



NEUROENDOCRINE NEOPLASMS: RETROSPECTIVE CLINICOPATHOLOGIC STUDY IN TERTIARY HOSPITAL

Histopathology

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ABSTRACT

Background: Neuroendocrine neoplasms are rare heterogenous tumors having common phenotype. They can be located in any organ and originate from endodermal cells which proliferate from epithelium or other tissues with or without endocrine function. **Aim:** The objective of the present study is to compare frequency, distribution, clinicopathological features and their prognostic importance in the neuroendocrine neoplasms. **Methodology:** A retrospective hospital based study of the data was carried out for a period of 8 years from September 2015 to September 2023 after getting approval from institutional ethical committee. Clinicopathological data of Neuroendocrine neoplasms were collected by analyzing the hospital records. **Results:** Our study included 147 cases of NENs. Incidence of NENs was slightly higher in males (53.7%) and in the age group above 50 years (64.7%). Frequency of NENs were found to be highest in gastro intestinal tract (41 cases, 27.8%). Maximum number of NENs were localized and tumors with distant metastasis were seen in small bowel. Grade 1 tumors were seen most commonly in stomach, small bowel, pancreas and appendix. Maximum number of grade 2 tumors and grade 3 tumors were seen in stomach and liver. Neuroendocrine carcinomas were seen commonly in lung. Tumors with distant metastasis were seen in grade 3 Neuroendocrine neoplasms and neuroendocrine carcinomas. **Conclusion:** Male gender, elderly age and high grade were associated with worse prognosis. Gastrointestinal tract is the most common organ involved and were of lower grade. Lung had highest incidence of high grade tumors, but distant metastasis were seen in tumors of small intestine.

KEYWORDS

Neuroendocrine Neoplasm, Clinicopathological Features, Prognostic Factors.

INTRODUCTION:

Neuroendocrine neoplasms (NEN) originate from endodermal cells present in tissue with or without endocrine functions.^[1] Frequently involved sites are gastrointestinal tract (70%) and pancreas followed by broncho-pulmonary system (20%- 30%).^[2] Spectrum of neuroendocrine tumors ranges from low-grade to high-grade carcinomas expressing neuroendocrine markers.^[3] These tumors can have indolent behavior and can be aggressive with resistance to therapy.^[4] Incidence of NEN has been increasing in the past few decades which can be either because of increased recognition of these neoplasms or increased true incidence of these neoplasms.^[5] In our study we tried to analyze the frequency, distribution, clinico pathological features and their prognostic importance in the neuroendocrine neoplasms.

MATERIALS AND METHODS:

A retrospective hospital based study of data was carried in the department of pathology, for a period of 8 years from September 2015 to September 2023 after getting approval from institutional ethical committee with IEC No. 1349. Informed consent was obtained from all the participants. Neuroendocrine neoplasms were diagnosed histopathologically and confirmed by immunohistochemistry with Synaptophysin and Chromogranin A. Ki 67 was used to grade the tumor. Tumors were reclassified based on 2022 WHO classification of neuroendocrine neoplasms. Clinicopathological data of Neuro endocrine tumors like age, gender, site, grade and stage were collected by analyzing the hospital records. Association between grade and stage with site, age, gender was studied.

Inclusion criteria:

All the cases of NENs which were histopathologically diagnosed, with complete clinical details and immunohistochemistry status were included in the study

Exclusion criteria:

NEN cases which were not having immunohistochemistry status but diagnosed on morphology in routine Hematoxylin and eosin stain and without complete clinical details were excluded

As there is no single staging system to be applied to all the NENs at different sites, staging system is simplified as local, regional and distant. Localized tumor is confined to organ of its origin. Regional tumor is defined as invasive tumor infiltrating into the adjacent organ or tissue and/or regional lymph nodes. Distant tumors are the tumors which had spread to the distant sites away from the site of origin.^[5] Grading system is based on proliferation which is assessed by Ki67 and mitotic rate. NENs are graded as Grade 1 (low grade), grade 2 (intermediate grade), grade 3 (high-grade) and neuroendocrine carcinoma (NEC) according to 2022 WHO classification of neuroendocrine neoplasms.^[6]

Statistical Analysis:

collected data was entered in Microsoft excel 2019. Chi-square test was performed between proportions. SPSS 26th version was used for statistical analysis. P value less than 0.05 is considered as statistically significant.

Frequency of NENs in different age groups and gender were analyzed. Incidence of these tumors in different organs were studied. Grades and stage of NENs were studied and their association with age, gender, site, and size of the tumor were analyzed. Association between the grade and stage of NENs were also evaluated.

RESULTS

Our study included 147 cases of NEN, details of which were taken from hospital records from September 2015 to September 2023. Of 147 cases of NEN, 78 (53.7%) were in males and 69 (46.3%) were in female showing male predominance (Table 1)

Frequency of neuroendocrine neoplasms in different age groups were

studied and maximum number of cases were found in the age group above 50 years (64.7%). Maximum cases were in 51-60 years of age (25.2%) and minimum number of cases were noted in 21-30 years and <20 years (2% respectively in each age group). We assessed the association of age groups with gender in NENs. We found that NENs in age group below 50 years were found to be more common in women where as in elderly age group (above 50 years) showed male predominance (Table 1). This association showed statistical significance with p value of 0.001.

Table 1: Association of different genders with age groups in NENs

Age group	Gender		Total
	Male	Female	
< 20 years	3 (4.3%)	0 (0%)	3 (2%)
21 – 30 years	3 (4.3%)	0 (0%)	3 (2%)
31 – 40 years	14 (20.3%)	4 (5.1%)	18 (12.2%)
41 – 50 years	17 (24.6%)	11 (14.1%)	28 (19.0%)
51 – 60 years	14 (20.3%)	23 (29.5%)	37 (25.2%)
61- 70 years	10 (14.5%)	22 (28.2%)	32 (21.8%)
> 70 years	8 (11.6%)	18 (23.1%)	26 (17.7%)
Total	69 (100%)	78 (100%)	147 (100%)
Chi-square test – P is 0.001			

Frequency of NENs were found to be highest in gastro intestinal tract (41 cases, 27.8%) with maximum number of cases in stomach (19 cases, 12.9%). Next in frequency are lung (30 cases, 20.4%), lymph node (14 cases, 9.5%), cervix (14 cases, 9.5%), liver (12 cases, 8.2%), pancreas (7 cases, 4.8%) and thyroid (4 cases, 2.7%) (Table 2). In the GIT, maximum number of cases were seen in males except in small intestine and appendix which showed female predominance. In other organs, NEN showed male predominance. This association showed statistical significance with p value of <0.001. (Table 2)

Table 2: Distribution of NENs in different gender and organs

Organ involved	Females	Males
Appendix (n=2)	2 (2.9%)	0 (0.0%)
Cervix (n=14)	14 (20.3%)	0 (0.0%)
Colon (n=3)	1 (1.4%)	2 (2.6%)
Cecum (n=1)	0 (0.0%)	1 (1.3%)
Rectum (n=2)	0 (0.0%)	2 (2.6%)
small bowel (n=14)	5 (7.2%)	9 (11.5%)
Stomach (n=19)	5 (7.2%)	14 (17.9%)
Liver (n=3)	2 (2.9%)	1 (1.3%)
Pancreas (n=7)	3 (4.3%)	4 (5.1%)
Lung (n=30)	10 (14.5%)	20 (25.6%)
lymph node (n=14)	3 (4.3%)	11 (14.1%)
Thyroid (n=4)	3 (4.3%)	1 (1.3%)
Other (n=34)	20 (30.4%)	14 (16.7%)
Total (n=147)	69 (100.0%)	78 (100.0%)
Chi-square test – P is < 0.001		

NEN tumors were divided according to the simplified staging system into distant, localized and regional. Maximum number of NENs were localized (81.6%) followed by regional (11.6%) and distant (6.8%). When different stages were studied in different genders, localized tumors were found to be more common in females (91.3%) when compared to males (73.1%). Distant and regional tumors were found to be more common in males. This association was found to be statistically significant with p value of 0.01 (Table 3)

Table 3: Association of stage and grade of tumor with gender

Stage of NEN	Female	Male	Total
Distant	2 (2.9%)	8 (10.3%)	10 (6.8%)
Localized	62 (92.6%)	58 (73.4%)	120 (81.6%)
Regional	4 (5.8%)	13 (16.7%)	17 (11.6%)
Chi-square test – P is 0.01			
Grade 1	19 (27.5%)	12 (15.4%)	31 (21.1%)
Grade 2	6 (6.7%)	13 (16.7%)	19 (12.9%)
Grade 3	0 (0.00%)	3 (3.8%)	3 (2.0%)
Neuroendocrine carcinoma	37 (53.6%)	49 (62.8%)	86 (58.5%)
Paraganglioma	5 (7.2%)	1 (1.3%)	6 (4.1%)
Pheochromocytoma	2 (2.9%)	0 (0%)	2 (1.4%)
Chi-square test – P is 0.02			

When the stage of NEN in different organs were studied, maximum number of localized cases were seen in lung (24.2%) followed by stomach (14.2%). Maximum number of regional cases were seen in lymphnode (76.5%) and maximum number of tumor with distant metastasis were seen in small bowel (50%). (Table 4)

Table 4: Association between stage of the NEN and various organs

Organ involved	Distant	Localized	Regional	Total
Appendix	0 (0%)	2 (1.7%)	0 (0%)	2 (1.4%)
Colon	1 (10%)	2 (1.7%)	0 (0%)	3 (2%)
Cecum	0 (0%)	1 (0.8%)	0 (0%)	1 (0.7%)
Rectum	0 (0%)	2 (1.7%)	0 (0%)	2 (1.4%)
Small bowel	5 (50%)	8 (6.7%)	1 (5.8%)	14 (9.5%)
Stomach	1 (10%)	17 (14.2%)	1 (5.8%)	19 (12.9%)
Lymph node	1 (10%)	0 (0%)	13 (76.5%)	14 (9.5%)
Pancreas	0 (0%)	6 (5%)	1 (5.8%)	7 (4.8%)
Liver	0 (0%)	3 (2.5%)	0 (0.0%)	3 (2.0%)
Lung	0 (0%)	29 (24.2%)	1 (5.8%)	30 (20.4%)
Cervix	1 (10%)	13 (10.8%)	0 (0%)	14 (9.5%)
Thyroid	0 (0%)	4 (3.3%)	0 (0%)	4 (2.7%)
Other	1 (10%)	33 (27.5%)	0 (0%)	34 (23.1%)
Total	10 (100%)	120 (100%)	17 (100%)	147 (100%)
Chi-square test – P is 0.001				

All the NEN tumors are graded into four categories as grade 1, 2, 3 and neuroendocrine carcinoma. In our study maximum number of cases are neuroendocrine carcinoma (58.5%) and were seen mostly in men. Next in common are grade 1 tumors followed by grade 2 and grade 3 tumors. Grade 1 tumors were common in females and grade 2, 3 tumors were common in men. (Table 3)

Grades of neuroendocrine tumors in different organs were studied. Grade 1 tumors were seen most commonly in stomach, small bowel, pancreas and appendix. Maximum number of grade 2 tumors and grade 3 tumors were seen in small intestine. Neuroendocrine carcinomas were seen most commonly in lung followed by cervix. (Table 5)

Table 5: Relationship between grade of the tumor and site

Site	Grade 1	Grade 2	Grade 3	Neuroendocrine carcinoma
Appendix (n=2)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cervix (n=14)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (16.3%)
Colon (n=3)	1 (3.2%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
Cecum (n=1)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rectum (n=2)	1 (3.2%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Small bowel (n=14)	6 (19.4%)	4 (21.1%)	2 (66.7%)	2 (2.3%)
Stomach (n=19)	10 (32.3%)	3 (15.8%)	0 (0.0%)	6 (6.97%)
Liver (n=3)	0 (0.0%)	2 (10.5%)	0 (0.0%)	1 (1.2%)
Lung (n=30)	3 (9.7%)	3 (15.8%)	1 (33.3%)	23 (26.7%)
Pancreas (n=7)	4 (12.9%)	1 (5.3%)	0 (0.0%)	2 (2.3%)
Thyroid (n=4)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.7%)
Lymph node (n=14)	0 (0.0%)	2 (10.5%)	0 (0.0%)	12 (14.0%)
Others (n=26)	3 (9.7%)	1 (5.3%)	0 (0.0%)	22 (25.6%)
Total	31 (100%)	19 (100%)	3 (100%)	86 (100%)
Chi-square test – P is 0.001				

Grades of tumors in association with stage were studied. Most of the grade 1, grade 2 tumors and neuroendocrine carcinomas were localized. Tumors with distant metastasis were seen in grade 3 and neuroendocrine carcinomas. This association was statistically significant with p value of 0.001 (Table 6)

Table 6: Association between grade and stage of the neuroendocrine neoplasms

Grade of the tumor	Localized	Regional	Distant	Total
Grade 1	30 (25%)	1 (5.9%)	0 (0.0%)	31 (21.1%)

Grade 2	17 (14.2%)	2 (11.8%)	0 (0.0%)	19 (12.9%)
Grade 3	1 (0.8%)	0 (0.0%)	2 (20.0%)	3 (2.0%)
Neuroendocrine carcinoma	64 (53.3%)	14 (82.4%)	8 (80%)	86 (58.5%)
Paraganglioma	6 (5.0%)	0 (0.0%)	0 (0.0%)	6 (4.1%)
Pheochromocytoma	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.4%)
Total	120 (100%)	17 (100%)	10 (100%)	147 (100%)
Chi-square test – P is 0.001				

DISCUSSION:

Oberndorfer first identified Neuroendocrine neoplasm in intestine and named it as carcinoid in 1907 which was associated with flushing and diarrhoea.^[6] NEN are epithelial type originating in endocrine and non-endocrine organs where as neural type originating in the neuronal structures. paraganglioma represent NEN of neuronal type.^[7]

Incidence of NENs increased from 2.48 to 5.86 per 100,000 per year as per SEER and Norway cancer Registry data.^[8] Incidence is lower in Europe and Asia ranging from 1.1 to 3.24 per 100,000 per year.^[9] Advanced age, male gender along with rural residency and low socioeconomic status were associated with worse over-all survival of patient.^[10]

In our study most common age at presentation was more than 50 years which coincided with studies done by Paul E. Sackstein et al (2018)^[5] and Adele Caldarella et al (2011).^[3] Advancing age is associated with increased incidence and increased grade, possibly due to decreased immunity and increased comorbidities with increase in age.

NEN were more common in males in our study which coincided with study done by Adele Caldarella et al (2011)^[3] but did not coincide with study done by Paul E. Sackstein et al (2018).^[5] (Table 7)

Table 7: Gender distribution of NENs in different studies

Various studies	Male	Female
Our study (n=147)	53.7%	46.3%
Paul E. Sackstein et al ,2018 (n=85133)	47.6%	52.4%
Adele Caldarella et al, 2011(n=455)	52.7%	47.3%

In the present study, most common organ involved was GIT followed by lung, which did not coincide with study done by Felipe Silveira et al (2017)^[11], where lung showed maximum number of cases followed by GIT (Table 8).

Table 8: Distribution of NENs in different organs in different studies

Site of involvement	Present study (n=147)	Felipe Silveira et al, 2017 (n=250)
GIT	21.8%	30%
Lung	20.4%	36%
Lymphnode	9.5%	-
Liver	2%	2%
Thyroid	2.7%	8%
Cervix	9.5%	0.1%
Other	23.1%	23.9%

Among GIT (39 cases), maximum cases were seen in stomach (19 cases, 48.7%), followed by small intestine which does not coincide with study done Megha S Uppin et al (2017). In their study maximum cases in GIT were seen in small intestine followed by stomach.^[12] (Table 9)

Table 9: Distribution of NENs in GIT in different study

GIT	Our study (n=39)	Megha S. Uppin et al (2017) (n=28)
Stomach	19 (48.7%)	7 (25%)
Small intestine	14 (35.9%)	13 (46.4%)
Cecum	1 (2.6%)	0 (0%)
Colon	3 (7.6%)	2 (7.1%)
Rectum	2 (5.1%)	6 (21.4%)

Differences in the occurrence at various sites is thought to be due to combination of biological differences and environmental factors due to differences in demographic conditions. Increasing incidence in GIT

is probably due to better detection with the use of radiographic imaging, availability and utilization of endoscopies and colonoscopies.

Most of the neuroendocrine tumors were localized and were of grade 1 in our study which coincided with the study done by Paul E. Sackstein et al (2018)^[5] (Table 10). This might be due to detection of tumors at early stage because of availability of improved diagnostic modality.

Table 10: Different stages of NENs in various studies

Stage of NET	Our study (n=147)	Paul E. Sackstein et al (2018) (n=85133)
Localized	81.6%	52.4%
Regional	11.6%	20.2%
Distant	6.8%	27.4%

Grade 1 and Grade 2 tumors were more common in stomach and grade 3 tumors and neuroendocrine carcinoma are more common in lungs in our study which coincided by the study done by Paul E. Sackstein et al (2018).^[5]

In our study we correlated the grade and stage of the tumor to assess the prognostic importance of grade. Our data showed that Grade 3 tumors and neuroendocrine carcinomas showed distant metastasis. But when the site of the tumor and stage was studied, small intestinal NETs showed more distant metastasis when compared to other organs.

CONCLUSION:

Incidence of NENs was highest in gastrointestinal tract when compared to other organs but were mostly of low grade. In GIT, grade 2 and grade 3 tumors were seen in small intestine and were associated with metastasis. Next in frequency was lung with high incidence of neuroendocrine carcinoma. Male gender, elderly age and high grade were associated with worse prognosis.

Limitation of the study:

Our study is single institute study and results are applicable to tertiary care hospital with limited number of cases.

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