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Overview of Advanced Neuroendocrine Tumors (NETs)

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Classification of Neuroendocrine Neoplasms

Neuroendocrine tumors (NETs) belong to the family of malignant neoplasms that are believed to originate from neuroendocrine cells found throughout the body.[1,2] According to the North American Neuroendocrine Tumor Society (NANETS) and the World Health Organization (WHO) guidelines, neuroendocrine neoplasms are separated into 3 grades: low grade (G1) and intermediate grade (G2) NETs, and high grade (G3) neuroendocrine carcinomas. **Grade** refers to the aggressiveness of the tumor.[3-5] NETs are also classified as **well differentiated or poorly differentiated**. **Differentiation** refers to the extent to which neoplastic cells resemble their nonneoplastic counterparts.[6]

The proliferative rate (either mitotic count or Ki-67 index) is also very important in grading NETs. The Ki-67 index can usually be determined, even in cases of small biopsies. The mitotic count is not feasible in small biopsies.[6]

2010 WHO and NANETS Grading of NETs[6]

Grade	GI tract and pancreas	Lung and thymus (WHO 2004)	Lung and thymus (Moran et al, 2009)
Low grade (G1) NET (carcinoid)	<2 mitoses/10 HPF, *AND* ≤2% Ki-67 index	<2 mitoses/10 HPF, *AND* no necrosis	≤3 mitoses/10 HPF, *AND* no necrosis
Intermediate grade (G2) NET	2-20 mitoses/10 HPF, *OR* 3%-20% Ki-67 index	2-20 mitoses/10 HPF, *OR* foci of necrosis	4-10 mitoses/10 HPF, *OR* foci of necrosis
High grade (G3) neuroendocrine carcinoma	>20 mitoses/10 HPF, *OR* >20% Ki-67 index	>10 mitoses/10 HPF	>10 mitoses/10 HPF *AND* necrosis present

Adapted from Klimstra D et al with permission.[6]

Abbreviations: GI, gastrointestinal; **HPF**, high-power field.

The grading requires mitotic count in at least 50 HPFs (1 HPF = 2 mm^2) and Ki-67 index using the MIB antibody as a percentage of 500 to 2000 cells counted in areas of strongest nuclear labeling ("hot spots"). If grade differs for mitotic count compared with Ki-67 index, it is suggested that the higher grade be assumed.[7]

A word about neuroendocrine nomenclature

This brochure uses the nomenclature established in the 2010 *WHO Classification of Tumours of the Digestive System*[8] to classify different types of neuroendocrine neoplasms.

The WHO naming convention categorizes these neoplasms into 2 groups:

- Neuroendocrine tumors (NETs): well-differentiated neoplasms that can be divided into grade 1 (G1) and grade 2 (G2) depending on proliferation and histology
- Neuroendocrine carcinomas: poorly differentiated grade 3 (G3) neuroendocrine neoplasms

Use of "tumor" instead of "neoplasm" is debated and both terms are used interchangeably in the literature. All of the entities under discussion are neoplastic, so "neoplasm" is therefore a more accurate term than "tumor," which means only "mass." These terms are used interchangeably throughout this brochure.

Advanced NETs: Symptoms, Incidence, and Survival

According to the US Surveillance, Epidemiology, and End Results (SEER) Program registries, there has been an approximate 5-fold increase in the diagnosed incidence of NETs over the past 30 years.[2] A continued increase in reported incidence is predicted.[9]

NETs are more prevalent than stomach and pancreatic cancer combined[2,10] and are often **advanced** at the time of diagnosis, meaning that they have metastasized to distant sites.[2] Many NETs secrete hormones or substances when they metastasize that cause disabling symptoms and can lead to serious complications. The most common primary tumor sites, symptoms, syndromes, and survival data for advanced NETs are shown in the following tables.

Primary tumor site	Overall incidence (cases per 100,000)[2]	Predominant hormone involvement	Major symptoms	Associated syndrome	5-year survival in advanced NETs (%)
Lung	1.35	Serotonin, ACTH, GHRH, ADH[11]	Weight loss, malaise, fever, cough, dyspnea, wheeze, stridor, hemoptysis, chest/back pain[12]	• Carcinoid syndrome in less than 5% of patients (but may be found in up to 50% of patients with metastases)[11] • Cushing syndrome[11] • Acromegaly[11]	Atypical carcinoid, 61% Typical carcinoid, 90%[12]
Thymus	0.02	ACTH[11]	Shortness of breath, superior vena cava syndrome[8]	Cushing syndrome[11]	28%[8]
Stomach	0.30	Serotonin, somatostatin, gastrin[11,13]	Abdominal pain, small-bowel obstruction[9]	Carcinoid syndrome[11]	10%[9]
Small intestine Duodenum Jejunum/ileum	 0.19 0.67	Serotonin, somatostatin, secretin, cholecystokinin, motilin, GIP[11,13]	Abdominal pain, small-bowel obstruction[11]	Carcinoid syndrome[11]	36%-79%[11]
Appendix	0.15	Serotonin, substance P[9]	Nonspecific symptoms, signs of acute appendicitis[9]	Carcinoid syndrome may be present in patients with metastases[11]	34%[11]
Colon	0.20	Somatostatin, enteroglucagon, peptide YY, neurotensin[13]	Pain, anorexia, weight loss[11]	–	20%[11]
Rectum	0.86	Glucagon, PP, glicentin-like peptides[11]	Rectal bleeding, pain, constipation[11]	–	18%[11]

Advanced Pancreatic NETs

Pancreatic NETs vary in clinical aggressiveness, depending on subtype and histologic features. Although they share similarities with other NETS, pancreatic NETs can be difficult to diagnose and manage. Presentation is highly variable and depends mainly on the functional status of the tumor.[14] In *functional* NETs, symptoms and corresponding syndromes are usually determined by the type of hormone product secreted. *Nonfunctional* NETs are not associated with secretion of hormone products related to a syndrome; in these NETs, symptoms reflect tumor growth or spread.[14,15]

The table below lists the major pancreatic NET subtypes, associated symptoms and syndromes, and 5-year survival data.

Pancreatic NET subtypes	Pancreatic NET cases per million[11]	Predominant hormone involved	Major symptoms	Associated syndrome	5-year survival in advanced NETs (%)
Gastrinoma	1.0-1.5	Gastrin, ACTH[11,16,17]	Recurrent peptic ulcer, diarrhea[11,16,17]	Zollinger-Ellison syndrome (ZES)[11]	30% (10-yr survival)[11]
Insulinoma	1.0-2.0	Insulin, proinsulin[11,17]	Hypoglycemia (fasting or nocturnal), neuroglycopenia, headache, lethargy, dizziness, diplopia, blurred vision, amnesia, seizures, coma, neurologic deficit[11]	Hypoglycemia syndrome (Whipple's triad)[11]	29% (10-yr survival)[11]
Glucagonoma	0.01-0.10	Glucagon, PTH, gastrin, serotonin, VIP, MSH[11,17]	Migratory necrolytic erythema, weight loss, diabetes mellitus, cheilosis or stomatitis, diarrhea[11,16]	–	60%[11]
Somatostatinoma	<0.10	Somatostatin[11]	Hyperglycemia, cholelithiasis, diarrhea, steatorrhea, hypochlorhydria, abdominal pain, weight loss, anemia[11]	–	60%[11]
VIPoma	0.10	VIP[11]	Severe watery diarrhea, carbohydrate intolerance, facial flushing[11]	Verner-Morrison syndrome[18]	59%[18]
ACTHoma	<0.1	ACTH[11]	Excessive torso fat, muscle fatigue	Cushing syndrome[11]	NA
GRFoma	<0.1	GRF[11]	Bone deformity, heart failure, vision problems	Acromegaly[11]	NA

Abbreviations: ACTH, adenocorticotropic hormone; **ADH**, antidiuretic hormone; **GHRH**, growth hormone-releasing hormone; **GIP**, gastric inhibitory peptide; **GRF**, growth hormone-releasing factor; **MSH**, melanocyte-stimulating hormone; **NA**, not available; **PP**, pancreatic polypeptide; **PTH**, parathyroid hormone; **VIP**, vasoactive intestinal polypeptide.

Monitoring Progression in Advanced NETs

NETs are progressive neoplasms that need to be monitored. An essential aspect of monitoring is periodic imaging, which helps to determine extent of disease, changes in disease status, and response to management interventions. The measurement of biochemical markers is also an important tool.

Imaging

Computed tomography (CT) may be used for surgical candidates as part of preoperative planning, and may help identify the spread of disease.[19,20]

Magnetic resonance imaging (MRI) is a well-recognized imaging technique. Injection of a contrast medium (such as gadolinium) facilitates the visualization of NETs, as these tumors may appear isodense with the surrounding tissue.[21] MRI has been shown to be effective in the detection of hepatic and bone metastases.[19,22-24]

Octreoscan™ somatostatin receptor scintigraphy (SRS) is a whole-body imaging technique that specifically identifies tumors that express somatostatin receptor (over 90% of NETs).[1] Patients are intravenously administered a radiolabeled somatostatin analog (^{111}In-octreotide or ^{111}In-pentetreotide) prior to scintigraphy with a large-field gamma camera.[24] Octreoscan may be particularly helpful in identifying previously unsuspected extrahepatic and lymph node metastases.[22,24]

^{131}Iodine metaiodobenzylguanidine (MIBG) scintigraphy: MIBG scintigraphy is an imaging test that uses injected radioisotope and a specialized scanner to locate, confirm the presence of, and monitor primary and/or metastatic pheochromocytomas and neuroblastomas. Only a minority of other NETs are MIBG-avid, however, so the technique typically is not used as a standard imaging technique for most NETs.[25-27]

Positron emission tomography (PET) is also a radiolabeled imaging modality that is used to detect metastasis. When used with certain radioactive agents (eg, C-5-HTP), PET may be helpful in monitoring more aggressive types of NETs and is being investigated in the detection of carcinoid tumors.[9,28]

Important General Biochemical Markers of NETs

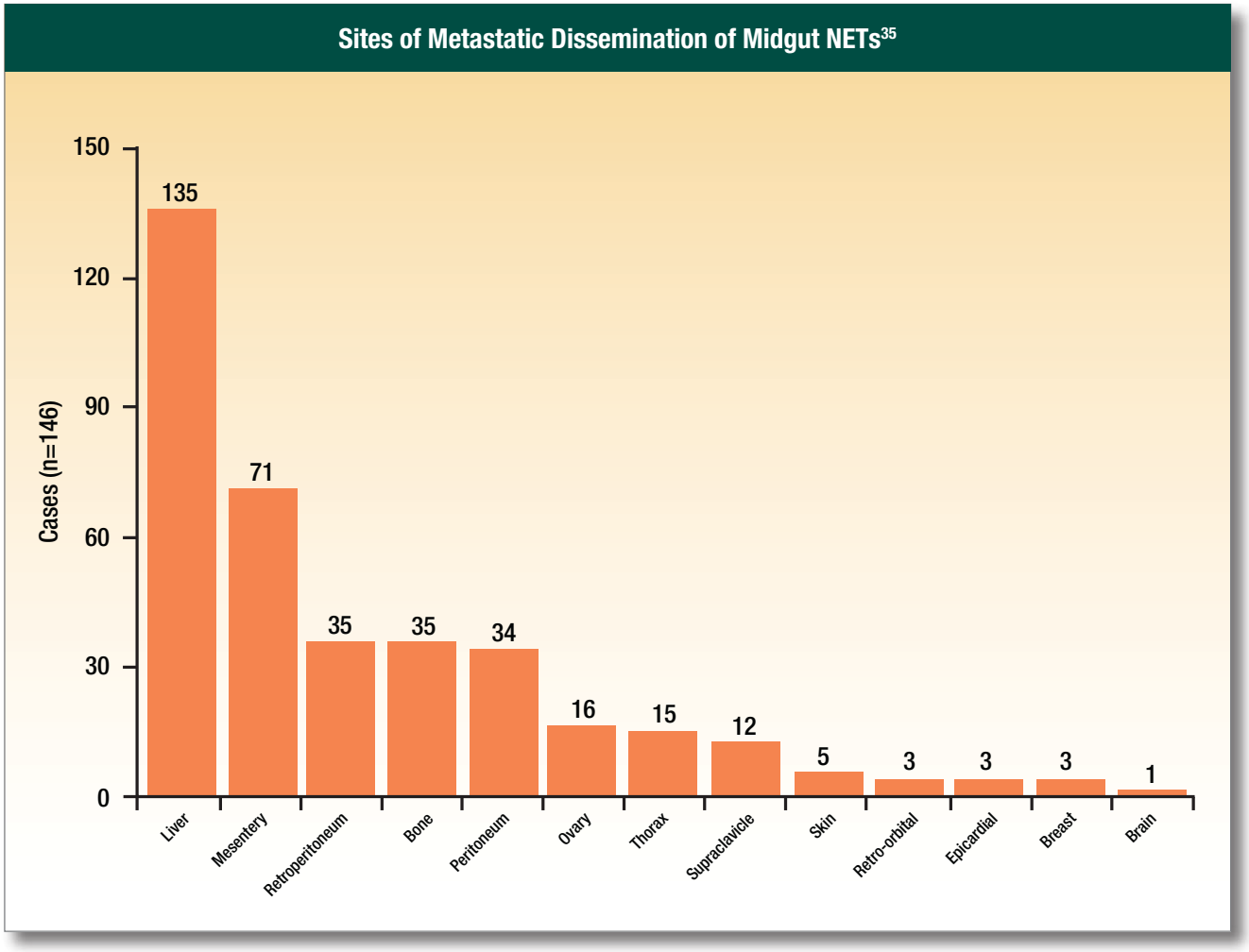
Marker	Relevance	Sensitivity[29]	Specificity[29]
CgA	Currently the most useful circulating marker for GEP-NETs, elevated in up to 90% of NETs.[30-32] Levels are typically highest in metastatic disease, particularly in patients with multiple liver metastases[31,32]	In most NETs: 60%-90% In MTC: <50%	68%-100%
5-HIAA	Only elevated in NETs and metastases that secrete serotonin. Elevated levels are associated with increased tumor mass[1,33,34]	In ileal NETs: 65%-85% In other NETs: 5%-50%	~100%
NSE	High levels correlate with a poor prognosis, especially in small cell lung NETs[29]	In GEP-NETs: 38%-70% In small cell lung NETs: >70%	30%-85%
PP	Although considered a nonspecific marker, is elevated in the majority of pancreatic NETs[29]	In GI NETs: 30% In pancreatic NETs: 70%	67%

Abbreviations: CgA, chromogranin A; **5-HIAA**, 5-hydroxyindoleacetic acid; **GEP**, gastroenteropancreatic; **MTC**, medullary thyroid carcinoma; **NSE**, neuronal-specific enolase; **PP**, pancreatic polypeptide.

Managing Advanced NETs: Sites of Progression, Management Options, and Survival

Common sites of metastases

For midgut NETs, the most common site of distant metastasis is the liver; however, other areas may also be affected, as shown in the graph below.



Management of advanced NETs

In patients with metastatic NETs, management strategies depend on location of the primary neoplasm, patterns of metastatic spread, and hormonal activity.[20]

Management Options for Advanced NETs	
Surgery	Surgery is rarely curative in the setting of metastatic disease, but it can have an important role in achieving palliation in select patients.[36] Surgical debulking may be an option in appropriate patients for relief of symptoms. Patients with advanced NETs may also benefit from a multidisciplinary combination of surgery and other interventions[37]
Chemotherapy	The usefulness of chemotherapy for NETs is limited. However, in patients with advanced pancreatic NETs, the antitumor activity of chemotherapy may be of benefit[14]
Radiofrequency ablation (RFA)	When surgery is not an option, RFA may be an appropriate management modality. RFA can be effective in both relieving the symptoms of NET liver metastases and achieving local control of metastases.[38] However, in most cases, a neoplasm >5 cm in diameter is considered unsuitable for this modality[38]
Targeted radionuclide therapy	Iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) is currently the only licensed therapy that serves as a palliative option for certain patients with inoperable or metastatic neoplasms.[39] Other forms of radionuclide therapy are currently under development
Liver-directed therapy	When liver surgery is not an option, hepatic embolization may be a useful management modality. Selective hepatic transcatheter arterial embolization (TAE) or chemoembolization (TACE) with hepatic artery occlusion can be employed in the management of liver metastases in appropriate patients. The goal is to reduce neoplasm size and hormone output[39]
Peptide receptor radionuclide therapy (PRRT)	Using radiolabeled somatostatin analogs, PRRT is a management modality for inoperable or metastatic NETs.[14,15,40] PRRT is currently available only in certain centers in Europe and is still investigational in the United States.
Clinical trials	Entering patients into formal trials of new agents, when feasible, should be considered[41,42]

Survival statistics

Long-term SEER data (1973-2004) demonstrate the malignant potential of NETs and variability of outcomes.[2] Median duration of survival and 5-year survival rates ***decrease*** with the degree of neoplasm differentiation and extent of disease.

Survival Based on Degree of Differentiation and Extent of Disease[2]			
	Local disease (50%)	**Regional disease (23%)**	**Distant metastases (27%)**
Well-differentiated NETs (G1/G2)			
Median survival duration	223 months	111 months	33 months
5-year survival	82%	68%	35%
Poorly differentiated neuroendocrine carcinomas (G3)			
Median survival duration	34 months	14 months	5 months
5-year survival	38%	21%	4%

Strong correlation between primary neoplasm site and extent of disease: In the SEER data analysis of 28,515 patients, certain primary neoplasm sites were associated with distant disease at diagnosis, for example, pancreas 64%, cecum 44%, colon 32%, thymus 31%, and jejunum/ileum 30%.[2]