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ORIGINAL ARTICLE

Single institutional series of neuroendocrine tumors managed in the Australian Capital Territory

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Abstract

***Aims*:** Retrospective review of neuroendocrine tumors (NETs) treated within the Australian Capital Territory to describe the local epidemiology and assess prognostic clinicopathological factors.

***Methods*:** Patients with histologically proven non-pulmonary low to intermediate grade NETs were identified from our hospital clinical database. Data were analyzed according to epidemiological, clinical and histopathological characteristics.

***Results*:** Of the 107 included patients, the most common primary tumor site was jejunum/ileum (32%), followed by rectum (22%) and pancreas (11.2%). In total, 32% had distant metastases at presentation, most commonly in the liver. Most patients were symptomatic at diagnosis, while 22.4% of cases were found incidentally. Second malignancies, in particular of gastrointestinal origin, were diagnosed in 33.6%. Surgical debulking was the most common treatment (59.8%) while 18% had multimodality therapy. With a median follow-up of 25 months from diagnosis, about 78% of patients are still alive. Median time to first relapse was 15 months and the 5-year survival rate was 80% for NETs of jejunum/ileum. Univariate survival analysis revealed tumor location, high Ki67 index, raised plasma chromogranin A, and urine 5-hydroxyindoleacetic acid upon diagnosis to be associated with shorter 5-year survival.

***Conclusion*:** The epidemiologic characteristics and long-term outcome in our series are comparable to other reported studies. This analysis presents some important prognostic factors which could be used for risk stratification in patients with NETs.

Key words: chromogranin A, epidemiology, neuroendocrine tumors, prognostic factors, survival.

INTRODUCTION

Neuroendocrine tumors (NETs) consist of a broad spectrum of malignancies that arise from neuroendocrine cells throughout the body. Fifteen different endocrine cell types are known, some of which produce amines and neuropeptides.[1] Despite their diversity in tissue of origin, these tumors share common features, including growth pattern and expression of neuroendocrine markers.

The epidemiology of NETs is only recently beginning to be understood. They appear to be much more common than previously believed, although it is unclear whether this is due to a true increase in the incidence or an artifact of an increase in diagnoses due to improvements in diagnostic techniques. Other factors such as better awareness among health care professionals may also be contributory. Tumors of gastroenteropancreatic (GEP) origin are the most common of all NETs and can present as an incidental finding, liver metastases, bowel obstruction and less commonly "carcinoid syndrome."

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Historically, sites of predilection have been reported to be the appendix (43%), small intestine (15%) and rectum (15%) based on case series from small population-based cohorts and tertiary referral centers.[2] However, some recent studies suggest a change in anatomical distribution.[3] We have attempted to determine if the change in anatomical distribution of GEP-NETs as seen in other studies is reflected in our patient population.

Various prognostic indices have been identified in several recent studies to predict tumor behavior and survival.[4] A literature review of PubMed identified prognostic variables which included age, urinary 5-hydroxyindoleacetic acid (5-HIAA), chromogranin A (CgA), tumor size and Ki67 count. We also examined the prognostic significance of previously stated indices in our study population.

METHODS

The major inclusion criteria were histologically confirmed low to intermediate grade NET of extra pulmonary origin using European NET Society grading system (ENETS grades 1 and 2).[5] Of 125 patients with histologically proven NETs, 107 patients were eligible for the study and 18 patients with either poorly differentiated NETs (small cell type) or of lung origin were excluded. This analysis also includes patients who were initially diagnosed at our institution but followed up elsewhere. Every possible effort was made to obtain an update on such patients and those who were lost to follow-up from their general practitioner.

A retrospective analysis was performed from the medical records of 107 patients treated by the Medical Oncology Unit of The Canberra Hospital, Australian Capital Territory (ACT), between 1998 and 2011. Our oncology unit is the main tertiary referral center for the Australian Capital Territory and southern New South Wales servicing a population of over 500 000. This population is predominantly of white Australian or European ancestry. The project was approved by the ACT Health and Calvary Healthcare ACT Human Research Ethics Committees.

Data collection

The cases were identified from individual specialist's databases and the records of hospital pharmacies as well as histopathology providers. The necessary data for this study were obtained by review of eligible patients' medical records. More specifically, the information gathered included date of initial diagnosis, date of death and the cause of death if available, time to first progression, localization of the primary tumor, extent of metastasis if present, baseline CgA, urine 5-HIAA, treatment details and clinical outcome. When the diagnosing institution was external to the hospital, the histopathology was reviewed and revised when appropriate by a staff pathologist from our institution. Follow-up data up to June 30, 2011 were included.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 software (Armonk, NY, USA). Survival analysis was performed using the Kaplan–Meier method and differences were compared using the log-rank test. Overall survival was calculated from date of diagnosis to date of death.

RESULTS

General characteristics of cohort

The median age at diagnosis was 62 years (range 18–91 years) with a slight male predominance (female to male ratio of 0.94). NETs were slightly more common in never smokers with smoker and nonsmoker ratio of 0.88. About 33.6% of patients had a diagnosis of second malignancy made at some point in life ($n = 36$/107 patients). One-third of second malignancies originated from gastrointestinal tract. Less common second malignancies such as sarcomas and endometrial cancer were also seen. The baseline characteristics of cohort are presented in Table 1.

The median follow-up period was 25 months (range 1 month to 12 years) and median time to first relapse of about 15 months. In total, 21 patients died during this period; the cause of death was disseminated neuroendocrine malignancy in the majority, but in six cases the cause was either unknown or an unrelated event. Only 10 patients (9.3%) were lost to follow-up, reflecting the centralized nature of the medical services in this region.

Primary tumor site and size

The most common primary tumor site was jejunum or ileum (32%), followed by rectum (22%) and pancreas (11%). The pancreatic NETs were mostly nonfunctioning except a minority which secreted gastrin, glucagon or insulin. It was observed that NETs could originate from some unusual sites including the breasts, ovaries, larynx and anal canal. A primary could not be identified

Table 1 Baseline characteristics of the patients

Age (years)	
Median	62
Range	18–91
Sex (no, %)	
Male	55 (51)
Female	52 (49)
Tumor size (no, %)	
Less than 1 cm	25 (23)
More than 1 cm	35 (32)
Data missing (primary unknown or metastatic/not resected)	47 (43)
Prior local or systemic therapy (no, %)	
Surgery	64 (60)
Local therapy	24 (22)
Chemotherapy	17 (15)
Somatostatin analog therapy	14 (13)
Radiotherapy	10 (9)
Radioactive yttrium-90 microspheres to liver	11 (10)
I-131 MIBG	9 (8)
Biological agent	4 (3)
Distant metastases (no, %)	
None	71 (67)
Any	30 (32)
Distant sites of metastases (%)	
Liver	22
Multiple sites	20
Bone	11
Non-regional node	11
Brain	5
Sites of second malignancy (no, %)	
Colorectal	14 (13)
Skin including melanoma	12 (11)
Prostate	5 (4)
Lung	3 (4)
Head and neck	3 (3)
GIST	2 (2)
Primary tumor site (no, %)	
Jejunal/Ileum	35 (32.7)
Rectum	24 (22.4)
Pancreas	12 (11.2)
Unknown primary	10 (9.3)
Duodenum	6 (5.6)
Gastric	5 (4.6)
Colon/Cecum	5 (4.6)
Appendix	4 (3.7)
Anal	3 (2.8)
Other (breast, ovary)	3 (2.8)

GIST, gastrointestinal stromal tumor; I-131 MIBG, radioiodine-labeled metaiodobenzylguanidine.

for 9% of those with metastatic disease. The median size of primary tumor was 1.2 cm (range 0.1–7 cm).

Extent of disease at diagnosis

Most of the patients had localized disease at initial diagnosis. The distant metastases were seen in 32% cases with liver being the most common site of remote disease. This is quite similar to reported US SEER (Surveillance, Epidemiology, and End Results program) data of 59% patients with locoregional disease and 21% with distant metastases. We also observed that NETs could metastasize to any site, including the lung, peritoneal, subcutaneous, adrenal, pleura and ovaries. Multiple sites of metastatic involvement at initial diagnosis were present in 20% patients including liver, bone and adrenal as most common. In fact, liver metastases were always present in the setting of metastases to the adrenal, lung and other sites.

Clinical presentation

A substantial proportion of patients were asymptomatic upon diagnosis (22%). The most common symptom at diagnosis was nonspecific abdominal pain. Other presenting symptoms included small bowel obstruction and local complications from metastatic deposits. Classical carcinoid symptoms were seen in only minority (4%) of cases.

Treatment

Most common treatments included surgical resection with curative intent in the majority (59.8%), local treatment such as endoscopic resection (22.4%) and chemotherapy (15%). About one-fourth (26%) of patients received more than three treatment modalities. Somatostatin analog (SSA) therapy use was less common, reflecting clinical practice at the time and the Pharmaceutical Benefits Scheme restricting treatment to the patients with carcinoid syndrome or vasointestinal polypeptide secreting tumors only. Similarly, the use of biologically targeted agents was even more limited, as clinical trial results supporting their efficacy in this disease were not yet available. Only 3% of patients were treated with everolimus and bevacizumab. Around 10% of patients had implantation of SIR spheres (selective internal radiation therapy with radioactive yttrium-90 resin microspheres) to liver metastases. About 8% of patients received treatment with radioiodine-labeled metaiodobenzylguanidine (I-131 MIBG). Palliative radiotherapy to bony metastases was also used in some cases for pain relief.

Survival

The primary tumor site was an important prognostic marker in our patient population. The estimated 5-year survival rates using Kaplan–Meier analysis were 80% for NETs of jejunal or ileal origin, 85% for rectal and 60 % for pancreatic tumors (Fig. 1).

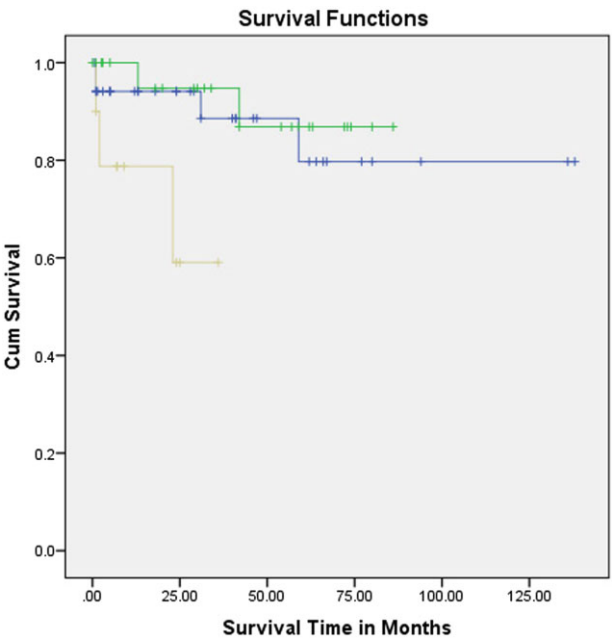

Figure 1 Cumulative survival of neuroendocrine tumors according to tumor site. Tumor site: +, ileum/jejunum censored; +, rectum censored; +, pancreas censored.

Tumors with Ki67 of 2% or less had more favorable outcome as compared to their counterparts with higher proliferation index. The estimated 5-year survival was 65% in the cohort with high Ki67 (ENETS grade 2) whereas no death was observed in the group with low proliferative index (ENETS grade 1). Similarly, the 5-year survival measured lower (although not statistically significant) when plasma CgA was raised (87% *vs* 83%). Urine 5-HIAA can also provide useful prognostic information. Those patients who had elevated results (twofold or higher) at diagnosis had shorter mean survival (74 m *vs* 52 m) although the results again did not reach statistical significance due to small sample size. The information on Ki67, plasma CgA and urine 5-HIAA was only available in two-third cases which may raise the possibility of selection bias.

The overall outcome was better in young patients (<50 years) and those with small tumors (<1 cm) as expected. The impact of these prognostic factors has been shown in a forest plot in Figure 2.

DISCUSSION

NETs are much more common than previously believed. A large population-based study analyzing the SEER data reported overall incidence rate of 38.4 per 1 million individuals in the year 1997.[6] This analysis also suggested that the incidence of NETs is increasing. The majority of NETs appear to be sporadic, but may also arise in the context of inherited genetic syndromes such as multiple endocrine neoplasia types 1 and 2.[7]

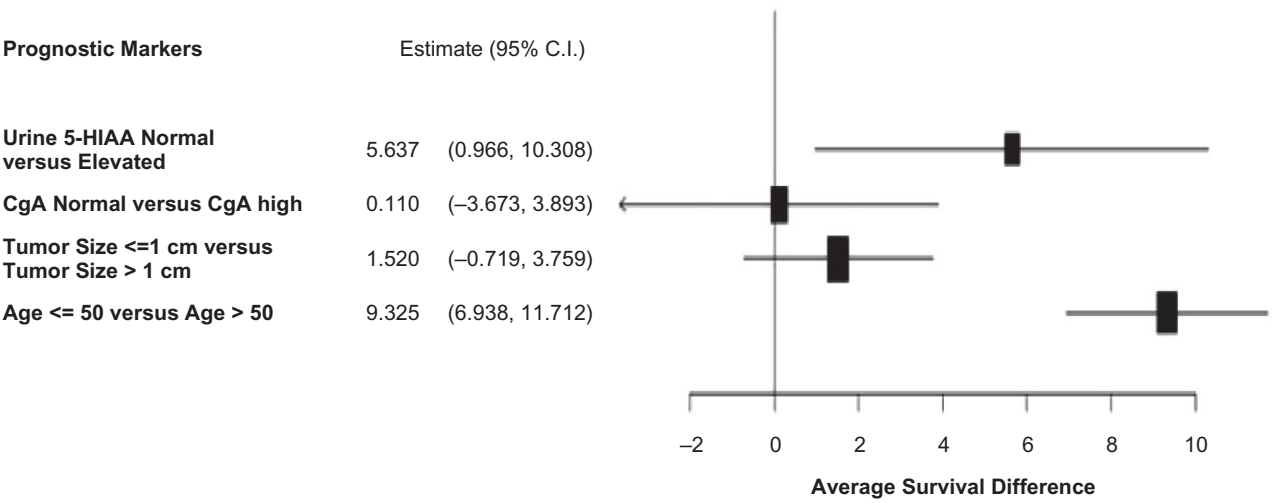

Figure 2 Impact of prognostic markers on survival (5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A, Ki67 could not be included as no deaths have occurred in the European NET Society grading system, grade 1 cohort).

Table 2 Primary tumor site: A comparison with other studies (NETs distribution by percentage)

Site	Our data	Soga *et al.*[37]	Shebani *et al.*[9]	SEER data (1973–1999)	Luke *et al.*[38]
Appendix	3.7	9.6	30	7.4	9.5
Jejunal/Ileum	32	12	38	26	20.6
Rectum	22	15	12	21	NA
Duodenum	5.6	8.3	1.3	4.3	NA
Unknown primary	9.3	3.6	NA	11	15
Stomach	4.6	11	5.3	4.2	3.7

NA, not applicable; NET, neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results program.

Approximately two-thirds of NETs arise in the gastrointestinal tract. As we have demonstrated in our study, they can initially present in several ways. Most appendiceal NETs occur in the distal appendix and do not cause any difficulties. Similarly, tumors occur in the ileum/small intestine although more prevalent but often asymptomatic unless of size greater than 2 cm.[8] They can rarely lead to complications such as bowel obstruction, gastrointestinal bleeding, small bowel ischemia due to desmoplastic reaction, and hydronephrosis from retroperitoneal fibrosis. Rectal tumors are increasing in incidence, often found incidentally by endoscopy, usually quite small and rarely metastasize.[9]

From distribution perspective, a comparison has been drawn with some of the other studies as shown in Table 2. The distribution of NETs in our series was quite comparable to reported studies from other centers with the major difference being that we had fewer appendiceal NETs. It is possible that some functioning pancreatic NETs and small appendiceal carcinoids were not captured in our databases and followed up elsewhere.

Our analysis of patients with low to intermediate grade NETs over a period of 12 years resulted in the identification of a spectrum of second malignancies that occurred in a third of these patients. A large series of 8331 small intestinal NETs from the SEER dataset reported the occurrence rate of second malignancy of 29% with prostate being the most common site, followed by breast, colon, lung and bladder cancers.[10] The investigators observed that most of the second malignancies were diagnosed before NETs and had worse mean survival (57.9 *vs* 40.9 months). Patients with GEP-NETs as first tumor also had increased risk of development of another gastrointestinal malignancy in the future. This association has also been described in other smaller series.[11,12] The higher than expected incidence of metachronous second primaries observed would suggest that this may represent a true increased risk rather than surveillance bias. Longer follow-up, larger studies and perhaps a case control design may further help to distinguish whether there is a common predisposition syndrome between NETs and other malignancies.

Plasma chromogranin (CgA) is a reliable and sensitive marker for small intestinal tumors. It reflects tumor burden and has prognostic value.[13–16] Unfortunately, because this study is underpowered, its prognostic role has not been very well demonstrated. Importantly, the results may vary depending on the assay used and also affected by proton pump inhibitor use, chronic atrophic gastritis, chronic renal failure and liver cirrhosis. Measurement of 24-h urinary 5-HIAA under dietary restrictions has replaced serum serotonin because of higher sensitivity and specificity.[13,17] Elevated urinary level of 5-HIAA is highly specific for midgut tumors. This is because foregut and hindgut carcinoids cannot convert 5-hydroxytryptophan to serotonin or 5-HIAA. It aids in diagnosis and follow-up of patients with carcinoid syndrome. Similar to our series, some other studies have also reported shortened survival for those patients with elevated 5-HIAA at diagnosis.[18] The utility of 5-HIAA as a marker of prognosis has been limited due to wide variability in measurement range in the setting of metastatic disease, false positivity from drugs and food.[19] Nevertheless, plasma CgA and urine 5-HIAA should be performed at first visit, then for follow-up, and at suspicion of tumor recurrence or progression. Plasma CgA levels better correlate with treatment response as compared to 5-HIAA.

Ki67 index is useful to grade the disease and determine the therapy. The best cutoff value has previously been variable, but use of a 2% cutoff point to stratify prognosis among low to intermediate grade NETs is supported by most groups.[20] This has also been shown to correlate with patient survival independently of tumor stage.[21–25] We have found more favorable outcome in tumors with low Ki67 as compared to their

counterparts with higher proliferation index. Other factors such as age, tumor size and carcinoid heart disease have very little supporting data to assign them a prognostic role and clearly more research is warranted to establish this. These factors have recently been incorporated into a nomogram which may provide potentially useful prognostic information and help with management decisions.[4] This model has its own limitations and needs external validation to establish its role in routine clinical practice.

Patients with low to intermediate grade GEP-NETs are less responsive to systemic chemotherapy than those with poorly differentiated tumors. In such patients, objective radiologic responses are rare, and no chemotherapy regimen has demonstrated a significant overall survival benefit. Cytotoxic agents such as 5-fluorouracil, capecitabine, dacarbazine, temozolamide and interferon alpha either as a single agent or in combination have been used in patients with progressive low-grade tumors.[26] A variety of chemotherapy regimens were used in our series including single-agent capecitabine, 5-fluorouracil, 5-fluorouracil with streptozocin, modified FOLFOX6 and carboplatin with etoposide. A single patient in our series with primary NET of the breast was treated with adjuvant 5-fluorouracil, epirubicin and cyclophosphamide regimen because of the rarity of this disease.

SSA therapy has been in use to treat symptoms of hormonal excess in patients with functioning GEP-NETs for a long time. However, its antitumor effect in low-grade small intestinal NETs has only recently been demonstrated in a phase 3 study, where it significantly improved median time to tumor progression.[27] In our series, it was only used in patients who met the reimbursement criteria in being functionally active with carcinoid symptoms.

Local treatment options for liver metastasis from GEP-NETs include hepatic resection providing symptomatic benefit and a chance for cure, although overall recurrence rate is quite high. Debulking of the tumor without possibility of complete resection may improve symptoms and longer disease control. Unresectable liver metastases are often treated with hepatic directed therapies such as chemoembolization, hepatic arterial embolization or radioembolization (radioactive yttrium-90 resin microspheres). In our center, only the spheres were employed. A small prospective study of radioactive yttrium-90 resin microspheres in patients with unresectable liver metastases demonstrated long-term clinical, biochemical and radiological response in a significant proportion of patients.[28]

Recently, sunitinib has demonstrated to have activity in advanced NETs including carcinoids with objective response rate (ORR) of 9.3% and further 63% had stable disease.[29] Other biological agents with recent evidence of activity in NETs include everolimus, temsirolimus, pazopanib, sorafenib and bevacizumab.[30–34] Their low usage in the series reflects the lack of reimbursement for these high-cost agents and the relative recent data regarding efficacy.

Use of targeted radiation in the form of peptide receptor radiotherapy (PRRT) with radionuclides yttrium (^{90}Y)-DOTA octreotide or lutetium (^{177}Lu)-DOTA octreotate is associated with ORR of 30–34%.[35] An important prerequisite for this therapy is that disease be avid on somatostatin receptor scintigraphy. These PRRT treatments are available at a few centers in Australia and are supported by evidence from large case series but prospective randomized data are lacking at present. This was not an available therapy in our center and I-131 MIBG was used as a systemic radioisotope therapy.

This case series has limitations in being from a single institution and not prospective. It only includes those who were diagnosed/treated at our tertiary institute or regional subcenters, whereas our center is now an active contributor to national NETs database.

Registry data from Norway and SEER program have observed 5-year survival rates for small intestinal NETs in the range of 60–70%, which is slightly lower than that observed in our study. This is significantly lower in the presence of liver metastases and for pancreatic tumors (27–43%).[36] This may further improve as the evidence of efficacy of targeted therapy accumulates and opens new horizons for the treatment of these rare tumors. This series suggests that low Ki67 index is a favorable prognostic factor. Larger prospective studies are needed to further evaluate the role of other prognostic markers such as CgA and 5-HIAA and whether they are useful for guiding management, as is currently assumed.

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