NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors

Well-Differentiated Neuroendocrine Tumors of the Thorax (Includes Lung and Thymus)

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Abstract: Neuroendocrine tumors (NETs) of the thorax, including bronchial and thymic neuroendocrine NETs, are often referred to as NETs of the foregut. The incidence and prevalence of NETs are increasing in the United States as demonstrated in the Surveillance, Epidemiology, and End Results from 1973 to 2004 (*J Clin Oncol*. 2008;26[18]:3063–3072). Although the majority of bronchial and thymic NETs are sporadic, approximately 5% to 10% can be associated with hereditary syndrome, multiple endocrine neoplasms type 1 (*Nat Rev Cancer*. 2005;5[5]: 367–375). Diagnosis is made by tissue pathology, allowing for characterization and classification of the NET. Radiologic evaluation is performed to determine the extent of disease involvement. Clinical symptoms from hormonal overproduction or from paraneoplastic processes are medically managed to improve patients' quality of life. Locoregional disease can be curative with surgery; however, distant or metastatic disease is rarely curable. Therapeutic options for metastatic/advanced NETs of the thorax are mainly to palliate symptoms. Final treatment recommendations for patients with either bronchial or thymic NETs should be individualized, weighing the risks and benefits of therapy.

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Carcinoid was a term introduced by Siegfried Oberndorfer in 1907 to describe neuroendocrine tumors (NETs) because they were noted to be slow growing and "cancer-like" rather than a true cancer.[1] Since the 1999 World Health Organization (WHO) classification, carcinoid is considered an inadequate description for well-differentiated NETs, which consist of a heterogeneous group of cancers, occurring in many different body sites with diverse clinical, histological, and genetic characteristics. The incidence and prevalence of NETs are increasing in the United States as demonstrated in the Surveillance, Epidemiology, and End Results (SEER) databases from 1973 to 2004.[2] Among the epithelial NETs, primary sites are further classified by embryonic divisions of the alimentary tract, such as foregut, midgut, and hindgut. Foregut NETs consist of those originating from the thymus, lung, stomach, pancreas, and duodenum. In this article, we will concentrate on NETs of the thorax, specifically bronchial and thymic NETs.

Patients with NETs of the thorax can present with symptoms resulting either from the overproduction of hormones/active amines or from the effect of tumor burden. Carcinoid syndrome, most commonly experienced by patients with metastatic NETs of the midgut, can also occur in patients with NETs of the thorax. Cutaneous flushing, diarrhea, wheezing, and symptoms of valvular heart disease are symptoms frequently ascribed to classic carcinoid syndrome. Although generally less common, bronchial variant carcinoid syndrome is strikingly unique in its skin manifestation and is more common among patients with NETs of the lung than those with NETs of thymus. Patients suspected of having thoracic NETs, based on biomarkers or clinical symptoms, should undergo confirmation of diagnosis with pathology, followed by radiologic assessment to determine the extent of disease involvement. The cause of NETs is not entirely elucidated, but approximately 5% to 10% of patients with bronchial or thymic NETs are associated with multiple endocrine neoplasms type 1 (MEN1).[3] Collectively, thoracic NETs share common anatomic primary sites and consist of a heterogeneous group of diseases with different histological diagnoses, clinical behaviors, and natural histories. In general, patients with localized bronchial or thymic NETs should be evaluated for curative resections. Therapeutic objectives for metastatic or advanced NETs of the thorax are mainly to palliate symptoms. Patients with symptoms, resulting from hormonal overproduction or paraneoplastic syndromes of their disease processes, should be treated medically or with supportive measures to control hormonal secretion. The final treatment recommendation for patients with either bronchial or thymic NETs should be individualized, weighing the risks and benefits of each option.

Epidemiology

For many decades, NETs have been considered to be rare malignancies that were only incidentally discovered. Perhaps the earliest report on the incidence of NETs was from an autopsy series from 1958 to 1969 in Malmo, Sweden, where the incidence was 8.4 per 100,000 per year.[4] Although these authors and subsequent others have described the incidence of NETs, much still remains to be learned about the race, sex , primary tumor site distribution, and survival patterns in patients with these diseases.[4–7] In 2008, using the SEER data set of 35,618 patients with NETs from 1973 to 2004, Yao et al[2] reported an increasing age-adjusted incidence of NETs, from 1.09 per 100,000 persons in 1973 to 5.25 per 100,000 persons in 2004, in the United States annually. Data obtained from the SEER registries likely

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underestimated the total number of patients with NETs because the SEER data contain incomplete representation of the US patient population. In addition, only patients with malignant NETs are included in the SEER registries. Whereas histological evidence of basement membrane invasion defines malignant behavior for most epithelial malignancies, the definition of malignant behavior for NETs is more complex. In the absence of obvious malignant behavior, such as direct invasion of adjacent organs and metastasis to regional lymph nodes or distant sites, classifying a NET as benign or malignant may be difficult. Neuroendocrine tumors are believed to derive from the diffuse neuroendocrine system located throughout the body, and thus, the primary site of disease can be from any part of the body. The most common site of NETs is the gastrointestinal tract, and the next frequent is the thorax.

Among NETs of the thorax, bronchial NETs are more common than thymic NETs. On the basis of most recent SEER database analysis, the incidences of bronchial and thymic NETs are 1.35 and 0.02 per 100,000 population per year, respectively.[2] Bronchial NETs account for approximately 1% to 2% of all lung malignancies in adults and approximately 20% to 30% of all NETs.[7] A thymic NET is an uncommon neoplasm and accounts for 2% of all mediastinal tumors and 5% of thymic lesions.[8] Median ages of patients at presentation with bronchial and thymic NETs are 64 and 59 years, respectively.[2] Published reports have been variable regarding the environmental risk factors associated with thoracic NETs. Therefore, even in bronchial NETs, the causality of smoking is not proven despite various retrospective reviews, suggesting a higher association with atypical bronchial NETs.[9–11] Stage distribution at diagnosis from the SEER program database for grade 1/2 well-differentiated NETs by primary site is depicted in Table 1.

Bronchial NETs are usually judged to be sporadic, although approximately 10% have some feature suggesting hereditary origin. These features are either tumor multiplicity (5%) or association with MEN1 (5%). Bronchial NET in MEN1 has the added feature of being a disease with female preponderance (5:1 ratio); explanation for this remains unclear.

Similarly, thymic NETs are usually sporadic; however, these can occur in 5% to 10% of cases with MEN1. However, a specific *MEN1* genotype has note been identified.[12] There is a striking male preponderance (10:1) in thymic NETs with MEN1. Surprisingly, several studies have failed to find loss of heterozygosity at 11q13 in thymic NETs of the MEN1 syndrome, despite being malignant. Inactivation of the normal *MEN1* copy without mutation perhaps by promoter methylation seems likely. Involvement of the *MEN1* gene has not been tested directly in sporadic thymic NETs.

Pathology and Molecular Genetics

A variety of proposals regarding the classification and nomenclature of NETs has appeared, and many of these differ somewhat regarding specific terminology and criteria for grading and staging. Most proposed systems have indeed proven useful to stratify prognostic subgroups of NETs. However, the differences in criteria have resulted in much confusion. It would be of great benefit if a single system of nomenclature, grading, and staging could be developed; however, some of the systems that have arisen independently are now firmly established or recognized by organizations charged with standardizing terminology such as WHO. Also, compelling clinical data favoring one system over another does not exist. Thus, abandoning some of the current systems in favor of a single, uniform proposal has proven impractical. On the other hand, careful examination of the existing proposals reveals many common features that underlie the classification and form the basis for grading and staging. Features such as the proliferative rate of the tumor and the extent of local spread (assessed based on similar parameters used for nonneuroendocrine carcinomas of the same anatomic sites) are shared by most systems. Therefore, it is recommended that these basic data elements used to stratify NETs be specified and documented in pathology reports, in addition to the utilization of a specified system of nomenclature, grading, and staging. By doing this, we ensure that the fundamental data necessary for prognostic assessment and therapy determination are recorded, allowing retrospective comparison of the characteristics of NETs, irrespective of the specific classification system that may currently be in vogue. A "minimum pathology data set" of features to be included in pathology reports on NETs of the lung and thymus is proposed in Table 2.

TABLE 1. Stage Distribution at Time of Diagnosis Based on the SEER Program Database (1973–2004)

Primary Site	Stage, %		
	Localized	Regional	Distant
Thymus	49	23	28
Lung	28	41	31

Adapted from Yao et al.[2]

Nomenclature

The terminology for NETs varies by anatomic site but is uniform for these tumors in the lung and thymus. In general, NETs are sharply divided into well-differentiated and poorly differentiated categories. Well-differentiated NETs are also referred to as carcinoid tumors and include both low- and intermediate-grade groups. Poorly differentiated NETs are considered high grade by definition ("high-grade neuroendocrine carcinomas") and include small cell carcinoma and large cell neuroendocrine carcinoma. Cell size and nuclear morphology are used to distinguish small cell carcinoma from large cell neuroendocrine carcinoma. Combined (mixed) forms with elements of both high-grade neuroendocrine carcinoma and nonneuroendocrine carcinoma (usually adenocarcinoma) are also well recognized. Table 3 compares the various synonyms that exist for these different categories of neuroendocrine neoplasms of the lung and thymus. Although the criteria that define each category do not perfectly match between the various systems, there are several common themes. Each system recognizes 3 grades. In each, the low and intermediate grades are closely related, well differentiated, and distinguished largely by proliferative rate or necrosis. Finally, each system generally recognizes that well-differentiated and poorly differentiated features are rarely encountered within the same tumor. It is important to recognize that the unqualified terms "neuroendocrine carcinoma" or "neuroendocrine tumor," without reference to grade or differentiation are inadequate for prognostication or therapy and are considered inappropriate in pathology reports.

Bronchial carcinoid tumors less than 0.5 cm in size are defined as "carcinoid tumorlets" because of the negligible risk for malignant behavior.

Grading

Grading of thoracic NETs relies extensively on the proliferative rate to separate low, intermediate, and high grades. The grading system recently proposed for all thoracic NETs by WHO and the International Association for the Study of Lung Cancer

TABLE 2. Minimum Pathology Data Set: Information to Be Included in Pathology Reports on NETs of the Lung and Thymus

For resection of primary tumors:
- Anatomic site of tumor
- Diagnosis (functional status need not be included in pathology report)
- Size (in 3 dimensions)
- Presence of unusual histologic features (oncocytic, clear cell, gland forming, etc)
- Presence of multicentric disease
- *[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]*
  - *Chromogranin*
  - *Synaptophysin*
- Grade (specify grading system used)
- Mitotic rate (no. mitoses per 10 high-power fields [HPFs] or 2 mm^2; count 50 HPFs in the most active regions)
- *[OPTIONAL: Ki67 labeling index (count multiple regions with highest labeling density, report average percentage; "eyeballed" estimate is adequate)]*
- Presence of nonischemic tumor necrosis
- Presence of other pathological components (eg, nonneuroendocrine components)
- Extent of invasion
  - Presence of invasion into pleura, main stem bronchus, pericardium, chest wall tissues, diaphragm, or other adjacent structures (lung primary)
  - Presence of invasion through tumor capsule or into, pleura, pericardium, lung, or other adjacent structures (thymus primary)
- Presence of vascular invasion *[OPTIONAL: perform immunohistochemical stains for endothelial markers if needed]*
- Presence of perineural invasion
- Lymph node metastases
  - Presence of lymph node metastases
  - Mediastinal level of involved and uninvolved nodes examined
- TNM staging (specify staging system used)
- Resection margins (positive/negative /close) *[OPTIONAL: measure distance from margin if within 0.5 cm]*
- Proliferative changes or other abnormalities in nonneoplastic neuroendocrine cells

For biopsy of primary tumors:
- Anatomic site of tumor
- Diagnosis (functional status need not be included in pathology report)
- Presence of unusual histologic features (oncocytic, clear cell, gland forming, etc)
- *[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]*
  - *Chromogranin*
  - *Synaptophysin*
- Grade (specify grading system used)
- Mitotic rate (no. mitoses per 10 HPFs or 2 mm^2; count to 50 HPFs)
- Ki67 labeling index, for biopsies in which a diagnosis of high-grade neuroendocrine carcinoma cannot be excluded (count multiple regions with highest labeling density, report average percentage; "eyeballed" estimate is adequate)
- Presence of nonischemic tumor necrosis
- Presence of other pathological components (eg, nonneuroendocrine components)

(IASLC) uses either mitotic rate (expressed as mitoses per 10 HPF or 2 mm^2) or the presence and extent of necrosis. This grading system is shown in Table 4. Considerable clinical data exist to validate this grading system, although some authors have proposed further assessment of the mitotic cut points used to separate the 3 grades to determine whether the current thresholds are optimal. Thus, it is recommended to specify the actual proliferative rate in the pathology report, in addition to designating a grade based on a system that is specifically referenced.

Staging

As recently as a few years ago, no formal TNM-based staging systems existed for NETs for any anatomic sites. Recently, TNM

TABLE 3. Nomenclature for NETs of the Lung and Thymus

Grade	WHO, IASLC	Moran et al
Low	Carcinoid tumor	Neuroendocrine carcinoma, grade 1
Intermediate	Atypical carcinoid tumor	Neuroendocrine carcinoma, grade 2
High	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine

TABLE 4. Grading Systems for NETs of the Lung and Thymus

	Criteria	
Grade	**WHO/IASLC**	**Moran et al**
Low	<2 mitoses/10 HPF, AND no necrosis	≤3 mitoses/10 HPF, AND no necrosis
Intermediate	2–10 mitoses/10 HPF, OF foci of necrosis	4–10 mitoses/10 HPF, OR foci of necrosis
High	>10 mitoses/10 HPF	>10 mitoses/10 HPF

staging systems have been proposed. The American Joint Committee on Cancer (AJCC) and the IASLC have recently published a TNM staging system for NETs of the lung, which is displayed in Table 5. However, because data are yet to be collected to validate the parameters used for separating different stages, it is recommended that the extent of involvement of the primary organ and adjacent tissues and structures be specifically indicated in the pathology reports. This will allow easy conversion to any newer, data-based staging systems that may emerge. Reports should provide a TNM stage based on a system that is specifically referenced.

Other Pathology Information

A variety of other pathologic findings may be useful in the prognostication and management of patients with NETs (Table 3). Immunolabeling for general neuroendocrine markers (chromogranin A [CgA] and synaptophysin) may not be needed in histologically typical resected primary tumors, but these stains are very important in many biopsy specimens to confirm the nature of the tumor. Immunolabeling for specific peptide hormones is only useful in highly defined circumstances, however. Assessment of the Ki67 labeling index is not part of the classification of NETs of the lung and thymus (in contrast to gastroenteropancreatic NETs), but it may be useful to separate well-differentiated NETs (carcinoid tumors) from poorly differentiated (high grade) neuroendocrine carcinomas on biopsy specimens. The Ki67 index in resected carcinoid tumors reportedly has prognostic significance. Thus, the Ki67 index may be reported optionally. Adverse prognostic factors not included in grading and staging, such as vascular or perineural invasion should be documented. Adequacy of surgical resection should be indicated, and the number of involved lymph nodes (as well as the total number of nodes examined) should also be stated. A variety of prognostic or treatment-related biomarkers has been investigated, and some may have significant utility in the future; however, currently, none is recommended to be used routinely outside specific research settings. Histological abnormalities of the neuroendocrine cells in the surrounding tissues should be described.

Imaging and Biochemical Markers

Imaging

Patients suspected of having a diagnosis of a NET based on biomarkers and clinical symptoms should undergo imaging. Some NETs may not have elevated biomarkers, and patients with specific symptoms but no abnormal biomarkers should also be evaluated with imaging. Types and extent of radiologic evaluation should be guided by clinical symptoms. Imaging studies for NETs are generally done at the initial evaluation, to determine the extent of disease, and with subsequent follow-up, to evaluate disease status. Goals for the initial evaluation include identification of the primary tumor site as lung versus thymus and assessment of the extent of disease; this information will help with the formulation of treatment planning. Subsequent follow-up imaging studies are done for surveillance after complete resection or during periods of stability and for evaluation of response after treatment. Imaging modalities commonly used include the following:

- computed tomography (CT)
- magnetic resonance imaging (MRI)
- indium In 111-DTPA0 octreotide scintigraphy ([^{111}In-DTPA0] octreotide scintigraphy; Octreoscan)
- metaiodobenzylguanidine (MIBG) scintigraphy
- positron emission tomography (PET)

Initial Imaging Evaluation for Extent of Disease in Thymic and Bronchial NETs

Imaging studies generally recommended at the initial evaluation of patients with a tissue diagnosis of a NET include cross-sectional imaging (CT) of the soft tissues of the head and neck and the chest, cross-sectional imaging (CT or MRI) of the abdomen and pelvis, and [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan). In cases of thymic NETs, an ultrasound of the head and neck may be necessary to further assess nodal and vascular distribution of the disease.

Typical radiograph abnormalities for bronchial NETs include round or ovoid opacities that are usually less than 5 cm with an associated hilar or perihilar mass. The positive predictive value of CT-detected lymphadenopathy as an indication of nodal metastases in NETs was only 20% in 1 study.[13] Cavitation and pleural effusions are not common findings on a chest radiograph for bronchial NETs.[14,15] The typical radiologic finding for thymic NETs is a well-circumcised anterior mediastinal mass. Efforts should be made to exclude metastatic foci from other primary sites for radiologically discovered mediastinal masses. Generally, CT imaging may provide better resolution than plain radiographic studies of tumor extent, location, and the presence or absence of mediastinal adenopathy. However, because diagnosis is made ultimately by pathology, CT or ultrasound should be performed to determine whether the location of one or more suspicious lesions allows for image-guided needle biopsy to verify the diagnosis. Pathologic diagnosis can often be made safely with a biopsy specimen obtained from bronchoscopy because pulmonary lesions in bronchial NETs are usually located centrally.[16–18]

Follow-Up Imaging of Thymic and Bronchial NETs

Among patients undergoing surveillance after complete resection, we recommend cross-sectional imaging (CT) of the soft tissues of the head and neck and the chest and periodic (every 6–12 months) cross-sectional imaging (CT or MRI) of the abdomen and pelvis. The role of routine [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) has not been defined by prospective studies. Many experts, however, would advocate the use of [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) yearly as follow-up for patients without evidence of disease or on an as-needed basis to define indeterminate radiologic findings.

For patients with advanced disease, we generally recommend the use of cross-sectional imaging for known sites of disease. [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) can be used to test in vivo for the presence of somatostatin receptors 2 and 5. It can also be used to evaluate if peptide receptor radiotherapy represents a reasonable treatment option.

Techniques for Cross-Sectional Imaging of NETs

Neuroendocrine tumors are generally vascular tumors that enhance intensely with intravenous contrast during early arterial

TABLE 5. The 2010 AJCC TNM Staging of NETs of the Lung

AJCC Staging of NETs of the Lung			
Primary tumor (T)			
TX	Primary tumor cannot be assessed or tumor was proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy		
T0	No evidence of primary tumor		
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)		
T1a	Tumor ≤2 cm in greatest dimension		
T1b	Tumor ≥2 cm but ≤3 cm in greatest dimension		
T2	Tumor ≥3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm): involves main bronchus, ≥2 cm distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T2a	Tumor ≥3 cm but ≤5 cm in greatest dimension		
T2b	Tumor ≥5 cm but ≤7 cm in greatest dimension		
T3	Tumor ≥7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; tumor in the main bronchus (<2 cm distal to the carina but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe		
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or separate tumor nodule(s) in a different ipsilateral lobe		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion		
M1b	Distant metastasis		
Anatomic stage/prognostic groups			
Occult carcinoma	TX	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0

phases of imaging with washout during the delayed portal venous phase. The key to detect small NETs on CT is to maximize the contrast between the tumor and the adjacent normal parenchyma. For abdominal and pelvic imaging, we recommend multiphasic CT that includes the arterial phase and the portal venous phase. Rapid intravenous bolus of intravenous contrast is also recommended.

Magnetic resonance imaging is preferred over CT for patients with a history of allergy to iodine contrast material or for those with renal insufficiency. Neuroendocrine tumors can have variable appearances on noncontrast MRI. They can be hypointense or isointense on T1-weighted images. Metastases to the liver typically are usually of high signal on T2-weighted images.[19] Because T2-weighted images are obtained without intravenous contrast, they do not have the problem of variations in the timing of phases of contrast enhancement. T2-weighted imaging can be especially useful for patients unable to receive contrast. However, these metastases, especially when cystic or necrotic, can mimic the appearance of other T2 high signal intensity lesions, such as hemangiomas and, occasionally, cysts.[20] Dynamic contrast-enhanced imaging can provide additional information about the nature of the lesions and help to detect smaller lesions. We recommend T1- or T2-weighted imaging and multiphasic (arterial, portal venous, and delayed) dynamic MRI for NETs.[19,21]

Some published studies have suggested that MRI may be more sensitive than CT for the detection of small liver metastases.[22,23] However, it is also recognized that CT may be better

for the evaluation of peritoneal and mesenteric diseases. Whether CT or MRI is better overall for NETs will continue to be debated and will likely depend on the expertise of the local imaging center.

Techniques for Nuclear Imaging of NETs

Once a pathologic diagnosis is made, somatostatin analog molecular imaging using indium In 111 pentetreotide (^{111}In-DTPA-pentetreotide; Octreoscan) is advised because this has the highest sensitivity for detecting NETs. Somatostatin analog images should be acquired with high-count planar technique (15 minutes for each abdomen and thoracic scan). Single photon emission CT (SPECT; tomographic gamma camera imaging) with CT fusion hybrid imaging (SPECT/CT) or, if not available, SPECT imaging with a separately acquired CT scan of the soft tissue of the neck and chest should be obtained, depending on the planar gamma camera image findings and the area of clinical suspicion. About 70% to 80% of thoracic NETs express somatostatin receptors and can be imaged with radiolabeled octreotide (Octreoscan).[13,24] The ^{111}In-labeled somatostatin analog [^{111}In-DTPA0]octreotide shares the receptor-binding profile of octreotide, making it a good radiopharmaceutical for imaging of somatostatin receptors 2 and 5–positive NETs.[25] The overall sensitivity of [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) seems to be approximately 80% to 90%.[25] Unlike cross-sectional imaging, which is generally site-directed, [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) is done as whole-body imaging and thus can detect disease at unsuspected sites.

Imaging is generally performed at 4 to 6 hours and at 24 hours.[26] Imaging at 24 hours provides better contrast because of a lower background activity. However, there is often physiologic bowel activity that may produce false-positive results. At 4 to 6 hours, some lesions may be obscured by the relatively high background activity. In some cases, additional imaging at 48 hours may be needed when there is significant bowel activity at the 24-hour scan, which may potentially obscure lesions. Imaging using SPECT with CT fusion may be helpful in resolving the nature of the indeterminate lesions found on CT and in enhancing the sensitivity and specificity of the study.

[^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) can be performed for patients on long-acting octreotide but is best performed at the end of the dosing interval (3-6 weeks after the last dose). For patients on octreotide delivered via a continuous infusional pump or receiving intermittent short-acting octreotide, we would recommend that these be stopped for 48 hours before and during testing if possible. Although [^{111}In-DTPA0] octreotide scintigraphy (Octreoscan) can provide useful information about site of disease, it does not give information about size. Some agents such as interferon (IFN) may upregulate somatostatin receptors and thus can lead to increased uptake without disease progression. [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) is sometimes performed to evaluate the feasibility of peptide receptor radiotherapy because a scan with intense uptake at all known sites of disease is associated with a higher response rate after radiotherapy with somatostatin receptor targeting.

Iodine I 131 MIBG (^{131}I-MIBG) and, more recently, iodine I 123 MIBG (^{123}I-MIBG) molecular imaging have also been used for NETs, but these have the greatest efficacy in patients with pheochromocytoma, paraganglioma, or neuroblastoma. Nonetheless, some NETs being negative on [^{111}In-DTPA0] octreotide scintigraphy (Octreoscan) can be better identified with ^{123}I-MIBG.

Positron emission tomography with fluoride F 18 [^{18}F]-fluorodeoxyglucose (FDG) imaging, although successful for many solid tumors, has generally not provided additional information about the extent of the disease for well-differentiated NETs because of their generally lower proliferative activity. Although most well-differentiated NETs are not well imaged by FDG-PET, FDG imaging in undifferentiated and nonsecretory tumors may be more sensitive. Imaging with FDG-PET should be used for undifferentiated tumors or when [^{111}In-DTPA0] octreotide or ^{123}I-MIBG is negative or equivocal. Imaging with FDG-PET may also be used to characterize tumor aggressiveness with higher FDG uptake (expressed as SUV values) having a worse prognosis. This may be helpful when the tumor seems more aggressive than the histologic diagnosis indicates, and additional information from FDG-PET imaging may result in treatment changes.

Published studies have suggested carbon C 11 (^{11}C)-5-hydroxy-tryptophan (HTP) PET to be a promising imaging modality for the detection of NETs.[27] The serotonin precursor 5-HTP labeled with ^{11}C had increased uptake and irreversible trapping of this tracer in NETs.[27] [^{11}C]-5-HTP-PET proved better than somatostatin receptor scintigraphy for tumor visualization. However, the short half-life of ^{11}C ($t_{1/2}$ = 20 minutes) makes it difficult to apply in clinical practice. Other new PET imaging agents for NETs include ^{18}F-fluoro-L-4-dihydroxyphenylalanine, gallium Ga 68 (^{68}Ga)-tetraazacyclododecanetetraacetic acid - Tyr3-octreotide, ^{68}Ga-tetraazacyclododecanetetraacetic acid - 1-Nal3-octreotide, and ^{18}F-(1-deoxy-D-fructosyl)-*N*-(2-[^{18}F]fluoropropionyl)-Lys^0-Tyr^3-octreotate (Gluc-Lys). In addition, technetium Tc 99m depreotide, which has a greater affinity to somatostatin receptor 3, has also been used for imaging NETs. Although these novel imaging techniques are promising, clinical experiences are limited. Furthermore, many of these novel techniques are generally not available in the United States.

Staging in Thymic and Bronchial NETs

As discussed above, radiologic evaluations are done mainly for 3 purposes: (1) to localize the primary site of disease; (2) to assess extent of disease, that is, staging; and (3) to evaluate radiologic response to therapy, that is, restaging to determine disease status. After tissue diagnosis is confirmed, staging of bronchial NETs consists mainly of [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan), CT scans, and/or MRI. [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) can be helpful in evaluating distant sites of metastases among patients expressing somatostatin receptors, particularly somatostatin receptors type 2 and 5. Computed tomographic scans of chest and abdomen are necessary for a better resolution of tumor extent, location, and the presence or absence of mediastinal adenopathy. The most common metastatic site of all NETs is the liver, and because NETs are vascular tumors, abdominal CT with delayed phase and/or dedicated liver MRI is necessary to assess for liver metastasis.

The extent of disease or stage of disease in bronchial NETs is determined by using the current 2010 7th AJCC TNM classification for non–small cell lung carcinoma. The modifications in the 7th edition are based on recommendations of the IASLC to allow for better prediction of prognosis for bronchial NETs.[28] The Masaoka staging scheme is still applied for thymic NETs.[29] In addition, for thymic NETs, a simplified staging system has been proposed by Suster and Moran,[30] in which stage I lesions are encapsulated, stage II tumors are locally invasive, and stage III tumors present with lymph node or visceral metastasis. However, because of the rarity of thymic NETs, there is currently no well-recognized staging system specific to NETs of the thymus that can accurately reflect prognosis.

TABLE 6. Survival by Disease Stage and Primary Tumor Site in Patients With Well-Differentiated Thoracic NETs Diagnosed From 1988 to 2004

	Localized			Regional			Distant		
Primary Tumor Site	Median Survival Duration, mo	5-yr Survival Rate, %	10-yr Survival Rate, %	Median Survival Duration, mo	5-yr Survival Rate, %	10-yr Survival Rate, %	Median Survival Duration, mo	5-yr Survival Rate, %	10-yr Survival Rate, %
Thymus	92	93	49	68	65	49	40	32	0
Lung	NR	84	56	151	72	56	17	27	15

Adapted from Yao et al.[2]
NR indicates not reached.

Information about NETs as a whole came from the analyses of large databases such as the SEER registries in the United States. SEER staging systems are currently being used to determine prognosis and survival rates of NETs. A *localized* stage is defined as an invasive neoplasm confined entirely to the organ of origin. On the other hand, a *regional* stage is defined as a neoplasm that (1) extends beyond the limits of the organ of origin directly into surrounding organs or tissue, (2) involves regional lymph nodes, or (3) fulfills both of the aforementioned criteria. Finally, a *distant* stage is defined as a neoplasm that has already spread to parts of the body remote from the primary tumor.[31] In the most recent SEER database analysis of NETs, survival outcomes are consistently associated with histological grade and stage of disease. Among patients with well-differentiated bronchial NETs, 5-year survival rates are 84%, 72%, and 27% among patients with *localized*, *regional*, and *distant* diseases, respectively (Table 6).[2]

In summary, molecular scintigraphy using SPECT/CT combined with selective CT and MRI imaging is used for staging, restaging, and treatment monitoring and is vital to the quality care of patients with NETs. The staging system for bronchial NETs with the recently modified AJCC staging classification will accurately reflect disease prognosis. However, because of its rarity, a staging system to accurately predict the prognosis of patients with thymic NETs has not been formulated.

Biochemical Markers

Several circulating tumor markers have been evaluated for the diagnosis and follow-up management of NETs. Although these can be very useful for follow-up, an isolated elevation of marker levels is generally not sufficient for diagnosis without tissue confirmation. The most important of these markers is CgA, a 49-kd acidic polypeptide that is widely present in the secretory granules of neuroendocrine cells. Depending on the extent of the disease, plasma CgA is elevated in 60% to 100% of patients with either functioning or nonfunctioning NETs. The sensitivity and specificity of CgA for the detection of NETs range between 70% and 100%.[32–35] Levels of CgA may correlate with tumor volume; however, care should be taken in measuring CgA and in interpreting the results. For example, because somatostatin analogs are known to alter blood levels of CgA, serial CgA levels should be measured at approximately the same interval from injection in patients receiving long-acting somatostatin analogs. Spuriously elevated levels of CgA have also been reported in patients taking proton pump inhibitors, with renal or liver failure, and those with chronic gastritis. When used to monitor for recurrence after complete surgical resection, patients should discontinue proton pump inhibitors for 2 weeks if possible before measurements of CgA.

Although urinary 5-hydroxyindoleacetic acid (5-HIAA; 24-hour collection) is a useful laboratory marker for well-differentiated midgut NETs, its clinical usefulness in thoracic NETs is variable because more often than not, 5-HIAA levels are normal in patients with thoracic NETs. 5-Hydroxyindoleacetic acid is a surrogate measure of serotonin metabolism, which is tightly linked to the presence of carcinoid syndrome. 5-Hydroxyindoleacetic acid is more useful than the direct measurement of serotonin because serum serotonin varies considerably during the day according to activity and stress level. The specificity of this test has been reported to be 88%.[36] However, certain foods and medications (Table 7) can increase urinary 5-HIAA levels and should be avoided during specimen collection.[37]

For many NETs, including NETs of the lungs and thymus, another useful blood marker is neuron-specific enolase (NSE). Like most blood markers, blood sampling for NSE should be drawn in a fasting state. Among patients on somatostatin analogs, the NSE level should be drawn at a consistent time point relative to timing for the administration of long-acting analogs. Neuron-specific enolase is a dimer of the glycolytic enzyme enolase, which is present in the cytoplasmic compartment of the cell and its serum level is thought to be unrelated to the secretory activity of the tumor.[32] Although less specific than CgA, NSE may be a useful marker for follow-up of patients

TABLE 7. Foods and Medications to Be Avoided During 5-HIAA Urine Collection

Foods and Beverages	Medications
Alcoholic beverages	Phenacetin
Banana	Cough and cold remedies containing expectorants
Black walnuts	Muscle relaxants methocarbamol
Butternuts	Phenathiazines chlorpromazine, prochlorperazine, promethazine, etc
English walnuts	Methanamines
Kiwi	
Mockernut	
Nuts	
Pecans	
Pineapple	
Plantain	
Plums	
Shagbark	
Tomatoes	

with known diagnosis of NETs. A variety of other secreted amines can be measured among patients with NETs, but these (chromogranins B and C, pancreastatin, substance P, neurotensin, neurokinin A, and fasting pancreatic polypeptide) have less clinical applicability in the management of patients with bronchial and thymic NETs.

It is recognized that during a course of disease, NETs occasionally can produce different hormones. Therefore, the general principle of biomarker measurement is to evaluate a large panel of markers at key points such as at diagnosis or relapse, to identify which biomarkers are elevated in a particular patient, and then to follow the trend of these biochemical assays over time. Checking every biomarker at every visit is impractical, cost-ineffective, and not necessary.

Management of Local-Regional Disease

Principle of Surgery for Bronchial and Thymic NETs

Before embarking on surgical intervention, identifying the extent of NET invasion, pinpointing the exact location of the tumor, and assessing the functional capacity of the patient to withstand the planned operation are mandatory. A complete surgical resection is imperative, which may limit the use of thoracoscopic techniques. However, in select cases, thoracoscopic surgical intervention does have a role, particularly in managing resection of isolated metastasis. The best chance for a cure lies with the initial surgical procedure. In an attempt to precisely guide the surgical resection, FDG-CT imaging and the availability of completing a [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) intraoperatively have enhanced the surgeon's ability to remove all viable tumor tissues.

Bronchial NETs

Typical bronchial NETs often present with symptoms mimicking asthma and therefore often have a delay in diagnosis. Hence, bronchial NETs are generally advanced at the diagnosis, limiting the possibility of curative surgical resection. Rarely are bronchial NETs completely resected via endoscopic measures, and the risk of significant bleeding from endoscopic resection is significant. Endoscopic laser debulking to allow recovery from a distal obstructive pneumonia can potentially result in a more conservative resection to be performed.[38]

In the absence of locally advanced disease, a sleeve resection can often be performed with minimal loss of functional lung tissue.[39] The 5- and 10-year survival rates for typical bronchial NETs are 87% to 100% and 82% to 87%, respectively; subtotal resection at the initial surgery is linked to poor survival.[16,18,40–48] For bronchial lesions with potential for significant hemorrhage, sleeve resection is ill-advised. Extensive blood in the bronchus distal to the lesion as well as blood in the unaffected lung predisposes a patient to postoperative pneumonia and anastomotic complications secondary to local infection as well as a need for prolonged mechanical ventilation. Every effort should be made to avoid unnecessary contamination of the contralateral bronchial tree with blood and infected secretions. Use of a double-lumen bronchial endotracheal tube is highly recommended.

When a sleeve resection is undertaken, it is imperative that a frozen section of both bronchial margins be unequivocally free of tumor. Intraoperative flexible bronchoscopy is useful in confirming the patency of the bronchial anastomosis at the conclusion of the procedure as well as in direct endotracheal suctioning. The use of intraoperative ^{111}I-labeled octreotide is helpful in identifying tissue involved with tumor, which may not be distinguishable by the naked eye, particularly if the surgeon is performing a second operation where inflammation or scar tissue can limit the efficacy of direct visualization. Lymph node sampling is recommended when operating on well-differentiated bronchial NETs.[13,18,41,49–52] Peripheral-based lesions can be resected thoracoscopicaly. However, these lesions often have atypical features and can be associated with local-regional lymph node metastases. Correct staging of the tumor and, perhaps more importantly, enhancing the chance of curative surgery require a thorough lymph node dissection.[41,43,44]

It is noteworthy to discuss the management of a special group of bronchial NETs, referred to as bronchial carcinoid tumorlets. By definition, these tumorlets must have a maximum diameter of less than 0.5 cm and are generally not associated with any clinical symptoms. Because bronchial carcinoid tumorlets are often incidentally discovered on pathological review, the real incidence and prevalence of tumorlets are difficult to establish. They can be multifocal, bilateral, and frequently associated with inflammatory processes like bronchiectasis and interstitial fibrosis. An accurate histological diagnosis requires an accurate serial dissection of the pulmonary parenchyma. The real significance of these lesions is still not completely understood, and thus, formal recommendations, regarding surgical resection and follow-up, remain vague. Perhaps the most important consideration in the management of these bronchial carcinoid tumorlets is their correct diagnosis.

Thymic NETs

Thymic NETs are rare and often aggressive in their clinical behavior, resulting in difficult challenges to surgical cure. Thymic NETs tend to be diagnosed late and are often locally advanced at the time of presentation. Often, the tumors can invade vital structures and, in addition to CT and [^{111}In-DTPA0] octreotide scintigraphy (Octreoscan), MRI may also be helpful in planning for the surgical resection. Resection of thymic NETs is a major operation, occasionally requiring cardiopulmonary bypass with cardioplegic arrest of the heart, and should not be undertaken if there is widespread metastases outside the chest or if the patient is a marginal operative candidate. However, complete surgical resection is the only chance for a cure, and this should always be carefully considered. Curative resection of thymic NETs often requires a median sternotomy approach. A complete mediastinal lymphadenectomy is desirable for both staging and ensuring the best chance of disease-free survival.

Adjuvant Therapy

There are currently no data to suggest that adjuvant therapy (radiation, chemotherapy, or chemoradiation) will prolong a disease-free interval or median survival.[53,54] Therefore, at this time, there are insufficient data to recommend the use of adjuvant therapy after complete resection of local-regional disease.

Follow-Up and Surveillance

Follow-up recommendations based on a risk model framework for specific NETs presenting with local and extensive disease as "level 1" data (randomized clinical trials) are lacking.[55] General guidelines consist of identifying any disease-related symptom(s), biochemical markers (specific and nonspecific), and imaging assessment to determine the precise tumor localization and possible metastases by CT or MRI and [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan). After surgery, patients are typically reevaluated 3 months postoperatively to establish a new "baseline." The term "as clinically indicated" refers to changes of symptoms or signs from baseline, rising tumor marker(s), and CT/MRI changes suggestive of tumor growth. Tumor markers to consider are dependent on the primary NET site. Serum CgA is the most

sensitive but the least specific, whereas urine 5-HIAA is the most specific but not sensitive for diagnosing early disease.[35,56–60] Serotonin is recognized as a variable and labile tumor marker when followed serially, but it may be useful in making a diagnosis. Elevated or abnormal 24-hour urinary 5-HIAA level has a sensitivity of 75% and a specificity of up to 100% in making a diagnosis of thymic or bronchial NET.[56] Although this test may help to confirm the diagnosis, it is fraught with human errors that may be induced by certain drugs or activities. In fact, thymic or bronchial NET cells often lack aromatic amino acid decarboxylase, which is necessary to convert tryptophan to serotonin and ultimately to urine 5-HIAA. Thus, in patients with thymic or bronchial NETs, measurement for urine 5-HIAA is not as helpful or as useful as urinary serotonin.

Triple-phase helical CT and MRI are the preferred imaging modality when hepatic tumor infiltration is present or strongly suspected. For NET patients with contrast allergy, MRI (enhanced and unenhanced) is recommended. Ultimately, for patients unable to undergo CT or MRI, serial [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan) is suggested. Although no prospective study has been attempted to demonstrate the utility of any specific follow-up protocol, it is generally accepted that after curative resection, an active surveillance program can detect early tumor relapse. Theoretically, early detection of tumor recurrence or relapse can lead to an improved chance of achieving complete resection and allow for early initiation of therapy. Because of the indolent nature of well-differentiated NETs, patients need not be followed up at short intervals, but they can be followed up with long-intervening periods. We recommend that patients with NETs be reassessed once between 3 and 6 months after complete curative resection. Subsequently, patients should be evaluated every 6 to 12 months for at least 7 years after curative surgical resection. Follow-up evaluation should consist of interval history, physical examination, and laboratory testing including CgA and 5-HIAA at a minimum. Multiphasic CT or MRI is recommended by many experts. [^{111}In-DTPA0]octreotide scintigraphy can be performed as clinically indicated.

Management of Hormonal Syndromes

Control of symptoms from hormone overproduction is critical for improving quality of life for patients with NETs. Carcinoid syndrome is often associated with well-differentiated NETs; management of classic carcinoid syndrome is discussed elsewhere. However, because patients with thoracic NETs most likely will require surgical intervention, attention to perioperative management of carcinoid syndrome will be discussed in the next paragraphs. Management of refractory carcinoid syndrome is also discussed in the next paragraphs. In addition, for thoracic NETs, particularly bronchial NETs, Cushing syndrome and acromegaly are other hormonal syndromes that can be encountered.

Perioperative Management of Carcinoid Syndrome

Patients with carcinoid syndrome can be particularly challenging in the perioperative setting because they are at risk of developing carcinoid crisis from what may seem to be a relatively minor procedure such as colonoscopy, bronchoscopy, percutaneous biopsy, chemoembolization, or other non–NET-related procedures.[61] The degree of risk and severity of a crisis is difficult to predict. Every attempt at controlling the syndrome preoperatively should be undertaken. Manifestations of carcinoid crisis include hypotension or hypertension, flushing, tachycardia or bradycardia, bronchospasm, and complete vasomotor collapse. Treatment is centered on prevention. General preoperative preparation should include correction of nutritional deficiencies and electrolyte imbalances whenever possible. Premedication with octreotide, such as a single subcutaneous injection of 250 to 500 μg, should be a sufficient prevention for most minor procedures.[62] We recommend having extra doses available in the operating room or treatment area, to be given in 250 μg amounts or greater, should the need arise. For major procedures, a preoperative intravenous bolus of 250 to 500 μg, followed by a continuous infusion of 100 to 500 μg/h during the procedure, has been reported.[61,63] The infusion is then weaned by 50% daily for a few days until it can be safely discontinued and is sometimes supplemented by a dose of long-acting depot somatostatin analog. Additional preoperative preparation can include short-acting corticosteroids and antihistamines (H1- and H2-blocking agents).[64] Hypotension, which is not attributable to acute blood loss, should be treated with boluses of octreotide, steroids, and volume expansion.[61,63] Bronchospasm can also be reversed similarly to most allergic reactions with steroids.[63] Vasopressors should be avoided because these agents are known to potentiate the release of serotonin and vasoactive amines from these tumors.[61] Low doses of dopamine, vasopressin, and neosynephrine after pretreatment with a high-dose octreotide infusion can effectively prevent perioperative precipitation of carcinoid crises.[61]

Management of Refractory Carcinoid Syndrome

The commercial introduction of somatostatin analogs has resulted in vast outcome improvements for patients with carcinoid syndrome. However, refractory flushing and diarrhea to somatostatin can be quite challenging to manage. There can be multiple reasons patients develop refractory symptoms. A most important step is to reevaluate the status of disease and rule out disease progression. Imaging with CT or MRI, obtaining appropriate biomarkers, and carefully assessing history can help in determining the cause of symptoms and selecting an optimal therapeutic approach. The causes for refractory carcinoid syndrome in NETs, particularly refractory diarrhea, include an increase in hormone production by the tumor, development of steatorrhea because of pancreatic exocrine insufficiency secondary to somatostatin analogs, and development of pellagra because of niacin deficiency.

Serotonin, capable of inducing diarrhea in carcinoid syndrome, is secreted, and thus, serotonin-dependent diarrhea can occur with or without food ingestion. A consistent rise in urinary 5-IAA or imaging studies demonstrating disease progression would suggest that increased hormone production from a progressive disease is likely responsible for the refractory diarrhea. Escalating the dose of long-acting somatostatin analogs, shortening the period between injections, or adding a short-acting agent is often the most effective solution. Other options may include adding nonspecific diarrheal agents, debulking the tumor, or adding IFN. Somatostatin analogs given in high doses can also cause a malabsorptive diarrhea. In this scenario, patients often describe foul-smelling, floating, foaming, and greasy stools after meals. Malabsorptive diarrhea is often best managed by the addition of pancreatic enzymes with meals. Finally, refractory diarrhea can also be a result of vitamin deficiency. Patients with longstanding uncontrolled or poorly controlled carcinoid syndrome can develop niacin deficiency. Classic symptoms of niacin deficiency, known as pellagra, include diarrhea, dementia, and dermatitis. For patients in this scenario, supplementation with niacinamide or niacin in meals can help offset diarrhea.

As mentioned previously, therapeutic agents used for managing carcinoid syndrome include somatostatin analogs, IFN, serotonin receptor antagonists, and antidiarrheal agents.

Somatostatin Analogs

The use of somatostatin analogs to block the release of bioactive peptides and amines is the mainstay for the control of the symptoms of carcinoid syndrome. In the United States, octreotide is the only somatostatin analog currently approved for the treatment of carcinoid syndrome. In Europe and in other parts of the world, lanreotide is also approved for the control of the flushing, diarrhea, and wheezing associated with carcinoid syndrome. Octreotide acetate comes in 2 forms: an aqueous immediate release [short-acting] and a sustained release [long-acting] form. The short-acting somatostatin analog is administered initially as a test compound to determine safety and tolerability of the long-acting formulation and as a rescue injection for periods when the patient is exhibiting severe or recalcitrant symptoms. Currently, the long-acting release form of octreotide is offered in 10-, 20-, and 30-mg formulations, and the currently recommended starting dosage is 20 mg/mo. Careful review of the octreotide drug registration data reveals that octreotide blood levels are weight dependent.[65–67] Recent data suggest that up to 40% of patients who are treated with the long-acting release formulation may need additional rescue injections of short-acting somatostatin at some point during their disease course.[68] The need for a short-acting rescue medication to optimize symptom management is further supported by the data from the registration trial for octreotide long-acting release. In that trial, 40% of patients required weekly rescue medication (regardless of long-acting release dose) and 70% of patients required rescue injections at some time during the registration trial.[66]

Interferon alpha

Interferon α 2a and 2b (IFN-α-2a and IFN-α-2b) bind to specific IFN receptors on NET cells. After binding of IFN to its receptor, a signal transduction cascade is activated, leading to the transcription of multiple tumor suppressor genes. Interferon acts on specific enzymes (ie, 2′,5′-α-synthetase and P-68 kinase), leading to the degradation of peptide hormones and inhibition of protein synthesis. In NETs, the indications for IFN are similar (except carcinoid crisis) to those of somatostatin analogs.

Most investigational trials have studied recombinant IFN-α-2a or IFN-α-2b. In 30% to 70% of the patients with carcinoid syndrome, symptomatic remission with IFN therapy is observed, with a superior effect on flushing compared with diarrhea.[69–78] The effectiveness of IFN to control the symptoms of carcinoid syndrome is similar to that of somatostatin analogs, but the onset of response is more delayed. In patients with the carcinoid syndrome, comparing IFN to somatostatin analog, remission or stabilization of tumor markers and/or urinary 5-HIAA excretion was observed in 36% to 44% and in 30% to 35%, respectively. In most patients, symptoms of flulike syndrome occur during the first 5 days of IFN administration. Other common adverse effects include anorexia, weight loss, fatigue, and dose-dependent bone marrow toxicity including anemia, leucopenia, and thrombocytopenia. Less common adverse effects include hepatotoxicity, depression, mental disturbances, and visual impairment.[69–72,74,76–81]

The combination of octreotide and IFN-α has also been studied. Patients for whom octreotide alone produced suboptimal symptom control were included in 3 studies of 24, 19, and 9 patients.[73,82,83] Patients for whom monotherapy with IFN had no benefit were also included in 1 of these studies.[73] Biochemical responses were reported in 77%, 72%, and 75% of patients treated with combination therapy. Results of these studies suggest that there may be synergism between somatostatin analogs and IFN in controlling symptoms of carcinoid syndrome.

Serotonin Receptor Antagonists

Serotonin receptor subtype 5-HT_1 and 5-HT_2 antagonists, such as methysergide, cyproheptadine, and ketanserin, and 5-HT_3 antagonists, such as ondansetron, have also been used in patients with the carcinoid syndrome. These drugs generally result in symptomatic improvements of diarrhea and nausea but not of flushing.[84–89]

Antidiarrheal Agents

Like in other causes of secretory diarrhea, opiates and loperamide have been used for a symptomatic improvement of diarrhea in patients with the carcinoid syndrome.

Cushing Syndrome

Bronchial and thymic NETs can cause Cushing syndrome because of the ectopic production of adrenocorticotropic hormone (ACTH).[90–93] A bronchial NET is the most common cause of ectopic ACTH production. Symptoms of Cushing syndrome are seen in 1% to 2% of patients with a bronchial NET and can be the initial reason for seeking medical attention. The onset is usually immediate, and hypokalemia is often present. The diagnosis may be difficult because the production of ACTH by bronchial NETs can be suppressed by dexamethasone, unlike other tumors that produce ectopic ACTH. Sometimes these symptoms are not well controlled either by cytotoxic or biological treatment and require additional specific medical treatment.

Cushing syndrome could be treated with commonly available agents such as ketoconazole, metyrapone, aminoglutethimide, etomidate, mitotane, or mifepristone. Ketoconazole is the most popular and effective; it acts on several of the P450 enzymes, including the first step in cortisol synthesis, cholesterol side-chain cleavage, and conversion of 11-deoxycortisol to cortisol. A daily dose of 600 to 800 mg of ketoconazole can effectively decrease cortisol production. Adverse effects of ketoconazole include headache, sedation, nausea, irregular menses, decreased libido, impotence, gynecomastia, and elevated liver function tests. Metyrapone blocks 11-β-hydroxylase activity, the final step in cortisol synthesis. Therapy with metyrapone starts at 1 g/d divided into 4 doses and increases to a maximum dose of 4.5 g/d. Adverse effects are secondary to an increase in androgen and mineralocorticoid precursors and include hypertension, acne, and hirsutism. Aminoglutethimide is an anticonvulsant agent that blocks cholesterol side-chain cleavage to pregnenolone, with a relatively weak adrenal enzyme inhibitor at doses that patients can tolerate. Currently, aminoglutethimide is not commercially available for use. Similar to metyrapone, etomidate, an imidazole-derivative anesthetic agent, blocks 11-β-hydroxylase. Unfortunately, its use is limited to short-term duration because it has a short half-life and its route of administration is intravenous. Etomidate dosage is usually started at 0.3 mg/kg per hour. Mitotane is an adrenolytic agent that acts by inhibiting 11-β-hydroxylase and cholesterol side-chain cleavage enzymes. This drug also leads to mitochondrial destruction and necrosis of the adrenocortical cells in the zona fasciculate and reticularis. For this reason, it is used in the treatment of patients with adrenal cortical carcinoma. Mitotane can be used in combination with metyrapone. Unfortunately, mitotane is expensive with a very narrow therapeutic index. Adverse effects include moderate gastrointestinal and neurologic toxicity—nausea, vomiting, diarrhea, dizziness, and ataxia. Another important limitation of mitotane is that it is potentially teratogenic and can cause abortion. Mifepristone (RU 486) is an antiprogestational agent, which, at high doses, competitively binds to the glucocorticoid and progesterone receptors.

Although it may be effective, availability and use are currently restricted. In some patients, bilateral adrenalectomy may be necessary to control for Cushing syndrome when all medical therapy failed. For ectopic growth hormone–releasing hormone (GHRH) secretion and acromegaly, somatostatin analogs can be of value. Some patients with ectopic ACTH syndrome might respond to a somatostatin analog as well.

Acromegaly

Acromegaly from the ectopic production of GHRH is a rare manifestation of bronchial NETs.[94–97] However, bronchial NETs are the most common cause of extrapituitary GHRH secretion. These patients will likely respond to Somatostatin Analog or to surgical debulking.

Management of Advanced Disease

Approach to the Management of Advanced Disease

The decision to initiate therapy is based on a number of clinical and pathological factors including tumor grade, symptoms, performance status, and organ functions. Poorly differentiated NETs are more aggressive but are more likely to respond to platinum–based chemotherapy. Because of the rapid rate of growth and spread, treatment should be initiated quickly (see poorly differentiated NETs section). If tumor grade cannot be determined based on the available tumor specimen, a second core needle biopsy should be strongly considered because the results may determine treatment options.

For well-differentiated NETs of the lung and thymus, we recommend surgical resection if all gross disease can be reasonably resected. Palliative resection can also be considered to alleviate symptoms or prevent complications. Initiation of therapy for progressive disease should be considered if patients have symptoms, bulky disease, or evidence of tumor growth. Treatment of asymptomatic patients with limited evaluable disease and no evidence of progression can also be considered using agents with a favorable safety profile such as a somatostatin analog. For patients with unresectable disease confined to the liver, liver-directed therapy should be considered.

Peptide receptor radiotherapy is not approved in the United States. For those who can access such therapy, it presents an additional therapeutic option, especially for those patients with significant uptake on [^{111}In-DTPA0]octreotide scintigraphy (Octreoscan).

Systemic Therapy

Although substantial improvements in the management of carcinoid syndrome have been made, no new agent has been approved for the control of tumor growth during the last 3 decades. Several agents have been found to have varying degrees of activity in stabilizing tumor growth. Tumor regressions, however, are rare. Novel targeted agents such as vascular endothelial growth factor and mammalian target of rapamyacin inhibitors have been found to be promising in NETs and are under development. However, their clinical applications are still considered investigational.

Somatostatin Analogs

Somatostatin analogs have been widely used in NETs for the control of hormonal syndromes. Although somatostatin analogs have also been frequently used for theoretical cytostatic activity, until recently there were no prospective data to support the antiproliferative role of somatostatin analogs. In 2009, a somatostatin analog was demonstrated to have an antiproliferative activity, where progression-free survival duration of patients with well-differentiated NETs treated with 30 mg of octreotide long-acting release was prolonged compared with those patients who only received placebo (median progression-free survival, 14 vs 6 months; hazard ratio, 0.34; 95% confidence interval, 0.2–0.6; $P < 0.0001$).[98]

Interferon

Interferon-α has been reported to induce disease stabilization and to lead to objective responses in a small number of patients. Most of these studies, however, are underpowered. Pooling the data from patients with NETs involved in these studies, only 37 (12%) of 309 had objective tumor responses.[99]

Combining somatostatin analogs with IFN can theoretically enhance antitumor activity. Two underpowered random assignment studies have attempted to compare single-agent and combination therapy. In 1 study, NET patients who have undergone debulking by surgery and hepatic artery embolization were randomly assigned to octreotide or octreotide plus IFN. A significant improvement in time to progression was observed in the IFN arm (hazard ratio, 0.28; 95% confidence interval, 0.16–0.45).[100] In a second random assignment trial, patients were treated with lanreotide, IFN, or lanreotide plus IFN. Objective response rates were 4%, 4%, and 7%, respectively.[101] Although there is no defined standard therapy for NET patients with progressive disease, somatostatin analog plus IFN can be considered as an accepted option.

Chemotherapy

For metastatic well-differentiated NETs as a group, multiple cytotoxic drugs have been tried in various combinations; however, randomized trials have revealed only minor activity. As a result, there is no standard regimen, and the role of chemotherapy for advanced well-differentiated NETs, in general, continues to be debated. However, patients with foregut NETs such as those originating from the lung and thymus may derive some benefit from cytotoxic chemotherapy. Results from a published phase 2 study suggest antitumor activity with single-agent temozolomide for well-differentiated NETs, particularly those with foregut NETs.[102] Patients with metastatic or inoperable advanced NETs included 13 bronchial NETs (10 typical and 3 atypical); all received oral temozolomide for 5 consecutive days every 28 days.[102] Four (31%) had a partial response, whereas 4 others (31%) had stable disease.

The limited efficacy of chemotherapy has prompted investigation of novel therapeutic approaches for patients with advanced NETs. These include targeted radiotherapy (eg, therapeutic ^{131}I-MIBG, lutetium Lu 177 octreotate), inhibitors of angiogenesis (eg, bevacizumab), small molecule tyrosine kinase inhibitors (eg, sunitinib), and mammalian target of rapamyacin small molecule inhibitor (eg, everolimus). These novel treatments, although demonstrating promising efficacy in clinical studies, are still considered investigational therapy and are currently only available to patients on clinical trials.

Liver-Directed Therapy

The most frequent cause of death in patients with NETs is liver failure due to hepatic replacement by tumor. The goals of treatment include symptom control, biochemical control, objective tumor control, and improvement in quality of life.[103] Hepatic cytoreductive surgery can provide long-lasting benefit. Options include formal hepatic lobe resections, nonanatomic metastectomies, intraoperative radiofrequency ablation or cryoablation, or some combination thereof. In selected cases, liver transplant may

be an option for patients in whom extrahepatic disease has been controlled or eliminated.[103] Generally accepted criteria of candidacy for liver transplant include favorable histologic grade, low mitotic index, and adequate physiologic or nutritional status. Liver-directed cytoreduction can also be performed with minimally invasive, image-guided techniques. These include radiofrequency, cryoablation, and microwave ablation as well as laser-induced interstitial thermotherapy. Thermal ablative therapies can be used percutaneously, treating with CT, ultrasound, or MRI guidance. These therapies are typically reserved for patients with relatively small tumor burden. Both percutaneous heating and freezing probes have been successful in providing local tumor control and palliating symptoms.[104,105]

Many patients with NETs have extensive liver involvement and may require regional liver therapy. Regional arterial therapies are administered through angiographic catheters and can be delivered in a segmental, lobar, or whole liver distribution. These include bland embolization, chemoembolization, radioactive microsphere embolization, and percutaneous hepatic perfusion. Particle embolization with or without chemotherapy has long been the standard therapy for NET patients with extensive liver involvement.[106,107] Patients can frequently develop postembolization syndrome (fever, pain, nausea, and vomiting), requiring a short stay in the hospital.

Prospective randomized controlled comparison of hepatic artery embolization and chemoembolization is lacking. Therefore, the question of whether hepatic chemoembolization is better than hepatic bland embolization for patients with NETs remains unresolved. In recent years, radioactive microsphere embolization is emerging as a well-tolerated outpatient procedure, providing symptom relief and encouraging response rates.[108–111] Preliminary data with percutaneous hepatic perfusion using melphalan in patients with NETs are also encouraging.[112] Regional treatments have also been used to convert patients with unresectable to resectable disease; the frequency of conversion remains rare.

In general, these nonsurgical therapies are reserved for patients who have no surgical options. A multidisciplinary team approach to formulate individual therapy specific and optimal for each NET patient consisting of surgical and/or nonsurgical treatment is highly recommended. Often, hepatic tumor burden can be safely cytoreduced using a multispecialty approach involving experienced interventional radiologists, hepatobiliary surgeons, and medical oncologists. Even in the setting of unresectable disease, patients with NETs should be periodically assessed for disease status (stable or progressive disease) and surgical candidacy.

Role of Surgery in Advanced Disease

Patients with NET with limited metastatic disease for which the disease has been indolent should be considered for surgical resection, particularly if surgical intervention would result in the patient reaching a "no-evidence-of-disease" status. Surgical resection may result in symptomatic control as well as prolonged disease-free survival duration and potential cure. Retrospective analyses of cohorts of NET patients with surgical resection for limited hepatic metastasis suggest that approximately 20% of these patients can be cured (durable no-evidence-of-disease status) of the disease with appropriate surgical intervention. Surgical intervention should also be considered to palliate local symptoms.[113]

Conclusions and Future Looking Statements

The majority of bronchial and thymic NETs occur sporadically; however, 5% to 10% can be associated with the MEN1 hereditary syndrome. Although a definitive staging system for bronchial NETs has been formulated in 7th edition of the 2010 AJCC staging classification to provide more accurate prognosis, the rarity of thymic NETs has resulted in no similar staging classification. Nevertheless, the prognosis of NETs is mainly dependent on the tumor grade and on the extent of the disease (local vs locoregional vs distant). Patients with a well-differentiated NET that is localized have a better prognosis than those with a poorly differentiated NET with locoregional or distant metastases. Thymic NETs are often more aggressive than other NETs, associated with less favorable prognosis. After appropriate imaging with CT, MRI, and/or [^{111}In-DTPA0] octreotide scintigraphy (Octreoscan), complete resection including lymph node dissection, if appropriate, is the only curative approach. Therapeutic options for advanced or metastatic NETs of the thorax and thymus are mainly to palliate symptoms. Final treatment recommendations for patients with either bronchial or thymic NETs should be individualized and capitalized on the knowledge of the multidisciplinary team.

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