# RESEARCH ARTICLE

## A REGIONAL CANCER CENTER EXPERIENCE OF NEUROENDOCRINE TUMORS: CLINICO-EPIDEMIOLOGICAL PROFILE AND TREATMENT OUTCOMES

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**ABSTRACT**

**Background:** Neuro Endocrine Tumors (NET) comprises a family of neoplasms derived from the diffuse neuroendocrine system, with a wide range of morphologic, functional and behavioral characteristics. NETs are very uncommon and studies on their clinical profile, management and outcomes are very rare. This study was undertaken to document the clinico-epidemiological profile and outcomes of NETs presenting to a regional cancer centre in South India. **Materials and Methods:** From a retrospective records review, 252 patients with NET presenting to the Kidwai Memorial Institute of Oncology, Bangalore. The tumor location, clinical symptoms, stage at presentation, sites of metastasis, grading, and modalities of treatment received and their outcomes were studied. **Results:** The mean age was 53.74 years (± 13.97) (range 19- 85 years) and male: female ratio was 1.6:1. The most common site of presentation was foregut (49.5%), followed by bronchus and lung (17.58%). Among the NETs arising in gastrointestinal tract, esophageal NETs (23.6%) were the most common. Among the oesophageal NETs, nearly 80 % of tumors were located in the lower third of esophagus and gastro-esophageal junction. Metastases seen in 51% of cases, with the majority in liver. Nearly 10% were secretory NETs. Serum Chromogranin levels performed in 10 patients showed a median of 765ng/ml (range 56-2550 ng/ml). Over 70% were classified as poorly differentiated tumors. Nearly 51% received chemotherapy, with 35% receiving cisplatin + etoposide. Almost 15% underwent surgery and 14% received concurrent chemo radiotherapy. Progressive disease was seen in 11% treated cases. The overall survival in the treated cases was 11.25 months for the localized NETs and 4.75 months for the metastatic NETs. **Conclusion:** NECs occurred more commonly in males and in the foregut, mostly in the lower third of the oesophagus. Metastases were seen in over half the cases, with a large proportion of cases treated with chemotherapy and performed well with intervention.

## INTRODUCTION

Neuro-Endocrine Tumors (NET) comprises a family of neoplasms derived from the diffuse neuroendocrine system, with a wide range of morphologic, functional and behavioural characteristics. The incidence of NETs is 2.5-5 per 100,000 populations and has been steadily rising (Modlin, 2007). The increasing incidence of NETs reported in recent studies is likely multifactorial and includes increased awareness and improved diagnostic methods for detection.

In general, NETs are very uncommon, and studies on their clinical profile, management and outcomes are very rare, with only a few studies published worldwide and in Indian settings (Modlin, 2007; Edge, 2010; Doherty, 2011). Hence this study was undertaken to document the clinico-epidemiological profile of NETs presenting to a regional cancer centre in South India. In this study we report a series of 182 cases of NETs diagnosed between 2005 and 2015 in our regional cancer center. We describe the incidence, clinicopathologic features, immunohistochemical (IHC) findings, treatment modality and prognosis of the NETs that were treated in our institute.

## MATERIALS AND METHODS

Using a retrospective records review, all cases presenting with or diagnosed to have NET at the Kidwai Memorial Institute of Oncology, Bangalore between January 2005 and January 2015 were included in this study. The study was approved by the Institutional Ethics Committee. All pathologically confirmed NETs between 2005 and 2015 were included and their clinical data were collected. Patients with poorly differentiated carcinoma without IHC testing were excluded. Patient age, gender, presenting symptoms, the presenting Eastern Co-operative Oncology Group Performance Status (ECOG-PS), smoking, tobacco chewing and alcohol abuse habits, secretory or non secretory,  Ki-67 labeling index, IHC expression of synaptophysin and chromogranin, lymph node and visceral metastasis, bone scan involvement, bone marrow involvement, types of treatment and overall survival were all recorded and analyzed. Grading of the NETs was done according to the 2010 ENETS/WHO classification for neuroendocrine tumors based on the Ki-67 labeling index (2,3). The Ki-67-labeling index was recorded as Grade 1 ($\leq$2%), Grade 2 (3–20%) or Grade 3 (>20%). The differentiation of the tumor was also recorded as well differentiated, intermediate differentiated and poorly differentiated based on the histology (2,3). The various treatment modality was noted, surgical, radiotherapy, chemotherapy or concurrent chemoradiation. Overall survival was calculated from the date of diagnosis to the date of death or last follow-up (months).

**Statistical analysis:** Calculation of median and the range was done using Microsoft excel, and overall survival (OS) was calculated from diagnosis to the last follow up or death due to any cause. The actuarial survival analysis was performed according to the method described by Kaplan-Meier and the univariate analysis was performed for each parameters mentioned. *P* values 0.05 were considered to indicate statistical significance. Data were analyzed with the Statistical Package for the Social Sciences SPSS (version 16) statistical software.

## RESULTS

**Demographic profile:** The baseline characteristics of the patients are as outlined in Table 1 and Table 2. The mean age of the patients was 53.74 ($\pm$13.97) years; range 19- 85 years. 77.5% patients were aged more than 40 years. The male to female ratio was 1.6:1. The most common symptom at presentation was abdominal pain (60.4%). The other common symptoms were loss of weight and/or loss of appetite (25%) and melena (5%). 10 % of the patients had carcinoid syndrome. 52.75% presented with ECOG PS 1 or PS 2; and 35.7% patients were ECOG PS 3.

**Staging:** Among the 182 cases, the most common site of presentation was foregut (49.5%), followed by bronchus and lung (17.58%), head & neck (7.14%) and hindgut (7.14%) respectively. Among the NETs arising in different gastrointestinal sites, esophageal NETs (23.6%) were the most common followed by pancreas and stomach. Among the oesophageal NETs, nearly 80 % of tumors were located in the lower third of esophagus and gastro-esophageal junction. Pancreatic NETs were seen in 27 (14.8%). Metastases were found in nearly 51% with the Liver being most common site. Bone marrow involvement was seen in 5% cases.  Nearly 10% were secretory NETs. Serum Chromogranin levels performed in 10 patients showed a median of 765ng/ml (Range 56-2550

ng/ml). Serum Serotonin Levels (in 4 pts) ranged from 29.4 mg/dl -81.3 mg/dl. Over 70% were classified as poorly differentiated tumors. 70 % patients had grade 3 tumors, 17.5 % patients had grade 2 tumors; 12.5 % patients had grade 1 tumor. On IHC Synaptophysin and Chromogranin staining was positive in 97.5 % and 90 % patients respectively.

**Treatment:** Almost 51% received chemotherapy, with approximately 35% receiving cisplatin + etoposide as the chemotherapy regimen. Almost 15% underwent some form of surgical intervention and 14% received Radiotherapy. 17% received only best supportive care after diagnosis. Progressive disease was seen in 11% patients. The Overall survival was calculated using Kaplan Meier Graph. The median overall survival of stage IV patients was 4.75 months. The median overall survival of non-metastatic disease was 11.25 months. Of the 182 patients 28 patients (15%) underwent upfront radical surgery followed by adjuvant chemotherapy of cisplatin and etoposide combination. Twenty five patients (14%) underwent concurrent chemoradiation along with cisplatin. Of the patients with stage IV disease, ten were grade 2 NETs who underwent treatment with monthly long acting Octreotide injection (Octreotide LAR). The Grade 3 metastatic NETs were treated with palliative cisplatin and etoposide chemotherapy or a combination of Octreotide LAR and Everolimus.

## DISCUSSION

Neuroendocrine tumors generally pursue an indolent clinical course and hence maybe asymptomatic in the early stages. Ultimately patients will become symptomatic either as a result of increasing tumour bulk or hormonal hypersecretion (3-10). In the present study we analyzed 182 cases of NETs and as per literature review this is one of the largest studies published  till date [Doherty, 2011; Kapoor et al., 2014; Klimstra, 2010; Lawrence, 2011; Lee et al., 2014; Metz, 2008; Anthony, 2013; Janson et al., 1997; Ardill, 2003; Rinke, 2009] NETs form 2.5% of all cancers in the body. As per our Institution registry data the incidence of NETs is 2.5/1 lakh poulation. In the present study we found only 10% of the NETs were secretory and classified them as functional NETs (Lee et al., 2014; Metz, 2008; Anthony, 2013). In the study by Lee CG *et al*, the incidence of NETs of all the GIT-NETs was 1.3 %. (Lee, 2014). The rarity of this malignancy has meant that there are no validated protocols for the management of this rare disease. [Lawrence Lee et al., 2014; Metz, 2008]. The comparison between features of our study and similar study from India is highlighted in Table 2. The mean age of patients in our study was 53.74 ±13.97 years, ranging from 19- 85 years. This finding is slightly higher than that of the Study by Kapoor et al. [2014]. The male: female ratio in our study was 1.6 which was lower than the Indian study Kapoor et al.(4) Similar to the other studies, most of the patients had vague symptoms and the most common presenting symptom was abdominal pain. The proportion of smokers and tobacco chewers in our study was 37.5% almost similar to the study by Ku et al showing 41 % smokers.[7, 16]The various sites of presentation are as shown in figure 1. The most common sites were foregut, lung and bronchus, hindgut, head and neck, midgut, genitourinary and breast. In literature among GI NETs midgut is the most common site (Doherty, 2011). However in our study we observed foregut as the most common site of NETs the reason for which cannnot be described. 70 % of the patients had grade 3 disease, which confirms the finding across all the studies that

**Table 1. Baseline characteristics of NETs**

| Variable | Number (percentage) |
|---|---|
| AGE | Mean 53.74 years (± 13.97) |
| | Range 19 – 85 years |
| GENDER | |
| Male | 112 (62%) |
| Female | 70(38%) |
| Male Female Ratio | 1.6:1 |
| SYMPTOMS | |
| Abdominal pain | 110 (%) |
| Loss of weight or loss of appetite | 25(22.5%) |
| Dysphagia | 37 (%) |
| GI Bleed | 2 (5%) |
| Carcinoid Syndrome | 10 |
| PERFORMANCE STATUS | |
| 1/2 | 34 (85%) |
| 3 | 6 (15%) |
| TUMOR LOCATION | |
| Foregut | 90 |
| Midgut | 11 |
| Hindgut | 13 |
| Head and Neck | 13 |
| Bronchus and lung | 32 |
| Genitourinary | 10 |
| Breast | 8 |

**Table 2. Chemotherapy Regimens**

| | |
|---|---|
| Differentiation : | 32 (17.5%) |
| Well differentiated | 23 (12.5%) |
| Intermediate differentiated | 127(70.0%) |
| Poorly differentiated | |
| ENETS/WHO Grade (Ki67 Labeling Index) | |
| < 2% | 32 (17.5%) |
| 3-20% | 23 (12.5%) |
| >20% | 127 (70%) |
| *9DISEASE STAGE | |
| Non metastatic | 89 (49%) |
| Metastatic(IV) | 93 (51%) |

**Table 3. Comparison of Features of neuroendocrine tumor characteristics**

| Patient characteristics | Kapoor et al | Saldanha et al ( Present study) |
|---|---|---|
| Study population | 51 | 182 |
| Age- mean | 44 (25-66) | 53.74 (19- 85) |
| Sex | | |
| Male | 35 | 112 |
| Female | 16 | 70 |
| Ratio | 2.2:1 | 1.6:1 |
| Stage | | |
| Localized /regionally advanced | 29 | 89 |
| Metastatic | | |
| | 22 | 93 |
| Grade | | |
| 1 | 5 | 32 |
| 2 | 15 | 23 |
| 3 | 31 | 127 |
| Treatment | | |
| Adjuvant Ɍ post radical surgery | 7 | 25 |
| Chemotherapy | | |
| Cisplatin + Etoposide | 13 | 64 (35.2%) |
| Octreotide - LAR | 6 | 10 (5.5%) |
| Octreotide LAR + Everolimus | 5 | 5 (2.7%) |
| Weekly Cisplatin + RT | 14 | 6 (3.3%) |
| Others | 3 | 7 (3.8%) |
| Best Supportive Care | | 30 (16.5 |
| No Chemotherapy , follow up only | 23 | 60 (33%) |
| Median OS | | |
| Non metastatic | | 11.25 months |
| Metastatic | 14 months(0-60) | 4.75 months |
| Post radical Surgery | 2.5 months | 14 months |
| | 13months | |

NETs are predominantly high grade and metastatic. The proportion of stage IV disease in our study was 51%, which is the largest number of advanced/metastatic disease in literature.

At our center, we consider patients for upfront surgery if resectable in all NETs. Following complete resection adjuvant chemotherapy is given to improve survival.

Chemotherapy with cisplatin and etoposide regimen is given only when tumors are grade 3 or in the metastatic setting. Somatostatin analogues have proven successful in reducing symptoms of the carcinoid syndrome but its benefit in survival is unclear (Rinke, 2009). The Grade 1/2 tumors which are not completely resected or metastatic are treated with long acting somatostatin analogues. In the present study 8.2% received long acting octreotide therapy. Streptozocin and DTIC-based regimens have been tested with only modest activity and maybe associated with significant toxicity (Doherty et al., 2011; Moertel, 1983). As conventional systemic approaches remain insufficient and highly toxic, there is an obvious need for novel therapies in this tumour population. The median survival of non-metastatic disease was 11.25 months; the survival in this subset was improved with surgery and if completely resected. In the locally advanced group, lymph node positivity and unresected disease status were associated with the poorest outcome in the non-metastatic group. The median survival of patients with metastatic disease was 5.75 months with better outcome noted in the ten patients with grade 2 disease treated with octreotide LAR. This confirms the fact that for a presenting stage of disease, higher grade adversely impacts the outcome. In our experience Chemotherapy has shown a benefit in not only overall survival but also in improving the performance status; the benefit is however short-lived.

## Conclusion

This is the largest study from India on the clinical and epidemiological profiles and outcomes of neuroendocrine tumors. Although the general incidence of neuroendocrine cancers is increasing, the recognition of NETs is still rare and requires a high index of suscipicion. In the present study, NETs most commonly presented in the metastatic stage and metastasis was associated with poor prognosis. It also showed that grade 2 NETs had a better outcome than grade 3 NETs and that lymph node metastasis and unresectable disease had poorer outcomes. Whenever feasible, surgery should be attempted. In metastatic disease, chemotherapy or somatostatin analogues as per tumor grade, helps in symptom palliation and improving survival rates. Larger studies are required to determine optimal diagnosis and management of neuroendocrine tumors.

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