

Review

*Corresponding author

Kui Hin Liao, MBBS, MMed, FRCS, FAMS
 Medical Director and Senior Consultant Surgeon
 Department of Surgery and Surgical Oncology
 Nexus Surgical Associates Pte. Ltd.
 Liao KH Consulting Pte. Ltd.
 Mount Elizabeth Medical Centre
 3 Mt Elizabeth, 228510 Singapore
 E-mail: drliau@outlook.com

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Surgery in the Era of Molecular Medicine: Review of Gastroenteropancreatic Neuroendocrine Tumours

Kui Hin Liao, MBBS, MMed (Surgery), FRCS (Ed), FAMS (Surgery)*

Medical Director and Senior Consultant Surgeon, Department of Surgery and Surgical Oncology, Nexus Surgical Associates Pte. Ltd., Liao KH Consulting Pte. Ltd., Mount Elizabeth Medical Centre, 3 Mount Elizabeth, 228510 Singapore

ABSTRACT

The management of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) has evolved rapidly in the last two decades. Therefore, it is important that surgeons practicing in molecular medicine era have a clear understanding of the ever-changing landscape in GEP-NETs treatment and specifically how it influences the thinking and concepts of surgical treatment and research, in the context of transdisciplinary management.

KEY WORDS: Neuroendocrine tumour; Neuroendocrine neoplasm; Carcinoids; NETs; GEP-NETs; Molecular medicine era.

ABBREVIATIONS: NETs: Neuroendocrine tumors; PNETs: Pancreatic Neuroendocrine Tumours; DES: Diffuse Endocrine System; GEP: Gastroenteropancreatic; PD: Poorly Differentiated; ZES: Zollinger-Ellison Syndrome; VIP: Vaso-active intestinal peptide; PYY: Peptide YY; PP: Pancreatic Polypeptide; EUS: Endoscopic ultrasonography; TAE: Trans Arterial Embolization; TACE: Trans Arterial Chemo-Embolization; VEGF: Vascular Endothelium Growth Factor; PPPD: Pylorus Preserving Pancreaticoduodenectomy; mTOR: mammalian target of rapamycin; FDG: Fluorodeoxyglucose; PET: Positron Emission Tomography.

INTRODUCTION

Neuroendocrine tumours (NETs), are historically known as carcinoid. Siegfried Oberndorfer called it “Karzinoid Tumoren” when he first described seven cases of tumourlets in 1907.¹ Phenotypically, NETs cells exhibit features of both endocrine and neural cells. NETs have a wide spectrum of biologic behavior and natural history, ranging from indolent to aggressive and benign to malignant. Majority of NETs are found within the gastroenteropancreatic (GEP) axis, mirroring pattern of distribution on endocrine cells of the diffuse endocrine system (DES) within the digestive tract. Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) is a huge family of diverse functional and non-functional tumours, including all variety of pancreatic neuroendocrine tumours (PNETs), gastric NET (GNETs), peri-ampullary NETs, biliary tract NETs (BNET), duodenal NET (DNETs), jejunal-ileum NETs (JiNETs), appendiceal NET (ANETs), colonic and rectal NETs. By and large, JiNETs and PNETs constitute the largest subgroup within the GEP system. Only in recent decades, clinicians and scientists are beginning to understand NETs better, not withstanding more research and clinical trials are needed. This article covers an overview on the general principles in GEP-NETs management which may guide future research and trial questions in the molecular medicine era.

CLASSIFICATION

Due to the limited clinical utility and poor correlation with clinical behavior and prognosis,

the obsolete classification of NETs according to the embryologic origin into foregut, midgut and hindgut has fallen in clinical disuse. With better understanding on the natural history, NETs classification has evolved. The latest version of World Health Organization (WHO) 2017 classification has gained widespread acceptance in guiding diagnosis and strategizing clinical therapy (Table1).²

In the WHO 2000 and 2017 classification, the main change was the switch from cell differentiation to tumour cells grading. Tumour grading schemes in GEP-NETs classification are based on three parameters, i.e., differentiation, mitotic count and Ki-67 index for cellular proliferation (Table 2).² Further observation on the discordance between cell differentiation and tumour grading, based on mitosis and proliferation index, prompted revision to the new WHO 2017 classification, where a separate category of poorly differentiated (PD) neuroendocrine carcinoma NEC Grade 3(G3) was appended.

With the new WHO 2017 classification, clinical data on the biological behaviors, clinical management and survival outcomes on the different classes of tumours are needed. Along with the advances in molecular sciences, incorporating molecular onco-taxonomy will refine the future version of NET classification and staging.²

GEP-NETs Family and Clinical Presentation

GEP-NETs are a group of heterogeneous tumours, encompassing GNETs, DNETs, peri-ampullary NETs, BNETs, PNETs, JINETs, ANETs, colonic and rectal NETs.

Pathophysiologically, these tumours are either functional or non-functional tumours. Functional NETs secrete one or more bioactive compounds which produce paraneoplastic syndromes. Non-functional tumours are either non-secretory tumours or secrete bioinactive compounds. The biologic compounds can be hormones or peptide such as glucagon, insulin, somatostatin, serotonin, histamine, gastrin, cholecystokinin, gastric inhibitory peptide, glucagon-like peptide, secretin, ghrelin, motilin, vaso-active intestinal peptide (VIP), neurotensin, peptide YY (PYY) and pancreatic polypeptide (PP).

Gastric NETs

GNETs are a heterogeneous group of neoplasms and its classification has evolved along with the recent WHO 2017 version. Currently, GNETs are classified into GNET G1 and G2, gastric neuroendocrine carcinoma (NEC G3). A NEC can be either large cell or small cell.

Table 1: WHO Classifications of Neuroendocrine Tumours.

WHO 1980	WHO 2000	WHO 2010	WHO 2017
Carcinoid	Well differentiated (WD) endocrine tumour	NET* G1 (carcinoid)	NET G1
	WD endocrine carcinoma	NET* G2	NET G2 NET G3 WD NEN®
	Poorly differentiated endocrine/small cell carcinoma	NEC# (large cell or small cell type)	NEC G3 Poorly differentiated NEN, large or small cell type
Mucocarcinoid	Mixed exocrine-endocrine carcinoma	Mixed adenoneuroendocrine carcinoma MANEC	Mixed neuroendocrine-nonendocrine neoplasm, MiNEN
Mixed forms carcinoid-adenocarcinoma			
Pseudo tumour lesions	Tumour-like lesions	Hyperplastic and preneoplastic lesions	

NEC#: neuroendocrine carcinoma; NET*: neuroendocrine tumour; NEN®: Neuroendocrine Neoplasia.

Table 2: Tumour Grading for GEP-NETs (WHO 2010 Classification).²

GEP-NETs Grade	Mitotic Index	Ki-67 Index
Grade 1 (G1)	Mitotic Count <2 per 10 High Power Fields (HPF)	≤2%
Grade 2 (G2)	Mitotic Count 2-20 per 10 High Power Fields (HPF)	3-20%
Grade 3 (G3)	Mitotic Count >20 per 10 High Power Fields (HPF)	>20%

The sub-classification of GNETs are enterochromaffin-like (ECL) NETs cells, Type I GNETs [associated with immune chronic atrophic gastritis], Type II GNETs [associated with Zollinger-Ellison Syndrome (ZES) and multiple endocrine neoplasia (MEN) Type 1] and Type III sporadic GNETs.

Type I GNETs are usually limited to the gastric mucosa and submucosa in contradistinction to Type III GNETs, which frequently invade beyond the submucosa and extend into the regional lymph nodes. Gastrinoma tends to occur in multiple sites within the gastrinoma triangle as defined by three points, superiorly by the confluence of the cystic and common bile ducts, inferiorly by the junction of the second and third parts of duodenum and medially by the junction of the neck and body of pancreas. GNETs may co-exist with adenocarcinoma as part of the same tumour or independently. Recent research reviewed its association with the over-expression of p53 protein and PDX-1 transcription factor.^{3,4}

Biliary Tract NETs

Among the GEP-NETs, BNETs are the rarest and mostly located at the common hepatic duct (CHD) and proximal common bile duct.⁵ Generally, they are non-functioning tumours, although they may express gastrin, serotonin and PP. The high grade BNETs and mixed adenoneuroendocrine carcinomas are more common than the well differentiated (WD) NETs.⁶

Duodenal NETs

The commonest DNETs are gastrin producing G-cell tumour and somatostatin-producing D-cell tumours. The gastrin producing DNET variety is known as gastrinoma. It presents as Zollinger-Ellison Syndrome (ZES), characterized by abdominal pain, recurrent gastric and duodenal ulceration, gastroesophageal reflux symptoms and diarrhea. Majority are associated with multiple endocrine neoplasia (MEN) syndrome Type 1. On the other hand, the somatostatin-producing NETs are associated

with neurofibromatosis Type I.⁷

D-cell DNETs usually arise in the periampullary region and patients may present with obstructive jaundice when the tumour occludes the ampulla of Vater.⁸

Pancreatic NETs

PNETs are a diverse group of cancer and account for less than 3% of all pancreatic tumours.⁹ Most PNETs are diagnosed incidentally. These cancers arise from pancreatic endocrine cells when some PNETs secrete active hormones which cause symptoms related to the hormones. They are called functional PNETs. Most PNETs are non-functional tumours, i.e., either inactive hormones and do not have hormone related symptoms. Non-functional PNETs are generally asymptomatic in the early stage and for that reason they are often diagnosed in the advanced stage of the disease. Hormones secreted are diverse including insulin, glucagon, VIP, gastrin and somatostatin.

PNETs are classified by the nature of hormones they secrete such as insulinoma, glucagonoma, gastrinoma, PPoma, VIPoma and somatostatinoma as illustrated in Table 3. The presenting symptoms correspond to the nature of hormone secreted. Some of the well-known clinical syndromes are associated with PNETs, e.g., hyperinsulinemic-hypoglycemic syndrome or Whipple's triad in insulinoma, ZES in gastrinoma, Vernal Morison Syndrome or watery diarrhea, hypokalemia, hypochlorhydria and acidosis (WDHHA) in VIPoma patients (Table 3). Some PNETs are associated with hereditary tumour syndromes such as MEN syndrome and Von Hippel-Lindau (VHL) syndrome. In MEN syndrome, the clinical clue is often gleaned from a positive family history of pancreatic, parathyroid and pituitary tumour in young family members. Menin gene mutation is the underlying genetic pathology.

While most of PNETs are WD tumours, a small group is PD NECs. They are sub-classified into small cell carcinomas

Table 3: Pancreatic NETs and Symptomatology.

PNETs Type	Hormones	Symptoms
Insulinoma	Insulin	Neuroglycopenia symptoms e.g., lethargy, giddiness, blurring of vision (Whipple's Triad)
Gastrinoma	Gastrin	Gastric ulcer May be associated with MEN Syndrome
Glucagonoma	Glucagon	May present with skin rash (necrolytic migratory erythema)
VIPoma	VIP	Watery diarrhea, hypokalemia and achlorhydria (Vernal Morrison Syndrome)
Somatostatinoma	Somatostatin	Steatorrhea
Pancreatic Polypeptodomas (PPoma)	Pancreatic polypeptide	Change in satiety
Non-functioning Tumour	Inactive hormones or none	Mass effects of tumour

and large cell carcinomas. The later is more common.¹⁰

Jejuno-ileal NETs

Most of JiNETs are diagnosed during investigation for the primary tumour in an asymptomatic metastatic liver tumour or incidentally during a health screening. The commonest symptom in JiNETs is abdominal pain which could be due to one or many of these reasons: bowel dysmotility, subacute bowel obstruction and mesenteric angina secondary to mesentery fibrosis. Other presenting symptoms may be secondary to mass effect and hormones hypersecretion. Serotonin hypersecretion causes secretory diarrhea, flushing and intermittent bronchial wheezing and Hедinger's syndrome, collectively, known as carcinoid syndrome. More than 95% of these cases are associated with liver metastasis where serotonin and peptide hormones are released from the metastases. Carcinoid crisis characterized by hypo- or hypertension, severe bronchospasm and cardiac arrhythmias may be precipitated by anaesthesia and surgery in some patients.

Majority of JiNETs are G1 NETs. Rarely are they highly proliferative with poor histological differentiation variety. About 30% of patients with JiNETs present with carcinoid syndrome.

Appendiceal NETs

ANETs are often diagnosed incidentally after an appendix operation. A large majority of these patients are asymptomatic. Carcinoid syndrome is not common unless patients present with extensive local disease or metastatic tumour. More than one third of ANETs are located at the tip of the appendix.

In addition to the classic serotonin-secreting ANETs, there are L-cell type NETs, tubular and goblet cell ANETs. Histologically, the Goblet cell type is a mixed adenoendocrine carcinoma and is biologically more aggressive.¹¹ Till date, genetic association has not been reported.

Colonic and Rectal NETs

The natural history of NETs arising from colon and rectum is distinctly different. Majority of the colorectal NETs occur in the rectum and rarely in the caecum.¹² Most of the colonic NETs patients are asymptomatic in the early stage. Some patients may present with occult or overt bleeding per rectum, pain and constipation. Often, at the time of presentation, the colonic NETs already metastasize to the liver, lymph nodes and peritoneum.

Rectal NETs may be small or polypoid at the time of initial detection. Majority of rectal NETs are non-functional; however, they may secrete PP, somatostatin and PYY. Unlike metastatic colonic NETs, carcinoid syndrome is not typical of metastatic rectal NETs.¹³

The current unresolved issue centers on the classifica-

tion and biologic behavior of L-cell type NETs which are detected in 50% to 80% of rectal NETs using a combination of L-cell markers, GLP1, GLP2, PYY and PPY, immune-typing.^{14,15}

DIAGNOSTIC APPROACH

The diagnostic approach runs systematically starting from the assessment of clinical presentation and syndrome, followed by diagnosis and tumour stage confirmation. The diagnosis could be suspected from symptomatology or clinical syndromes, supported by an initial biochemistry and biomarkers. Serum chromogranin A is a useful general biomarker for the diagnosis of neuroendocrine tumour.¹⁶ In PD G3 GEP-NETs, Chromogranin A (CgA) may be normal and in such situations neuron-specific enolase (NSE) is an alternative tumour marker. Specific biomarkers such as serum serotonin, insulin, glucagon, PP and gastrin may be helpful, e.g., for JiNETs, the recommended biochemistry tests are CgA and 24 Hours urine 5-HIAA or serum serotonin, if available.

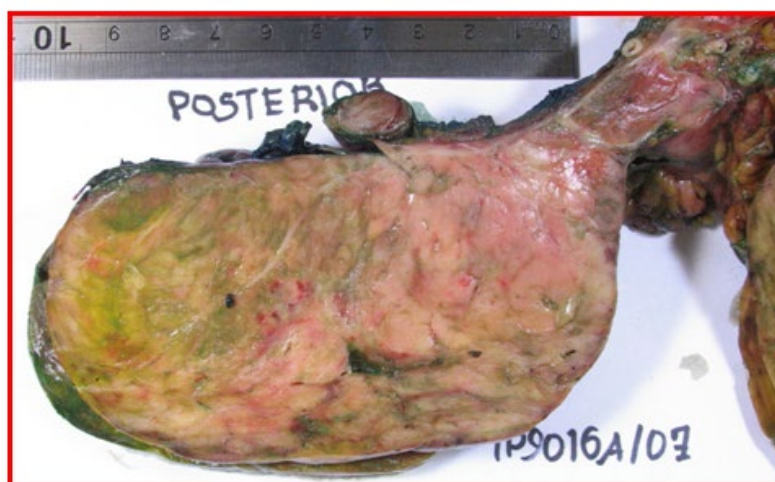
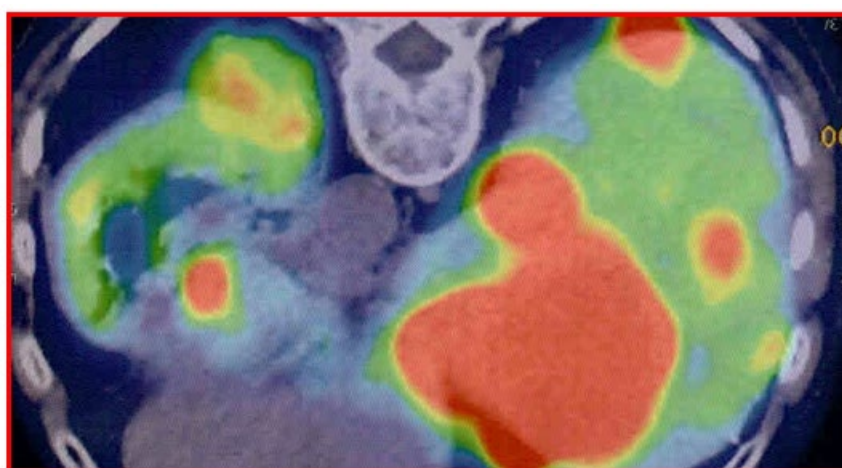
To confirm GEP-NETs, immunohistochemistry (IHC) remains the gold standard (Figure 1). CgA and synaptophysin immunohistochemistry are the key diagnostic markers. From WHO 2010 classification, Ki-67(MIB-1) is imperative to grade GEP-NETs. For the biopsy of tumour tissues, endoscopy is helpful in visualizing gastrointestinal NETs while endoscopic ultrasonography (EUS) guides PNETs biopsy. CT scan guided percutaneous approach is an excellent approach to target liver metastasis.

Multiphasic CT scan of the abdomen, pelvis and thorax is helpful in localizing and assessing the primary loco-regional and metastatic extent of GEP-NETs. Other imaging modalities such as magnetic resonance imaging (MRI), trans-abdominal ultrasonography, EUS and positron emission tomography (PET) scan may be considered where appropriate. PET CT or MRI scans using Fluoro-Deoxy-Glucose (FDG) and Ga-Doctate tracers are ordered to assess the metabolic activity of the tumours and the presence of somatostatin receptors respectively (Figure 2). Accurate staging greatly helps in clinical management stratification.

The clinical investigation algorithms are individualized to specific type of GEP-NETs. A combination of biochemistry, tumour biomarkers, imaging, endoscopy and biopsy are necessary to gather enough clinical information for therapeutic planning. The European Neuroendocrine Tumor Society (ENETS) has published the consensus statements on the clinical diagnostic approach of GEP-NETs in 2004, 2009, 2012 and 2016.¹⁷⁻²⁰

PRINCIPLES OF MANAGEMENT

Complex GEP-NETs patients are best evaluated and managed by a multidisciplinary team in a network of interdisciplinary and transdisciplinary setting. Curative treatments should be offered to all potential patients as far as the current available therapies

Figure 1: Pancreas NETs.**Figure 2:** F-18 FDG PET.

are concerned.

The principles and goals of managing GEP-NETs are to control hormone and tumour related symptoms, if present, and to improve survivorship by curative surgery or tumour ablation. Tumour sites, grade and stage, hormone functionality and performance status of patients, guide the choice of therapeutic options available for symptoms and tumour control. Current therapeutic repertoire in the management of GEP-NETs include surgery, organ transplantation, liver directed chemotherapy and ablative therapy, selective internal radiotherapy, hormonal therapy, immunotherapy, systemic chemotherapy and targeted molecular therapy.

The salient points on the therapeutic options are summarized and highlighted in the management of GEP-NETs.

Surgery

A rule of thumb in the management of early stage GEP-NETs is that, all patients with local disease should be considered for R0 curative surgery to completely remove the primary tumour unless patients are not fit for surgery. The other roles of surgery are debulking or cytoreductive surgery and palliative surgery.

Curative oncologic surgery aims at R0 surgical resection of the primary tumour and locoregional lymph nodes. For GNETs, depending on the site, size and depth of invasion of the tumour, the surgical options are endoscopic mucosal resection, subtotal gastrectomy with lymphadenectomy and total gastrectomy with lymphadenectomy. For JiNETs, segmental enterectomy with clearance of mesenteric and retroperitoneal lymph nodes is indicated. ANETs with low risk factors, i.e., tumour

size <1 cm, invasion up to submucosa and clear surgical margin, simple appendectomy is an adequate treatment.¹⁸ Patients with high risk factors in ANETs, right hemicolectomy with lymphadenectomy is necessary if R0 resection is the goal. Likewise, for colonic NETs, right or left hemicolectomy with resection of the accompanied lymph nodes is recommended depending on the location and extent of primary tumour. Anterior resection and abdominoperineal resection are options for rectal NETs. Less invasive surgery such as transanal minimally invasive surgery and transanal endoscopic microsurgical resection may be indicated for early small rectal NETs.¹⁹

Curative pancreatic surgery may involve enucleation of tumour, segmental pancreatectomy, Whipple's operation, pylorus preserving pancreaticoduodenectomy (PPPD) and subtotal distal pancreatectomy. In advanced surgical centers with minimal invasive expertise, some of these operations can be performed laparoscopically or with robotic surgery. The choice on the nature of operation is determined by the location and extent of tumours, e.g. early small periampullary NETs is amenable with curative PPPD. High cure rate can be expected when R0 surgical resection is performed. For instance, a cure rate of more than 90% of the patients has been reported for sporadic insulinoma.²⁰

Debulking, cytoreductive surgery or complete liver metastatectomy in selected patients with liver-only diseases in metastatic GEP-NETs, confer both improved symptoms control and long-term survivorship.²¹ It also has an added benefit of rendering medical therapy more effectively in controlling the residual tumour.

Palliative surgery may be necessary to relieve the intestinal obstruction caused by mesenteric fibrosis or tumour mass effects in patients with advanced GEP-NETs.

Organ Transplantation

Due to organ scarcity, orthotopic liver transplantation remains an option for only highly selected patients. The current selection criteria take into account patients showing an absence of extrahepatic metastasis with the involvement of less than 50% of the hepatic volume, undergoing pre-transplantation R0 resection of the primary tumour and those who are unresponsive or have exhausted all medical therapies. Aggressive GEP-NETs

is an exclusion criterion.²² When a strict inclusion for liver transplantation is adopted, the 5-year overall survival rate of 52% can be expected.²³

Liver Directed Loco-regional Therapy

For metastatic GEP-NETs patients who have liver-only disease and are not surgical candidates, the choice of loco-regional therapies include radiofrequency ablation (RFA), transarterial embolization (TAE) or chemoembolization (TACE) and radioactive isotope Yttrium-90 microsphere radioembolization therapy (RET).²⁴ These modalities of treatment can be used in combination with systemic chemotherapy or molecular therapy. RFA is recommended for the treatment of tumours less than 5 cm. Trans-arterial embolization (TAE) and trans-arterial chemoembolization (TACE) are indicated as a diagnostic approach for treating G1 and G2 NETs in patients showing reasonable liver function and those who are free from portal vein thrombosis. Although, a good objective response has been reported for Yttrium-90 microspheres RET, comparative randomized trial between Yttrium-90 microspheres RET and TACE is not available.²⁵

Hormonal Therapy

Somatostatin analogues (SSA) have been proven to have significant impacts in terms of controlling both, the symptoms and anti-tumour proliferation.^{26,27} SSA acts by reducing and blocking hormone secretion by the tumour, inhibiting neuroendocrine tumour growth, reducing gastrointestinal secretion and inhibiting peristalsis. These effects are achieved by binding with five subtypes of somatostatin receptors (sst1-5). Clinical response in terms of anti-proliferative effects is significant in JiNETs patients and, in term of hormone related symptoms, it can be observed prominently in PNETs.²⁸ In patients with VIPoma, SSA rapidly reverses the watery diarrhea, hypokalemia, hypochlorhydria, acidosis (WDHHA) syndrome and glucagonoma symptoms,²⁹ and is used to treat necrolytic migratory erythema rash.³⁰ In the carcinoid syndrome, SSA promptly palliates flushing and blushing symptoms.³¹

Octreotide, lanreotide and pasireotide are somatostatin analogues which are currently available for clinical use (Tables 4 and 5). They have different somatostatin receptor affinities. Octreotide and lanreotide bind avidly to sst2 receptor and have

Table 4: Molecular Directed Therapy for PNETs.

Study Phase (References)	Therapy	Response Rate	Survival (Months)
Phase II ⁴¹	Sorafenib	10%	PFS=11.9
Phase III ³⁷	Sunitinib	9.3%	PFS=11.4
Phase II ⁴²	Pazopanib/Octreotide	17%	PFS=11.7
Phase III ³⁸	Everolimus	73%	PFS=11
Phase II ⁴⁰	Temsirolimus	6.7%	TTP=6

PFS: Progression free survival; TTP: Time-To-Progression.

Table 5: Molecular Directed Therapy for Advanced NETs.

Study Phase (References)	Therapy	Stable Disease	Survival
Phase III ²⁹	Octreotide	66.7%	PFS=14.3 months
Phase II ⁴³	Bevacizumab/Octreotide	77%	PFS at 18 months 95%
Phase III ⁴⁴	Everolimus/Octreotide	84%	PFS=16.4 months
Phase II ⁴⁵	Imatinib	63%	PFS=24 weeks
Phase II ⁴⁰	Temsirolimus	58.3%	TTP=6 months

PFS: Progression free survival; TTP: Time-To-Progression.

moderate binding affinity to the sst3 and 5 receptors while pasireotide binds with greater affinity to the somatostatin receptors (sst1, 2, 3 and 5). Pasireotide has a higher affinity for sst5 receptor than octreotide.³² Somatostatin analogues are generally effective as a therapeutic approach for mitotically inactive tumours with avid somatostatin receptor expression. It is recommended as a first-line medical therapy for patients with WD G1 PNETs.³³ Generally, SSA is contraindicated in PD G3 GEP-NETs because majority of the G3 NETs lack somatostatin receptors and the likelihood of its resistance to SSA therapy is higher. In metastatic G1 and G2 non-functional pancreatic NETs, lanreotide has been shown to prolong progression-free survival.³⁴ Somatostatin analogues are generally well tolerated having good safety and adverse effect profiles.

However, trials to define its use as adjuvant therapy following R0 surgical resection of GEP-NETs are currently ongoing.

Systemic Cytotoxic Chemotherapy

The chemosensitivity of GEP-NETs is predicted from its tumour grade, tumour differentiation and primary tumour site. PD high grade NETs are generally very responsive to chemotherapy while the WD G1 NETs are resistant to cytotoxic chemotherapy. Therefore, systemic chemotherapy is recommended for patients who are diagnosed with metastatic G2 NETs, G3 NEC and those with inoperable progressive liver metastases in G1 or G2 NETs. In patients with G1 NETs, the response rate to systemic chemotherapy remains poor. The commonly considered cytotoxic drugs include cisplatin, etoposide, streptozotocin and 5-fluorouracil (5-FU) or doxorubicin.³⁵ Temozolomide based chemotherapy, alone or in combination with capecitabine, has been shown to have anti-tumour effects generating a good tumour response.³⁶

Biologic Targeted Therapy

Most GEP-NETs are characterized by hypervascularity with a frequent expression of VEGF ligand and receptors. Anti-VEGF agent that inhibits vascular endothelium growth factor (VEGF) pathway ultimately disrupts the drivers of angiogenesis. Anti-VEGF can be targeted at either the tyrosine kinase VEGF receptors on the tumour cell membranes or the circulating VEGF. Tyrosine kinase VEGF receptor inhibitors, sunitinib and pazopanib have been shown to be effective in controlling the

progression of advanced PNETs.³⁷ Bevacizumab is a monoclonal antibody that targets the circulating VEGF-A.

The mammalian target of rapamycin (mTOR) inhibitor targets the mTOR enzyme in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway that is responsible for cell growth, proliferation and metabolism. Everolimus, an mTOR inhibitor, has been tested in advanced PNETs which indicated anti-tumour effect with significant improvement in progression-free survival.³⁸ Everolimus has an additional advantage in decreasing the insulin release from the pancreatic beta cells in metastatic insulinoma patients.³⁹ Patients with metastatic insulinoma requiring a high dosage of diazoxide to control the overproduction of insulin hormones and hypoglycemia may show a favorable response to the treatment. Temsirolimus is the other mTOR inhibitor which has been tested clinically for advanced neuroendocrine carcinomas.⁴⁰

The clinical outcomes, measured by response rate, stable disease rate, progression free survival (PFS) and time-to-progression (TTP), of some of these molecular directed therapies for PNETs and advanced NETs are summarized in Tables 4 and 5 respectively.⁴¹⁻⁴⁵

Immunotherapy

Alpha-Interferon (IFN) therapy is one of the possible treatment options for GEP-NETs. Both, JiNETs and functioning PNETs are sensitive to the anti-secretory and anti-proliferative effects of alpha-IFN.⁴⁶ It controls symptoms and tumour growth effectively through immune stimulation, inhibition of angiogenesis and induction of cell cycle arrest.⁴⁷ However, its use is limited by the adverse effects of flu-like symptoms, depression and myelosuppression.⁴⁸ Therefore, it is usually implemented as a second line therapy. Fever, fatigue, anorexia and weight loss are common symptoms associated with this method of treatment. Interferon combined with somatostatin analogues has a synergistic effect in the symptoms and tumour control, an example being, patients with carcinoid syndrome who are refractory to octreotide treatment.

The impact of anti-PD1 and anti-PD-L1 on the treatment of neuroendocrine carcinoma has yet to be extensively explored. While clinical success has been witnessed in other types of cancers, clinical trials and research lack sufficient evidences

in GEP-NETs currently.

Peptide Receptor Targeted Radiotherapy (PRRT)

Emerging data on PRRT in the treatment of metastatic GEP-NETs using ⁹⁰Yttrium and ¹⁷⁷Lutetium labelled Doctatate PRRT has been promising. Patients who have either functioning or non-functioning GEP-NETs with dense somatostatin receptors on tumours as demonstrated by positive Ga-Doctatate PET/CT scan are considered as a suitable recipient of PRRT.⁴⁹ Objective response rates in the range of 20% to 40% have been clinically reported.⁵⁰ The main adverse effects of this treatment modality are bone marrow and renal toxicities. Further studies and clinical trials are currently underway to clarify its roles and indications in the management of GEP-NETs.⁵¹

The first preliminary PRRT phase III trial NETTER-1 result was published in 2016.⁵² In comparison to the octreotide LAR 60 mg, PRRT using ¹⁷⁷Lutetium significantly improved the treatment response rate and progression-free survival of patients with advanced metastatic midgut NETs.⁵³ A few other Phase III clinical trials for PRRT are currently underway and clinicians are eagerly awaiting the final outcome of the study.

Potentially, PRRT may have a role in the neoadjuvant setting to downstage an unresectable to resectable tumour, or render the safety of cytoreductive surgery. Surgeons must keep an eye on this emerging modality that could potentially have a tremendous impact on the surgical management of GEP-NETs.

Longitudinal Evaluation

Depending on the biology and grade of GEP-NETs, a regular medical review of clinical, biochemical parameters and imaging at an interval between 3 to 6 months is recommended. A clinical review at a closer interval is recommended for aggressive G3

GEP-NETs. Serum CgA and NSE remain useful general non-specific biomarker for follow-up in the affected patients. Other relevant tumour-specific markers and imaging are helpful in the assessment of treatment response, tumour recurrence, tumour progression, tumour dedifferentiation and prognostication. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan or dual-tracer PET/CT scans using FDG and Ga-Doctatate may be recommended (Figure 3). The dual-tracer PET scan has the advantage with respect to the assessment of 'flip-flop' phenomenon which results in a poor prognosis in NETs patients. It happens when tumours lose the expression of somatostatin receptors and exhibit an increased FDG hypermetabolism during the process of tumour dedifferentiation. When GEP-NETs progress rapidly or fail to respond to therapy or whenever imaging is unhelpful, a re-biopsy of liver metastases to reassess proliferative activity of the tumour is recommended.

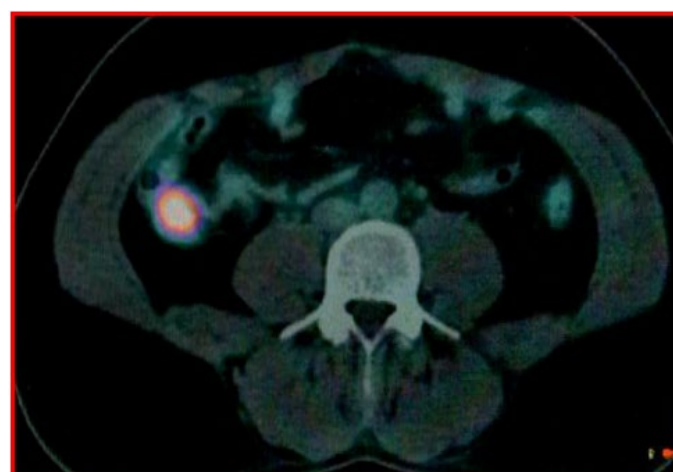
Prognosis and Survivorship

In general, G1 and G2 NETs show an indolent clinical tumour progression marked by several years of survivorship and good performance status, while the G3 NETs have a more aggressive clinical course with shorter survivorship.

The main prognostic factors for GEP-NETs include the site of origin of NETs, grade and classification of malignant tumours (TNM staging of the tumour).⁵⁴ Clinical prognosis can be adversely affected by the presence of high urinary 5-HIAA and CgA, carcinoid heart syndrome and carcinoid syndrome.

The 5-year overall survival rates for patients with non-functioning PNETs are estimated to be 26% to 58%.⁵⁵ Localized PNETs following R0 surgical resection show excellent prognosis and a 5-year survival is estimated in the range of 60% to 100%.^{56,57} In patients with liver metastasis, the overall 5-year survival rate ranges from 20% to 38%.⁵⁸

Figure 3: Ga-Doctatate PET Scan-Ileal NETs.



CONCLUSION

GEP-NETs is a heterogeneous group of tumours originating from the digestive diffuse endocrine system. They have a wide spectrum of biologic and oncologic diversity. With a better understanding of GEP-NETs, clinical diagnosis could be made more prompt and precise, such that therapeutic intervention could be more tumour type specific and prognostication could be more accurate.

Multimodal management provided by a multi- and trans-disciplinary team remains the key element for ensuring the clinical success and good outcome. More basic science research and clinical trials on classification, oncobiology, diagnostic and prognostic biomarkers, imaging technology and innovative therapeutics are needed to push the frontier in GEP-NETs management.⁵⁹

REFERENCES

1. Oberndorfer S. Karzinoide tumoren des dunndarms [In German]. *Frankfurt Z Pathol*. 1907; 426-432.
2. WHO. Neuroendocrine Tumour Grading System. 2017. Web site. http://www.agps.org.au/resources/AGPS_AGM_programs/2016_AGM_presentations/Gill_WHO%202017%20Neuroendocrine%20October%2027.pdf. Accessed June 25, 2017.
3. Nishikura K, Watanabe H, Iwafuchi M, Fujiwara T, Kojima K, Ajioka Y. Carcinogenesis of gastric endocrine cell carcinoma: Analysis of histopathology and p53 gene alteration. *Gastric Cancer*. 2003; 6(4): 203-209. doi: [10.1007/s10120-003-0249-0](https://doi.org/10.1007/s10120-003-0249-0)
4. Buettner M, Dimmler A, Magener A, et al. Gastric PDX-1 expression in pancreatic metaplasia and endocrine cell hyperplasia in atrophic corpus gastritis. *Mod Pathol*. 2004; 17(1): 56-61. doi: [10.1038/sj.modpathol.3800015](https://doi.org/10.1038/sj.modpathol.3800015)
5. Michalopoulos N, Papavramidis TS, Karayannopoulou G, et al. Neuroendocrine tumours of extrahepatic biliary tract. *Pathol Oncol Res*. 2014; 20(4): 765-775. doi: [10.1007/s12253-014-9808-4](https://doi.org/10.1007/s12253-014-9808-4)
6. Noronha YS, Raza AS. Well differentiated neuroendocrine carcinoid_ tumours of the extrahepatic biliary ducts. *Arch Pathol Lab Med*. 2010; 134(7): 1075-1079. doi: [10.1043/2008-0764-RS.1](https://doi.org/10.1043/2008-0764-RS.1)
7. Garbrecht N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumours of the duodenum and pancreas: Incidence, types, biologic behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer*. 2008; 15(1): 229-241. doi: [10.1677/ERC-07-0157](https://doi.org/10.1677/ERC-07-0157)
8. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ. Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. *Am J Surg Pathol*. 1986; 10 (5): 348-357.
9. Öberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol*. 2005; 19(5): 753-781. doi: [10.1016/j.bpg.2005.06.002](https://doi.org/10.1016/j.bpg.2005.06.002)
10. Shi C, Klimstra DS. Pancreatic neuroendocrine tumours: Pathologic and molecular characteristics. *Semin Diagn Pathol*. 2014; 31(6): 498-511. doi: [10.1053/j.semdp.2014.08.008](https://doi.org/10.1053/j.semdp.2014.08.008)
11. Deschamps L, Couvelard A. Endocrine tumours of the appendix: A pathologic review. *Arch Pathol Lab Med*. 2010; 134(6): 871-875. doi: [10.1043/1543-2165-134.6.871](https://doi.org/10.1043/1543-2165-134.6.871)
12. Jetmore AB, Ray JE, Gathright JB Jr, McMullen KM, Hicks TC, Timmcke AE. Rectal carcinoids: The most frequent carcinoid tumor. *Dis Colon Rectum*. 1992; 35 (8): 717-725. doi: [10.1007/BF02050318](https://doi.org/10.1007/BF02050318)
13. Levy AD, Sobin LH. From the archives of the AFIP. Gastrointestinal carcinoids: Imaging features with clinicopathologic comparison. *Radiographics*. 2007; 27(1): 237-257. doi: [10.1148/rg.271065169](https://doi.org/10.1148/rg.271065169)
14. Kim JY, Kim KS, Kim KJ, et al. Non-L cell immunophenotype and large tumour size in rectal neuroendocrine tumours are associated with aggressive clinical behaviour and worse prognosis. *Am J Surg Pathol*. 2015; 39(5): 632-643. doi: [10.1097/PAS.0000000000000400](https://doi.org/10.1097/PAS.0000000000000400)
15. Sohn JH, Cho MY, Park Y, et al. Prognostic significance of defining L-cell type on the biologic behavior of rectal neuroendocrine tumours in relation with pathological parameters. *Cancer Res Treat*. 2015; 47(4): 813-822. doi: [10.4143/crt.2014.238](https://doi.org/10.4143/crt.2014.238)
16. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: Is it a useful marker of neuroendocrine tumors? *J Clin Oncol*. 2007; 25: 1967-1973. doi: [10.1200/JCO.2006.10.1535](https://doi.org/10.1200/JCO.2006.10.1535)
17. Plöckinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004; 80(6): 394-424. doi: [10.1159/000085237](https://doi.org/10.1159/000085237)
18. Prommegger R, Obrist P, Ensinger C, et al. Retrospective evaluation of carcinoid tumours of the appendix in children. *World J Surg*. 2002; 26: 1489-1492. doi: [10.1007/s00268-002-6440-3](https://doi.org/10.1007/s00268-002-6440-3)
19. Yamaguchi N, Isomoto H, Nishiyama H, et al. Endoscopic submucosal dissection for rectal carcinoid tumours. *Surg Endosc*. 2010; 24(3): 504-508. doi: [10.1007/s00464-009-0606-0](https://doi.org/10.1007/s00464-009-0606-0)
20. Rothmund M, Angelini L, Brunt M. et al. Surgery for benign

- insulinoma: An international review. *World J Surg.* 1990; 14(3): 393-399. doi: [10.1007/BF01658536](https://doi.org/10.1007/BF01658536)
21. Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg.* 1995; 169(1): 36-43. doi: [10.1016/S0002-9610\(99\)80107-X](https://doi.org/10.1016/S0002-9610(99)80107-X)
22. Le Treut P, Delperio JR, Dousset B, et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors: A 31-case French multicentric report. *Ann Surg.* 1997; 225(4): 355-364.
23. Le Treut YP, Gregoire E, Klempnauer J, et al. Liver transplantation for neuroendocrine tumours in Europe – results and trends in patient selection: A 213 case Europe Liver Transplant Registry study. *Ann Surg.* 2013; 257: 807-815. doi: [10.1097/SLA.0b013e31828ee17c](https://doi.org/10.1097/SLA.0b013e31828ee17c)
24. Eriksson BK, Larsson EG, Skogseid BM, Lofberg AM, Lorellius LE, Oberg KE. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer.* 1998; 83: 2293-2301. doi: [10.1002/\(SICI\)1097-0142\(19981201\)83:11<2293::AID-CNCR8>3.0.CO;2-E](https://doi.org/10.1002/(SICI)1097-0142(19981201)83:11<2293::AID-CNCR8>3.0.CO;2-E)
25. Kennedy AS, Dezam WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: Early results in 148 patients. *Am J Clin Oncol.* 2008; 31: 271-279. doi: [10.1097/COC.0b013e31815e4557](https://doi.org/10.1097/COC.0b013e31815e4557)
26. Lamberts SWJ, van der Lely AJ, de Herder WW, Hofland LJ. Octreotide. *N Engl J Med.* 1996; 334: 246-254. doi: [10.1056/NEJM199601253340408](https://doi.org/10.1056/NEJM199601253340408)
27. Caplin ME, Pavel M, Cwikla JB. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. *N Engl J Med.* 2014; 371(3): 224-233. doi: [10.1056/NEJMoa1316158](https://doi.org/10.1056/NEJMoa1316158)
28. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-blind randomized trial. *J Intern Med.* 1995; 237(3): 369-275. doi: [10.1111/j.1365-2796.1995.tb01175.x](https://doi.org/10.1111/j.1365-2796.1995.tb01175.x)
29. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: A report from the PROMID Study Group. *J Clin Oncol.* 2009; 27: 4656-4663. doi: [10.1200/JCO.2009.22.8510](https://doi.org/10.1200/JCO.2009.22.8510)
30. O'Dorisio TM, Gagginella TS, Mekhjian HS, Rao B, O'Dorisio MS. Somatostatin and analogues in the treatment of VIPoma. *Ann N Y Acad Sci.* 1988; 527: 528-535. doi: [10.1111/j.1749-6632.1988.tb27006.x](https://doi.org/10.1111/j.1749-6632.1988.tb27006.x)
31. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of long-acting somatostatin analogue. *N Engl J Med.* 1986; 315: 663-666. doi: [10.1056/NEJM198609113151102](https://doi.org/10.1056/NEJM198609113151102)
32. Schmid HA, Schoeffter P. Functional activity of the multitigand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. *Neuroendocrinology.* 2004; 80(Suppl 1): 47-50. doi: [10.1159/000080741](https://doi.org/10.1159/000080741)
33. Eriksson B, Kloppel G, Krenning E, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors – well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology.* 2008; 87(1): 8-19. doi: [10.1159/000111034](https://doi.org/10.1159/000111034)
34. Caplin M, Ruzsniwski P, Pavel M, et al. A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic Neuro Endocrine Tumors (CLARINET). *Eur J Cancer.* 2013; 49.
35. Janson ET, Ronnblom L, Ahlstrom H, et al. Treatment with alpha-interferon versus alpha-interferon in combination with streptozocin and doxorubicin in patients with malignant carcinoid tumors: A randomized trial. *Ann Oncol.* 1992; 3(8): 635-638. doi: [10.1093/oxfordjournals.annonc.a058291](https://doi.org/10.1093/oxfordjournals.annonc.a058291)
36. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer.* 2011; 117(2): 268-275. doi: [10.1002/cncr.25425](https://doi.org/10.1002/cncr.25425)
37. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011; 364: 501-513. doi: [10.1056/NEJMoa1003825](https://doi.org/10.1056/NEJMoa1003825)
38. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011; 364: 514-523. doi: [10.1056/NEJMoa1009290](https://doi.org/10.1056/NEJMoa1009290)
39. Fuhrer DK, Kobayashi M, Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporine A are through regulation of the ATP-sensitive potassium channel. *Diabetes Obes Metab.* 2001; 3(6): 393-402. doi: [10.1046/j.1463-1326.2001.00150.x](https://doi.org/10.1046/j.1463-1326.2001.00150.x)
40. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer.* 2006; 95(9): 1148-1154. doi: [10.1038/sj.bjc.6603419](https://doi.org/10.1038/sj.bjc.6603419)
41. Hobday TJ, Rubin J, Holen K, et al. MC044h, a phase II trial of sorafenib in patients with metastatic neuroendocrine tumours (NET): A Phase II Consortium study. *J Clin Oncol.* 2007 ASCO Annual Meeting Proceedings Part 1, 2007; 25(Suppl 18): 4504. doi: [10.1200/jco.2007.25.18_suppl.4504](https://doi.org/10.1200/jco.2007.25.18_suppl.4504)

42. Phan AT, Yao JC, Fogelman DR, et al. A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (santostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC). *J Clin Oncol.* 2010; 28(Suppl 15): 4001.
43. Yao JC, Phan A, Hoff PM et al. Targeting vascular endothelial growth factor in advanced carcinoid tumour: A random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol.* 2008; 26: 1316-1323. doi: [10.1200/JCO.2007.13.6374](https://doi.org/10.1200/JCO.2007.13.6374)
44. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomized, placebo-controlled, phase 3 study. *Lancet.* 2011; 378: 2005-2012. doi: [10.1016/S0140-6736\(11\)61742-X](https://doi.org/10.1016/S0140-6736(11)61742-X)
45. Yao JC, Zhang JX, Rashid A, et al. Clinical and in vitro studies of imatinib in advanced carcinoid tumour. *Clin Cancer Res.* 2007; 13(1): 234-240. doi: [10.1158/1078-0432.CCR-06-1618](https://doi.org/10.1158/1078-0432.CCR-06-1618)
46. Biesma B, Willemse PH, Mulder NH, et al. Recombinant interferon alpha-2b in patients with metastatic apudomas: Effect on tumours and tumour markers. *Br J Cancer.* 1992; 66(5): 850-855.
47. Oberg K. Interferons in the management of neuroendocrine tumours and their possible mechanism of action. *Yale J Biol Med.* 1992; 65: 519-529; discussion 531-536.
48. Oberg K, Eriksson B, Janson ET. Interferon alone or in combination with chemotherapy or other biologicals in the treatment of neuroendocrine gut and pancreatic tumors. *Digestion.* 1994; 3: 64-69. doi: [10.1159/000201204](https://doi.org/10.1159/000201204)
49. Forrer F, Valkema R, Kwekkeboom DJ, de Jong M, Krenning EP. Neuroendocrine tumors. Peptide receptor radionuclide therapy. *Best Pract Res Clin Endocrinol Metab.* 2007; 21(1): 111-129. doi: [10.1016/j.beem.2007.01.007](https://doi.org/10.1016/j.beem.2007.01.007)
50. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3] octreotate: Toxicity, efficacy, and survival. *J Clin Oncol.* 2008; 26(13): 2124-2130. doi: [10.1200/JCO.2007.15.2553](https://doi.org/10.1200/JCO.2007.15.2553)
51. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med.* 2006; 36(2): 147-156. doi: [10.1053/j.semnucmed.2006.01.001](https://doi.org/10.1053/j.semnucmed.2006.01.001)
52. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumours treated with 177-Lu-Dotatate. *J Clin Oncol.* 2016; 34(4): 194-194. doi: [10.1200/jco.2016.34.4_suppl.194](https://doi.org/10.1200/jco.2016.34.4_suppl.194)
53. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of ¹⁷⁷Lu-Dotatate for midgut neuroendocrine tumours. *N Engl J Med.* 2017; 376(2): 125-135. doi: [10.1056/NEJMoa1607427](https://doi.org/10.1056/NEJMoa1607427)
54. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol.* 2005; 89(3): 151-160. doi: [10.1002/jso.20179](https://doi.org/10.1002/jso.20179)
55. Halfdanarson TR, Rubin J, Farnell MB, et al. Pancreatic endocrine neoplasms: Epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer.* 2008; 15(2): 409-427. doi: [10.1677/ERC-07-0221](https://doi.org/10.1677/ERC-07-0221)
56. Madeira I, Terris B, Voss M. et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut.* 1998; 43: 422-427. doi: [10.1136/gut.43.3.422](https://doi.org/10.1136/gut.43.3.422)
57. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factor and survival in 324 patients with pancreatic endocrine tumour treated at a single institution. *Clin Cancer Res.* 2008; 14: 7798-7803. doi: [10.1158/1078-0432.CCR-08-0734](https://doi.org/10.1158/1078-0432.CCR-08-0734)
58. Carty S, Jensen RT, Norton JA, et al. Prospective study of aggressive resection of metastatic pancreatic endocrine tumour. *Surgery.* 1992; 112(6): 1024-1031.
59. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *J Clin Oncol.* 2011; 29(7): 934-943. doi: [10.1200/JCO.2010.33.2056](https://doi.org/10.1200/JCO.2010.33.2056)