Neuroendocrine Tumors: Review and Clinical Update

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Neuroendocrine tumors (NETs) comprise a heterogenous group of neoplasms derived from peptide- and amine-producing cells of the neuroendocrine system. They are characterized histologically by the intracellular presence of markers of endocrine tissue, such as chromogranin A, synaptophysin, and neuron-specific enolase (**Figure 1**), which can be used in the diagnosis of these tumors. NETs are broadly subcategorized as carcinoid tumors or functional and nonfunctional NETs. Functional NETs and carcinoid tumors overproduce endogenous hormones or vasoactive substances, which can cause dramatic clinical symptoms. These tumors may arise sporadically or in the context of a heritable tumor syndrome.

The incidence of NETs is 2 cases per 100,000 persons, and they account for 0.5% of all malignancies.[1] Although most NETs are found in the gastrointestinal (GI) tract, carcinoids and other NETs make up only 1.5% and 0.3% of GI cancers in the United States.[2,3] Despite their relatively low incidence, NETs represent a significant clinical challenge because they have varied presentations and initial imaging studies to locate the tumor may be inconclusive. Additionally, management can be complicated if surgery is not possible. This article presents an overview of NETs, with a focus on heritable syndromes associated with NETs, clinical presentation, diagnostic work-up, treatment options, and prognosis.

TAKE HOME POINTS

- Neuroendocrine tumors (NETs) are a rare form of hormone-secreting neoplasms that present with varied clinical syndromes.
- The evaluation of NET is initially focused on obtaining tissue diagnosis through methods such as endoscopic ultrasound–directed fine-needle aspiration and then identifying potentially resectable disease.
- If patient health and tumor burden are amenable, the preferred treatment is surgical resection.
- Palliative therapies (eg, tumor debulking) can prolong survival, and symptomatic treatment with somatostatin analogues is effective for palliation.
- Current chemotherapy regimens are not considered first-line therapy, as they lack the effectiveness of surgical treatments. Radiotherapy techniques are still under development.

EPIDEMIOLOGY

The majority of NETs are carcinoid tumors. These tumors arise from enterochromaffin cells distributed throughout the GI tract and are defined as lesions that release serotonin. Functional and nonfunctional tumors derived from the lung, pancreas, thymus, adrenal glands, and thyroid account for a smaller proportion (0.4%) of NETs.[3] Approximately two thirds of NETs are found in the GI tract, and approximately one quarter occur in the lung, with the remainder arising in other endocrine tissues.[1,2]

Large, population-based studies have not shown any association between smoking or alcohol use and risk of developing NETs.[1,2] Carcinoid tumors occur more frequently in African Americans as compared with other ethnicities. Surveillance Epidemiology and End Results (SEER) data indicate an incidence of 2.47 per 10,000 in white men compared with 4.48 per 10,000 in African American men.[3] Gastric carcinoid has been associated with hypergastrinemic syndromes.[4]

HERITABLE TUMOR SYNDROMES

Although most NETs develop sporadically, several genetic syndromes significantly increase the risk for

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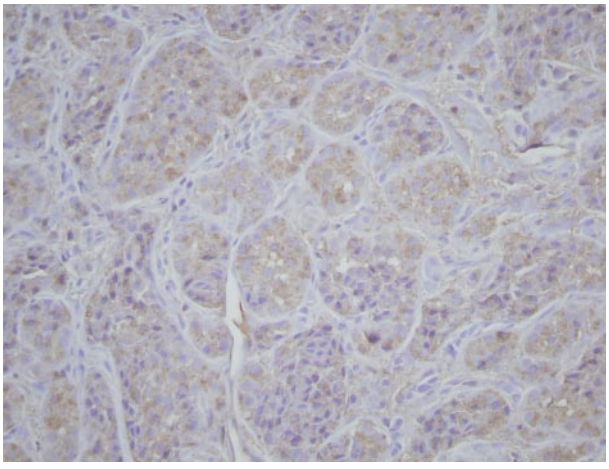

Figure 1. Positive staining with chromogranin A in a nonfunctioning neuroendocrine tumor (original magnification, 40×).

Table 1. Heritable Tumor Syndromes Associated with Neuroendocrine Tumors

Syndrome	Gene Product	Associated NET Type
MEN type 1	Menin	Gastrinoma > nonfunctional NET > insulinoma > other NET
MEN type 2	RET receptor tyrosine kinase	Medullary thyroid cancer, pheochromocytoma
Neurofibromatosis type 1	Hamartin	Somatostatinoma
VHL disease	pVHL tumor suppressor protein	Nonfunctional NET
Tuberous sclerosis	Tuberin	Rarely develop nonfunctional NET, insulinoma, and gastrinoma

MEN = multiple endocrine neoplasia; NET = neuroendocrine tumor; VHL = von Hippel-Lindau.

their development. Multiple endocrine neoplasia types 1 and 2 (MEN1; MEN2), neurofibromatosis type 1 (NF1), von Hippel-Lindau (VHL) disease, and tuberous sclerosis (TSC) are genetic syndromes that can be traced to alterations in cell regulatory proteins and signaling pathways (**Table 1**). The genetic alterations seen in sporadic lesions appear to be the same as those in the genetic syndromes.

MEN1 is a hereditary disorder resulting from a mutation of the MEN1 gene, which encodes the tumor suppressor protein menin.[5] Mutations of the MEN1 gene or loss of the gene locus (11q3) where the MEN1 gene is located account for 15% to 78% of the mutations found in sporadic NETs.[6,7] MEN1 manifests clinically via the development of enteropancreatic tumors, parathyroid hyperplasia, and anterior pituitary adenomas. The most common presenting feature of MEN1 is hyperparathyroidism, which is found in 90% of patients.[8] Over half of patients with MEN1 also have enteropancreatic tumors with varied secretory phenotypes, including gastrinoma (30%–50%), nonfunctioning tumors (20%), insulinoma (18%), gastrinoma/insulinoma (5%), glucagonoma (2%), vasoactive intestinal peptide–producing tumors (1%–9%), and somatostatinoma (1%).[8,9]

MEN2 results from a mutation of the RET protooncogene, a receptor tyrosine kinase. MEN2 is divided into 3 syndromes (ie, MEN2A, MEN2B, familial non-MEN medullary thyroid cancer [FMTC]), all of which have this genetic mutation as well as a near 100% association with medullary thyroid cancer (MTC). MEN2A is also associated with pheochromocytoma (30%–50%) and primary hyperparathyroidism (10%–20%).[10] MEN2B is associated with pheochromocytoma (44%), neuromas, mucosal neuromas, and a marfinoid habitus (94%–100%).[11] FMTC presents solely as MTC and is genetically similar to MEN2A, suggesting a MEN2A syndrome with reduced penetrance.[5] Due to the high incidence of MTC associated with these syndromes, prophylactic thyroidectomy has been advocated, with several case series demonstrating increased cancer-free survival at 10 years.[12,13]

NF1 involves loss of the NF1 gene on chromosome 17, which encodes a tumor suppressor protein involved in cell growth regulation.[14] Although typically characterized by plexiform neuromas, which in turn can develop into malignant peripheral sheath tumors, NF1 is also associated with nonfunctioning NETs[14] and somatostatinomas.[15]

VHL disease is classically characterized by central nervous system hemangioblastomas, retinal angiomas, and renal cell carcinomas. Approximately 65% of patients with VHL disease will develop NETs, most commonly pheochromocytomas or pancreatic NETs.[16]

TSC is conveyed on the TSC1 and TSC2 genes, which encode the proteins hamartin and tuberin, and is clinically manifested by multiple fibromas, hamartomas, and various other benign connective tissue lesions. In a few case reports, TSC has been associated with malignant islet cell tumors, but these are not a common feature of the disease.[17,18]

DIAGNOSIS

Clinical Symptoms

The presentation of NETs can vary widely. Patients with a functional NET may present with symptoms related to the overproduction of certain hormones or

Table 2. Clinical Neuroendocrine Tumor Syndromes Based on Hormone Overproduction

Hormone	Associated Syndrome	Clinical Features	Incidence per 100,000 Annually	Incidence in MEN1 per 100,000 Annually	Specific Symptomatic Treatment*	Malignant, %
Serotonin	Carcinoid	Flushing, diarrhea, asthma, carcinoid heart disease (fibrous endocardial thickening that usually causes right-sided valvular heart disease)	2–8.4†	Rare	Serotonin receptor antagonists, $histamine_1$ and $histamine_2$ antagonists, antidiarrheal agents	95–100
Insulin	Insulinoma	Hypoglycemia (confusion, headache, visual changes, diaphoresis, tremor)	1–2	872	Diet, IV dextrose, diazoxide	< 10
Gastrin	Zollinger-Ellison	Abdominal pain, diarrhea, gastroesophageal reflux, peptic ulcers	0.5–1.5	2545	Proton pump inhibitors	60–90
Vasoactive intestinal peptide	Verner-Morrison, pancreatic cholera, WDHA syndrome	Watery diarrhea, hypokalemia, achlorhydria, dehydration	0.05–0.2	46	IV fluids	40–70
Glucagon	Glucagonoma	Dermatitis (migratory necrolytic erythema), hyperglycemia, weight loss, diarrhea, thromboembolism	0.01–0.1	82	Diet, insulin, anticoagulation	50–80
Somatostatin	Somatostatinoma	Diabetes, gallbladder disease, diarrhea, steatorrhea, achlorhydria, weight loss; typically only symptomatic with pancreatic lesions	Rare	27	Diet, insulin, pancreatic enzymes	> 70
None, pancreatic polypeptide	Nonfunctional NET	None	1–2	927	None	> 60

Data from Levy-Bohbot N, Merle C, Goudet P, et al. Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas: study from the GTE (Groupe des Tumeurs Endocrines) registry. Groupe des Tumeurs Endocrines. Gastroenterol Clin Biol 2004;28:1075–81; Simon P, Spilcke-Liss E, Wallaschofski H. Endocrine tumors of the pancreas. Endocrinol Metab Clin North Am 2006;35:431–47, xii; *and* Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. Acta Pathol Microbiol Scand [A] 1976;84:322–30.

IV = intravenous; MEN1 = multiple endocrine neoplasia type 1; NET = neuroendocrine tumor; WDHA = watery diarrhea, hypokalemia, achlorhydria.

*Most functional NETs can be symptomatically treated with somatostatin analogues and tumor debulking. Exceptions include somatostatinoma, in which symptoms would be worsened by excess somatostatin but may respond well to tumor debulking.

†The large discrepancy in carcinoid incidence is due to the indolent nature of the disease. Epidemiologic studies based on autopsy specimens reveal a high prevalence, but those based on cancer databases have noted lower values.

physiologically active tumor products (**Table 2**). The average age at diagnosis is 64 years.[2] Nonfunctional tumors can present with symptoms such as abdominal pain (68%–78%), weight loss (32%–50%), jaundice due to biliary obstruction or metastases (21%–50%), or nausea and vomiting (36%).[19,20] Metastases are found in up to 22% of patients with functional noncarcinoid NETs at the time of diagnosis, with carcinoids specifically presenting as metastatic disease 19% of the time.[3] Nonfunctioning gastropancreatic tumors typically manifest as more advanced disease, resulting in a greater frequency of metastases at diagnosis (40%); the most common site of metastasis is the liver.[20] Patients with MEN1, MEN2, NF1, VHL disease, and TSC should receive appropriate screening for NETs, such as screening for hyperthyroidism in MEN1. There are no universally accepted guidelines

for routine screening for these tumors in populations with no known genetic predisposition.[21,22]

Imaging Studies

The initial evaluation of patients with a known or suspected NET should include identification of tumor type, presence or absence of metastases, and assessment of tumor malignancy and potential for resection. A strategy using anatomic imaging (computed tomography [CT], magnetic resonance imaging [MRI], transabdominal ultrasonography, GI endoscopy, and endoscopic ultrasonography [EUS]), functional imaging (somatostatin receptor scintigraphy [SRS], positron emission tomography [PET]), and tumor biopsy is usually employed. Combined use of anatomic and functional imaging has been proven to increase the accuracy of staging in the diagnosis of NET.[23]

Anatomic imaging. Conventional imaging, including CT, MRI, and transabdominal ultrasonography, is typically the initial imaging modality employed in the evaluation of patients with suspected NETs. Dual-phase thin-section multidetector CT has a sensitivity as high as 94% in the setting of known functional syndromes.[24] MRI that uses modern imaging protocols has demonstrated a sensitivity of 85%,[25] while transabdominal ultrasonography is less sensitive in detecting primary tumors (33%).[19] Of note, these anatomic imaging studies do not delineate biologic activity or histopathology, the next step in diagnosis.

Functional imaging. Functional imaging studies are an important part of staging and identifying metastases. These studies target receptors, uptake pathways, or metabolism unique to NETs.

SRS is a nuclear medicine imaging modality that takes advantage of the fact that over 80% of NETs express somatostatin receptors.[26] In SRS, octreotide, a synthetic analogue of somatostatin, is radiolabeled with ^{123}indium and ^{111}indium and administered intravenously. The radioactive octreotide binds to the somatostatin receptors, and the isotopes can be localized as they decay, which allows lesions with high somatostatin receptors to be visualized. The sensitivity of SRS varies according to tumor type, detecting lesions in 94% of patients with metastatic carcinoid[27] but less than 50% of lesions in patients with insulinomas.[28] Through the detection of hepatic or extrahepatic metastases, SRS may affect tumor staging in as many as 25% of patients and is a key component in the evaluation of NETs.[29]

Single photon emission computed tomography (SPECT) uses multiple gamma cameras to construct 3-dimensional images and has been used to enhance SRS. In a large series, SRS combined with SPECT detected 92% of liver metastases compared with only 52% for planar SRS and 80% for conventional imaging procedures.[30] Nuclear medicine imaging with meta-iodobenzylguanidine (^{123}I-MIBG) may also be used, although this test is not universally employed in the staging of NETs.[31]

PET with ^{11}C-5-hydroxytryptophan can be used to detect NETs and in 1 study identified lesions not found by SRS or conventional imaging in 58% of patients.[32] PET can be used with radiolabeled ligands to increase the rate of detection of liver metastases.[33] PET is often used in conjunction with CT and SRS.

Direct endoscopic techniques may be useful in identifying lesions such as carcinoid of the lung and GI tract. EUS is primarily used to evaluate and obtain tissue from gastroduodenal and pancreatic lesions (**Figure 2**). EUS can localize tumors as small as 0.5 cm[34] and, when combined with fine-needle aspiration (FNA), has a sensitivity of 82% to 98% and specificity of 86% to 100% for finding and correctly identifying pancreatic NETs.[35–38] EUS can play an important role in tumor staging. In a study by DeWitt et al,[38] EUS correctly identified 67% of lesions compared with 41% found by CT alone. However, even patients with a NET identified on CT may benefit from tissue sampling using EUS-guided FNA.[38]

Serologic Studies

Various circulating biochemical markers, including neuron-specific enolase and chromogranin A, have been evaluated as a means to detect NETs and as an indicator of tumor burden and response to therapy. Neuron-specific enolase has demonstrated variable sensitivity (43%–100%) and poor specificity (65%) as a serum marker for NETs.[39,40] Chromogranin A testing has been more successful, with a sensitivity of 68% to 92% and a specificity of 67% to 86% for assessment of tumors.[39,41] Chromogranin A levels are highest in carcinoid tumors, MTCs, and pheochromocytomas.[40] Serum levels may not correlate with the degree of tumor burden.[41,42] Measurement of chromogranin A levels should be a part of the initial and follow-up evaluation of NET but cannot be relied on as the sole marker of disease remission.

For functional NETs, specific markers exist according to the syndrome exhibited. In Zollinger-Ellison syndrome, elevated fasting gastrin levels had a sensitivity of 64% to 80% for detecting gastrinomas.[41,43] Hepatic venous sampling for insulin and proinsulin may detect and localize as many as 90% of insulinomas.[44] However, assessing other hormone levels has varying effectiveness. Functional NETs may change their primary secretory hormone over the course of the disease and manifest different syndromes over time.[45]

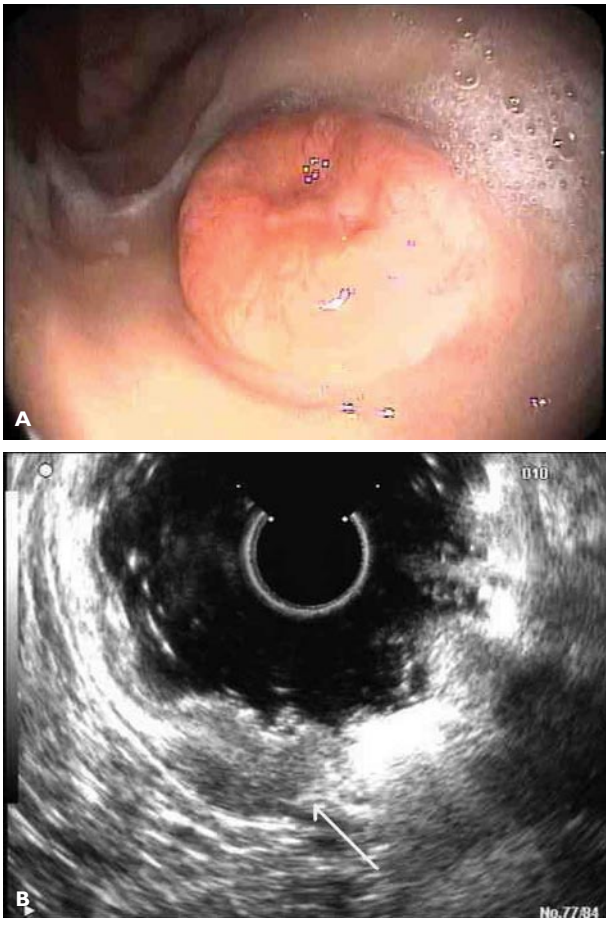

Figure 2. (**A**) Gastric neuroendocrine tumor seen in the gastric fundus on endoscopy and (**B**) endoscopic ultrasound of the same lesion (*arrow*). Note that the lesion invades all layers of the gastric wall but does not erode through the adventitia.

Diagnostic Approach

The heterogeneous nature of NETs creates difficulty in designing an algorithm for diagnosis. A typical initial work-up for a suspected or known NET usually begins with CT scans to evaluate for obvious primary and/or metastatic lesions. Serologic testing may be performed (eg, chromogranin A, CA19-9, carcinoembryonic antigen) along with laboratory testing for specific hormones as directed by clinical presentation (Table 2). EUS-guided FNA can be employed to define the borders of the lesion and obtain tissue. Except in cases of insulinoma, SRS is then used to further survey for metastases (**Figure 3**); if SPECT imaging is available, it may replace SRS. PET is an appropriate functional imaging modality for insulinomas and can be combined with MRI of the liver to ensure metastatic disease is fully evaluated.

In 1963, a classification system for carcinoid tumors was created based on histology and anatomic site.[46] Sites were divided into foregut (respiratory tract, stomach, duodenum, biliary system, pancreas), midgut (small bowel, appendix, cecum, colon), and hindgut (distal colon, rectum). This system may be helpful in estimating mortality, with 5-year survival rates at 70% for foregut, 61% for midgut, and 88% for hindgut tumors. However, a limitation of this system is that it groups the carcinoid tumors with the lowest overall 5-year survival rate—liver (18%) and pancreatic (38%) tumors—into a class with the highest predicted survival. The World Health Organization pathologic criteria published in 2000 are currently used for diagnosing NET and take into account both the site of tumor occurrence as well as histology found on biopsy.[47] However, a large number of tumors remain in the category of "benign or malignant behavior possible." The current system has not yet been shown to be better at predicting mortality.

TREATMENT

Surgery

Surgery is the preferred option for patients with resectable disease, but palliation with tumor debulking, chemotherapy, and targeted radionuclide therapy is often needed because of the high frequency of metastases. Management with somatostatin analogues has become a mainstay of therapy and is used in most symptomatic patients. Liver transplantation has been performed in patients with known liver metastases but is not widely used.[48]

When complete resection is not possible or if the patient has MEN1 or MEN2, surgery must still be considered for symptomatic relief as well as survival benefit. Compared with patients with sporadic mutations, patients with MEN1 who receive surgical resection have similar survival rates after 7 to 10 years but a higher rate of recurrence, with only 4.5% tumor-free at 10 years.[49,50] In patients believed to have localized NETs of pancreatic or duodenal origin, survival is 74% at 5 years and 43% at 10 years after pancreatoduodenectomy, distal pancreatectomy, or local excision.[51] The high probability of recurrence in cases of MEN1 or other genetic syndromes often makes the decision to attempt curative resection difficult. Approximately 75% of patients with MEN1 who undergo complete resection of their tumor will develop a new NET in the pancreatic remnant within 10 years.[52] Despite the high recurrence rate, current guidelines suggest resection in patients with MEN1 when possible to prevent the development of more malignant disease and to relieve symptoms of excessive hormone production.[22]

Tumor debulking of hepatic metastases, either via

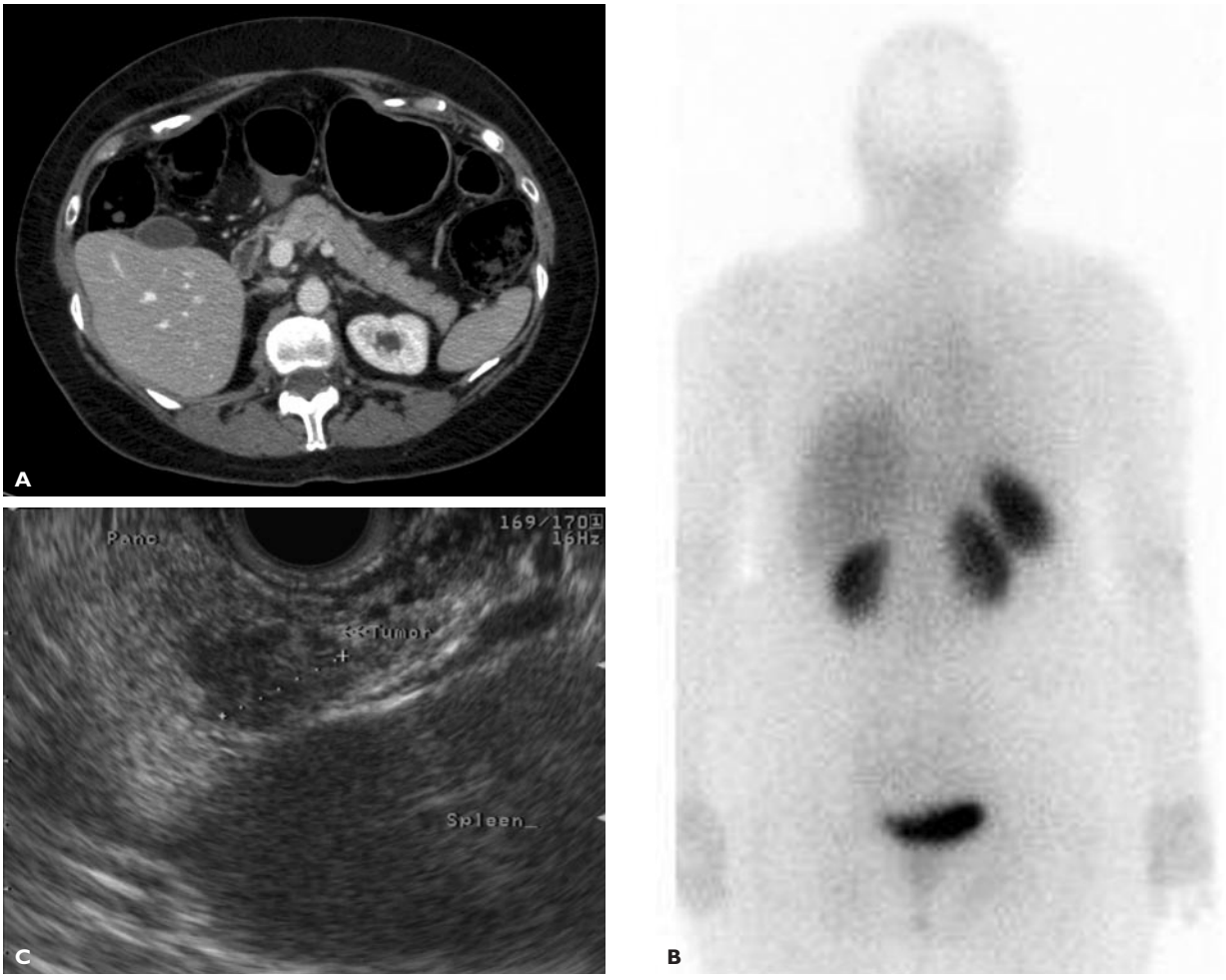

Figure 3. (**A**) Computed tomography scan in a patient with clinical manifestations suggestive of an insulinoma. No mass lesion is visible in the pancreas. (**B**) Somatostatin receptor scintigraphy in the same patient. No pathologic lesions were seen; however, normal renal and splenic uptake is noted as well as accumulation in the bladder. (**C**) Endoscopic ultrasound (EUS) images from the same patient disclose a 1-cm mass lesion in the tail of the pancreas. EUS-guided fine-needle aspiration confirmed insulinoma. (Images courtesy of Dr. David Schwartz, Vanderbilt University, Nashville, TN.)

surgery or the use of hepatic artery chemoembolization, has been shown to increase survival.[53,54] A chemoembolization technique used for metastases associated with hepatic NET is the injection of polyvinyl alcohol particles or gelfoam powder by interventional radiologists, which embolizes selected hepatic arteries and limits blood supply to areas of high tumor burden. Hepatic artery chemoembolization is a less invasive method for decreasing tumor burden, with rates that are comparable to surgery. Aggressive treatment of hepatic metastases may increase 5-year survival from 25% to between 50% and 72%, depending on the degree of liver involvement. Poor outcomes have been noted in patients with more than 50% liver involvement, and repeat embolizations are not as effective.[55]

Chemotherapy

Chemotherapy is not considered a part of first-line therapy for NETs, primarily because the regimens used to date are not as effective as surgical and other debulking treatments. Treatment with streptozocin and 5-fluorouracil (5-FU) is part of most current regimens after early case series showed that streptozocin used in combination with doxorubicin and 5-FU results in partial tumor response in half of patients, as measured by radiologic and serologic testing.[56] Up to two thirds of patients with MEN1 have a response to streptozocin and 5-FU treatment.[43] Regimens that do not include both streptozocin and 5-FU are not effective.[57,58] Interferon-α and interferon-β have also been used in some chemotherapy trials, with similar success. Treatment with lantreotide,

interferon-α, or both in combination in patients with known progressive disease showed no superiority to either monotherapy or dual therapy.[59] A recent small study using pegylated interferon-α demonstrated stabilization of disease in 75% of patients, and this agent may play a role in treatment in the future.[60]

Radiotherapy

Both external beam radiotherapy and targeted radionuclide therapy have been investigated for the treatment of NETs. Although some case reports describe the use of external beam radiotherapy in metastatic disease, it is not a common component of treatment.[61] Directed radionuclide therapies, which exploit the somatostatin receptors and the amine precursor uptake system, are becoming a more accepted part of treatment protocols. In patients with inoperable or metastatic tumors identified on SRS, treatment with ^{177}Lu-octreotide improved disease in up to 47% of patients.[62] Combining chemotherapy with radionuclide therapy appears to have an additive benefit. After receiving 5-FU and streptozocin, patients treated with ^{131}I-MIBG and ^{111}In-pentreotide as second-line therapy demonstrated improved survival compared with controls at 15-month follow-up; however, no long-term benefit has been found, emphasizing the palliative nature of this treatment.[63]

Somatostatin Analogues

The use of long-acting somatostatin analogues (typically lantreotide, octreotide, and vapreotide) has led to improved symptom control in NET of all types; the exact mechanism by which these agents work remains unknown. Use of long-acting somatostatin analogues has led to symptomatic response rates of up to 75% in functional NET[27,64] and temporary tumor shrinkage in 9%.[27] Side effects are generally mild, but asymptomatic gallbladder stones or sludge have been noted in 50% of treated patients.[65]

PROGNOSIS

The prognosis for patients with NETs has improved with the advent of more aggressive surgical intervention and the use of long-acting somatostatin agonists and targeted second-line therapy. Recent studies have demonstrated that malignant disease, defined by direct invasion of adjacent organs by tumor, lymph node metastases, or distant organ spread, may have 5-year survival rates as high as 77% to 95% when treated aggressively with resection of primary tumor and adjunctive therapy.[66,67] This represents a great improvement when compared with older studies that suggest a much lower survival rate of 36% at 5 years.[68] Favorable prognostic factors include curative resection of primary tumor, absence of liver metastases, metachronous liver metastases, and aggressive treatment of liver metastases.[68] Metachronous liver metastases may lead to a better prognosis as compared with synchronous liver metastases because of the association with less advanced disease at diagnosis.[68] Poor prognostic indicators include lymph node involvement, metastases detected at diagnosis,[51] and lymphovascular invasion.[69] Unfortunately, nearly all patients with metastatic disease have recurrence on 7-year follow-up, even after successful treatment of metastatic disease.[67]

FUTURE DIRECTIONS

The diagnosis of NET has been advanced significantly with the combined use of anatomic and functional imaging. Newer modalities such as SPECT and F^{18}-labeled somatostatin when used with EUS-guided FNA or other less invasive biopsy techniques are highly sensitive and specific for diagnosing NET. Because of the limited success of medical management and chemotherapy for NET, efforts should be made to further develop targeted therapies that exploit somatostatin receptors and the amine precursor uptake system. Until these therapies are better developed, the primary treatment for NET is surgical. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 40.

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