Neuroendocrine Tumors Symposium
(GIST & NETs: A Multidisciplinary Journey)

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Neuroendocrine tumors (NETs) are the second most prevalent gastrointestinal tumors (GEP-NETs) arising from cells of the diffuse neuroendocrine system such as the enterochromaffin (EC) cells. These cells possess secretory granules and release neurohormones.

The incidence of NETs is on the rise. Based on the United States registry, there has been a five-fold increase in the number of cases over the last 5 years (Figure 1). The incidence of NETs is reported to be 2.5 – 5 per 100,000 per year.1 The increase in incidence may partly be due to greater awareness and better imaging and diagnostic modalities.

Figure 1: Increase in NETs Incidence

Incidence of NETs Increasing

NETs are the second most prevalent gastrointestinal tumor after colon cancer in the United States and the survival of patients with localized disease (203 months) is better than those with distant metastases (39 months).2 Wide variability in presentation, lack of awareness and being seen by different specialists may explain the delayed diagnosis of NETs of up to 3-7 years. Functioning tumors are detected earlier because of recognizable symptoms. Non functioning tumors are mostly picked up incidentally and tend to present late with mass effects and metastases. NETs are also discovered during appendectomy, GI endoscopy, and routine imaging using CT scan or ultrasound. At the time of diagnosis, 30% of them have already progressed with either regional or distant metastases.

Serotoninomas are typical carcinoid tumors that secrete serotonin and only 10% of such patients demonstrate the constellation of symptoms typifying the carcinoid syndrome. Serotoninomas are mainly found in the gut (75%), lung (25%) and a small percentage in kidneys or ovary.1,2 Gut carcinoids are mostly seen in the small bowel and discovered during routine appendectomy. About 1 in 300 appendecomy will have benign carcinoid tumors.3 By the time these tumors are detected, liver metastases would have occurred.

Flushing and diarrhea are the most common symptoms in patients with carcinoid syndrome. 50% of patients with the Carcinoid Syndrome have valvular heart disease and some of them will have telangiectasia, wheezing, cyanosis and pellagra.4 The cardiac complications signify poor prognosis.

Pancreatic NETs may occur sporadically or as part of multiple endocrine neoplasia type 1. Also known as islet cell tumors, pancreatic NETs present with typical syndromes. These include insulinomas, gastrinomas, glucagonomas, VIPomas, somatostatinomas and non-syndromic pancreatic NETs which have a metastatic rate of up to 70%.5 NETs can be diagnosed using a combination of various methods such as biomarkers, imaging techniques, endoscopy and histopathology.6 Biomarker Chromogranin A (CgA) is expressed by almost 90% of NETs and is independent of their site of origin.6 CgA is also elevated in both functioning and non functioning tumors. It can be used to aid the diagnosis of NETs and help predict prognosis as well as monitor treatment progression. CgA results however may be affected by renal and hepatic dysfunction, inflammatory bowel disease and atrophic gastritis.

It is also elevated in patients taking proton pump inhibitors (PPIs). False negatives are occasionally seen in poorly differentiated tumors. CgA levels may correlate with severity of disease. Other biomarkers include 5-hydroxyindoleacetic acid (5-HIAA), serum gastrin for gastrinoma, serum glucagon for glucagonoma, serum insulin, proinsulin and C-peptide in insulinoma and also vasoactive intestinal peptide (VIP) for VIPoma.7 Immunohistochemical tumor tissue markers include CgA, synaptophysin, Ki-67 and Cg A gene expression. Pathological reports should use the Ki-67 index for tumors, which is a pathological marker for cell proliferation and indicates the aggressiveness of the tumor.7

Imaging of NETs is important as the location and extent of the disease needs to be ascertained. Endoscopic ultrasound is useful for detecting gastric, duodenal, rectal and pancreatic lesions but is highly operator dependent. CT and MRI scans are usually the investigation of choice and can detect metastatic disease. Radiouclide injections into the blood stream can bind to the neuroendocrine tumor cells and help localize the site of the tumor. Octreoscan,6,7 somatostatin receptor (SSTR) scintigraphy, is the best imaging modality for NETs, but is unfortunately not widely available.

Other diagnostic imaging that could be used are Hybrid SPECT/CT, bone scintigraphy, (MBIG) iodine-131-meta-iodobenzylguanidine scintigraphy and PET scanning using 68 Ga-DOTATATE. Despite having a combination of imaging techniques, primary tumors are located in less than 50% of all cases.8

Managing NETs requires a multidisciplinary team with surgery remaining the mainstay of therapy for unresectable tumors, symptomatic control and tumor growth reduction treatment with somatostatin analogues (SSAs), systemic chemotherapy, loco-regional therapy, ionizing radiation or targeted therapy are options. SSA, a natural polypeptide reduces gastric and pancreatic secretion.

The first SSA available was octreotide (Sandostatin, Novartis) with a half life of two hours. A slow release octreotide (Sandostatin LAR, Novartis) providing a half-life of 2-3 weeks was subsequently launched. Apart from symptomatic control, octreotide LAR reduces tumor growth progression as shown in the PROMID study.9 Lanreotide autogel injection, interferon alpha alone or in combination with SSA are other alternatives in the treatment of NETs. New targeted therapy could alter the treatment paradigm and these include antiangiogenic agents, peptide receptor radiotherapy (PRRT), mTOR inhibitors and VEGF inhibitors.

In summary, the majority of NETs are well differentiated and slow growing, but have high malignant potential and strong tendency for liver metastases. They have nonspecific presenting symptoms and a high index of suspicion is needed to make the diagnosis. A multidisciplinary team comprising of gastroenterologists, surgeons, oncologists, endocrinologists, radiologists and pathologists should be involved in managing NETs.

References:
profile for NETs. A tumor size of 3 mm in diameter will secrete detectable amounts of peptides in the blood stream for measurement.\(^3\) Of the three biomarkers, NSE secrete detectable amounts of peptides in the blood profile for NETs. A tumor size of 3 mm in diameter will be reported in one standard term as NETs once a NET is diagnosed, it should be sent to a pathologist to classify, grade and stage the tumor.

There is a role for biomarkers before diagnosis to confirm the suspicion of disease for further tests if needed. Should the biomarker results be positive, one can then justify sending patients for an MRI or CT scan to detect the location of the tumors. In addition, biomarkers can also be used to gauge treatment response. Once a NET is diagnosed, it is preferred to be a pathologist to classify, grade and stage the tumor.

All related tumors include carcinoid tumor, malignant carcinoid, pancreatic endocrine tumors, islet cell tumors, etc should be reported in one standard term as NETs.\(^3\) Up until recently, NETs have been classified following the WHO classification which basically separates tumors into poorly- or well-differentiated groups.\(^3\) Small and large cell carcinomas are classified under the poorly-differentiated group while benign tumors, tumors of uncertain malignant potential (TUMP) and low grade malignancy tumors are classified under the well-differentiated group.

Grading is then applied based on the mitotic count. The WHO NETs classification is however not sufficiently well defined as even small tumors have the probability of becoming malignant. Consensus published in the American Journal of Surgical Pathology 2010 clearly stated that no NETs should be reported as “benign.”\(^4\)

Staging was slightly different among different organs. In 2010, the American Joint Committee on Cancer (AJCC) developed a more definitive classification for NETs, TNM system with the inclusion of a staging system for various organs.\(^7\)

TNM for NET does not prominently in poorly-differentiated tumors and only apply to well-differentiated tumors. Tumor grading can separate poorly-differentiated tumors from well-differentiated tumors, but it does not separate among well-differentiated tumors.

There is no single treatment for NETs as the disease requires multimodal management. Surgery has a role in patients together with local-regional treatment as patients always present only with liver metastases. Somatostatin analogues (SSAs) provide a rational biological therapy because NETs express high amounts of somatostatin receptors.

Other available therapies include interferon and tumor-targeted radioactive therapy as well as chemotherapy which is normally for poorly differentiated NETs and high proliferation. If patients have progressive disease, biological therapy with SSA is required or it may be added to chemotherapy.

SSAs have standard indications for functional syndrome related to peptide-producing NETs, prevention of carcinoid crises before any invasive procedure and asymptomatic well-differentiated NETs with progressive disease. In addition, there are potential indications for asymptomatic, well-differentiated NETs with stable disease, adjuvant therapy with other therapy and somatostatin receptor positive in poorly differentiated NETs.\(^3\) SSAs show clinical efficacy in most of pancreatic NETs.

However, there are challenges in analyzing clinical trials on SSAs in NETs due to lack of controlled studies, small numbers, unclear inclusion criteria, different tumor subtypes, spontaneous variation of growth, different SSA therapies (doses, duration & follow up) and influence of previous or concomitant treatments.

The majority of NET studies indicate a clinical response to SSAs in patients with stable disease in 30%-80% of patients and hormonal responses in 30%-70% of patients.\(^2,3\) However tumor regression remains minimal with SSA treatment. Survival rates of NETs patients have improved with the introduction of SSAs despite them not being first line treatment.\(^4\)

In these studies, good responses were achieved with high doses of SSAs instead of the standard dose.\(^3\) A soon to be published study by Ferolla P et al on patients with progressive well-differentiated refractory NETs shows that a slight increase in octreotide LAR dosage (i.e. 30 mg every three weeks instead of four weeks) resulted in slower tumor and biochemical progression.

References:
7. American Joint Committee.
but the outcome is expected to change in the future as currently all the patients on placebo have died while a large number of patients from the octreotide LAR arm are still surviving. No treatment-related death was reported during the study.

The most frequent reported adverse events were gastrointestinal disorders, hematopoietic system disorders and reduced well-being. In conclusion, octreotide LAR should be considered the standard treatment in patients with NETs of the midgut which are newly diagnosed, functioning or non-functioning, well differentiated, metastatic & with little liver involvement, octreotide LAR is a promising treatment option after debulking surgery with little metastatic disease.

Overall survival should still be analyzed as median survival in patients treated with Octreotide LAR is not yet achieved. There are several potential explanations for the tachyphylaxis mechanism or resistance to SSA therapy but no one knows why it occurs.

Interferon-α (IFNa) still lacks clinical studies on efficacy. INFα in combination with a SSA had been suggested to improve treatment response. Chemotherapy may be used for poorly differentiated tumors. Temozolomide or etoposide-cisplatin are options for treating these SSA-resistant tumors.

Currently, there is growing interest in molecular target agents such as bevacizumab (VEGF monoclonal antibody) and everolimus (mammalian target of rapamycin (mTOR) inhibitor). The mTOR pathway is the most interesting as it affects tumor proliferation, angiogenesis and glucose metabolism. A phase II study on everolimus in combination with octreotide LAR demonstrated 70% of patients had >50% reduction in CgA levels and stable tumor, 22% of patients had partial tumor response with only 8% of patients experiencing progressive disease.

SOM230 (passireotide) is a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding for patients with progressive disease. With increasing developments in NET therapies, there is a possibility of changing future NET management. Biological therapy (i.e. SSA, INFα, SSA+INFα, SSA+everolimus, SSA+bevacizumab, SSA+sunitinib) may be recommended for patients with a Ki-67 index of <3%.

For patients with a Ki-67 index of between 3-20%, biological therapy with a combination of a mTOR inhibitor and a SSA or temozolomide with a SSA may be recommended. Chemotherapy in association with other target therapy may be recommended for patients with a Ki-67 index of >20%.

There is no one single expert for NETs. No one can work alone. Certainly it is essential to have surgeons, oncologists, pathologists, endocrinologists, gastroenterologists, and radiologists work towards a multidisciplinary approach in the management of NETs.

References:

Principles of Surgery in NETs Management

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The principle role of surgery in GEP-NETs is to provide relief from hormonally active tumors, the effects of tumor mass and, if possible, to be curative. Many studies conducted on resectable GEP-NETS had advocated surgery as the primary modality if it is resectable. The five-year survival rate is reported to be as high as 75% which we should be aiming for. In pancreatic NETs, 35%-52% are normally non-functioning tumors. Being functional or non-functional tumors, 92% of these are malignant. Clinical presentations of pancreatic NETs is similar to exocrine pancreatic adenocarcinomas but with higher resectability rates and significantly higher survival rates.

Insulinomas generally do not require radical surgery and can be mostly enucleated. However, 99% of insulinomas are inaprepacrine. Many of them are very small (<5 mm) and require intraoperative or pre-surgery ultrasonography of pancreas for detection. Post surgical disease- free survival rates for gastrinomas are between 45%-65% and 35% at five years. Routine duodenectomy or duodenal transillumination may help to locate gastrinomas. Overall survival for completely resected non-functioning pancreatic NETs vs functional pancreatic NETs is reportedly similar (45% of five-year survival rate for both groups). Recurrence or the development of metastases following complete resection of invasive pancreatic NETs is reported to be very high, up to 75%. Survival is limited by the completeness of surgical resection achieved.

Primary gastrointestinal NETs are generally very small (<1 cm), located mostly in the stomach, duodenum or rectum and endoscopy is recommended if they are uninnvasive. Tumor growth in small bowel NETs cause shrinking of the mesentery and lead to kinking of small intestines. This causes severe debilitating abdominal pain, disabling diarrhea, weight loss, malnutrition and possible death if uncorrected. If disease progresses, intestinal ischemia may develop as result from compression of main mesenteric vessels by nodal metastases, fibrosis or elastic vascular sclerosis. If possible, radical resection of the small bowel including the mesentery is recommended for such cases.

An appendiceal NET is considered the commonest GEP-NETs. The majority of these tumors were identified following appendectomy for suspected appendicitis and up to two per 100 appendectomy specimens may contain a NET.

Treatment includes appendectomy for small lesions with no other unfavourable features. If the lesion is >2 cm, situated at the base of appendix with involvement of mesoappendical and/or vascular invasion then a right hemicolectomy is recommended with follow-up for a minimum of five years.

Colonic NETs pose the worst problem as they are commonly found at the ceacum, mostly right sided with abdominal pain & weight loss. It often presents with multiple tumors around the region of the main tumor. The probability of lymph node metastases for a tumor size >2 cm can be as high as 80%. Recommended treatment is standard resection with regional node clearance and endoscopical treatment may be required or colonic NETs <1 cm. Survival improves with regional lymph node clearance. The five-year survival rate is around 40%.

Figure 4: GEP NETs – The role of surgery

As for liver metastases, complete resection of the hepatic metastases improves five-year survival by 75% compared to only 20%-30% without surgery. Indications for curative resection are fit patients, no unresectable extrahepatic disease and sufficient residual liver volume.

Aggressive surgical debulking is important as symptomatic relief can be achieved in the majority of patients with functional GEP-NETS. Simultaneous resection of primary and hepatic metastases is done in selected patients with acceptable morbidity and mortality. Of late, liver transplants have shown very favourable five-year survival of up to 80% but the risk of extensive surgery and long-term immunosuppression needs to be considered.

Current literature supports aggressive surgical resection for GEP-NETS, even in advanced disease. The extent of radical surgery should be determined on an individual basis. Management of GEP-NETS should be multidisciplinary in approach and focused at experienced & high volume centers.

Appreciation and understanding of each individual’s tumor biology based on prognostic indicators and response to therapies should guide the surgeon as to the indications and goals of surgical intervention.

References: