Neuroendocrine Tumors of the Lung

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KEYWORDS

• Neuroendocrine tumors • Carcinoid • Bronchoscopy • Sleeve lobectomy

KEY POINTS

- Pulmonary neuroendocrine tumors (NETs) are a group of rare tumors arising from neuroendocrine cells.
- Anatomic resection with nodal sampling and/or dissection is the mainstay in management of these patients.
- Grade I NET has an excellent prognosis with surgical resection.
- Patients with grade II NETs are significantly more likely to develop recurrent disease.
- Grade III NETs are aggressive lung cancers with poor prognosis.

DEFINITION

Neuroendocrine tumors (NETs) are a heterogeneous group of uncommon cancers that arise from specialized, peptide- and amine-producing cells dispersed throughout the diffuse endocrine system. They are broadly categorized into foregut (bronchial, gastric, duodenal, and pancreas), midgut (jejunal, ileal, appendiceal, and ascending/transverse colon), and hindgut (distal colon and rectum) tumors.

Because of their rarity, heterogeneity, and variable natural history, NETs remain a poorly understood disease. An SEER database analysis suggested that the incidence of some NETs (including lung) in the United States is steadily increasing, and currently 2000 to 4500 patients are diagnosed with a lung NET every year,[1] which amounts to 1% to 2% of all lung cancers. This is likely attributable to an improvement in diagnostic tools, including the dramatic diffusion of lung cancer screening programs worldwide. Moreover, because of the commonly indolent nature of this disease, the prevalence of individuals with NETs is also increasing and is currently greater than 170,000 for all-comers. This also applies to the lung subcategory, as median survivals for patients with localized or low-grade disease can be in excess of 15 years.

Lung NETs are the second most common site for NETs after the gastrointestinal (GI) system, accounting for 30.6% of all NETs.[2] Most of them are sporadic lesions with poorly understood risk factors; smoking does not seem to be a risk factor, in contrary to the more common bronchogenic counterparts. Hereditary NETs can be associated with familial syndromes, some of which include multiple endocrine neoplasia types 1 (MEN1) and 2 (MEN2), von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.

Some patients with lung NETs may have symptoms attributable to hormonal hypersecretion, and these tumors are considered to be "functional," whereas those without any associated hormonal symptoms are considered "nonfunctional" tumors. In contrast to the GI counterparts, serotonin hypersecretion and the classic "carcinoid syndrome" are not very common, even in metastatic disease. Functional tumors, however, can be associated with severe, prolonged flushing or adrenocorticotrophin hormone (ACTH) hypersecretion that can cause Cushing syndrome.[3] There is also a

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pathologic entity called diffuse intrapulmonary neuroendocrine cell hyperplasia (DIPNECH) that is considered a premalignant form of the disease and can be associated with chronic cough and episodic shortness of breath.

Most patients with lung NETs have proximal tumors and nonspecific presentation symptoms that can result in delayed diagnosis. These include shortness of breath, cough, and hemoptysis or recurrent pneumonia in the same lung segment. Timely diagnosis and appropriate management of primitive neuroectodermal tumors (PNETs) can be achieved using a multidisciplinary approach comprising specialized pathologists, endocrinologists, pulmonologists, and medical, radiation, and thoracic surgical oncologists.

CLASSIFICATION AND PATHOLOGY

According to the 2015 World Health Organization (WHO) classification of lung, NETs fall into 3 categories: low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), and high-grade (large-cell neuroendocrine and small-cell carcinoma) (Fig. 1). The higher grade counterparts usually denote a more aggressive disease and carry a worse prognosis.

Well-differentiated NETs of the lung are subcategorized into typical or atypical using histologic criteria. Typical carcinoid tumors have fewer than 2 mitoses/10 per high-power field (HPF) and lack any evidence of necrosis. Atypical carcinoid tumors have 2 to 10 mitoses/10 HPF with necrotic features or architectural disruption. High-grade, poorly differentiated NETs have greater than 10 mitoses/10 HPF and extensive foci of necrosis. NETs of the lung and bronchi follow the tumor-node-metastasis (TNM) staging system as for lung carcinomas. As in squamous and adenocarcinoma lung cancer, the prognosis becomes poorer with increasing stage at diagnosis.

IMAGING AND ADDITIONAL TESTING

Pulmonary NETs are traditionally divided into central and peripheral lesions based on their origin with respect to the bronchial tree. Patients with DIPNECH will complain of chronic cough spanning multiple years in the setting of negative standard chest radiographs. Most patients with peripheral tumors will be diagnosed incidentally on imaging

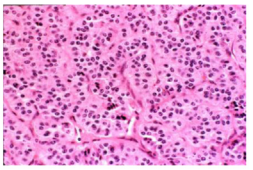
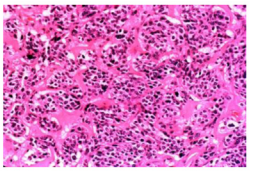
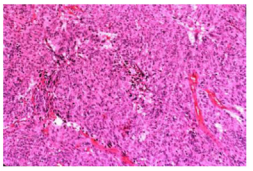
	Histology	Cytology
Grade I (Typical) 	Nested growth pattern Absent mitoses	Monomorphic Eosinophilic cytoplasm
Grade II (Atypical) 	Presence of necrosis Loss of nested growth Mitotic activity (> 5/ 10 HPF)	Pleomorphic Variation in nuclear size
Grade III (Large cell) 	Extensive necrosis Mitotic activity (> 10/ 10 HPF)	Hyperchromatic nuclei Large cell (4-6 X lymphocyte) Small cell (1-3 X lymphocyte)

Fig. 1. Pulmonary NETs grading system.

performed for other reasons. However, patients with central tumors can be symptomatic and will complain of obstructive respiratory symptoms such as recurrent chest infections, cough, hemoptysis, chest pain, dyspnea, and wheezing. Patients who present with symptoms suspicious of lung NETs should be discussed within a multidisciplinary tumor board and undergo evaluation with both biochemical testing as well as imaging studies to assess disease burden.

BIOCHEMICAL TESTING

Those who have clinical symptoms that suggest hormonal hyper secretion such as Cushing or flushing/diarrhea should undergo testing for serum cortisol, ACTH, serum serotonin levels, or urine 5-hydroxyindoleacetic acid as indicated. Patients presenting with Cushing syndrome must undergo a complete evaluation and workup with input from endocrinology,[4] as some of the diagnostic tests for ectopic ACTH secretion might be inconclusive. Screening for hormone hypersecretion in asymptomatic individuals is not routinely recommended; however, obtaining a baseline serum chromogranin-A is sometimes recommended in nonfunctioning tumors and can be followed during treatment if abnormal.[5]

DIAGNOSTIC IMAGING

Computed Tomography of the Chest

The most commonly used imaging modality for diagnosis of lung NETs is multiphase contrast-enhanced computed tomography (CT) of the chest. These tumors frequently seem as a smooth, rounded, homogenous nodule or mass within the lung parenchyma or in an endobronchial location with an associated postobstructive process (**Fig. 2**A, B). NETs of the lung are characterized by good blood flow that leads to higher uptake of contrast medium; this allows a differentiation of benign round nodules, which mostly show only a low-contrast medium uptake.

For DIPNECH, high-resolution CT with an expiration study shows mosaic attenuation or air trapping along with multiple nodules due to multiple tumorlets and carcinoid tumors.

PET-Computed Tomography

Most patients with a lung lesion will at some point undergo a PET with fludeoxyglucose F 18 (FDG-PET) as part of their evaluation. Bronchial NETs can present as either central lesions (suggesting lung adenocarcinoma) or peripheral solitary nodules on chest imaging and are included in a wide range of differentials such as lung carcinoma, hamartoma, inflammatory, or infectious lesions. FDG-PET-CT, however, is unreliable for diagnosis of low-grade tumors such as DIPNECH, tumorlets, and typical carcinoid due to their low metabolic activity and FDG uptake. Most of the slow-growing tumors do not take up FDG and thus seem “cold” on imaging. Conversely, aggressive varieties such as large and small cell lung cancer will demonstrate significant FDG uptake.

About 80% of low-grade and 60% of intermediate-grade lung NETs express somatostatin receptors on their surfaces, making them eligible for functional imaging using somatostatin analogues. These imagings include radiolabeled octreotide imaging (a relatively older modality), as well as the newer somatostatin receptor PET/CT scans.

The current Food and Drug Administration–approved tracers are 68-Gallium dotatate and 68-Ga dotatoc. Somatostatin receptor PET can provide useful information on overall tumor burden, as well as confirm the presence of somatostatin receptors, which can have therapeutic implications (somatostatin receptor positive disease carries usually a better prognosis and can be associated with response to somatostatin analogue treatments). A meta-analysis of 22 studies determined that 68-Ga dotatate had a

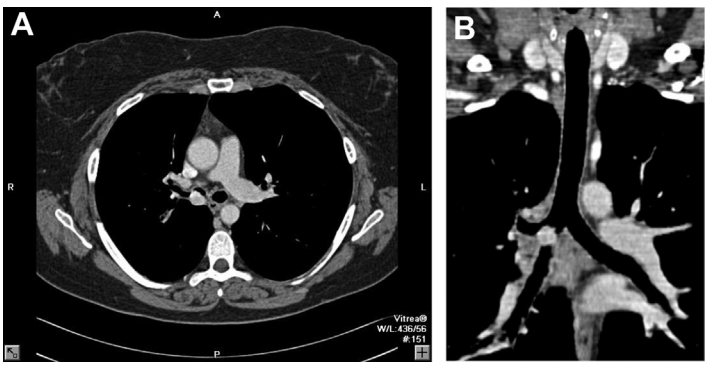


Fig. 2. CT imaging. CT chest showing a solitary well-defined, round, homogeneous mass in the right main stem bronchus (*A*) seen extending to the BI in sagittal views (*B*).

pooled sensitivity and specificity of 91% and 94%, respectively, for the initial diagnosis of NETs.[6] There are limited data on whether long-acting somatostatin receptor inhibition in the therapeutic setting can interfere with 68-Ga Dotatate PET/CT scans, one study showed that timing did not make a difference.[7] 68-Ga dotatate PET/CT or PET/MRI is currently preferred over radiolabeled octreotide scanning, as it is more sensitive than SSR scintigraphy for determining somatostatin receptor status.

Luminal Imaging

Imaging is no substitute for tissue sampling in the setting of lung NETs and flexible bronchoscopy, and biopsy is the most important diagnostic test for central lesions. On bronchoscopy, these tumors are pathognomonically characterized by a strongly vascularized mass covered by bronchial epithelium (**Fig. 3**). They are mostly broad-based and grow intraluminally as well as extraluminally—the so-called iceberg phenomenon. For more peripheral lesions, navigational bronchoscopy or percutaneous techniques may be used to establish diagnosis. In spite of vascularization, serious problems with hemorrhage are rare during the biopsy procedure (<1%). In the event of hemorrhage, endobronchial interventions such as cryotherapy, injection of dilute epinephrine, or occasionally, use of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser can be helpful with hemostasis.

Endobronchial ultrasound-guided transbronchial needle aspiration (EPBUS-TBNA) or mediastinoscopy is also recommended for the purpose of staging according to the TNM classification for lung cancer. EBUS-TBNA is unlikely to differentiate typical from atypical carcinoids, and hence its utility is primarily in detection of nodal involvement.

Echocardiography

Carcinoid heart disease is a feared complication of almost half of the patients with long-standing carcinoid syndrome and can be particularly debilitating in its later stages. Affected patients have pathognomonic plaquelike deposits of fibrous tissue on cardiac valves, leaflets, and papillary muscles. Most commonly affected areas are the tricuspid and pulmonic valve leading to right-sided heart failure. For those diagnosed with bronchial carcinoid, echocardiography and evaluation of left- and right-sided heart valves is recommended to assess the presence of carcinoid heart disease; this is particularly important as part of preoperative evaluation.

Therapeutic Options and Treatment Guidelines

Management of lung NETs depends on tumor size, stage, and the general condition of the patient. As a general rule, patients with asymptomatic, nonfunctional, slow-growing disease have the option of observation, whereas all others should consider surgery or systemic treatments. Unfortunately, most approaches are based on low-quality data and medium-strength evidence with the exception of small cell lung cancer (SCLC). Current consensus supports surgical resection as the primary treatment of choice and the only curative option for localized, resectable disease.

For patients with locoregional or metastatic, unresectable disease and symptoms of hormone hyper secretion, symptom control with somatostatin analogues such as octreotide or lanreotide is of paramount importance. Somatostatin analogues are also suggested perioperatively in surgical patients in whom there is concern for hormone hypersecretion from tumor manipulation during resection, also known as carcinoid crisis.

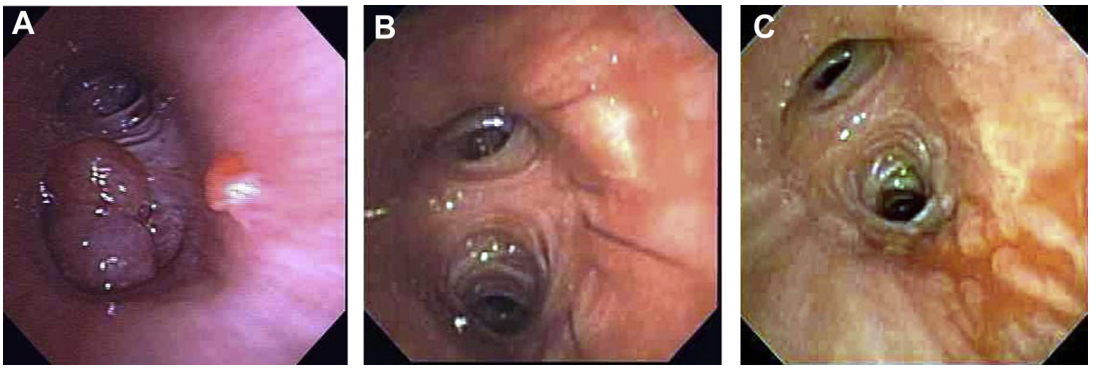


Fig. 3. Bronchoscopic features. Bronchoscopy images showing round, smooth mass covered by bronchial epithelium in the left upper lobe orifice highly suspicious for typical carcinoid (*A*). Postoperative bronchoscopy after left upper lobe sleeve resection (*B*) and subsequent bronchoscopy months later showing completely healed anastomotic sites (*C*).

Surgery for localized disease

For patients with peripheral lung tumors, the surgical extent of choice is complete anatomic resection (lobectomy and segmentectomy) with hilar/mediastinal lymph node dissection or sampling. The most important objective is a microscopically tumor-free resection margin (R0), which is associated with a good prognosis and best outcomes. Small (<2 cm), peripheral typical carcinoid tumors with clinically negative lymph nodes can be successfully treated with sublobar resection with frozen section confirmation of negative margins. There are multiple retrospective database studies comparing the survival difference between wedge resections and segmentectomies for stage I typical carcinoids. Although some report a survival advantage with anatomic resections,[8] others have shown no difference in cancer-specific or disease-free survival with wedge resections for stage I typical carcinoids.[9,10] A randomized clinical trial is the only tool capable of providing an accurate answer, but it is difficult to conduct such a study for a rare disease as this.

For larger or central typical carcinoids, atypical carcinoids, or tumors with clinically positive lymph nodes, lobar resection is preferred along with lymph node assessment. An important tenet of surgical treatment of lung NETs is the sparing of normal lung parenchyma especially due to the low malignant and recurrence potential. Where possible, bronchial sleeve resection or a sleeve lobectomy should be carried out in preference to pneumonectomy (ideally with intraoperative frozen section of the resection margins).[11] Achieving a negative margin should suffice from an oncologic standpoint, and there is no current consensus on a specific distance or margin associated with improved long-term outcomes.[12]

There is little evidence to guide on surgical resection as part of management of recurrent locoregional disease or isolated distant metastatic disease.[13] Surgery is considered in selected patients with adequate performance status, with limited disease and curative intent after a multidisciplinary discussion.

Where possible, surgical resection of liver metastases can be considered with curative intent, to aid symptom control or for debulking when greater than 90% of tumor can be removed. Complete resection of liver metastases can increase 5-year overall survival rates to greater than 70%.[14]

Endobronchial

Inoperable tumors requiring palliative treatment can be resected bronchoscopically, in order to alleviate symptoms such as retention pneumonia. Even in case of the rare endobronchial growth without expansion through the cartilage, bronchoscopic resection should not be undertaken due to the increased risk of local recurrence. Endobronchial resection should hence only be reserved for patients unable to tolerate formal surgical resection.

Cryotherapy is a safe and effective adjunct to endobronchial resection to decrease local recurrence rates with lower risks of bronchial stenosis.[15] Laser bronchoscopy is another option that can also be used along with other therapies and offers the advantages of being rapid, immediately effective, and repeatable.[16]

Endobronchial resection can also be used as a potential bridge to surgery in cases of central PNETs presenting with postobstructive pneumonitis and destroyed lung parenchyma. An initial local endobronchial resection can be performed to open the airway and enable drainage before reassessment for lung parenchymal-sparing surgery.

On occasion, small carcinoid tumorlets (<5 mm) are observed on bronchoscopy or cross-sectional imaging. In this case, a diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) can be made. This condition is thought to be generally indolent, and such tumorlets should not be routinely resected. These patients can be observed with chest CT scans every 12 to 24 months or as clinically indicated. The use of somatostatin analogues for symptom control is debatable and currently investigated.

Locoregional therapy

Current National Comprehensive Cancer Network (NCCN) guidelines recommend use of stereotactic body radiation therapy as an option for patients who are not medically fit for surgery, and thermal ablation can be recommended in cases where both surgery and radiation therapy are contraindicated.[17]

Adjuvant radiation is recommended in atypical and high-grade carcinoids with mediastinal N2 or greater disease[18] but the survival benefit has not been established in a high-quality randomized study. For patients with localized unresectable disease, definitive radiation can be offered, with chemotherapy, but the optimal dose and sequence is yet unclear. Common practice has been modeled after the regimens used in similar settings for either non–small-cell or small-cell cancers.

For metastatic lung NETs, palliative radiation is considered for symptomatic lesions. Radiofrequency ablation can be considered in cases of liver, lung, or bone metastasis.

Systemic therapy

Metastatic or unresectable disease is generally considered incurable, thus management is

palliative and requires a multidisciplinary evaluation. The treatment goals are to both control hormone-related symptoms (if any) as well as prevent tumor growth. Systemic therapy options depend on the histology and functional status of the tumor and include somatostatin analogues, mTOR inhibitors (everolimus), peptide receptor radionuclide therapy, and chemotherapy. As in every rare tumor, participation in clinical trials is highly encouraged.

As in the GI counterparts, somatostatin analogues such as octreotide or lanreotide have the potential to control the carcinoid syndrome and inhibit tumor growth; cytoreduction is less common. The NCCN guidelines recommend initiation of somatostatin analogues for advanced low- and intermediate-grade and all functional tumors. Additional options include initiation of everolimus based on results of phase III RADIANT-4 study, which included about 30% lung NETs and showed a 52% reduction in the estimated risk of progression or death.[19] Other oral pathway inhibitors are currently being studied in large clinical trials.

Chemotherapy has been generally somewhat effective in high-grade tumors with a good amount of randomized data in the SCLC pathology. Much less is known for atypical carcinoids and large-cell lung neuroendocrine neoplasms. Regimens are borrowed from the SCLC literature and include cisplatin with etoposide, carboplatin with etoposide, or temozolomide. Its role in the adjuvant treatment of resected, high-grade tumors is debatable and currently studied. Some small studies have shown a 19% to 22% response rate in patients with atypical NETs treated with chemotherapeutic agents.[20,21]

Immunotherapy with checkpoint inhibitors such as nivolumab, pembrolizumab, or CTL4 inhibitors such as ipilimumab has shown positive results in high-grade tumors such as SCLC but its efficacy is limited in well-differentiated, slow-growing histologies (consistent with the experience in GI NETs).

As previously mentioned, lung NETs can express somatostatin receptors on their surface, and this has led to a growing interest in the use of peptide receptor radionuclide therapy (PRRT) with (177)Lu-DOTATATE. PRRT attaches radiolabeled ligands to somatostatin analogues to deliver a radiation dose to somatostatin receptor positive tumors and has been particularly successful in GI NETs.[22] Several studies[23–26] have reported the use of PRRT as a potential therapeutic option in advanced lung NETs. Overall response rates ranged from 13% to 30%, whereas progression-free survival ranged from 19 to 28 months and overall survival ranged from 32 to 59 months. Data are mostly retrospective and of average quality, but large studies are being planned to effectively answer that question.

In general, results with systemic therapy have been largely disappointing, and survival data have to be interpreted with caution due to the small numbers of patients and data from retrospective single-institutional series, with several limitations. As such, benefits of systemic therapy are at best, modest, with no clear benefits in overall survival.

Prognosis and Follow-Up

The prognosis of PNETs is significantly associated with the degree of differentiation and lymph node metastases. Long-term results from numerous surgical series suggest that the histologic subtype of a bronchial carcinoid is the most important prognostic factor. Tumor-node-metastasis (TNM) stage seems less critical.

After complete resection, typical carcinoids have the best prognosis, with a 10-year survival rate of more than 80%. The 5-year survival rate in atypical carcinoid without lymph node metastases is 80% and with lymph node metastases is 60%.

Because recurrences and distant metastases can develop years after resection of the primary tumor, prolonged follow-up care is indicated. For patients with typical carcinoid, conventional CT can be performed at 3 and 6 months and then annually. For atypical carcinoids, closer monitoring is recommended: first at 3 and 6 months and then at 6-month intervals. After 10 years, surveillance should be considered as clinically indicated. Chromogranin-A levels can be used as a tumor marker and elevated levels, although not diagnostic, can be associated with recurrence.[27,28] Their use is not encouraged after curative resection, and the levels can be affected by certain medications, making the interpretation difficult.

CLINICS CARE POINTS

Pearls:

- Pulmonary NETs are the second most common NETs after the GI system.
- Most patients are asymptomatic; however, some patients can have symptoms related to hormone overproduction (most commonly Cushing syndrome) and should be worked up accordingly.
- CT chest is the most commonly used imaging modality; however, bronchoscopy and biopsy are pertinent to diagnosing and classifying pulmonary NET.

- Small (<2 cm), peripheral typical carcinoid tumors with clinically negative lymph nodes can be successfully treated with sublobar resection with frozen section confirmation of negative margins.
- For larger or central typical carcinoids, atypical carcinoids, or tumors with clinically positive lymph nodes, lobar resection is preferred along with lymph node dissection. R0 resection is key.

Pitfalls:

- Despite the vascularity, chances of hemorrhage with biopsy of these tumors is less than 1%. Any bleeding can be controlled by endoscopic interventions such as cryotherapy, epinephrine, or Nd:YAG laser.
- Carcinoid heart disease is a feared complication in patients with long-standing carcinoid syndrome related to NETs, and preoperative ECHO of the heart is important to assess the valves.
- Even in a case of endobronchial growth without expansion through the cartilage, bronchoscopic resection should not be undertaken due to the increased risk of local recurrence. Endobronchial resection should only be reserved for symptomatic patients unable to tolerate formal surgical resection.
- Results with use of systemic therapy for pulmonary NETs have been largely disappointing in terms of overall survival.

DISCLOSURE

The authors have nothing to disclose.

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