bladder, retroperitoneum NENs was identified. Out of the 8 cases of pancreatic NEN, 5 were arising from head of the pancreas, 1 from the body of pancreas, and 2 from tail of the pancreas. Pictograph representation of the location of NENs has been depicted in Fig.2.

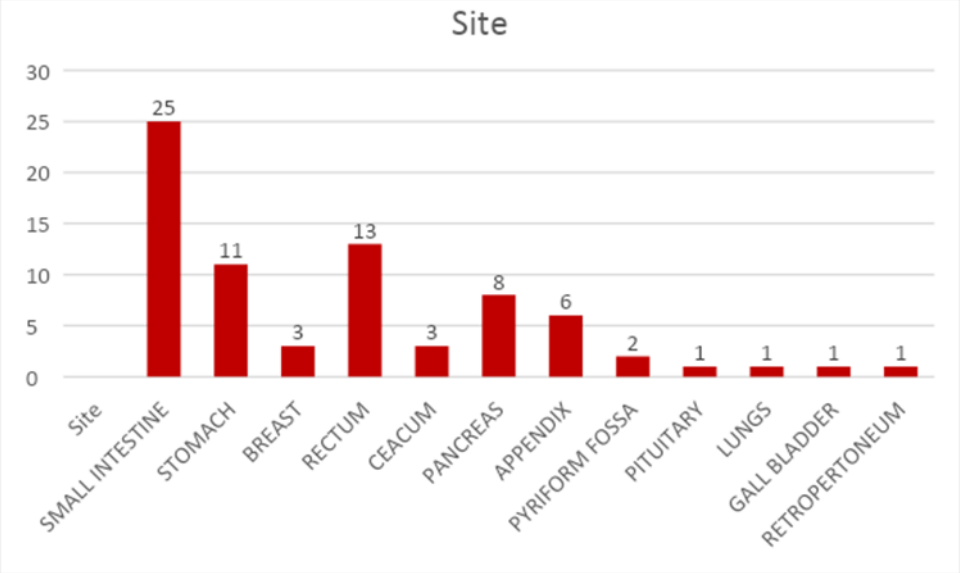

Fig 2: location of NENs

Resectability

Among 75 patients diagnosed with NENs, 47(63%) patients underwent surgery for surgical clearance of the tumor. Among 47 cases, 6 were found to be unresectable due to extensive local/distant spread and various factors. Hence, 87% of NENs were resectable (Pre-op systemic chemotherapy and other treatments are not discussed here, as it is beyond the scope of this article). The following Fig.3 depicts the percentage of unresectability.

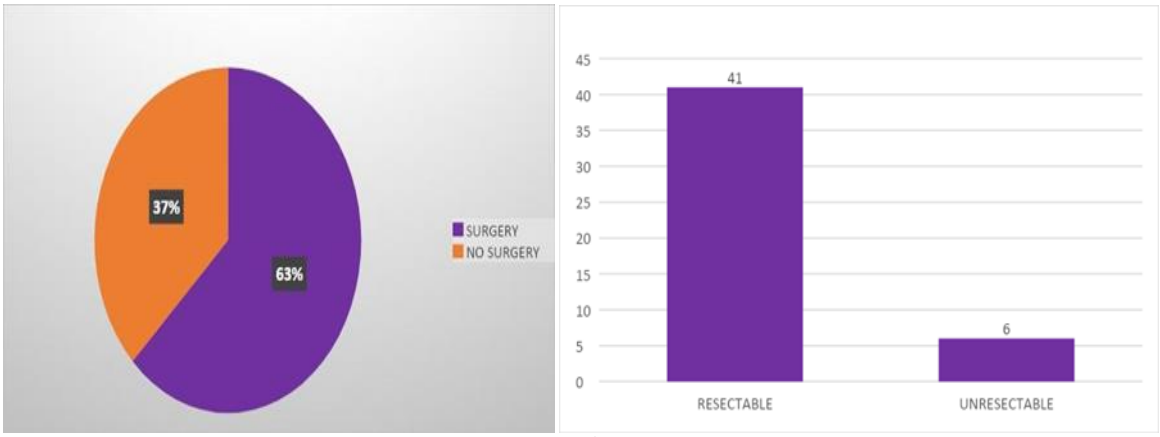

Fig 3: percentage of unresectability.

Tumor Grades:

WHO guidelines for grading GI and pancreatic NENs has been depicted in Table **2**. In our study, most of the NENs were Grade 1 (57%), followed by Grade 2 (33%) and Grade 3 (10%) as shown in **Table 3**.

Table 2: WHO guidelines for grading GI and pancreatic NENs

WHO Grade	Mitotic Count/10 HPFs	Ki-67Labeling Index, %
NEN Grade 1	<2	<3
NEN Grade 2	2-20	3-20
NEN Grade 3	>20	>20
	Frequency	**Percent**
Grade 1	42	57%
Grade 2	24	33%
Grade 3	7	10%

Table 3: Grading GI and pancreatic NENs

Location	NETG1	NETG2	NET G3
Stomach	5	4	2
Duodenum	17	8	-
Pancreas	1	6	1
Ileum	-	1	-
Colon andrectum	13	1	2
Appendix	4	2	-
Other sites	2	-	4

Grade 1 is a NET with a mitotic count of less than 2 per 10 high-power fields (HPFs) and/or less than 3% Ki-67 labeling index; G2 is a NET with a mitotic count of 2 to 20 per 10 HPFs and/or a 3% to 20% Ki-67 labeling index, and NEC is a small cell carcinoma or large cell carcinoma with a mitotic rate of more than 20 per 10 HPFs and/or greater than a 20% Ki-67 labeling index. For precise evaluation of the grading, a minimum of 50 HPFs for the mitotic count and at least 500 cells for the Ki-67 labeling index should be counted from hot spots[10,11]

Differentiation of NENs: The WHO 2000 classification divided NETs from the GI and pancreaticobiliary tracts into well-differentiated endocrine tumors, well-differentiated endocrine carcinomas, and poorly differentiated endocrine carcinomas, based on the degree of differentiation[12]. Among 75 cases, 77% (n=57) of NENs were found to be well-differentiated, in our study, as depicted in **Table 4.**

Table 4: Differentiation of NENs

Differentiation	Frequency	Percent (%)
Well-differentiated	58	77%
Poorly Differentiated	17	23%

Discussion

As there is a continuous and significant evolution in the nomenclature and classification of NENs since the last few years, and as there are very few studies regarding the entire clinicopathological spectrum of NENs, we have attempted to put forward our experience with neuroendocrine tumors. NENs belong to a group of malignancies, which arises from a special type of cells called 'neuroendocrine cells' which have traits similar to those of nerve cells and hormone-producing cells. NENs are rare kind of tumors which can arise anywhere from the body, most commonly in GI tract followed by lungs.There are various classifications w.r.t. NENs. Slow and rapidly growing tumors depending on their rate of growth. Functional NENs are those NENs that produce excess hormones, that give rise to symptoms, which will finally lead to a diagnosis of such tumors. Nonfunctional neuroendocrine tumors don't release hormones at all or don't release enough to cause symptoms and are usually diagnosed as an incidental finding.The WHO 2000 classification divided NENs from the GI and pancreaticobiliary tracts into well-differentiated endocrine tumors, well-differentiated endocrine carcinomas, and poorly differentiated endocrine carcinomas, based on the degree of differentiation[12]. Well-differentiated endocrine tumors were further classified into benign tumors and low-grade malignant tumors, based on the tumor size, mitotic rate, Ki-67 labeling index, lymphovascular invasion, and symptoms, in association with hormonal oversecretion [12], whereas poorly differentiated endocrine carcinomas usually indicate small cell and large cell carcinomas.Well-differentiated NECs have been regarded as low-grade malignancies, and poorly differentiated NECs were considered high-grade malignant tumors. Both well-differentiated and poorly differentiated endocrine carcinomas are invasive cancers with the ability to metastasize to distant organs. The term neuroendocrine neoplasm has been accepted as general nomenclature instead of carcinoid because carcinoid does not convey the malignant nature of the tumors and can be confused with carcinoid syndrome. GEPNENs (Gatroenteropancreatic NENs) are rare tumors accounting for 2.5 to 5 cases per 100, 000[3] The increasing use of endoscopic study and rising trend of performing endoscopic biopsies from suspicious foci with easy availability of IHC stains perhaps have useful in documenting more and more number of GEPNENs.

In our study, which included 75 patients over a duration of 5 years, 44 were male patients and 31 were female patients and 80% of them were >40 years. Among them, the diagnosis was made on endoscopic biopsies in 41 cases and surgical specimens were used for diagnosis in 34 cases.In our study, a maximum number of patients were asymptomatic, as most of them were incidentally diagnosed on endoscopic procedures. Among the remaining patients, most of them presented with nonspecific symptoms of abdominal pain and vomiting. Whereas, Amarapurkar et al. who reported 74 cases of NETs of GIT-pancreas reported most of their patients presented with vague non-specific symptoms[12].Megha S. Uppin, Shantveer G. Uppin et al. also opined the same[13]We gave special emphasis on the location of NENs in our study, as there is a wide range of opinions regarding the most common sites of NENs, in the limited available data. In our study, we found small intestine (1st part of duodenum followed by 2nd part) was the most common site of NENs (32%). Similar findings were also noted by Maggardet al[13] Small intestine was the most common site accounting for 44.7%. Whereas Amarapurkar et al. reported the stomach as the most common site (30.2%) followed by the pancreas (23.3%), in their study.In our study, the duodenum was the most common site (32%) and this doesn't include any NENs of the ampulla region. The clinical course of the ampullary NETs is different from duodenal NETs, as they have a more aggressive phenotype, with generally higher-grade tumor[14-16].NENs of the stomach is divided into three types and the most frequent subtype is type I arising in the fundus or body and these are associated with chronic atrophic gastritis[17].Our study also depicted the same, where most of the gastric carcinoids were type I (45%) followed by type I (36%). Estrozi B noted stomach followed by small intestine and pancreas as common sites with the majority being G1 tumors[18]In our study, there was only one case of bowel NENs, which was found in a resected specimen of ileum in the form of multiple polyps.Colorectal NENs account for 4–8% of the GIT NETs. But incidence in our study, the incidence of colorectal NENs (16 cases, 21%) was a bit on the higher side. Almost similar incidence of colorectal NENs was reported by Megha S. Uppin https://www.ncbi.nlm.nih.gov/pubmed/?term=Uppin%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=28280618et al. These are regarded as "low-grade malignant", even in the presence of metastasis.Furthermore, the

WHO classification defines colorectal carcinoids as "benign" if the tumors are localized in the submucosa, measuring 20 mm or less and lack vascular invasion[19].

Table 5: A comparative analysis of the pancreatic NETs

Parameters	Goodell et al[19]	Nadler et al[20]	Megha S. Uppin et al[13]	Present study
Mean age(in years)	59.4	52	46.77	51.6
Male: Female	1.04:1	1:1.1	1.1.2	1.6:1
Grading				
Grade 1	13(28.89%)	18(47%)	9(81.81%)	1(12.5%)
Grade 2	26(57.7%)	16(42%)	2(18.18%)	6(75%)
Grade 3	6(13.33%)	3(8%)	-	1(25%)

We had given special emphasis on the surgical/ clearance/ resectability of NENs. *Schurr PG et al*. reported aggressive surgical treatment improves long-term survival[21] In our study, among 75 patients diagnosed with NENs, 47(63%) patients required surgery for surgical clearance of tumor. Among 47 cases, 6 were found to be unresectable due to extensive local/distant spread and various factors. Hence, 87% of NENs were resectable.

Conclusion

The duodenum followed by colorectal, stomach was found to be the most common sites of NENs. The majority of tumors are NET G1 and were classified based on WHO classification and most of the G3 tumors were not amenable to surgical clearance. 87% of the NENs were completely resectable, in our study. Still, limited available studies opine differently in most of the parameters pertaining to NENs. Hence, more studies with a large number of subjects, are required in this regard.

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