A ten-year retrospective analysis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Malaysia

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SUMMARY

Gastroenteropancreatic neuroendocrine tumours (GEP- NETs) are rare neoplasms with a complex spectrum of presentation. The study cohort (n=64) included the diagnoses of carcinoid, (n=26, 41%), insulinoma, (n=25, 39%), undetermined (n=10, 16%), VIPoma, glucagonoma and multiple endocrine neoplasia (MEN-1) (n= 3). Almost half of the patients (n=31) had distant metastasis at diagnosis, the commonest being carcinoid tumours. Presenting symptoms were due to either hormonal expressions or mass effects. Diagnoses in all patients were made based on positive immunohistochemical staining for chromogranin and synaptophysin. Less than half (n=30) had either serum chromogranin A, urinary 5-hydroxyindole acetic acid (5-HIAA), serum insulin or C-peptide levels performed. Commonest diagnostic imaging modalities were computed tomography (CT) scan (94%) and abdominal ultrasound (15%). Curative or palliative surgery was performed in 58 patients. Systemic therapy included long acting somatostatin analogues (n=14), chemotherapy (n=7) and interferon-α2b (n=1). Nine patients died, all of who had metastatic disease at diagnosis. All patients with insulinoma (n=25) were assessed by endocrinologists whilst carcinoid tumours were mainly managed by surgeons (n=16/26). Involvements of oncologists and gastroenterologists were minimal. This study showed that patients with GEP-NETs in Malaysia commonly presented late in the disease with presence of distant metastases. Less than half had adequate hormonal and biochemical examinations performed for diagnostic as well as prognostic purposes, and only a third received systemic therapy. Lack of institutional-based database, clinical expertise and multi-disciplinary involvement contributed to the inadequate surveillance and management of the disease.

KEY WORDS: *Gastroenteropancreatic tumour (GEP-NETs), functional tumours, metastasis, carcinoid, insulinoma*

INTRODUCTION

Endocrine tumours of the gastroenteropancreatic (GEP-NET) structures comprised of a group of cells capable of amine precursor uptake and decarboxylation. These tumours are relatively rare with an overall incidence of 2-3 cases per 100,000 in Caucasian populations[1, 2]. The reported incidence has substantially increased over the last decade, partly due to advancements in diagnostic techniques and increased vigilance among clinicians. These tumours have similar clinical features, often unpredictable with unusual biological behaviour, frequently presenting late and therefore resulted in marked delays in the diagnosis[3]. Carcinoid, gastrinoma, insulinoma, somatostatinoma, glucagonoma, and watery diarrhoea (WDHHA) syndromes are described as individual syndromes according to their respective secretory hormones and peptides. Distinguishing signs and symptoms of each syndrome will aid in the diagnostic work-up[4].

The majority of these tumours are carcinoid tumours, accounting for more than half of those presenting each year. The incidence of carcinoid has risen in the last 10 years, particularly those found in the stomach and ileum. Insulinomas, gastrinomas, and pancreatic polypeptide secreting tumours (PPomas) account for 17%, 15%, and 9%, respectively, with the rest being less than 1%[4]. However, the overall incidence rates and individual anatomic sites are variable.

GEP-NET tumours are classified according to their site of origin and defined broadly according to their differentiation. Hormonal and biochemical markers such as serum insulin, C-peptide, serum chromogranin A, pancreatic polypeptide (PP) or urinary 5- hydroxyindoleacetic acid (5-HIAA) levels are performed to support the diagnoses. Histopathological examinations with specific staining media such as chromogranin, synaptophysin and neuron specific enolase are confirmatory whilst immunohistochemistry for Ki67 (MIB-1) is mandatory for tumour grading[17].

The imaging modalities commonly used for the diagnosis of GEP-NET tumours are computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) and somatostatin receptor scintigraphy (SRS)/ octreotide scintigraphy. EUS in experienced hands is the most sensitive technique for detecting a pancreatic NET and permits fine needle aspiration of a lesion[5, 6]. The most sensitive imaging modality for metastatic disease is SRS, except for metastatic insulinomas, of which only 50% express type 2 somatostatin receptors (SST_2). Positron emission tomography (PET) has become a valuable tool in detecting small NETs[5].

Surgery remains the mainstay of treatment for GEP-NETs, aimed as curative whenever possible. The goal is to prolong symptom- and disease-free conditions for all patients. There is increasing evidence for more aggressive debulking surgery, defined by at least 90% removal of tumour, as medical therapies have better efficacy when prescribed in smaller neoplasms. When the tumour is unresectable, the treatment has two objectives: to control potentially life-threatening symptoms produced by hormone secretions and to extend patient survival by means of therapies that enable a reduction in the tumour volume or at least a retardation of the tumour growth[5, 7].

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The somatostatin analogues are the standard therapies for the control of hormonal syndromes in functioning tumours. In addition, these agents also have some antitumor effects and stabilizing ability[5]. Interferon have consistently been shown to have a biochemical response rate of 40-70% in GEP-NETs, but their inferiority in comparison to the somatostatin analogues indicate that interferon should not be recommended as first-line therapy for symptomatic control[16]. Chemotherapy can be effective in selected NETs, namely streptozosin based regime, in progressive well-differentiated neoplasms of the pancreatic origin, with a response rate of 35-55%, but they have limited role in midgut or hindgut endocrine tumours. In poorly differentiated endocrine neoplasms, chemotherapy would be considered as first-line treatment, often using a platinum based regime[8]. Although the response rate to such treatment can be up to 60%, there is often an early relapse[5, 8].

Liver metastases is often the main prognostic factor in GEP–NETs. Patients with liver metastases have been shown to have a worse survival rate when compared to those without liver involvement survival rate to 5 years of patients with untreated liver metastasis is about 13–54%, against 75–99% in patients without liver metastases[15]. Unfortunately, between 60-75% of patients with either midgut or hindgut tumours present with liver metastases, more often seen in non- functioning tumours[9].

To date, there has been no study or any form of reported data on GEP-NETs in Malaysia. The objective of this study is to describe the spectrum of presenting symptoms, the various subtypes of GEP-NETs, the methods of which diagnoses were made and the different treatment modalities offered to these patients. This data would serve as a catalyst in our effort to increase the awareness on the importance of the disease and encourage clinicians to participate in the creation of a database for effective monitoring of the disease and to emphasize the need for multidisciplinary involvement for a comprehensive management plan.

MATERIALS AND METHODS

The study population was identified from 6 tertiary centers in Malaysia. These hospitals were chosen based on their past experiences in managing GEP-NETs. Letters of invitation to participate in this survey were given to the respective specialists involved in the management of these patients. Patient selection was based on confirmed diagnoses of GEP-NETs made between January 2000 and April 2010. All patients who had confirmed diagnosis of GEP-NET based on histopathological findings were included in the study. These patients were managed either by general physicians, gastroenterologists, endocrinologists, endocrine surgeons, general surgeons or hepatobiliary surgeons. Subjects were also identified through the participating pathology departments through the histopathological reports.

A total of 69 cases were identified but only 64 of them were included. Two of them did not have histopathology confirmations and the other three were lost to follow up after their initial diagnoses. Their medical records were systematically reviewed to collect data on age, gender, race, type of GEP-NET, site of primary tumour, tumour stage at diagnosis, presenting symptoms, duration of symptoms before diagnosis, imaging modality, hormonal and biochemical confirmations, treatment modality, specialty involved in the management and duration of follow-up. Tumour stage was classified as localized (confined to the organ of origin) or distant metastasis (spread to distant organs).

Descriptive statistical analysis was used to describe the results of the study. Statistical Package for the Social Sciences (SPSS) package version-17 was used for the analysis.

RESULTS

1) Patient population

Out of the 64 patients with GEP-NET included in the study, 30 (47%) were males and 34 were females (53%). There was equal proportion of Malay and Chinese patients (39%) and 14% were Indians. The mean age was 49 years (20–75) (Table I).

2) Tumor characteristics

The most common type of tumour was carcinoid, (n=26, 41%), followed by insulinoma, (n=25, 39%) and undetermined (n=10, 16%). Vasoactive intestinal polypeptide (VIPoma), glucagonoma and multiple endocrine neoplasia (MEN-1) were represented equally in 4.8% of the patients (Fig. 1).

The sites of the primary tumors were pancreas (67.2%), stomach and rectum (9.4% each), ileocaecal (3.1%), duodenum (4.7%), colon (1.6%) and undetermined (4.7%). Among the carcinoids 10.9% were found in the pancreas, 9.4% were found in the rectum and stomach, 3.1% in the ileocaecal, duodenum and undetermined site and 1.6% was found in the colon. The most common pancreatic-NET was insulinoma followed by carcinoid, VIPoma, glucagonoma and undetermined type.

At diagnosis, almost half of the patients had distant metastasis (48.4%). Carcinoid tumours were the commonest type presenting with distant metastasis (29.7%), followed by the undetermined type of GEP-NETs (10.9%). Out of the 25 cases of insulinoma, only 3 had distant metastasis at presentation. There was no significant gender difference in the stages of the disease at presentation.

3) Presenting symptoms and duration of symptoms before diagnosis

The presenting symptoms were very variable, ranging from hypoglycaemic symptoms, epigastric pain, altered bowel habits, lower and upper gastrointestinal bleeding, right iliac fossa pain and intestinal obstruction. All of the patients with insulinoma presented with hypoglycaemia, which was accompanied by epigastric pain in one of them. The undetermined group mainly presented with epigastric pain (Fig. 2). Epigastric pain was the commonest symptoms in 12 out of 24 patients with carcinoid tumors, followed by lower gastrointestinal bleeding in 5 patients. One patient presented with right iliac fossa pain and another presented with intestinal obstruction.

Duration of symptoms prior to diagnosis, ranged from 3 days to 10 years (120 months). The median duration of insulinoma, was 17.8 months. Insulinoma was most commonly diagnosed late although the symptoms were present for a long time. Carcinoid tumors were diagnosed relatively early as compared to the other tumors (presented less than 2 years).

4) Diagnostic procedures

The most common imaging diagnostic investigation include computed tomography (CT) scan (94%) followed by abdominal ultrasound (15%), endoscopic ultrasound (15%) and magnetic resonance imaging (8%). Endoscopic procedures were carried out for most of the gastrointestinal carcinoids and for the VIPoma (Fig. 3).

With regards to functional assessment and biochemical tests, 30 patients (46.9%) had either serum chromogranin A, urinary 5-hydroxyindole acetic acid (5-HIAA), serum insulin or c-peptide levels performed. All of the patients with insulinoma

Table I: Characteristics of the study population and their GEP-NET (n= 64)

	Total n(%)
Age (years)	
Mean	49
Gender	
Male	30 (47)
Female	34 (53)
Ethnicity	
Malay	25 (39)
Chinese	25 (39)
Indians	9 (14)
Others	5 (8)
Tumor type	
Carcinoid	26 (40.6)
Insulinoma	25 (39.1)
Undetermined	10 (15.6)
MEN 1	1 (1.6)
VIPoma	1 (1.6)
Glucagonoma	1 (1.6)
Primary site	
Pancreas	43 (67)
Stomach	6 (9)
Duodenum	3 (5)
Ileocaecal	2 (3)
Colon	1 (2)
Rectum	6 (9)

had elevated serum insulin and c-peptide levels. However, only 4 (6.3%) patients with carcinoid had serum chromogranin A or urinary 5- hydroxyindole acetic acid (5-HIAA) performed. All the subjects included in this study had positive immunohistochemical staining for chromogranin and synaptophysin. In addition, eight of them also stained positive for neuron specific enolase (NSE).

5) Treatment modalities

Fifty-eight patients (91%) underwent surgery, either as curative or palliative procedures. Within the remaining six, 3 refused surgery, while the other 3 had poor co- morbidities and was deemed unfit for surgery. All the patients with insulinoma, with the exception of one, underwent curative surgery the latter having had a huge locally invasive pancreatic tumour. Although 33 patients had liver metastasis, liver resection, arterial chemoembolization or radiofrequency ablation was performed in less than 8% of the cases following surgery.

Systemic therapy was given to 22 patients (34%) who had metastatic disease, out of which 14 received somatostatin analogues, 7 received chemotherapy and 1 had interferon-α2b. The long acting somatostatin analogue was used in all of the patients. The combination chemotherapy regimens used consisted of either streptozosin plus 5-fluorouracil, etoposide plus cisplatinum or 5-fluorouracil plus folinic acid (Fig. 4).

6) Duration of follow up and mortality

The duration of follow up was between 1- 240 months with a median of 18 months. Insulinoma was the longest GEP-NET on follow up (240 months). Out of the 64 patients, 9 died (glucagonoma, n=1 : insulinoma, n =1 : carcinoid tumour, n= 3: undetermined type of tumour, n= 4), all of whom had metastatic disease at diagnosis.

7) Multidisciplinary involvement

Patients were followed up in the respective clinics of the disciplines involved in the management of the patients. The specialists involved in the management of these patients were endocrinologists, gastroenterologists, endocrine surgeons, hepatobiliary surgeons and oncologists. Endocrinologists were involved in the initial management of all patients with insulinoma (n=25), out of which 4 were subsequently lost to follow up. Carcinoid tumours, on the other hand, were managed mainly by surgeons in 16 out of 26 patients. Five of them were on both surgical and oncologist follow ups, 3 were monitored by a gastroenterologist, one by an oncologist and one patient was seen by both the surgeon and endocrinologist. Both glucagonoma and MEN 1 (carcinoid and gastrinoma) were on both surgical and endocrinologists follow up whereas the VIPoma patient was under a surgeon's follow up.

DISCUSSION

There is limited data on GEP-NETs from Asia with current studies emerging mostly from the USA and the European countries[10, 11, 12]. To date, this is the first descriptive study on the management of GEP-NETs in Malaysia, which has provided an insight into the spectrum of GEP-NETs, its epidemiology, presentation and pattern of care. Our results were consistent with previous data which showed that GEP-NETs consist of a broad spectrum of tumours with a wide range of clinical presentations and outcome[10]. Carcinoid appear to be most prevalent followed by insulinoma, which is in consistence with previous published data[4,12]. However, whilst the gastrointestinal tract had been described as the primary site in all the published series, the pancreas (67.2%) appeared to be the commonest site within our survey which may reflect an unintended preselected patients from specialised hepatobiliary units within two participating tertiary medical institutions.

Presence of tumour metastasis at diagnosis represents an important prognostic marker[10]. Distant metastasis was detected in a significant proportion of our patients (48.4%) which is in consistence with previous studies which is most likely attributed to late presentation of the disease[11]. Patients who were diagnosed as having carcinoid were the highest group with distant metastasis at diagnosis (29.7%), followed by the undetermined type (10.9%). This survey demonstrated the pancreas as the most common primary site in patients with metastatic disease. This is similar to some data[10] but differed from others which showed intestinal tumours being commoner primary sites[14].

Biochemical and hormonal levels for serum chromogranin A, urinary 5-HIAA, C-peptide or serum insulin levels were performed in only 46.9% of the patients. Insulinoma was the only tumour which had consistent biochemical confirmation in all of the 25 cases. The hormonal and biochemical testing are important not only for diagnostic purposes but also for monitoring of treatment responses. The inadequate assessment of the hormonal and biochemical functions could have been attributed to limited laboratory support and restricted funding in most of the medical institutions in the country, which further highlight the inadequate treatment plan for GEP-NETs in the country.

With regards to treatment, surgical resection was done in 90.9% of patients. Pharmacotherapy following surgical intervention include somatostatin analogue (Octreotide LAR), interferon alpha-2b and chemotherapy (streptozosin plus 5-fluorouracil, etoposide plus cisplatinum or 5-fluorouracil plus folinic acid). Somatostatin analogues have been widely used in GEP- NETs

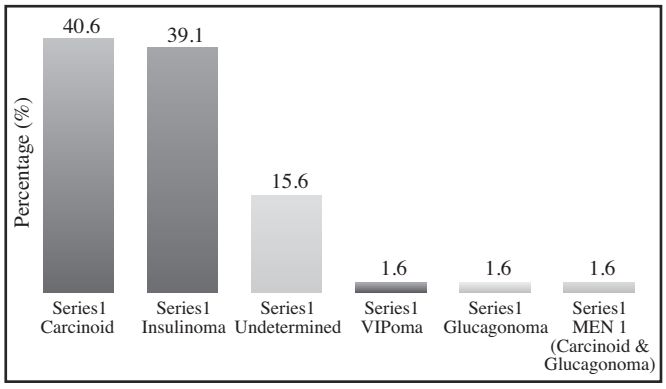

Fig. 1: Types of GEP-NETs.

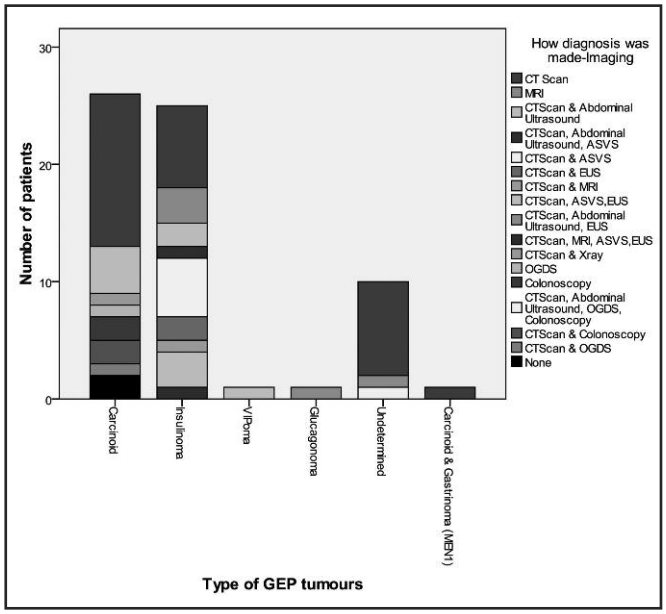

Fig. 3: Imaging modalities used for the diagnosis of the GEP-NETs.

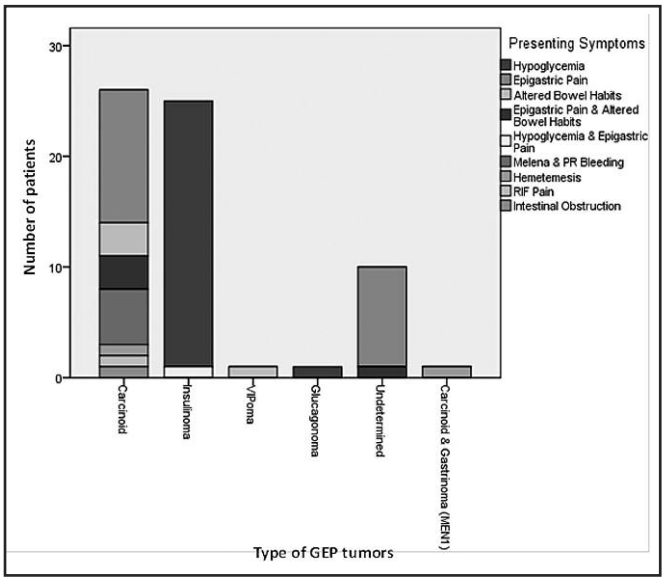

Fig. 2: Presenting symptoms before diagnosis.

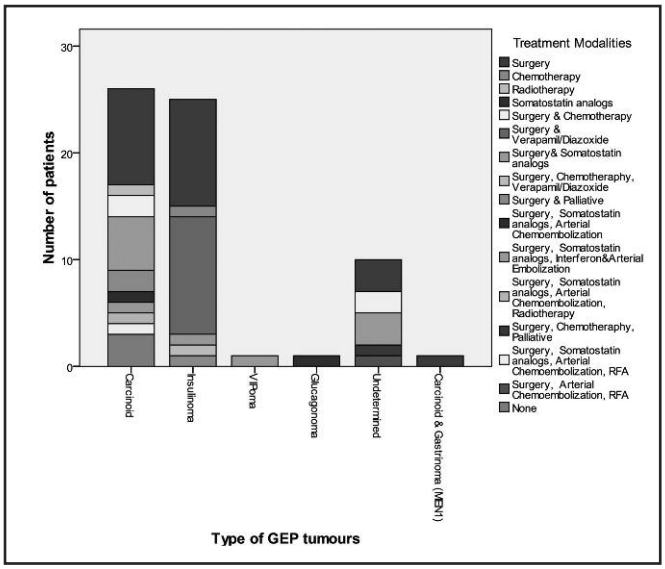

Fig. 4: Treatment modalities offered to the GEP-NET patients.

for the control of hormonal syndrome and recent data have shown antitumoural activity and significant improvement in time to progression (TTP)[12]. Unfortunately, the use of these analogues in our setting is very limited due to its high cost. In this study, chemotherapy was used in patients with advanced disease. The use of chemotherapy has been shown to be disappointing in the management of GEP-NETs, mainly carcinoid of the mid and hindgut, though this can be an alternative treatment for patients who have exhausted standard and investigational therapeutic options[13]. Newer therapies such as the mammalian target of rapamycin (mTOR) inhibitors and vascular endothelial growth factor (VEGF) inhibitors were not used for any of the subjects.

The most frequent cause of death in patients with GEP-NETs is liver failure due to hepatic invasion by the tumour[12]. Within the study cohort, liver metastasis was detected in all of the patients who succumbed to the disease (n=9). Despite 48.4% of our patients having distant metastasis, local-regional ablative therapy such as liver resection, arterial chemoembolisation, radiofrequency ablation and radiotherapy were only administered to 8% of the patients. This could be explained by lack of clinical expertise and inadequate involvement of the various medical and surgical disciplines relevant to a comprehensive management of GEP-NETs.

The management of GEP-NETs should involve multiple disciplines throughout the course of the disease from diagnosis to addressing its complications, thus ensuring appropriate and accurate investigations, functional assessment, precise histological grading, and to predict prognosis by mitotic count and proliferative indices. However, our data had higlighted inefficiencies in various aspects of the disease managment. Most of the carcinoid tumours were only managed by surgeons. Insulinoma was the only GEP-NET that had the appropriate multidisciplinary involvement. Oncologists, gastroenterologists, general physicians, endocrine surgeons and other clinicians should be more involved in the management of GEP-NETs to improve the diagnostic rate, prevent late presentations and ensure a more effective treatment plan.

One of the major limitations of this survey is the absence of any systematic GEP-NET database which explained the low number of cases collected from the 6 participating centres over the last ten years (2000-2010). Therefore, a national database for GEP-NETs should be promptly initiated to highlight the importance and to ensure a systematic surveillance of the disease.

CONCLUSION

This study demonstrated the inefficiencies in the management of GEP-NETs in Malaysia which included delayed presentations, delayed diagnosis, inadequate hormonal, biochemical and histopathological examinations, and the lack of multidisciplinary approach in managing such a complex disease. A concerted effort to address all of the above issues must be initiated with formation of a GEP-NET clinical team in a national referral centre and setting up of a GEP-NET comprehensive database. These would be pivotal towards improving the management of GEP-NETs in the country.

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