0163-769X/04/$20.00/0
Printed in U.S.A.

Endocrine Reviews 25(3):458–511
Copyright © 2004 by The Endocrine Society
doi: 10.1210/er.2003-0014

The Diagnosis and Medical Management of Advanced Neuroendocrine Tumors

GREGORY A. KALTSAS, G. MICHAEL BESSER, AND ASHLEY B. GROSSMAN

Department of Endocrinology, St. Bartholomew's Hospital, London EC1A 7BE, United Kingdom

Neuroendocrine tumors (NETs) constitute a heterogeneous group of neoplasms that originate from endocrine glands such as the pituitary, the parathyroids, and the (neuroendocrine) adrenal, as well as endocrine islets within glandular tissue (thyroid or pancreatic) and cells dispersed between exocrine cells, such as endocrine cells of the digestive (gastroenteropancreatic) and respiratory tracts. Conventionally, NETs may present with a wide variety of functional or nonfunctional endocrine syndromes and may be familial and have other associated tumors. Assessment of specific or general tumor markers offers high sensitivity in establishing the diagnosis and can also have prognostic significance. Imaging modalities include endoscopic ultrasonography, computed tomography and magnetic resonance imaging, and particularly, scintigraphy with somatostatin analogs and metaiodobenzylguanidine. Successful treatment of disseminated NETs requires a multimodal approach; radical tumor surgery may be curative but is rarely possible. Well-differentiated and slow-growing gastroenteropancreatic tumors should be treated with somatostatin analogs or α-interferon, with chemotherapy being reserved for poorly differentiated and progressive tumors. Therapy with radionuclides may be used for tumors exhibiting uptake to a diagnostic scan, either after surgery to eradicate microscopic residual disease or later if conventional treatment or biotherapy fails. Maintenance of the quality of life should be a priority, particularly because patients with disseminated disease may experience prolonged survival. (*Endocrine Reviews* 25: 458–511, 2004)

Abbreviations: ADH, Antidiuretic hormone secretion; ASVS, arterial stimulation venous sampling; CAG, chronic atrophic gastritis; CCK, cholecystokinin; CEA, carcinoembryonic antigen; CgA, chromogranin A; CGRP, calcitonin gene-related peptide; CHD, carcinoid heart disease; CS, carcinoid syndrome; CT, computed tomography; CVD, cyclophosphamide, vincristine, and dacarbazine; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA, diethylene-triamine-penta acetic acid; ECL, enterochromaffin; EUS, endoscopic ultrasound; FDG, ^{18}F-labeled deoxyglucose; FMTC, familial MTC; 5-FU, 5-fluorouracil; GC, gastric carcinoid(s); GEP, gastroenteropancreatic; GI, gastrointestinal; GRP, gastrin-releasing peptide; hCG, human chorionic gonadotropin; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; INF, interferon; IOUS, intraoperative ultrasound; MEN, multiple endocrine neoplasia; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MTC, medullary thyroid carcinoma; NE, neuroendocrine; NET, NE tumor; NF, neurofibromatosis; NIPH, noninsulinoma pancreatogenous hypoglycemia; NME, necrolytic migratory erythema; NSE, neuron-specific enolase; PET, positron emission tomography; PP, pancreatic polypeptide; SCLC, small-cell lung carcinoma; SDH, succinate dehydrogenase; SPECT, single-photon emission CT; SS, somatostatin; STZ, streptozotocin; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau; VIP, vasointestinal peptide; ZES, Zollinger-Ellison syndrome.

***Endocrine Reviews* is published bimonthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

I. Introduction

ENDOCRINE TUMORS CONSTITUTE a heterogeneous group of neoplasms that have been postulated to originate from a common precursor cell population (1). The system includes endocrine glands, such as the pituitary, the parathyroids, and the [neuroendocrine (NE)] adrenal, as well as endocrine islets within glandular tissue (thyroid or pancreatic) and cells dispersed between exocrine cells, such as endocrine cells of the digestive and respiratory tracts, the diffuse endocrine system (2–4). Because these cells share a number of antigens with nerve elements, the term "neuroendocrine" is also used to connote such cell types and will be adopted in this review (4). Traditionally, this classification

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

has tended to exclude pituitary and parathyroid tissue, and these will not be further discussed in this review. NE tumors (NETs) originating from the gastrointestinal (GI) tract, along with similar tumors originating from the lungs and thymus, have traditionally been defined as "carcinoid tumors"; this term will still be used in this review because most of the literature regarding the diagnosis, management, and prognosis of these tumors uses the previously established classification (5). Some NETs may occasionally show very aggressive behavior and become highly malignant (poorly differentiated NETs), but the great majority tend to be relatively slow growing (well-differentiated NETs) and retain many multipotent differentiation capacities (3). Such features include the ability to produce and secrete a variety of metabolically active substances (amines and peptides) and cause distinct clinical syndromes (6). In addition, NETs possess neuroamine uptake mechanisms and/or specific receptors at the cell membrane, such as somatostatin (SS) receptors, which can be of great value in identifying and localizing these tumors as well as being useful in their therapy (7). NETs may occur either sporadically or as part of familial syndromes; the latter are associated with particular genetic defects, a number of which have recently been delineated at the molecular level (8).

This review will focus on the gastroenteropancreatic (GEP) NETs, NETs originating from chromaffin cells, and NETs originating from C (parafollicular) cells of the thyroid. The particular features of NETs that have recently been incorporated into their classification will be covered in an attempt to combine accurate diagnosis with biological behavior and prognosis. Recent developments involving the pathogenesis, earlier diagnosis, and screening for NETs, particularly in familial forms, will also be discussed. Classical symptoms of specific syndromes related to humoral secretion or other clinical presentation of such tumors and recent advances in their biochemical confirmation and localization methods will be presented, and a diagnostic algorithm will be formulated. Finally, evidence-based current medical therapeutic approaches aiming at humoral control and prevention of further tumor growth will be reviewed, and a possible therapeutic algorithm for each of these tumors will be proposed.

II. Histopathological Classification and Variables Used to Predict Biological Behavior

The major function of NE cells is to elaborate, store, and secrete small peptides and biogenic amines (6, 9). Their histopathological examination aims at classifying the tumors according to their tissue origin, biochemical behavior, and prognosis (10). The assessment of endocrine differentiation in tumors has traditionally been obtained using light microscopy, silver impregnation methods (histochemistry), and electron microscopy (1, 4). Currently, the diagnosis of NETs mainly relies on the positive assessment of markers of NE differentiation by immunohistochemistry (3, 4, 11). The most commonly used markers are general NE markers (applicable to all NE cells), either in the cytosol such as neuron-specific enolase (NSE) and the protein gene product 9.5 (12, 13) or granular markers such as chromogranin A (CgA) and synaptophysin (2, 4, 14). The cell-specific characterization of NETs requires hormone immunohistochemistry (4, 11). NETs associated with hyperfunctional syndromes are defined as functioning, whereas NETs exhibiting immunopositivity for endocrine markers and/or elevated serum markers but unassociated with a distinct clinical syndrome are called nonfunctioning tumors (3). Histological and hormonal features of specific cell types are integrated in a so-called "morphofunctional" classification, in an attempt to predict the natural history of the tumor (2, 3, 15). In the recent World Health Organization (WHO) classification, the following types of NETs have been recognized, at least for GEP tumors, but this is probably applicable to all NETs (1, 3, 4, 15–17): 1) well-differentiated endocrine tumor (benign or low grade malignant); 2) well-differentiated endocrine carcinoma; 3) poorly differentiated endocrine carcinoma (small cell carcinoma); and 4) mixed exocrine-endocrine carcinoma.

The differentiation is based on histomorphology, tumor size (in general larger tumors are more aggressive), and the presence or absence of gross local invasion and/or metastasis, thus reflecting biological behavior (2, 3). Most NETs are well-differentiated tumors that are characterized by a solid trabecular or glandular structure, tumor cell monomorphism with absent or low cytological atypia, and a low mitotic (<2 mitoses/mm^2) and proliferative status ($<2\%$ Ki-67 positive cells) (3). Such tumors are slowly growing but can occasionally exhibit more aggressive behavior (>2 mitoses/mm^2 and/or proliferation index $>2\%$ Ki-67 positive cells); however, only in the presence of metastasis and/or invasiveness is the tumor defined as a well-differentiated NE carcinoma (2, 18). Poorly differentiated NETs are invariably malignant, are defined as poorly differentiated NE carcinomas, and are characterized by a predominantly solid structure with abundant necrosis, cellular atypia with a high mitotic index (≥ 10 mitoses/mm^2) and proliferative status ($>15\%$ Ki-67 positive cells), diffuse reactivity for cytosolic markers, and scant or weak reactivity for granular markers or neurosecretory products (3). Mixed exocrine-endocrine carcinomas are epithelial tumors with a predominant exocrine component admixed with an endocrine component comprising at least one third of the entire tumor cell population. Their biological behavior is essentially dictated by the exocrine component, which may be acinar or ductal type (18). It is hoped that, in the future, other factors such as the angiogenic capacity of tumor cells and specific genetic changes may prove to be valuable tools in determining prognosis, biological behavior, and response to therapy (10).

III. Tumor Biology

A. Genetic defects

NETs can occur sporadically or in a familial context of autosomal dominant inherited syndromes such as multiple endocrine neoplasia (MEN) (8, 19). Four major MEN syndromes, MEN I, MEN II, von Hippel-Lindau (VHL) disease, and Carney complex, represent the most common forms of inherited predisposition to NETs with variable but high penetrance in various NE tissue; early screening can be used for presymptomatic diagnosis (8, 19). Less commonly, endocrine

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

tumors of the pancreas, parathyroids, and adrenal glands have been observed in phacomatoses, such as neurofibromatosis (NF) type 1 and tuberous sclerosis (19). In addition, familial occurrence of single endocrine lesions such as primary hyperparathyroidism, pituitary adenomas, medullary thyroid carcinoma (MTC), or pheochromocytomas have been identified as putative genetic diseases for most of which the genetic pathways remain to be identified (20).

Most NET-predisposing diseases have been related to inactivation of tumor growth suppressor genes, except in MEN II and the inherited form of MTC, which occur through dominant activation of the RET protooncogene (19, 21). The RET protooncogene encodes a transmembrane tyrosine-kinase receptor that causes cellular proliferation, differentiation, and increased cell motility (8, 21). MEN II comprises three clinical subtypes, MEN IIA, MEN IIB, and familial MTC (FMTC) (21); in MEN IIA, all patients develop MTC, about 50% pheochromocytoma, and about 15% primary hyperparathyroidism (21, 22). Patients with MEN IIB may have a marfanoid habitus and mucosal neuromas but not hyperparathyroidism; in these patients, MTC occurs at a younger age and behaves more aggressively compared with MEN IIA (19, 21). Approximately 95% of MEN II cases are accounted for by germline RET mutations (~98% of MEN IIA cases, 97% of MEN IIB cases, and 85% of FMTC cases) (21, 23). MEN I is an autosomal dominant syndrome characterized mainly by hyperplasia and/or multiple tumors of the parathyroid, endocrine pancreas, anterior pituitary, foregut-derived NE-tissues, and adrenocortical glands (24). Somatic mutations of the *MEN I* gene have been reported in sporadic forms of endocrine tumors with a variable incidence of 20–30% in parathyroid (25), endocrine pancreas (33% gastrinomas, 17% insulinomas) (26), 25% of lung carcinoids (27), but less than 1% in pituitary and adrenocortical tumors (4). In clinical practice, genetic analysis is useful to assess the syndromic diagnosis of MEN I, but the diagnosis cannot be excluded with certainty when a mutation is not found (8). Therefore, the clinical screening of patients remains a prerequisite for genetic analysis. The three major features of VHL disease are retinal angiomas, central nervous system hemangioblastomas, and clear cell renal cell carcinomas; the lifetime risk for each of these tumors has been estimated as greater than 70% (21, 28, 29). Other VHL-related lesions include pheochromocytomas, pancreatic islet cell tumors, and papillary cystadenomas of the pancreas, epididymis, the broad ligament, and the lymphatic sac of the middle ear (29). However, the incidence of specific tumors depends on the phenotypic class of VHL, of which four have been described (type 1 and types 2A, 2B, and 2C). The Carney complex is an autosomal dominant disease predisposing to various types of tumors, including cardiac and cutaneous myxomas, spotty pigmentation of the skin, and nonneoplastic hyperfunctioning endocrine states, such as nodular adrenocortical hyperplasia associated with Cushing's syndrome and pituitary and thyroid adenomas (30, 31). Approximately 1% of patients diagnosed with pheochromocytomas may have NF1, a dominantly inherited disorder with complete penetrance but highly variable expressivity (32). Diagnostic criteria for NF1 include cutaneous or sc neurofibromas, café-au-lait spots appearing early in life, optic glioma, benign iris hamartomas (Lisch nodules), and specific dysplastic bone lesions (32). Digestive tract carcinoid tumors have rarely been described in patients with NF1 and tuberous sclerosis (8, 33). Knowledge of the particular genetic defects in these familial syndromes is essential for the early screening and counseling of other family members.

B. Apoptosis

The protein product of the bcl-2 oncogene is an important modulator of apoptosis because it blocks programmed cell death without affecting cell proliferation (34–36), whereas the c-myc protooncogene, which inactivates key tumor suppressors such as p53 and retinoblastoma gene product, also plays a central role in some forms of apoptosis (36, 37). Coexpression of bcl-2 and c-myc leads to a synergism that may result from the ability of bcl-2 to directly interfere with the apoptotic cell death resulting from the dysregulated expression of c-myc (34–36). Such an association has recently been described for a number of NETs including MTC, pheochromocytomas, carotid body tumors, and some carcinoids (34).

C. Growth factors

Malignant progression of NETs may also be triggered by overexpression of growth factors involved in endocrine and endothelial cell proliferation such as TGFα, endothelial growth factor, nerve growth factor, and vascular endothelial growth factor (VEGF)/VEGF-related factors (19). Among various growth factors promoting angiogenesis, VEGF was found to be overexpressed, mainly in midgut carcinoid and some pancreatic tumors, suggesting that it may be involved indirectly in the growth of these tumors (38).

The genetic markers so far identified in various sporadic types of NETs are not specific enough to be used for diagnostic purposes, but they provide some clues as to the genetic mechanism of tumor development.

IV. Tumor Markers in Neuroendocrine Tumors

A. Serum and immunohistochemical tumor markers

The various cell types of the NE cell system can secrete specific products, such as peptides and biogenic amines, that are tumor-specific and may serve as markers for the diagnosis and follow-up of treatment (see *Section IV.A.1*); it is also probable that some tumor markers may have prognostic implications (6, 39) (Table 1). A number of other components specific for all NE cells and associated with secretory granules or cytosolic proteins can also be used as tumor markers; among these, the chromogranin family is the one most commonly used (see *Section IV.A.2*) (6, 39).

1. Specific tumor markers. Peptide hormones are synthesized as precursors, which are cleaved in a sequence- and tissue-specific manner to yield the biologically active peptides; however, their fine processing is usually deficient in NET cells (6). Therefore, direct measurement of these peptides, and when necessary of their precursors, establishes the diagnosis and occasionally also provides information regarding the size of the tumor (39). In addition, there are cases in

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

TABLE 1. Common tumor markers and distribution of SS receptors in patients with GEP tumors, chromaffin cell tumors, and MTCs

Tumor types	Specific serum tumor markers	Nonspecific serum tumor markers	SS receptors (positive scintigraphy with ^{111}In-octreotide)
Thymus	SS, serotonin	CgA, NSE	50–80%
C-thyroid cells	Calcitonin, CGRP, ACTH, SS, serotonin	CgA, CEA	70–75%
Lung	GRP, CT, SS, POMC, ACTH, ADH, serotonin, β-hCG	CgA, NSE	80%
GI tract	Gastrin, CCK, GIP, VIP, motilin, glucagon, GRP, PP, GHRH, POMC, ACTH, serotonin	CgA, NSE, hCG	80–90%
Pancreatic islet cells	Insulin, gastrin, VIP, glucagon, SS, serotonin	CgA, NSE, hCG	60–95%
Ovary	Serotonin, hCG, PTHrP, POMC, CGRP	CgA, NSE	
Chromaffin cells	Noradrenaline, adrenaline, dopamine, POMC, calcitonin, neuropeptide Y, neurotensin, SS	CgA, NSE	85–95%
Adenocarcinomas with NE differentiation	POMC, CGRP	CgA, NSE	20–35%

Derived from Krenning *et al.* (53); Olsen *et al.* (70); Lamberts *et al.* (6); Nobels *et al.* (40); Oberg (407); Norheim *et al.* (211); and Tomassetti *et al.* (213). POMC, Proopiomelanocortin; GIP, gastric inhibitory peptide.

which multiple hormone production is evident, which can also fluctuate throughout the course of the disease (39). The measurement of serum hormone concentrations can also be useful in the diagnosis of clinically nonfunctioning tumors in which the hormonal products may not be associated with clinical syndromes (6, 40). More recently, the α- and β-subunits of human chorionic gonadotropin (α- and β-hCG) have been shown to be markers of nonfunctioning GEP tumors, as well as MTC and small-cell lung carcinoma (SCLC) (6, 40).

2. Nonspecific tumor markers. In addition to specific hormones secreted by NE cells, other proteins that exert regulatory activities on the packaging, processing, and secretion of hormones are increasingly recognized as NET markers (6, 39, 41). CgA, CgB, and CgC form a group of acidic monomeric soluble proteins that are localized within secretory granules in which they are costored and cosecreted with the locally present peptides (39, 42). CgA is the granin mostly used in clinical practice, although the other chromogranins are relevant, particularly as CgA-negative, but CgB-positive tumors are increasingly being recognized (39, 43). Plasma CgA levels may be elevated in a variety of NETs, including pheochromocytomas (43–45), paragangliomas (40, 46), carcinoid and pancreatic islet cell tumors (43, 46, 47), MTC (43), parathyroid and pituitary adenomas (48), although much less (<60%) in SCLC (40, 44). The highest CgA levels have been found in metastatic carcinoids and GEP tumors (44, 45, 49, 50). Both tumor burden and secretory activity should be considered when interpreting CgA results, with a sensitivity and specificity varying between 10–100% and 68–100%, respectively (5, 43, 50). Renal insufficiency and hypergastrinemia are the main causes of false-positive CgA results (40, 43). Several assays for the measurement of intact CgA and the different cleavage products have been developed using either monoclonal or polyclonal antibodies, and thus exhibiting substantial differences in sensitivities and specificities (51). This must be taken into consideration until a recognized international standard for CgA is established (51). Comparative studies have shown that the sensitivity of CgA in relation to the reference biological specific markers is higher in foregut carcinoids, comprising bronchial, thymic, head and neck primaries (5, 40, 43), and comparable to specific tumor marker sensitivities in patients with ileal carcinoids and pheochromocytomas (43, 50). In addition, CgA has been shown to be an independent prognostic factor for midgut carcinoids because it correlates not only with tumor burden but also with biological activity (46, 47).

Synaptophysin and NSE are present diffusely in the cytoplasm of NETs, so they are consistently positive in most NETs (6). NSE is only present in neurons and NE cells and can also serve as a circulating marker for NETs (6). NSE is most frequently elevated in patients with SCLC (74%) but has also been found to be elevated in 30–50% of patients with carcinoids, MTC, islet cell tumors, and pheochromocytomas (40). Elevated levels of NSE are also roughly correlated with tumor size, although the specificity is lower than that of CgA; however, the combination of both CgA and NSE has a higher sensitivity than either parameter separately (40). Some oncogenic proteins are not specific for NETs but are frequently synthesized in these tumors, *i.e.*, carcinoembryonic antigen (CEA) in MTC (6).

3. Tumor markers and stimulation tests. When patients present with a high clinical suspicion of a functional syndrome but with normal basal measurements of specific tumor markers, a dynamic test can be used to increase sensitivity (39). Although the rationale of employing such tests has recently been questioned, several dynamic tests have traditionally been used (52). The dynamic tests that are still in use will be discussed later with reference to individual tumor types.

B. Amine and peptide receptor expression and visualization

The demonstration of the presence of amine uptake mechanisms and a high density of peptide receptors on several NETs, as well as their metastases, has been used for both diagnosis and monitoring of these tumors using radionuclide techniques (6, 53).

Metaiodobenzylguanidine (MIBG) is a guanidine derivative that exploits the specific type 1 amine uptake mechanism at the cell membrane and the subsequent uptake from the cytoplasm and storage within the intracellular storage vesicles (54). It shows little binding to postsynaptic receptors and has minimal or no intrinsic pharmacological effect (54, 55). MIBG localizes to adrenomedullary tumors, hyperplastic adrenal medulla and, to a lesser degree, in the healthy adrenal medulla (54, 56). In addition, several other NETs including carcinoids and MTC exhibit this specific uptake mechanism and can thus accumulate MIBG (54).

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

SS is a 14-amino acid peptide that is widely expressed throughout the central nervous system as well as in peripheral tissues including the endocrine pancreas, gut, thyroid, adrenals, and kidneys (57, 58). SS acts mostly as an inhibitory factor on neurotransmission, intestinal mobility, absorption of nutrients and ions, vascular contractility, and cell proliferation (57). Owing to its short half-life (1–2 min), many SS long-acting analogs have been synthesized, among which octreotide and lanreotide are the ones most commonly used in clinical practice (59, 60). These analogs are cyclic octapeptides that have a more prolonged half-life (1.5–2 h), and thus, biological activity (6, 59–61). The biological effects of SS are mediated by five specific SS receptors (1–5) that all bind the native peptide but show major differences in their affinities for SS analogs; the currently used analogs exhibit a very low affinity for SS receptors 1 and 4 but bind with high affinity to SS receptors 2 (predominantly) and 5 and with moderate affinity to SS receptor 3 (6, 57, 62, 63). Each receptor subtype is coupled to multiple intracellular transduction pathways, but all five are functionally coupled to inhibition of adenylate cyclase and decreased calcium influx, and thus generally inhibit hormonal secretion and intestinal mobility (57). SS also inhibits the proliferation of both normal and tumoral cells as a result of hypophosphorylation of the retinoblastoma gene product and G_1 cell cycle arrest (64). The antiproliferative effects of SS can also result from apoptosis through SS receptor 3 induced by p53 and Bax (39). The SS effect on tumor growth may also be the result of indirect effects through the inhibition of growth factors (65) and angiogenesis (66, 67).

SS receptors are found mainly in well-differentiated rather than poorly differentiated tumors and thus may exert prognostic significance as markers of differentiation (Table 1) (67–69). The high frequency of SS receptor 2 mRNA in NETs allows the localization of various human tumors and metastases using ^{111}In-labeled octreotide (57, 66); there is a close correlation between the presence of SS receptor 2 mRNA, tracer uptake using SS receptor autoradiography, and the therapeutic response to SS analog treatment (6, 39, 70). In addition, specific polyclonal antibodies against SS receptor 2 have been developed that correlate with ^{111}In-labeled octreotide uptake (71). Tumors and metastases that harbor uptake mechanisms and/or peptidic receptors can be visualized *in vivo* using a γ-camera after the injection of ^{123}I-MIBG and/or ^{111}In-pentetreotide (72, 73). In addition, other small peptidic receptors that are expressed in cell membranes of NE tissues include vasointestinal peptide (VIP), bombesin, cholecystokinin (CCK), gastrin and/or substance P (6, 67–69). Labeled analogs/peptides can also be used as markers for putative receptors for *in vivo* tumor visualization (69, 74).

C. Radionuclide imaging

Radionuclides provide a diagnostic modality in which radiolabeled amines or peptide analogs, based on their ability to bind to suitable ligands, are used for the identification and localization of NETs (7, 62, 63, 75).

1. Scintigraphy with MIBG (^{123}I-MIBG). The prolonged storage of MIBG within secretory vesicles permits high specific uptake and imaging after labeling with both ^{131}I- and ^{123}I-MIBG; however, imaging quality with ^{123}I-MIBG is superior, and it is currently the radiopharmaceutical of choice (76–79). The efficiency of ^{123}I-MIBG is excellent for the visualization of intraadrenal and extraadrenal sites of benign and malignant pheochromocytomas, showing a diagnostic sensitivity and specificity above 80 and 90%, respectively (80). Radiolabeled MIBG facilitates in the diagnosis of multiple tumors and paragangliomas, in the detection of suspected malignant chromaffin tumors, for the screening of individuals at risk in familial forms of the disease, and for the selection of patients for therapeutic MIBG based on a positive diagnostic scan (72, 78). It also has a complementary role in the diagnosis of other NETs such as carcinoids and MTC (78–80) (Fig. 1); its sensitivity is said to be enhanced with the preimaging administration of MIBG, but this remains controversial (81).

2. Scintigraphy with SS analogs (^{111}In-octreotide). Octreotide (Sandostatin, Novartis, Basel, Switzerland) was the first SS analog to be used in clinical practice, although considerable experience has also been obtained with lanreotide (Somatuline/Ipstyl, Ipsen, Paris, France) (73). These compounds have been conjugated with DTPA (diethylene-triamine-pentaacetic acid) (63, 64, 82), but more recently with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) as a way of coupling SS analogs with various radionuclides (83, 84). There is a predominance of renal clearance of the analog (73, 85, 86), although the uptake of ^{111}In-DTPA octreotide (pentetreotide) shows a bell-shaped function of the injected mass, explaining the increased uptake that follows prior administration of the unlabeled peptide (73, 87). Planar and single-photon emission CT (SPECT) lesions are performed 24 and 48 h after the injection of the radiopharmaceutical; normal visualization includes the thyroid, spleen, liver, kidneys, and part of the pituitary (73, 86) (Fig. 2). Scintigraphy with ^{111}In-octreotide has been shown to have a detection rate of 67–91% for all NETs and is used both for diagnosis and staging, and also in the follow-up of patients (7, 53, 59, 70, 83). In addition, it also exhibits high specificity (88–92), although occasional false-positive localizations may occur because uptake is also demonstrable in many other tumors, granulomas, and autoimmune diseases (7, 53, 54, 83, 86). A recent systematic study prospectively assessing the specificity of scintigraphy with ^{111}In-octreotide in patients with gastrinomas revealed an overall specificity of 86% (93, 94). Evidence from *in vitro* studies has shown increased uptake of radiolabeled octreotide in the presence of low concentrations of unlabeled octreotide (95, 96). During octreotide treatment, the uptake of ^{111}In-octreotide in SS receptor-positive tumors and the spleen is diminished (95). In general, NETs remain visible during treatment with octreotide, although tumor uptake may be less than without octreotide treatment (95).

The detection of an unsuspected lesion in a patient with a single known lesion is important in that it may affect the selection of curative surgery, which remains the treatment of choice in patients with NETs (83, 97–99); however, there are no clinical or biochemical predictors of a positive scan (7, 99). False-positive results have been reported, although this may be a misnomer because they may actually represent micrometastases (73). ^{111}In-DTPA-Tyr^3-octreotate, a newly synthesized SS analog, demonstrated higher tumor uptake than ^{111}In-DTPA-Tyr^3-octreotide, whereas kidney uptake was similar (73). More

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.