



Original Article

Clinico-Pathological Analysis of Neuroendocrine Neoplasms in a Tertiary Cancer Care Centre in India

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ABSTRACT

Background: Neuro-endocrine neoplasms represent a diverse group of tumors with varied presentations. Majority of them arise from gastro-entero-pancreatic (GEP) structures¹. Majority of NENs are neuroendocrine tumors (NETs) and possess an indolent disease biology. However, 10–20% of NENs are neuroendocrine carcinomas (NECs) and they are highly proliferative tumors characterized by rapid disease progression.

Materials And Methods: As a part of the initial diagnostic work up, all patients underwent diagnostic biopsy from the most accessible site. The primary site of all cases were noted and histopathological features including the grade of the tumor and differentiation were analysed in detail. Immunohistochemistry with synaptophysin, chromogranin and cytokeratin were done in all cases for confirmation of the diagnosis. Ki-67 was done for all cases except for neuro endocrine tumors of the lung and thymus. Patients with neuroendocrine carcinomas underwent FDG PET CT scan and those with neuroendocrine tumors underwent Ga 68 Dotatate PET CT scan. The maximum standard uptake value (SUV) and the site of maximum SUV in all PET CT scans were noted.

Results: We evaluated a total of 94 cases. Of these 48 cases were neuroendocrine carcinomas and 46 were neuroendocrine tumors. We evaluated neuroendocrine carcinomas and neuroendocrine tumors separately.

Conclusion: Lung is the most common site of neuroendocrine carcinoma followed by gastroenteropancreatic system. Among the GEPs, stomach was the most common site. Majority of cases presented in stage 4.

Keywords: Neuroendocrine neoplasms; Neuroendocrine tumors; Neuroendocrine carcinomas; Gastroenteropancreatic neoplasms; Positron emission tomography-computed tomography (PET-CT).

INTRODUCTION

Neuro-endocrine neoplasms represent a diverse group of tumors with varied presentations. Majority of them arise from gastro-entero-pancreatic (GEP) structures¹. Majority of NENs are neuroendocrine tumors (NETs) and possess an indolent disease biology. However, 10–20% of NENs are neuroendocrine carcinomas (NECs) and they are highly proliferative tumors characterized by rapid disease progression².

NET epidemiologic studies have been more commonly reported, whereas epidemiologic studies of NECs are comparatively rare, mainly due to issues pertaining to appropriate classification and disease rarity. The incidence and prevalence of NETs are rising globally, with the most significantly increased rates in nations such as the USA, Canada, and Norway³.

A longitudinal NET registry from India reported its findings in 2017. Incidence rates were not reported, but increase in the number of cases was reported as years passed by.⁴

Controversies existed regarding the classification of these tumors. More than 20 different classifications have been proposed, depending on the cell of origin, histological grade, tumor location, embryological origin, or secretory activity.

The intention of the latest WHO-ENETs classification is to standardize NET categorization and also to provide prognostic information of various types⁵

The clinical and pathological profile of NETs in the Indian population is different from that of Western countries. In our country, majority of patients present with metastatic disease. This raises a need for creating awareness among the public and medical fraternity and for formulating our own guidelines for optimal treatment.⁶

There are not so many Indian studies that looked into the incidence of various NETs and their clinicopathological correlation.

In our study, we have analysed the clinical and pathological features of various neuro endocrine neoplasms in detail.

AIM AND OBJECTIVES

Aim

To analyse and study the presentation and features of neuroendocrine neoplasms in our population

Primary Objective

To study the clinical and pathological features of neuroendocrine neoplasms in our population

Secondary Objectives

1. To correlate the radiological features with pathological features of neuro endocrine neoplasms
2. To study the demographic profile of the above-mentioned neoplasms.

MATERIALS AND METHODS:

Study site

Apollo Speciality Cancer Hospital and Tertiary Care Centre, Teynampet, Chennai (Tamil Nadu, India)

Study population

Patients presenting with neuroendocrine tumors or neuroendocrine carcinomas to Apollo speciality hospital during the study period

Study Duration

March 2021 to March 2023

Inclusion criteria

All patients who presented to Apollo cancer centre, Chennai with the diagnosis of neuroendocrine carcinoma or neuroendocrine tumour.

Exclusion criteria

Patients with synchronous malignancies at diagnosis

Sample size calculation

Being an observational study, all cases meeting the inclusion criteria during the study period were included in the study

Methodology

All cases of neuro endocrine neoplasms which includes neuroendocrine tumors and neuroendocrine carcinomas which presented to the department of Medical oncology, Apollo cancer centre during the study period were analysed.

As a part of the initial diagnostic work up, all patients underwent diagnostic biopsy from the most accessible site. The primary site of all cases were noted and histopathological features including the grade of the tumor and differentiation were analysed in detail. Immunohistochemistry with synaptophysin, chromogranin and cytokeratin were done in all cases for confirmation of the diagnosis. Ki-67 was done for all cases except for neuro endocrine tumors of the lung and thymus. Patients with neuroendocrine carcinomas underwent FDG PET CT scan and those with neuroendocrine tumors underwent Ga 68 Dotatate PET CT scan. The maximum standard uptake value (SUV) and the site of maximum SUV in all PET CT scans were noted.

Statistical analysis

Data entry was in MS Excel sheet and analysis was done in SPSS version 27.1.0. All categorical variables are expressed as percentage. All continuous variables are expressed as mean +/- SD. ANOVA test is done for finding statistical difference between various groups. Spearman correlation is used to find the correlation between variables

RESULTS:

We evaluated a total of 94 cases. Of these 48 cases were neuroendocrine carcinomas and 46 were neuroendocrine tumors. We evaluated neuroendocrine carcinomas and neuroendocrine tumors separately.

Neuroendocrine carcinomas (NEC)

Among the 48 cases, 33 (69%) were males and 15 (31%) were females.

Mean age of presentation was 60 years

Primary site of tumor

Lung was the most common site of primary with 16 (33%) cases. Gastro entero pancreatic NEC were the second in frequency with 15 (31%) cases which included esophagus, stomach, colon, rectum, pancreas and gall bladder. Prostate was the third most common primary site with 6(12.5%) cases. Among the 4 (8%) cases of unknown primary, one case presented with multiple liver metastases, one case with extensive lymphadenopathy, one case with rectus muscle deposit and one with mediastinal nodes. Other sites of primary included cervix, 2 (4%),paranasal sinuses, 2 (4%) vagina, 2 (4%), breast, 1(2%).

Site	Number	Percentage
Lung	16	32%
GEP	15	30%
Other sites	17	34%

Table1 Primary site of neuroendocrine carcinomas

Site	Number	Percentage
Stomach	5	31.25%
Esophagus	2	12.5%
Pancreas	2	12.5%
Gall bladder	2	12.5%
Colon	2	12.5%
Rectum	2	12.5%

Table 2 Primary site of GEP NECs

Site	Number	Percentage
Prostate	6	35%
Unknown primary	4	23%
Cervix	2	12%
Paranasal sinus	2	12%
Vagina	2	12%
Breast	1	6%

Table 3 NECs at sites other than lung and GEP

Symptoms at presentation

NECs of lung had various symptoms at presentation The most common symptoms were cough and shortness of breath followed by loss of weight and loss of appetite. Other respiratory symptoms were chest pain and haemoptysis The most common symptom due to metastases was back pain due to bone metastases. One patient presented with disorientation due to brain metastases.

Symptom	Count	Percentage
Cough	8	25.0%
Shortness of breath	8	25.0%
Loss of weight	5	15.6%
Loss of appetite	4	12.5%
Back pain	3	9.4%
Chest pain	3	9.4%
Hemoptysis	2	6.3%
Disorientation	1	3.1%

Table 4 Symptoms in NECs of lung

Symptoms of GEP NECs differed depending on the site of the tumor. 11(73%) of the patients had abdominal pain as a presenting symptom. Altered bowel habits was seen in 5(33%) of patients. 3 (20%) of patients had dysphagia and 5 (33%) patients had weight loss. 2 (10%) patients had jaundice on presentation.

Symptom	Count
Abdominal pain	11
Weight loss	5
Altered bowel habits	5
Dysphagia	3
Jaundice	2

Table 5 Symptoms in GEP NECs

There were 6 cases of NECs of prostate. All cases had the symptom of difficulty on in micturition. 2 cases had associated hematuria.

Among the 4 cases of unknown primary, the case with multiple liver metastases, had jaundice and weight loss on presentation. The patient with extensive lymphadenopathy had weight loss and loss of appetite. Patient case with rectus muscle deposit was asymptomatic except for the swelling over the thigh. And the one with mediastinal nodes had cough and dyspnoea on exertion.

There were two cases of NEC of cervix. One patient presented with cervical discharge and the other one had cervical discharge associated with lower pelvic pain. Among the two cases of NECs of paranasal sinuses, one case presented with head ache and the other presented with nasal blockade. Both cases of vaginal NECs presented with vaginal bleeding. Palpable breast mass was the presenting symptom of the only one case of breast NEC.

Pattern of spread

Liver was the most common site of visceral metastases for lung and GEP primaries. 31% of lung cases and 47% of gastrointestinal primaries had liver metastases. Bone was the second most common site of metastases. 4(25%) cases of lung cases and 3 (20%) of GEP NECs had bone metastases. Brain metastases was seen only in lung cases and was seen in 2(13%) cases.

PRIMARY SITE	PATTERN OF SPREAD

	CONFINED TO PRIMARY ORGAN	REGIONAL NODES ALONE	VISCERAL AND DISTANT NODES	BONE	BRAIN
LUNG	3(19%)	2(13%)	5(31%)	4(25%)	2(13%)
G.I TRACT	3(20%)	2(13%)	7(47%)	3(20%)	0
PROSTATE	0	2(33%)	4(67%)	0	0
FEMALE GENITAL TRACT	1(25%)	0	2(50%)	1(25%)	0
BREAST	0	1(100%)	0	0	0
PARANASAL SINUSES	0	0	1(50%)	1(50%)	0

Table 6: Pattern of spread of NECs

Among 48 cases of neuroendocrine carcinomas, majority 40(83%) were small cell carcinomas, 6(12.5%) were large cell carcinomas and 2 (4%) cases were mixed neuroendocrine carcinomas. Distribution of the pathological types across various primary sites are shown in the table given below. Among the large cell carcinomas two cases were in the lung and one each in the pancreas, rectum, vagina, and ethmoid sinus. Among the two cases having features of both neuro endocrine carcinoma and adenocarcinoma one was found in the lung and the other in the pancreas.

PRIMARY SITE	PATHOLOGICAL TYPE		
	SMALL CELL NEUROENDOCRINE CANCER	LARGE CELL NEUROENDOCRINE CANCER	MIXED TYPE
LUNG	13 (81%)	2 (13%)	1(6%)
G.I TRACT*	12(80%)	2(13%)	1(7%)
PROSTATE	6(100%)	0	0
UNKNOWN PRIMARY	4 (100%)	0	0
FEMALE GENITO URINARY TRACT**	3(75%)	1(25%)	0
BREAST	1 (100%)	0	0
PARANASAL SINUSES	1 (50%)	1 (50%)	0

Table 7: Pathological type of NECs

* G.I tract includes esophagus, stomach, colon, rectum ,anal canal, pancreas and gall bladder

**Female genito- urinary tract includes cervix and vagina

NEUROENDOCRINE TUMORS

We analysed 46 cases of neuro endocrine tumors. Among them 18 (39%)were females and 28 (61%) were males.

The mean age of presentation was 57 years (range 30-85 years).the mean age of various subsites were analysed and there was no significant difference between the age and subsite.

AGE	SITE OF NETs				P VALUE
	GEP	LUNG AND THYMUS	UNCOMMON SITES	UNKNOWN PRIMARY	
MEAN AGE	56	58	57	62	0.749

Table 8: Mean age of NETs

For better understanding, neuro endocrine tumors of different subsites were evaluated separately under the headings of 1.NETs of gastroenteropancreas (GEP) 2.NETs of lung and thymus. 3.NETs of uncommon sites.4.NETs of unknown primary. GEP NETs were the most common site comprising around 59% of cases. Lung and thymus contributed 15 % of cases.6 (13%) cases were from uncommon sites which included prostate, breast, kidney and urinary bladder and 6 (13%) cases presented as metastases from unknown primary.

Site	Count
Gastroenteropancreatic NETs	27
NETs of lung and thymus	7
NETs of uncommon sites	6
NETs of unknown primary	6

Table 9: Site wise distribution of neuroendocrine tumors

Among GEP NETs, most common site was small intestine with 10 (22%) cases and among the 10 cases,5 were in the duodenum,4 in the ileum and 1 in the jejunum. Pancreas was the second most common site with 8 (17%) cases. There were 6 (13%) cases arising from the lung. Other sites of primary were stomach 4 (9%) cases, prostate 3 (6%)cases, rectum 3 (6%) cases, , and one case each in the breast, colon, gall bladder, kidney , thymus and urinary bladder. 6 cases were from an unknown primary site.

Primary site	Count
Small intestine	10
Pancreas	8
Stomach	4
Rectum	3
Colon	1
Gall Bladder	1
Kidney	1
Urinary Bladder	1
Prostate	3
Breast	1
Lung	6
Thymus	1
Unknown Primary	3

Table 10: Primary site of neuroendocrine tumors

Symptoms at presentation

Abdominal pain associated with altered bowel habits was the present in all cases of tumors arising from the small intestine. 2 among 10 cases had additional symptom of loss of weight. Abdominal pain was the main presenting symptom in all pancreatic cases also. Pain radiating to back and jaundice was present in 2 (25%) cases each of pancreatic primary.

Cough and shortness of breath were the presenting complaints in 3 (50%) cases of lung primary. 3 (50%) patients had haemoptysis and 3 (50%) patients had chest pain as the presenting symptom.

Among the six cases from an unknown primary site, two patients presented with abdominal pain who were found to have abdominal nodes. One case with mediastinal nodes presented with cough. The patient with neck node was asymptomatic except for the neck swelling. Back pain due to vertebral metastases was the presentation in one case and a single sacral lesion with pain was the presenting symptom in one case

Stage at presentation

Among the total of 46 cases of neuro endocrine tumors, 35 (76%) cases presented as stage 4 disease. Only 7 (15%) cases were confined to the primary site at presentation. 4 (8.7%) cases had metastases to regional nodes. There was no significant difference between the primary site of the tumor and the stage of the disease.

STAGE	SITE OF NETs				P VALUE
	GEP	LUNG AND THYMUS	UNCOMMON SITES	UNKNOWN PRIMARY	
STAGE IV	17	7	5	6	0.294
STAGE I,II,III	10	0	1	0	
TOTAL	27	7	6	6	

Table 11: Cross table of site of NETs and stage of presentation

Pattern of spread

For GEP NETs distant nodes and viscera were the most common sites of metastases. 14(52%) of cases had metastases to distant nodes and viscera and liver was the most common visceral organ involved, 9 cases (33%).

Bone was the most common site of metastases for lung NETs. 4 (66%) cases of lung had bone metastases.

For uncommon sites also, bone was the most common site of metastases.

PATTERN OF SPREAD	SITE OF NETs		
	GEP	LUNG AND THYMUS	UNCOMMON SITES
REGIONAL NODES ONLY	6(22%)	0	1(17%)
DISTANT NODES AND VISCERA	14(52%)	2(29%)	1(17%)
BONE	3(11%)	4(58%)	3(50%)
BRAIN	0	1(14%)	1(17%)

Table 12: Cross table of site of NETs and pattern of spread

Grade of the tumor

Among the GEP NETs majority (48%) were intermediate grade tumors. 30% of them were low grade and only 22% were high grade tumors. But among tumors of the uncommon sites, majority were high grade (83%). Among the tumors of unknown primary also, majority were high grade (67%).

In neuro endocrine tumors of lung and thymus, 57% were atypical carcinoids (intermediate grade) and 43% were typical carcinoids. There was no significant association between the grade of the tumor and the primary site.

GRADE OF THE TUMOR*	SITE OF NETs				P VALUE
	GEP	UNCOMMON SITES	UNKNOWN PRIMARY	LUNG AND THYMUS	

LOW GRADE	8(30%)	0	0	3(43%)	0.075
INTERMEDIATE GRADE	13(48%)	1(17%)	2(33%)	4(57%)	
HIGH GRADE	6(22%)	5(83%)	4(67%)	-	

Table 13: Cross table of site of NETs and grade of the tumor

* There is no high grade attributed to NETs of lung. High grade neuro endocrine neoplasms of lung are either small cell or large cell neuroendocrine carcinomas.

Ki 67

The mean Ki 67 value is the lowest for the GEP NETs (12.69%). The highest value of mean Ki67 is for the uncommon sites, which comprised the maximum percentage of high grade tumors. The unknown primary subgroup had a mean Ki 67 of 31.67%. we could find a significant association between the site of the primary tumor and mean ki 67 value. P value 0.009.

Ki 67	SITE OF NETs			P value
	GEP N=27	UNCOMMON SITES N=6	UNKNOWN PRIMARY N=6	
MEAN VALUE	12.69%	46.67%	31.67%	0.009

Table14: Cross table of site of NETs and Ki 67

Maximum SUV Value

The mean of the maximum SUV value in the DOTATATE PET CT scan was calculated and was compared between each sub sites. The maximum value was for the GEP NETs (42.28) and the minimum value was for the unknown primary site with nodal disease. But the association between the Max SUV value and the site of the primary disease is not statistically significant (P value 0.084)

Max.SUV value	SITE OF NETs				P value
	GEP N=27	UNCOMMON SITES N=6	UNKNOWN PRIMARY N=6	LUNG AND THYMUS N=7	
MEAN VALUE	48.28	15.63	15.56	30.81	0.084

Table15: Cross table of site of NETs and Max SUV value in PET CT

MEAN OF THE MAX SUVs OF	GRADE OF THE NET			P VALUE
	LOW GRADE	INTERMEDIATE GRADE	HIGH GRADE	
GEP NETs	52.65	56.69	24.42	0.297
LUNG AND THYMUS	41.35	31.37	-	
UNKNOWN PRIMARY	14.42	5.50	18.88	
UNCOMMON SITES	-	11.4	16.4	
TOTAL	50.39	44.92	20.12	

Table16: Cross table of Grade of NETs and the mean of Max SUV value in PET CT

SUV value of each subsite is tabulated against the grade of the tumor. Lower grade NETs have a higher mean SUV value compared to the higher grade tumors when all NETs are considered together and for GEP NETs separately. this trend was not seen for NETs of rare uncommon sites and for those tumors of unknown sites with nodal disease.

Correlation analysis

Grade of the tumor and Ki 67

Ki 67 was done for all tumors except lung and thymus. Grade of the neuro endocrine tumor and Ki 67 shows a strong positive correlation with a spearman’s coefficient of 0.593. This correlation is expected as, when the grade increases from low grade to high grade, Ki 67 value also increases.

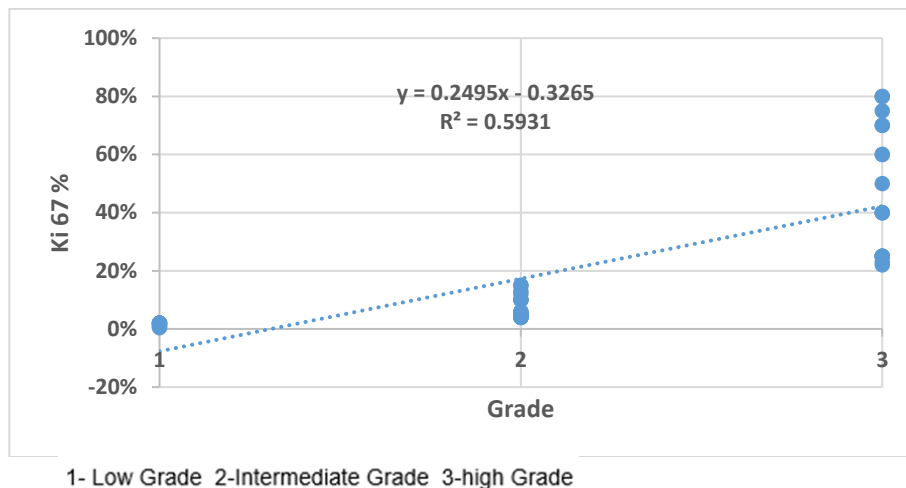


Figure 1: Correlation plot between grade of the tumor and Ki 67

Grade of tumor and Max SUV

Spearman’s correlation test was done to find out the association between the grade of the neuroendocrine tumor and the maximum SUV value in the DOTATATE PET CT scan. It shows a weak correlation with a coefficient value of -0.114. we could find that there is a negative correlation between the SUV max value and grade, meaning as the grade increases from low to high, the SUV value decreases, but the correlation is very weak.

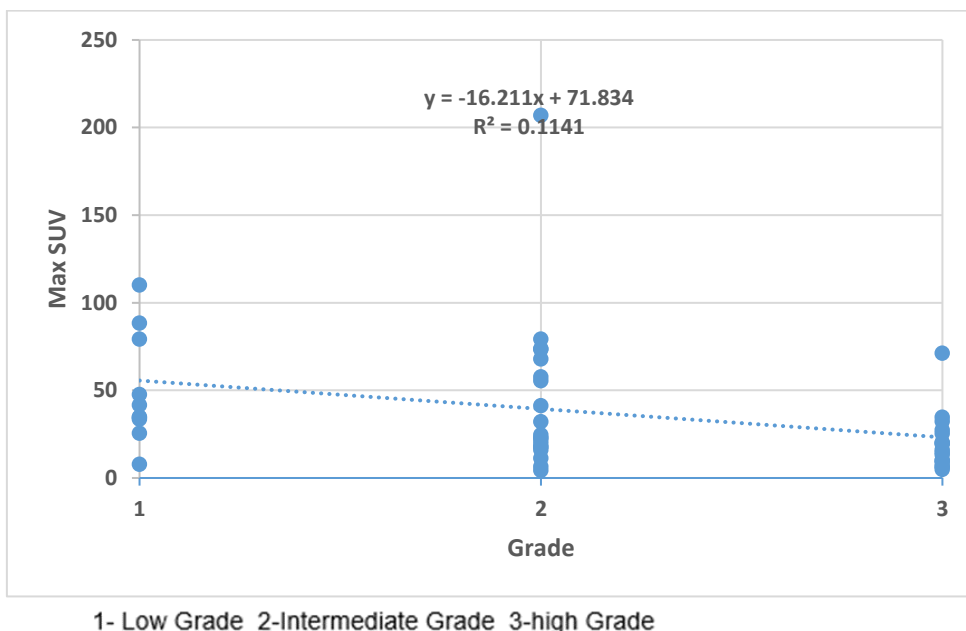


Figure 2: Correlation plot between grade of the tumor and Max SUV

Max SUV and Ki67

Spearman’s correlation coefficient between Max SUV value in the DOTATATE PET CT and ki67 value is -0.145 which is a very weak negative correlation.

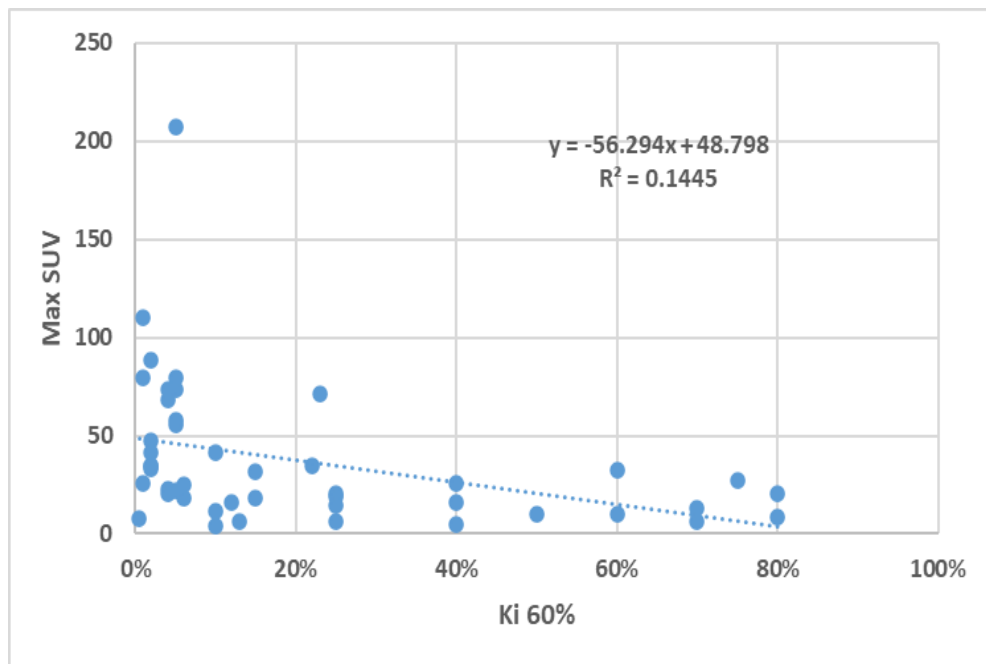


Figure 3: Correlation plot between Max SUV and Ki 67

DISCUSSION:

We evaluated neuro endocrine carcinomas and neuro endocrine tumors separately as their pathological and clinical behaviors are entirely different. Neuroendocrine carcinomas are pathologically high grade, have clinically aggressive course and poor prognosis compared to neuroendocrine tumors.

In our study we evaluated a total of 48 cases of neuro endocrine carcinomas. Majority of them were males (69%). A male gender predominance was observed in various other studies conducted in other parts of the world including the study by Sun et al.⁷. Our study also showed a similar pattern with male predominance.

It is usually a disease of the elderly, seen in those above 60 years of age as seen in the study by Sun et al.⁷ and in various other studies. The mean age in our study is 60 years.

Lung is the most common site of neuro endocrine carcinomas followed by gastroentero pancreatic system. other sites are usually rare. In this study lung was the most common site of neuroendocrine carcinomas (33%) followed by gastro intestinal system (32%). This pattern is consistent with the existing literature. We could find quite a few number of neuro endocrine carcinomas arising from rare sites which includes prostate ,vagina, cervix and paranasal sinuses which are usually rare.

Small cell and large cell carcinomas are the two histomorphological types of neuroendocrine carcinomas described. Various studies have shown that small cell carcinomas are the most common type of neuro endocrine carcinomas of the lung and large cell and mixed type are very rare entities.⁸ In this study also 81% of the NECs of lung were small cell type.

Nearly 70 % of NECs of lung present as stage 4 disease⁹. Our study also showed almost the same pattern in the stage of presentation. 69 % of the lung cases presented at stage 4 on their initial visit. Among the GEP NECs 67% presented in stage 4 disease. when considering all the neuroendocrine carcinomas, 64% presented as stage 4 disease.

Small-cell NEC of the prostate is a very rare entity and is responsible for only less than 0.5–1% of all prostate cancers. It is associated with a more aggressive clinical course and poor prognosis¹⁰. But we had a higher percentage of prostatic small cell neuroendocrine tumors compared to the literature data, i.e around 12.5%. All of them presented in stage 4 disease which indicate the aggressive nature of this disease.

NECs of the cervix are also very rare. They are seen in only 2% of all cervical tumors¹¹. They are usually locally aggressive and associated with early dissemination of the disease. There were two cases in this study and both of them presented as stage 4 disease with distant visceral metastases which shows the aggressive nature of the disease.

For neuroendocrine tumors, in the study done by Rahul.S.Kulkarni et al at a cancer centre in western India, the mean age of presentation was 49 years with a male : female ratio of 1.85:1⁶ In our study, it is 57 years with a male :female ratio of 1.6

In the same study mentioned above, pancreas was the most common primary site of origin (35%), followed by unknown primary origin (19%) and small intestine (9%). In a multicentre longitudinal NET registry from India reported in 2017, the most common primary sites of disease, in decreasing order, were the pancreas (42.9%), small intestine (22.1%), colorectum (9%), and appendix (2.7%).¹²

Compared to the above mentioned studies, the most common site of primary tumor was different in our study. Small intestine (22%) was the most common site followed by pancreas (17%). Other sites in the decreasing order were lung (13%), stomach (9%), prostate (6%) and rectum (6%). Difference in the primary site of neuro endocrine tumor may be due to the geographical differences where the studies are conducted and this demands further epidemiological studies of this tumor.

CONCLUSION:

Lung is the most common site of neuroendocrine carcinoma followed by gastroenteropancreatic system. Among the GEPs, stomach was the most common site. Majority of cases presented in stage 4. Small intestine is the most common site of neuro endocrine tumor followed by pancreas. Majority of the neuroendocrine tumors are of intermediate grade. Majority of the neuroendocrine tumors presented in stage 4. There is a moderate correlation between Ki 67 and grade of the tumor. The clinical profile of neuroendocrine tumors in the Indian population is different from that of the western population and there are differences between different regions of India also. Larger multi institutional studies are needed to throw more light into the nature of neuroendocrine neoplasms.

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