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REVIEW ARTICLE

Role of Endoscopic Ultrasound in Gastroenteropancreatic Neuroendocrine Tumors and Update on Their Treatment

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ABSTRACT

The gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are rare tumors and include all tumors arising from the gastrointestinal (GI) or pancreatic neuroendocrine cells. They can occur anywhere in the GI tract with the small intestine, pancreas and rectum being the common GI sites. Because of nonspecific symptoms they are difficult to diagnose and diagnosis is often delayed by years. Advancement in cross-sectional imaging techniques and advent of radionuclide-labeled somatostatin analogs have improved our accuracy of diagnosis and staging GEP NETs. Endoscopic ultrasound (EUS) with its unique combination of endoscopy and ultrasound provides high resolution images of GI tract wall as well as the surrounding solid parenchymal organs and therefore is an important investigation for the diagnosis and staging of GEP NETs. Surgery is the treatment of choice with good long-term results in patients with localized GEP-NETs. Control of symptoms in functional NETs is warranted to improve the quality of life of the patient. Somatostatin and its analogs like octreotide and lanreotide have been used to control symptoms because of functional NETs. The management of metastatic GEP NETs includes control of symptoms and therapy to decrease/stop tumor growth that includes somatostatin and its analogs and chemotherapy. Newer therapeutic modalities like peptide receptor radionuclide therapy (PRRT) and molecular therapy hold considerable promise.

Keywords: Endosonography, Pancreas, Carcinoids, Stomach, Computed tomography.

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INTRODUCTION

The neuroendocrine tumors (NETs) are a heterogeneous group of relatively rare, but now being increasingly recognized and diagnosed tumors that are seen most commonly in the gastrointestinal (GI) and the bronchopulmonary system.[1] The gastroenteropancreatic (GEP) NETs, is an umbrella term which includes all tumors arising from the GI or pancreatic neuroendocrine cells and encompasses the earlier recognized categories of carcinoids and pancreatic neuroendocrine tumors (PNET).[2,3] They can occur anywhere in the GI tract with the small intestine, pancreas and rectum being the common GI sites and these tumors have varying biological behavior.[2,3] The diverse and sometimes nonspecific clinical syndromes associated with pancreatic NET can make these malignancies difficult to diagnose at an early stage. These tumors present with variable symptoms that may include functional symptoms due to overproduction of hormones or nonspecific symptoms due to nonfunctional tumors. Majority of the GEP NETs are nonfunctional and usually present with symptoms of mass effect of the tumor or distant metastasis that is usually in the liver.[4] Because of these nonspecific symptoms of GEP NETs are difficult to diagnose and diagnosis is often delayed by years. Advancement in cross-sectional imaging techniques and advent of radionuclide-labeled somatostatin analogs have improved our accuracy of diagnosis and staging GEP NETs.[4] Endoscopic ultrasound (EUS) with its unique combination of endoscopy and ultrasound provides high resolution images of GI tract wall as well as the surrounding solid parenchymal organs. These detailed high resolution images obtained by the EUS are much better than those obtained by other cross-sectional imaging modalities and this allows identification of small lesions that may be missed by other cross-sectional imaging techniques. Also the ability to do fine needle aspiration (FNA) from the lesion is an added advantage of the EUS. These qualities of EUS make it an important investigation for the diagnosis and staging of GEP NETs. This review discusses the role of EUS in diagnosis, staging and treatment of GEP NET and also a brief update on various therapeutic modalities for these rare but unique tumors will be provided.

EUS FOR DIAGNOSIS AND LOCALIZATION OF GEP NET

GEP NET occur either in the bowel or the pancreas and approximately 40% of these tumors are seen in pancreas with the rest being seen in the intestines with small bowel and the rectum being the common sites.[5] EUS is helpful in both of these clinical situations. Because of its ability to obtain high resolution images of the GI tract and adjacent organs, EUS is the most sensitive test for detection these lesions especially the ones that are small and especially localized in the pancreas. It has been shown to be particularly useful for identification of smaller lesions that have been missed by other cross-sectional imaging modalities.[5-7] Although the diagnosis of intestinal NET can be achieved by endoscopic studies, EUS helps to determine the depth and extension and this helps in planning appropriate therapy.[5]

Pancreatic NET

Despite the advances in imaging modalities, up to 30% of PNETs can be missed during a preoperative assessment. As majority of NETs have somatostatin receptors, octreotide scintigraphy has high sensitivity and specificity for localizing NET. However, tumors that lack somatostatin receptors and are small can be missed even on scintigraphy. EUS obtains high resolution images of the pancreas because the transducer is placed very close to the pancreas, being separated only by the thin GI tract wall (Figs 1 to 3). Because of this EUS is particularly well suited for detection of small pancreatic lesions. Studies have demonstrated that EUS with or without FNA has a sensitivity ranging from 77 to 93% for the diagnosis of pancreatic NETs.[8-11] Varas Lorenzo et al reported the diagnostic yield of various imaging modalities in 37 patients (16 males) with pancreatic NET by sequentially examining them with abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), angiography, OctreoScan and radial and sectorial EUS. They found that the sensitivity, specificity and diagnostic accuracy of EUS to be 81, 80 and 78% and three pancreatic rumors of ≤1 cm size (all insulinomas) that were missed by other cross-sectional imaging modalities, were detected by EUS.[5] Versari et al compared the diagnostic yield of EUS, multidetector CT (MDCT) and Ga-68 DOTATOC PET/CT in patients with NETs and found that EUS, PET and MDCT correctly identified lesions in 13/13 (100%), 12/13 (92%) and 10/11 (91%) patients respectively.[12] De Angelis et al studied the role of EUS in PNET in 25 patients who underwent surgical resection and reported that EUS correctly localized 20/23 (87%) pancreatic tumors 11/12 (91.6%) insulinomas, 3/8 (37.5%) duodenal gastrinomas and 10/11 (90.9%) metastatic lymph nodes.[13] In contrast, correct localization was done on ultrasonography (US) in 17.4% patients, by CT in 30.4%, by MRI in 25%, by angiography in 26.6%, and by somatostatin receptor scintigraphy in 15.4% patients. EUS has been also found to be an excellent investigational modality for detecting pancreatic NETs in patients with multiple endocrine neoplasia (MEN) type 1 before the development of significant biochemical test abnormalities.[14]

On EUS, the pancreatic NET typically are well defined hypoechoic lesions with a homogeneous lesion appearance and majority of these lesions are solid.[2] Occasionally, these lesions may also have a cystic appearance. EUS may be falsely negative if the tumor has an isoechoic appearance, is very small in size, or is located at the tail end especially if it is pedunculated. A peripancreatic lymph node may mimic a PNET leading on to a false diagnosis of NET on

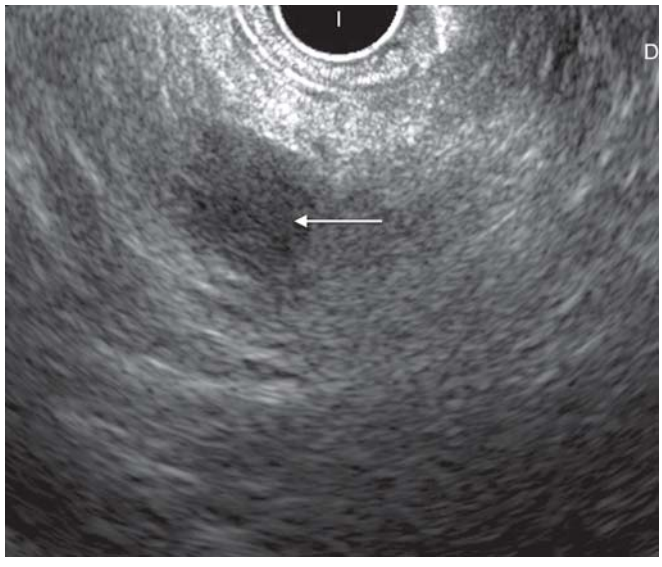

Fig. 2: EUS: A small pancreatic insulinomas localized on EUS (arrow)

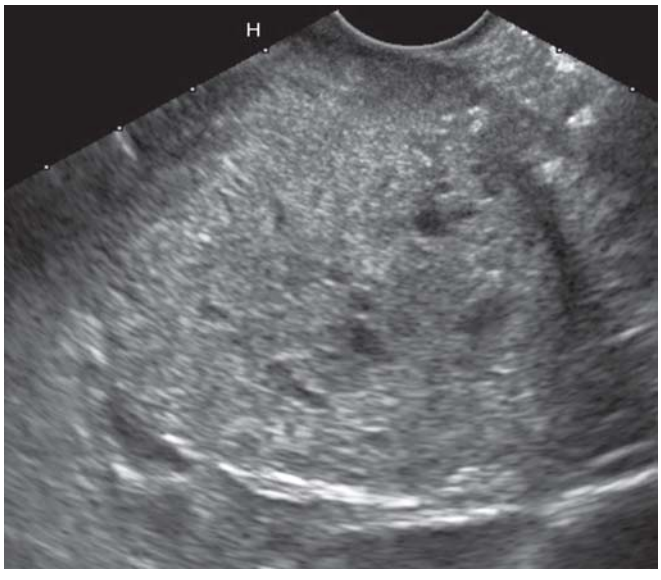

Fig. 1: EUS: Large nonfunctional pancreatic NET

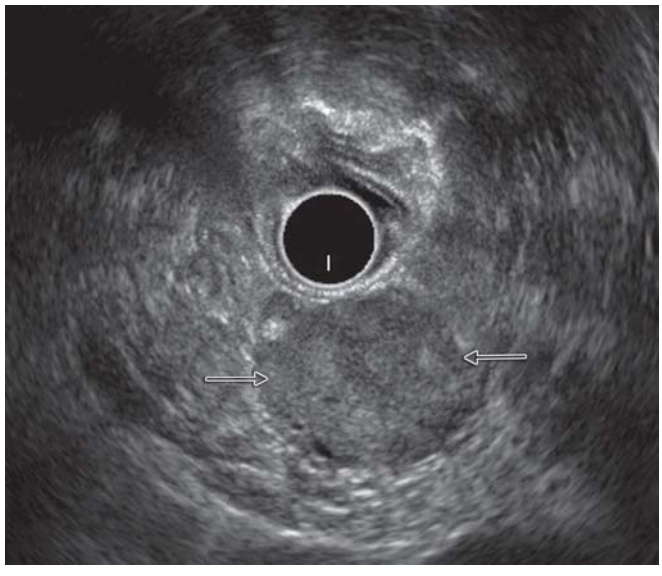

Fig. 3: EUS: Well-defined hypoechoic insulinomas (arrow)

EUS. Recently, contrast enhanced EUS (CEUS) has been used to detect small pancreatic tumors, differentiate between focal pancreatitis and pancreatic cancer as well as to differentiate and characterize various pancreatic tumors. Sakamoto et al[15] studied 156 patients of suspected pancreatic tumors by CEUS and they observed three types of vascular pattern: Hypovascular, isovascular and hypervascular lesions in comparison to the surrounding parenchyma. They observed that 96.2% of the hypovascular lesions were pancreatic carcinomas, 80% of the isovascular lesions were focal pancreatitis and 76% of the hypervascular lesions were NET. Ishikawa et al reported that heterogeneous ultrasonographic texture in the tumor, identified as filling defects in CEUS, was the most significant factor for malignancy and therefore concluded that CEUS has higher sensitivity in preoperative localization of PNETs and can also help in differentiating benign from malignant tumors.[16]

Thus, the available literature suggests that EUS is particularly able to localize gastrinomas and insulinomas. As most of the insulinomas are located in the pancreas, EUS is an excellent modality for diagnosing and localizing these lesions. The reported detection rates by EUS have ranged from 79 to 94%, with higher sensitivity in the head and lower sensitivity in the tail.[17] Similarly, pancreatic gastrinomas are also localized by EUS in 75 to 94% of cases. However, the extrapancreatic (duodenal) gastrinomas are less frequently detected by EUS possibly because of their generally smaller sizes.[3] CEUS is an upcoming promising new technique but more studies are needed.

EUS-GUIDED CYTOLOGICAL DIAGNOSIS OF PNET

EUS along with the localization of the tumor also allows FNA of the lesion (Fig. 4). This provides cytological material for cytology, histology and immunohistochemistry (IHC). Chatzipantelis et al reported that the helpful cytological findings for the diagnosis of NET on cytological material obtained via EUS FNA were a richly cellular sample with a monotonous, poorly cohesive population of small or medium-sized cells with granular chromatin (salt and pepper) and plasmacytoid morphology.[18] The IHC is commonly performed by using stains including chromogranin, synaptophysin, neuron specific enolase, CDX, and CD56 and various hormones like insulin, glucagon, etc.[2,18] Recently, attempts have been made to predict the biological behavior of the tumors by using the cytological or histological findings. Chatzipantelis et al retrospectively reviewed the cytopathological findings and proliferative activity (Ki-67) in EUS FNA specimens of 35 patients with PNET.[19] They found that 21/22 (95.4%)

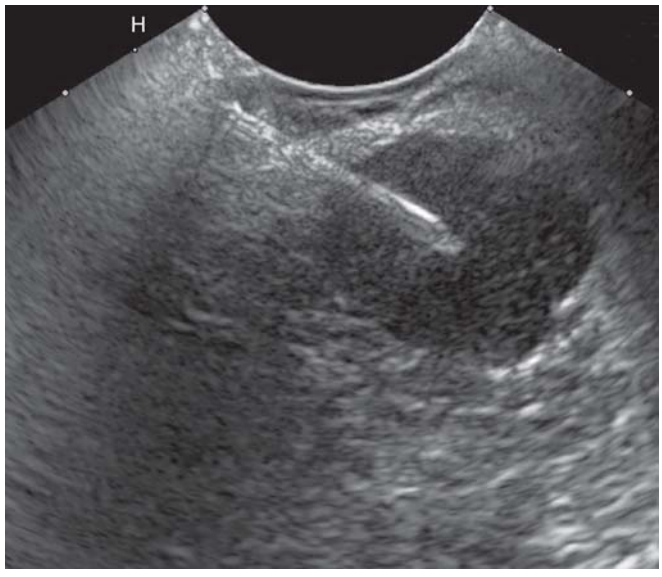

Fig. 4: EUS-guided FNA from pancreatic NET

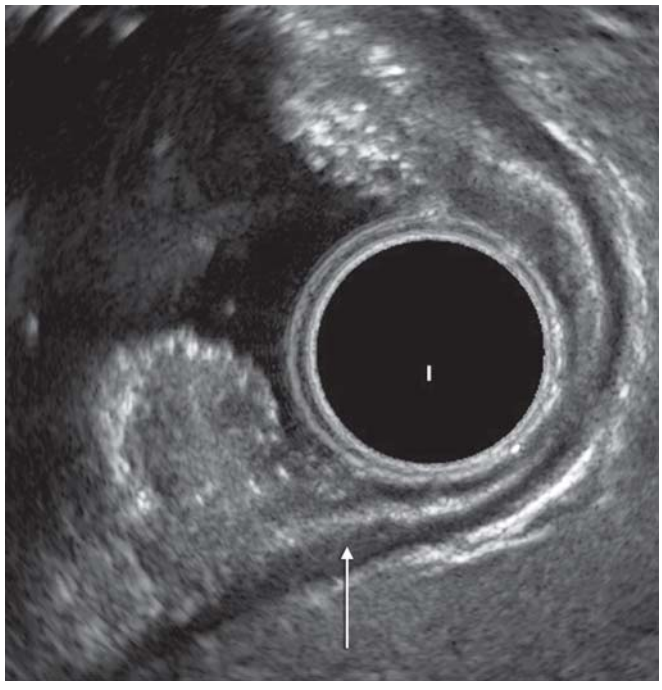

Fig. 5: EUS: Gastric carcinoid with muscularis propria intact (arrow)

malignant tumors had a high proliferative index (>2% Ki-67 cells) whereas Ki-67 was totally absent from tumors that were classified as WHO subgroup 1a (well-differentiated NETs confined to the pancreas) and was seen in a lesser proportion of tumors (42.86%) classified as WHO subgroup 1b (well-differentiated NETs of uncertain behavior confined to the pancreas). Thus, they concluded that Ki-67 evaluation in routine EUS-FNA cytology specimens can be used as a potential prognostic marker in pancreatic NET.

EUS for Staging of Luminal NET

NETs located in the stomach, duodenum and rectum can be diagnosed on endoscopy and if there is no extraintestinal

metastasis, the NETs can be resected endoscopically. But before proceeding on to the endoscopic resection, exact depth of the invasion of the NET needs to be determined so that appropriate therapeutic strategy can be planned. Yoshikane et al studied 29 patients with GI carcinoid tumors (five gastric, seven duodenal, and 17 rectal) by EUS and reported that accuracy of determining the depth of invasion using EUS was 75%. They concluded that EUS is useful for the staging of GI carcinoid tumors as it helps in determining depth of involvement as well as presence of perigastrointestinal lymph node involvement.[20] Kobayashi et al studied the depth of invasion of rectal carcinoids in 52 patients using EUS.[21] They found that the depth of invasion was correctly identified by EUS in all 52 patients with the tumors being localized to submucosa in 49 patients and infiltrating the muscularis propria in three patients. They concluded that rectal carcinoid tumors that are $\leq$ 10 mm in diameter with no invasion of the muscularis propria, and not having any depression or ulceration in the lesion can be resected endoscopically. Martinez-Ares et al resected 24 tumors in 21 patients endoscopically and found that EUS is the most precise diagnostic technique for evaluating tumor size, and showing the tumor-free state of the muscularis propria, the two most important factors that help in selecting the patients for endoscopic resection.[22] Also, endoscopic submucosal dissection (ESD) has also been described for rectal carcinoids and here also, EUS has been shown to be an useful technique for excluding muscularis propria invasion (Fig. 5).[23,24]

Although, EUS can also asses the depth of invasion in gastric NETs and thus help in selecting patients suitable for endoscopic resection, the therapy of gastric NETs is dependent upon multiple factors that include the type, size and number of NET and the readers are advised to consult other reviews on this topic.[25,26]

EUS-guided Antitumor Therapy

Because of its unique capability to simultaneously visualize both the pathological as well as normal structures in the real time along with the ability to avoid surrounding vascular structures, EUS has also been used to deliver therapeutic agents in to the tumor.[2] There are multiple reports of EUS-guided ablation of insulinomas.[27-31] Although, surgical resection is the preferred therapeutic approach in patients with insulinoma, some of the patients with insulinoma may not be good candidates for surgery because of comorbidities and therefore would need alternative minimally invasive treatment modalities for symptom control. EUS-guided alcohol ablation of the insulinomas has been described as case reports and although feasible and successful, its use has been associated with serious complications including life-threatening. A recent study by Levy et al in eight patients of insulinoma, used lower volumes of alcohol and repeated treatment sessions with the aim of symptom relief rather than complete ablation of the tumor.[32] In this study, EUS-guided injection was used in five patients and intraoperative ultrasound-guided alcohol injection in three patients. A volume of 0.8 ml (range: 0.12-3.0 ml) of alcohol was injected per session in small aliquots, typically 0.01 to 0.1 ml at a time using a 22 or 25G needle. The injections were repeated at the same site until a hyperechoic blush was seen expanding in the tumor and it was stopped when the blush was seen in close proximity to the edge of the tumor or whenever, there was concern for leakage beyond its border. Dependent upon the tumor size and pattern of spread after the initial injection, additional passes were made, avoiding the previous needle tracts. There were no peri- or postprocedural complications. In the first 24 hours after procedure, 3/5 patients needed intravenous glucose to control hypoglycemia whereas the remaining two patients did not need any intervention for control of blood sugars. On long-term follow-up, this treatment strategy effectively relieved symptoms and resulted in euglycemia without the need for medical therapy in two patients and with low dose diazoxide therapy in three patients. Thus, limited experience suggests that EUS-guided alcohol fine needle injection may be appropriate treatment modality for insulinomas requiring extensive resection and in patients who are poor surgical candidates.

Treatment of GEP NET: An Overview

NETs may manifest with symptoms related to the effects of hormone hypersecretion (carcinoid syndrome, gastrinoma, glucagonoma) or related to the mass effects associated with large lesions (nonfunctioning NETs) like pain, bowel obstruction and awareness of lump. The therapy for these tumors is decided on the site of disease and whether any distant spread has occurred or not. The therapy therefore needs to be individualized based upon the location, size, presence or absence of metastasis and the symptoms produced by it.[33]

Treatment of Nonmetastatic Disease

Surgical resection remains the therapy of choice for localized GEP-NET and is the only curative treatment.[4] As with all other tumors, the curative surgical resection depends upon the mode of presentation and the extent of the spread of the disease. If the lesion is less than 2 cm in diameter, the frequency of metastasis is usually low. The goals of the surgical therapy are to: (1) Prolong survival by resecting the primary tumor and any nodal or hepatic metastases, (2) control the symptoms related to hormonal secretion, (3) prevent or treat local complications.[34]

The usual approach for intestinal lesions is bowel resection with resection of draining lymph nodes. During surgery an attempt must be made to look for any synchronous lesions and to resect them. Concomitant cholecystectomy can be undertaken to prevent any gall bladder sludge formation that may accompany use of octreotide later. Smaller lesions may however be dealt with endoscopically.[2,34-37] For small duodenal lesions endoscopic resection may be done; larger lesions warrant transduodenal local excision or pancreatoduodenectomy. For lesions elsewhere in the small and the large intestine, surgical resection with lymphadenectomy is warranted. For appendiceal carcinoids, an appendectomy is sufficient for lesions smaller than 1 cm. The management of lesions between 1 and 2 cm is controversial with some advocating appendectomy and others preferring a right hemicolectomy. It is important to rule out lymphatic or distant metastasis in larger lesions. Rectal carcinoids smaller than 2 cm can be treated with endoscopic or transanal excision. However, examination under anesthesia and/or EUS before the procedure should be done for lesions larger than 1 cm. For lesions larger than 2 cm, or smaller lesions with invasion into the muscularis propria, or with lymph node involvement, low anterior resection or, in rare cases, an abdominoperineal resection is indicated. Close post-operative follow-up is needed in most of these patients to identify any recurrent disease early.

Gastric carcinoids are classified into three types.[4] The types I and II are associated with hypergastrinemia. Type I gastric carcinoids originate in the background of chronic atrophic gastritis while the type II carcinoids originate in the background of acid hypersecretion due to gastrinomas (Zollinger-Ellison syndrome). Type III carcinoids are sporadic lesions which occur in absence of hypergastrinemia and are usually larger and have more aggressive behavior. The frequency of metastasis increases from types I to III with rates of around 10, 10 to 30 and 50 to 60% respectively. Lesions in the stomach may be handled endoscopically or with surgical resection. For type I and II with lesions smaller than 2 cm the options include endoscopic resection of the lesions with biopsy of adjacent mucosa, or use of octreotide in gastrinoma and a policy of observation. Larger lesions (>2 cm) are usually resected surgically. In type III lesions, radical resection with locoregional lymphadenectomy is the therapy of choice.[33,38]

In nonfunctional PNETs, small tumors (<2 cm) can be enucleated, while larger lesions can be treated with a pancreaticoduodenectomy or a distal pancreatectomy with splenectomy depending on the site of the lesion. For functional PNETs which are localized, the therapy must attempt control of hormonal hypersecretion followed by surgical resection of lesion, if possible.[4,33,38]

Treatment of Metastatic GEP-NETs

The therapy of metastatic GEP-NETs must address two important issues: Control of symptoms due to secreted products and the control of the tumor load. Somatostatin and its analogs like octreotide and lanreotide can bind to the somatostatin receptor subtype (SSRT) 2 and 5.[39] They block the release and the synthesis of bioactive amines as also their peripheral actions. These analogs have a weak tumoricidal and a good tumoristatic effect.[39] Long acting formulations like lanreotide are preferred for the ease of use. A majority of patients will have some symptomatic response to therapy with a reduction in symptoms like flushing and diarrhea.[40] Side effects may include impaired blood sugar control, gallstone formation, steatorrhea, hypocalcemia, etc. Interferon-α, also, has a mild tumoricidal effect similar to somatostatin analogs.[41] Combination of interferon-α and octreotide has also been used especially in situations when one of the drugs becomes ineffective.[42,43] A number of chemotherapeutic agents have also been used but the response is dismal to most drugs. Various combinations of drugs which have been tried in treatment of metastatic disease include combination of streptozotocin with 5-flourouracil, or doxorubicin with 5-flourouracil.[44] Combination of etoposide and cisplatin may produce a significant antitumor response but their use is recommended only in patients advanced disease with high proliferative index.[45]

Newer therapeutic modalities have increased the armamentarium available for therapy in metastatic NETs. These include various molecularly targeted therapies and use of peptide receptor radionuclide therapy. Molecular targets are cellular molecules which have a role in cellular growth and division. Use of targeted approaches can stop the cells from abnormal proliferation and thus stop tumor growth. However, as multiple cellular pathways are involved in tumorigenesis, the benefits of targeted therapies do not last forever. Important molecules involved in tumorigenesis of NETs include mammalian target of rapamycin (mTOR), vascular endothelial growth factor (VEGF) for angiogenesis, insulin-like growth factor (IGF), transforming growth factor-alpha (TGF-α), platelet derived growth factor (PDGFR) and epidermal growth factor (EGFR) among others.[46]

Everolimus, an mTOR inhibitor, was compared with placebo in the RADIANT 3 trial in patients with NET. Everolimus (10 mg daily) prolonged the progression free survival in these patients.[47] A study has shown that Sunitinib, a multitarget tyrosine kinase inhibitor, in a dose of 37.5 mg daily improves survival in patients with NET vis-a-vis placebo.[48] Similarly bevacizumab, anti-VEGF monoclonal antibody, has been found superior to interferon in patients with NET who were already on octreotide.[49]

Table 1: Radionuclide agents used for PRRT

Radionuclide	*Mechanism*	*Utility*	*Half-life (in days)*	*Cons*
Indium-111	Gamma emitter, Auger electrons	Diagnostic	2.8	Minor therapeutic role
Yttrium-90	High energy pure beta emitter	Therapeutic, cross-fire effect to adjacent cells	2.7	Higher renal toxicity
Lutetium-177	Intermediate energy beta emitter, two gamma peaks	Therapeutic, less toxic, diagnostic utility also	6.7	—

Another therapeutic modality which has generated considerable interest is the use of radiolabeled somatostatin analogs. PRRT utilizes the high somatostatin receptor expression in NETs to ensure a targeted delivery of radiation to the tumor cells.[50] This has become possible with development of peptide with high receptor specificity (e.g. DOTA) and their tagging with various radionuclides (Table 1). The side effects of PRRT may include hematological, renal or hepatic effects. Usually the decrease in blood cells occurs due to bone marrow suppression and is transient. Renal toxicity may include thrombotic microangiopathy and tubular injury. Various approaches including amino acids infusion (lysine and arginine) to reduce renal toxicity are under evaluation. Hepatotoxicity is uncommon and usually mild. It manifests usually as an increase in transaminases but may result in significant toxicity in patients with large hepatic metastasis.[50]

TREATMENT OF LIVER METASTASIS

Liver is a common site of metastasis of the GEP-NETs due to the portal venous drainage of the GI tract and the pancreas where the primaries originate. The therapy of hepatic metastasis can be done using the previously mentioned systemic therapy or by using local ablative/resective approaches.[51,52] Local approaches include ablative therapy, surgical resection and hepatic transplantation for lesions of limited size and transarterial chemoembolization (TACE) for larger lesions. Local approaches to manage these lesions are done in cases where no other organs (except the primary lesion and the liver) are involved. Surgical resection is the preferred therapy in small resectable lesions and offers the best opportunity for long term survival. Ablation can be done using radiofrequency waves, microwaves or cryotherapy. Also, liver transplantation has been utilized as a therapeutic options in some patients but recurrence free 5-year survival has been less than 25%.[51,52]

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