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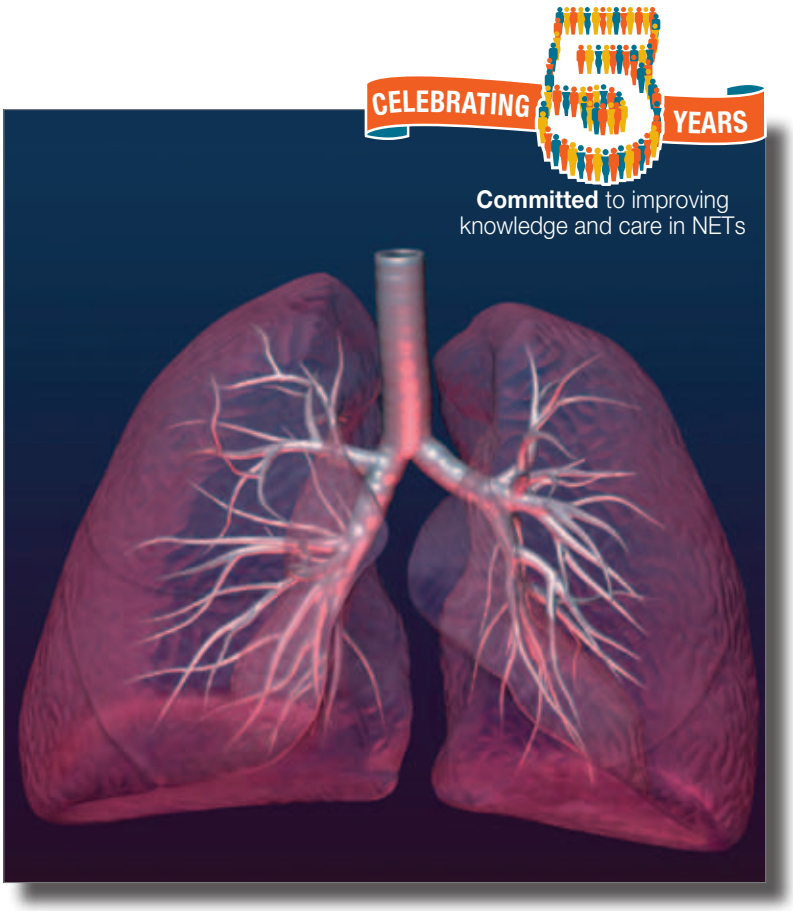

Bronchial Neuroendocrine Tumors

The disease and its management

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Overview of neuroendocrine tumors of the lungs and thymus

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that originate from neuroendocrine cells found throughout the body.[1,2] They arise in many different body sites and display diverse clinical, histologic, and genetic characteristics.[3]

The tracheobronchopulmonary complex is the most frequent extradigestive site for NETs.[4] Although the majority (>60%) of NETs originate in the gastrointestinal system, about 25% originate in the pulmonary system.[5] NETs of the thorax include both bronchial and thymic NETs.[3] Characteristics of these NETs are presented in Table 3.

Technically considered to be neuroendocrine neoplasms, small cell lung carcinoma (SCLC) and large cell lung carcinoma (LCLC) are generally highly aggressive malignancies and are approached using a different treatment paradigm.[5] This monograph will focus primarily on the diagnosis and treatment of well-differentiated (G1 and G2) bronchial NETs (also known as typical and atypical carcinoid tumors).[3] Although less aggressive than SCLC and LCLC, G1 and G2 bronchial NETs have a poor prognosis if they metastasize. According to long-term Surveillance, Epidemiology, and End Results (SEER) data,* 73% of patients diagnosed with well-differentiated (G1 and G2) bronchial NETs with distant metastases die within 5 years.[1]

*Patients diagnosed from 1988 to 2004.

A word about neuroendocrine nomenclature

This brochure uses the nomenclature established in the 2010 *WHO Classification of Tumours of the Digestive System*[6] to classify different types of neuroendocrine neoplasms.

The WHO naming convention categorizes these neoplasms into 2 groups:

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

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

Classification of G1/G2 bronchial NETs

There are a number of different systems for the classification of bronchial NETs.[3] Although most of these systems have proved helpful in stratifying patients into relevant prognostic subgroups, differences in the terminology and criteria have caused confusion.[3] To address these differences, a multidisciplinary group of specialists in the field of NETs recently recommended a "minimum pathology data set" that would capture the raw information on which staging and grading could be based (eg, extent of spread to adjacent tissues and proliferative rate).[3,7] One of the consensus recommendations was that the staging and grading systems used (examples of which are shown in Tables 1 and 2) should be clearly indicated on the pathology report.[7]

Stage

Differences in the many classification systems notwithstanding, the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC) recommend that G1/G2 bronchial NETs be staged using the tumor-node-metastasis (TNM) staging system.[8,9]

Table 1. WHO Staging System for Lung Cancer, Including G1/G2 Bronchial Neuroendocrine Tumors[8]

T-Primary Tumor	
TX	Primary tumor cannot be assessed, or tumor 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
Tis	Carcinoma in situ
T1	Tumor 3 cm or less 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)*
T2	Tumor with any of the following features of size or extent: • More than 3 cm in greatest dimension • Involves main bronchus, 2 cm or more distal to the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor nodule(s) in the same lobe; tumor with malignant pleural effusion†
N-Regional Lymph Nodes‡	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
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)
M-Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis, includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

Stage Grouping			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

† Most pleural effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, or T3.

‡ The regional lymph nodes are the intrathoracic, scalene, and supraclavicular nodes.

Adapted from *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. IARC, Lyon, 2004.

Grade

Bronchial NETs should also be classified by grade, a fundamental predictor of outcome.[3] The grading system proposed for all thoracic NETs by the WHO and the IASLC uses either mitotic rate or the presence and extent of necrosis.[3] Although clinical data exist to validate this grading system, some authors propose further assessment of the mitotic count to provide additional separation among the 3 grades. Therefore, experts agree that the actual proliferative rate should be specified in the pathology report, along with the grade and the grading system used.[3,7]

Table 2. Grading Systems for Neuroendocrine Neoplasms of the Lung and Thymus[3]

Grade	WHO/IASLC	Moran et al[10]
Low (G1)	<2 mitoses/10 HPF, AND no necrosis	≤3 mitoses/10 HPF, AND no necrosis
Intermediate (G2)	2-10 mitoses/10 HPF, OR foci of necrosis	4-10 mitoses/10 HPF, OR foci of necrosis
High (G3)	>10 mitoses/10 HPF	>10 mitoses/10 HPF

HPF, high-power field.
Adapted from Phan A et al. *Pancreas*. 2010;39(6):784-798.

Characteristics and epidemiology of bronchial NETs

Bronchial NETs are a distinct subset of NETs that share common anatomic primary sites but represent a spectrum of different histologic diagnoses, clinical behaviors, and natural histories.[3,8] Bronchial NETs comprise approximately 2% of primary lung neoplasms.[11]

G1 (also known as typical) bronchial NETs are classified as low-grade, well-differentiated pulmonary neuroendocrine neoplasms, and usually present in the fifth decade of life. They are most often central in location, causing symptoms of cough, wheezing, hemoptysis, and recurrent postobstructive pneumonia. G1 bronchial NETs are only rarely associated with the classic carcinoid syndrome; they have, however, been associated with ectopic adrenocorticotropic hormone (ACTH) secretion, resulting in Cushing syndrome.[11]

NETs of the thorax include thymic NETs

Thymic NETs are uncommon neoplasms and account for 2% of all mediastinal neoplasms.[3] Patients can remain asymptomatic even as their disease progresses[12]; therefore, thymic NETs are typically diagnosed late, and advanced disease is often discovered at presentation.[3] In some cases, patients with thymic NETs may present with Cushing syndrome due to ectopic production of ACTH. Thymic NETs are often more aggressive than other NETs and are associated with a less favorable prognosis compared with other NETs.[3]

The incidence is only 0.02 per 100,000 individuals.[1] Thymic NETs are usually sporadic. However, they can also occur in approximately 5% to 10% of patients with multiple endocrine neoplasia 1 (MEN-1).[3]

Table 3. Characteristics of Bronchial and Thymic Neuroendocrine Neoplasms

Differentiation[13]	Grade[13]	Mitotic count[6]	Traditional[6]	Current classification systems (ENETS, WHO)[13]
Well differentiated NETs	Low grade (G1)	<2/10 HPF	Typical carcinoid tumor	NET grade 1
	Intermediate grade (G2)	2-10/10 HPF	Atypical carcinoid tumor	NET grade 2
Poorly differentiated neuroendocrine carcinomas	High grade (G3)	>10/10 HPF	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
			Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell

ENETS, European Neuroendocrine Tumor Society.

Approximately one-third of bronchial NETs demonstrate atypical histologic features. Atypical, or G2, bronchial NETs are characterized by the presence of frequent mitoses or areas of necrosis. They tend to occur in older individuals, most commonly in the sixth decade of life and, unlike G1 NETs, are more common in smokers. They also tend to be larger in size than G1 bronchial NETs and are more commonly peripheral in location.[11]

Long-term SEER data of patients diagnosed from 1988 to 2004 in the United States demonstrate that prognosis can be poor: Overall 5-year survival is 27% in patients with well-differentiated G1/G2 bronchial NETs with distant metastases.[1]

G1 bronchial NETs are generally less aggressive, with metastases reported in less than 15% of cases. G2 bronchial NETs pursue a more aggressive clinical course, metastasizing to mediastinal lymph nodes in 30% to 50% of cases.[11]

After surgical resection, 5-year survival rates for patients with G1 bronchial NETs generally exceed 85%; however, even with resection, the 5-year survival rate for G2 bronchial NETs is only 44% to 71%.[11]

Histology also influences the choice of surgical procedure. Conservative resection, consisting of wedge or segmental resection, is currently the preferred form of treatment for localized bronchial NETs, whereas more aggressive procedures are often chosen for atypical (G2) bronchial NETs.[11]

Prognosis of G1/G2 bronchial NETs

The prognosis for patients with bronchial NETs is highly dependent on neoplasm histology and stage. Overall survival rates for G1 bronchial NETs are better than for G2 bronchial NETs.[11,14] Even with resection, the 5-year survival rates for patients with G2 bronchial NETs range from 31% to 75%.[11]

However, for both G1 and G2 bronchial NETs, prognosis is poor once distant metastases are present, with only a 27% survival rate (Table 4), comparable to pancreatic NETs.[1]

Table 4. Long-Term SEER Data (1988 to 2004) Showing Disease Stage at Diagnosis and Survival by Disease Stage in Patients With Well-Differentiated Bronchial NETs[1]

Bronchial primary tumor site	Disease stage at diagnosis	Median survival duration	5-yr survival rate
Localized disease	49%	NR	84%
Regional disease	23%	151 months	72%
Distant metastases	28%	17 months	27%

Adapted from Yao JC et al. *J Clin Oncol.* 2008;26(18):3063-3072.

Histopathologic prognostic factors

Negative predictors of prognosis in G2 bronchial NETs include size greater than 3.5 cm, mitotic rate, pleomorphism, and aerogenous spread. Favorable prognostic factors include palisading, papillary formation, and pseudoglandular patterns.[14]

Lymph node involvement

When systemic lymph node resection is performed routinely, lymphatic involvement can be found in 5% to 10% of patients with well-differentiated bronchial NETs.[15] Lymph node metastases are identified in more than 30% of patients with grade 2 NETs.[11]

Presentation and evaluation of G1/G2 bronchial NETs

Patients with G1/G2 bronchial NETs often present with nonspecific signs and symptoms, including coughing and wheezing, not unlike symptoms of asthma.[11] These symptoms prompt initial suspicion of asthma, which contributes to a delayed diagnosis.[3] Other symptoms include dyspnea, hemoptysis, obstructive pneumonia, pleuritic pain, and atelectasis. However, many patients with G1/G2 bronchial NETs are asymptomatic.[5]

Most G1/G2 bronchial NETs develop in the major bronchi (mainstem and lobar bronchi); the remainder develop in the peripheral lung (segmental bronchi or beyond).[16] G1 bronchial NETs are often centrally located, whereas G2 bronchial NETs are more commonly found peripherally in the lungs.[17]

Syndromes

G1/G2 bronchial NETs are the most common cause of Cushing syndrome, due to the ectopic production of ACTH. Symptoms of Cushing syndrome are seen in 1% to 2% of patients with bronchial NETs and can be the initial reason for seeking medical attention.[16] Acromegaly from the ectopic production of growth hormone-releasing hormone (GHRH) is a rare manifestation of bronchial NETs; however, bronchial NETs are the most common cause of extrapituitary GHRH secretion.[16] Carcinoid syndrome is rare but may occur in the presence of metastatic disease.[14]

Biomarkers

Circulating tumor biomarkers, along with imaging and pathology, may be helpful in monitoring bronchial NETs. An important biomarker is chromogranin A (CgA). CgA is a useful circulating marker, elevated in the blood levels of up to 90% of patients with NETs.[18,19] CgA levels have prognostic significance and may be used to help monitor disease progression. CgA levels have also been correlated with tumor burden and reduced survival,[20,21] and CgA concentration may reflect the degree of tumor differentiation.[23]

Other conditions (eg, chronic atrophic gastritis, renal or hepatic failure, and arterial hypertension) and proton pump inhibitor therapy can increase CgA levels and potentially cause a false-positive result.[22] Therefore, an isolated CgA elevation is not sufficient for diagnosis of a G1/G2 bronchial NET; tissue confirmation is required.[3]

For diagnostic accuracy and ongoing disease management, biomarker results should be confirmed with imaging studies and biopsy, when appropriate.[3]

Imaging and pathology

Patients suspected of having a bronchial NET, based on clinical symptoms, should undergo imaging to confirm the diagnosis. Imaging studies are generally performed at the initial evaluation to determine the extent of disease, and at follow-up, to evaluate disease status.[3]

Conventional chest x-ray may lead to a diagnosis, but computed tomography (CT) and bronchoscopy are the best procedures to detect an abnormal mass in the chest.[24]

In bronchial NETs

- CT and magnetic resonance imaging (MRI) have a much higher sensitivity in visualizing bronchial NETs than ultrasonography.[25] CT images of the chest are shown in Figures 1 and 2
- Octreoscan™ (octreotide scintigraphy) may also be considered, for initial evaluation[3]
- Endoscopic ultrasound (EUS) with biopsies are useful in detecting both the primary tumor and mediastinal lymph node metastases[24]

Follow-up imaging studies are performed for surveillance after complete resection or for evaluation of treatment response. Potentially useful follow-up imaging modalities include CT and MRI.[3]

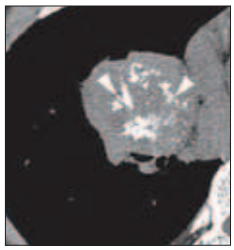
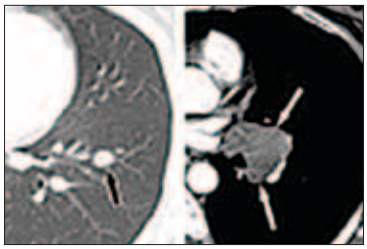


Figure 1. Bronchial NET in a 25-year-old man. Axial thin-section (1.0-mm section thickness) CT scan of the right middle lobe shows the large (60-mm diameter) mass with punctate calcifications (arrowheads).

Reprinted with permission from Chong S et al. *Radiographics*. 2006;26(1):41-57.[26]



(a) (b)

Figure 2. Bronchial NET in a 42-year-old woman. **(a)** Axial CT scan (5.0-mm section thickness) obtained at the level of the basal segmental bronchi shows a small (10-mm diameter), well-defined nodule (arrow) in the left lower lobe. **(b)** CT scan (mediastinal window) obtained at the level of the left basal trunk shows enlarged left hilar lymph nodes (arrows).

Reprinted with permission from Chong S et al. *Radiographics*. 2006;26(1):41-57.[26]

Pathology is essential for assessment of the histologic grade of bronchial NETs. Tissue sampling is most commonly obtained at the time of surgical resection for patients with localized, resectable disease. In patients with metastatic disease, tissue diagnosis is usually obtained with a biopsy during bronchoscopy or fine-needle aspiration.[5,14,27] However, the small cytology samples obtained with bronchoscopy or fine-needle aspiration may make it difficult to differentiate G1 (Figure 3) and G2 (Figure 4) bronchial NETs; repeat sampling with a core biopsy or other assessment may be required.[5,14]

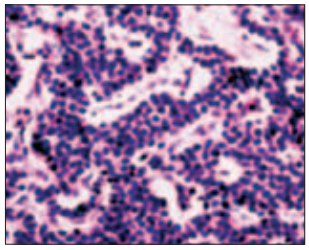


Figure 3. Photomicrograph of a G1 bronchial NET. Note the endocrine growth pattern (nests, trabeculae), uniformity of cells, and lack of necrosis.

Reprinted with permission from Gustafsson BI et al. *Cancer*. 2008;113(1):5-21. © Copyright John Wiley & Sons, Inc.[17]

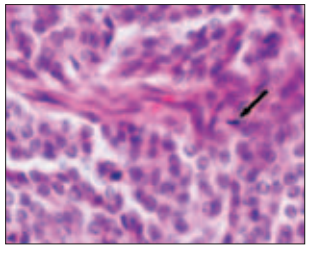


Figure 4. Photomicrograph of a G2 bronchial NET. Note the nuclear pleomorphism and mitosis (arrow).

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Management of G1/G2 bronchial NETs

Management of G1/G2 bronchial NETs is dependent primarily on tumor stage and grade. Patients with early-stage disease should generally undergo surgical resection with curative intent.[3] No adjuvant therapy is recommended for well-differentiated neoplasms.[3] Management of locoregional disease is focused on obtaining a cure, and treatment of advanced or metastatic disease is focused on palliation.[3] Treatment modalities by stage are shown in Table 5.

Patients usually benefit from the care of a multidisciplinary team, which may include an oncologist, interventional radiologist, surgeon, pathologist, and other specialists as needed.[3]

Table 5. G1/G2 Bronchial NETs Management by Stage

Locoregional disease	Advanced disease
Surgery Surgery is the primary treatment option for G1/G2 bronchial NETs[24]	**Surgery** Surgical resection may be considered in selected patients with isolated hepatic metastases.[3] Debulking surgery is an option with multiple liver metastases[25]
Adjuvant therapy At this time, there are no data to recommend adjuvant radiation, chemotherapy, or chemoradiation after complete resection of locoregional disease in patients with well-differentiated neoplasms[3]	**Systemic therapy** Currently, there are no standard systemic therapies for patients with advanced bronchial NETs.[3]
Related syndromes Palliative resections should be considered[24]	**Related syndromes** Cushing syndrome, acromegaly, and carcinoid syndrome may be caused by G1/G2 bronchial NETs.[3] Patients with carcinoid syndrome are at potential risk for developing carcinoid crisis during bronchoscopy or other non–NET-related procedures[3]
Radiation therapy (external radiotherapy) Consider after nonradical surgery in G2 bronchial NETs[24]	**Radiation therapy (external radiotherapy)** Consider in metastatic disease in both G1 and G2 bronchial NETs[24]
NA	**Liver-directed therapy** Liver-directed therapy may be used as a palliative technique in patients with hepatic-predominant disease[25]

Surgery

In patients with locoregional disease, the best chance for a cure lies with the initial surgery.[3] Data show that long-term survival in patients undergoing surgery for well-differentiated tumors is as high as 80% to 90%,[11] suggesting the vast majority of patients present with early-stage disease and are cured with surgery. Surgical resection of the primary tumor, together with metastases, can be considered in patients with more advanced disease if all gross disease can be reasonably resected.[3]

Related syndromes

In patients with locoregional G1/G2 bronchial NETs, Cushing syndrome, acromegaly, and carcinoid syndrome may be encountered.[3] Although rare in patients with bronchial NETs, carcinoid syndrome places patients at potential risk for developing carcinoid crisis during bronchoscopy or other non–NET-related procedures.[3]

Chemotherapy and other systemic agents

In the management of NETs, the role of chemotherapy and other systemic agents is evolving. Some medical therapies may be appropriate for certain patients, depending on the type of NET and treatment goals. Entering patients into clinical trials, when feasible, should be considered.[28]

Liver-directed therapy

The most common sites of metastases in patients with bronchial NETs are the regional/mesenteric and mediastinal lymph nodes; metastases to bone may also develop.[24] In patients with hepatic-limited or hepatic-predominant disease, liver-directed therapies may be considered. Such approaches may include debulking surgery, radiofrequency ablation, cryoablation, laser therapy, radiologic (chemo) embolization, or combinations of these.[25] Liver transplantation may be considered in young patients in whom all extrahepatic neoplasms and metastases have been removed and follow-up does not visualize recurrence of extrahepatic neoplasms. Hundreds of transplantations have been performed worldwide; however, practically all patients have developed recurrence within months to years later.[25]

Follow-up after complete curative resection of G1/G2 bronchial NETs

General follow-up recommendations include a reassessment once between 3 and 6 months after complete curative resection, then every 6 to 12 months for at least 7 years thereafter.[3]

Conclusion

G1/G2 bronchial NETs are complex neoplasms whose epidemiology, clinical behavior, and treatment may differ significantly from those of other lung cancers.[29] The prognosis of bronchial NETs depends on the neoplasm grade and the extent of disease.[3] Locoregional disease is often curable with surgery.[3] For patients with distant metastases, prognosis is poor; 73% of patients die within 5 years.[1] Ultimately, the management of G1/G2 bronchial NETs should be tailored to the needs of each patient, and should capitalize on the expertise of a multidisciplinary team.[3]

As classification systems and guidelines for the management of bronchial NETs evolve, existing treatment algorithms will also be tested. Clearly, there is room to improve outcomes in patients with bronchial NETs, and further research is warranted.[9]

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