CHEST

Advances in the Diagnosis and Management of Well-Differentiated and Intermediate-Differentiated Neuroendocrine Tumors of the Lung

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Neuroendocrine tumors (NETs) are a rare, heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body, with the lungs and GI tract being the most common sites of origin. Despite increasing incidence, awareness of lung NETs remains low among thoracic specialists who are often involved in the assessment and early treatment of these patients. Successful treatment requires accurate and timely diagnosis; however, classification can be challenging, particularly for well-differentiated and intermediate-differentiated lung NET types (typical carcinoids [TC] and atypical carcinoids [AC]). Diagnosis and management of lung NETs are further complicated by the nonspecificity of symptoms, variable natural history, and lack of high-level clinical evidence; a multidisciplinary approach is required, which has been shown to improve prognosis. Currently, surgery remains the only curative option for TC/AC. Inconsistencies between guideline recommendations for systemic therapies, especially for chemotherapy, result in a lack of consensus on a standardized treatment for unresectable disease. Recent data from the Phase III RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial (RADIANT-4), which contained a large population of patients with advanced, well-differentiated, nonfunctional lung NETs in addition to those with GI NETs, found a reduced risk of disease progression and death with everolimus compared with placebo, leading to US approval of everolimus in these patient populations. This study is the first high-level therapeutic evidence in patients with TC/AC, and everolimus is currently the only agent approved for treatment of TC/AC. Increased awareness, prompt diagnosis, and additional adequately powered controlled clinical trials of patients with well-differentiated and intermediate-differentiated lung NETs are needed to further improve evidence-based care.

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ABBREVIATIONS: AC = atypical carcinoids; ENETS = European Neuroendocrine Tumor Society; LCNEC = large cell neuroendocrine carcinoma; NCCN = National Comprehensive Cancer Network; NET = neuroendocrine tumor; PFS = progression-free survival; SCLC = small cell lung carcinoma; SSTR = somatostatin receptor; TC = typical carcinoids; WHO = World Health Organization

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Neuroendocrine tumors (NETs) are a heterogeneous group of rare malignancies found throughout the body, most commonly in the lungs and GI tract.[1,2] Lung carcinoid tumors account for approximately 25% of primary well-differentiated and intermediate-differentiated NETs[2,3] and 2.2% of primary lung neoplasms.[4] Peripherally located bronchopulmonary carcinoids (approximately 15% of all carcinoids[5]) are usually asymptomatic, whereas those with centrally located tumors often present with respiratory symptoms related to tumor mass, including cough, hemoptysis, dyspnea, chest pain, and wheezing.[6] These symptoms may manifest for many years before diagnosis due to the similarity with other conditions such as asthma.[5,7] Between 30% and 50% of lung carcinoids present as asymptomatic incidental findings,[8] and many may not be detected until autopsy.[5] Accurate and timely diagnosis of lung NETs is required for successful treatment and improved prognosis.[3,9]

Delayed diagnosis can increase the probability and incidence of metastases.[3] A cumulative analysis of 13,715 carcinoid tumors, identified by the Surveillance, Epidemiology, and End Results survey, noted that 12.9% of patients presented with metastasized tumors at the time of diagnosis, which would affect overall patient prognosis.[3] Further analysis of 28,515 cases using Surveillance, Epidemiology, and End Results data revealed a strong correlation between primary tumor site and disease stage as well as between histologic grade and disease stage in patient prognosis.[2] Prognosis was also observed to be associated with the degree of metastasis, in which patients with metastatic lung NETs had significantly shorter survival compared with those with localized lung NETs. These correlations further emphasize the importance of early and accurate diagnosis to improve overall prognosis.

The World Health Organization (WHO) 2015 classification of tumors of the lung, pleura, thymus, and heart identifies four distinct histologic variants of lung NET—typical carcinoids (TC), atypical carcinoids (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC)—which are grouped together in one category to facilitate differential diagnosis.[10] In the previous WHO classification of tumors (2004), carcinoids were grouped separately from LCNEC and SCLC.[11] Lung NET can also be classified according to grade: TC, low grade; AC, intermediate grade; or LCNEC/SCLC, high grade.[10] These classifications are based on histologic diagnostic criteria, including cell size, cell morphology, mitotic index, architectural growth patterns, and the presence of necrosis.[12,13] The focus of the present review is on TC and AC, which are classified as well-differentiated and intermediate-differentiated (low grade and intermediate grade), respectively.[4,10] TC and AC are defined as tumors $\geq$ 0.5 cm,[10] and histologic features include organoid growth patterns with uniform cytologic features and lung carcinoids generally present with a moderate amount of eosinophilic cytoplasm with nuclei containing finely granulated chromatin.[13] AC nuclei occasionally contain more coarsely granulated chromatin, and nucleoli are more prominent in AC, whereas they are inconspicuous in TC.

Diagnostic criteria differentiating TC from AC include the number of mitoses (per 2 mm^2) and the presence of necrosis (Table 1).[14] Criteria also include the proliferative index, as evaluated by immunohistochemistry using the Ki-67 antigen, a cellular marker for proliferation, which was a recent addition to the WHO classification (2015).[10,13,15] TC have $<$ 2 mitoses per 2 mm^2 per viable area of tumor, Ki-67 $\leq$ 5%, with no necrosis; AC can have between 2 and 10 mitoses per 2 mm^2 per viable area of tumor, Ki-67 $\leq$ 20%, and/or the presence of focal necrosis.[10,13] The recent WHO classification changed their recommended mitosis counting method: mitoses per 10 high-power fields are no longer recommended; mitoses should instead be counted within 2 mm^2 in the area of highest mitotic activity with the most viable tumor cells.[10,15]

TABLE 1] Classification of Lung NETs

NET	Mitotic Count per 2 mm^2	Necrosis	Cell Size
Typical carcinoid	$<$ 2	Absence	…
Atypical carcinoid	2-10	Absence or punctiform	…
Large cell neuroendocrine carcinoma, poorly differentiated	$>$ 10	Large	Larger
Small cell lung carcinoma, poorly differentiated	$>$ 10	Large	$<$ 3 lymphocytes

NET = neuroendocrine tumor. (Reprinted with permission from Hörsch et al.[14] Copyright © 2014 Karger Publishers, Basel, Switzerland.)

The subtle histopathologic differences between TC and AC make classification difficult, particularly in small biopsy samples or cytology samples; this difficulty affects selection of an appropriate treatment regimen and thus patient prognosis.[1,6] Furthermore, TC and AC may be mistaken for SCLC in crushed biopsy samples. The recent addition of Ki-67 to the WHO classification plays an important role in this diagnostic setting, allowing SCLC (Ki-67 $>$ 50%) to be distinguished from carcinoids (Ki-67 $\leq$ 20%).[10] However, the utility of Ki-67 to distinguish TC from AC has not yet been established, and there are conflicting data regarding TC/AC separation; thus, it is currently not recommended for use in this setting.[10,16] The task of diagnosis is further complicated by the existence of multiple guidelines featuring recommendations for diagnosis.[6,9,17-19]

There is no specific staging for lung NETs; current staging of lung carcinoids follows recommendations for non-NET lung cancers using the American Joint Committee on Cancer/International Association for the Study of Lung Cancer tumor node metastasis staging system.[10] However, some concern has been raised regarding the usefulness of this system due to the cutoff values of 3, 5, and 7 cm, when lung carcinoids are often $<$ 3 cm in diameter.[1] Although TC and AC are considered to be low-to-intermediate grade, both subtypes are capable of regional lymph node or distant metastasis.[18,20] Clinically, AC are observed to be more aggressive than TC, with poorer survival rates over 5 and 10 years.[20,21] Lymph node involvement at diagnosis was identified in 9% of TC and 36% of AC in a large multi-institutional study.[18] Furthermore, local recurrences affected 2% of TC and 7% of AC, and distant metastases affected 4% of TC and 26% of AC. Therefore, long-term follow-up over several years is recommended for patients with lung carcinoids, including those of low grade.

Due in part to the rarity of lung NETs, and carcinoids specifically, a relatively limited amount of evidence and accumulated knowledge are available compared with other cancers. Experts from the European Neuroendocrine Tumor Society (ENETS), the European Society of Thoracic Surgeons, and the National Comprehensive Cancer Network (NCCN) agree that a multidisciplinary approach is required for effective and efficient diagnosis and treatment of advanced lung NETs.[6,17,18] As mentioned previously, the diagnosis and management of lung NETs are complex due to a combination of the asymptomatic nature of lung NETs, nonspecificity of symptoms when present, and variable natural history. It is therefore recommended that each case be assessed in consultation with several experts within a multidisciplinary tumor board specializing in pulmonary carcinoids; this board should include surgeons, medical and radiation oncologists, pulmonologists, pathologists, endocrinologists, interventional radiologists, and gastroenterologists where required.[18] A multidisciplinary approach to more common cancers has been associated with improved diagnosis, treatment planning, patient prognosis, and patient satisfaction,[22] and it is a recommended approach for lung NET diagnosis and treatment.

Correct classification of lung NETs allows for selection of the most effective treatment regimen; however, until recently, limited prospective clinical data have been available for lung NETs, particularly in the case of TC and AC. A recent Phase III trial, RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial (RADIANT-4), assessed the efficacy of everolimus, a mammalian target of rapamycin inhibitor, in a large subgroup (n = 90) of patients with advanced, well-differentiated, nonfunctional lung NET.[23] The main RADIANT-4 study was a large randomized, placebo-controlled trial (N = 302) in which adults with advanced, progressive, nonfunctional NETs of lung or GI origin received everolimus 10 mg/d or placebo, both with best supportive care (excluding somatostatin analogues). The aim was to investigate whether everolimus prolonged progression-free survival (PFS) compared with placebo. Everolimus was shown to reduce the risk of disease progression or death by 52% in the overall population, while a retrospective post hoc analysis of the lung NET group corroborated these findings, demonstrating a 50% decrease in disease progression. Furthermore, an interim overall survival analysis suggested a numeric improvement in favor of everolimus (hazard ratio, 0.64 [95% confidence interval, 0.40-1.05]; P = .037 [boundary for significance at first interim analysis, .0002]). Observed adverse effects were primarily grade 1 or 2 in severity, and they were mostly manageable with dose modification or interruption with no need to change treatment duration. The most common adverse events related to everolimus treatment included stomatitis (63%), diarrhea (31%), fatigue (31%), infections (29%), and rash (27%). The findings from this trial support the use of everolimus as a new therapy for well-differentiated lung NETs. Based on these data, the indication for everolimus has recently been expanded in the United States to include the treatment of adults

with progressive, well-differentiated, nonfunctional NETs of lung or GI origin that are unresectable, locally advanced, or metastatic, in addition to the treatment of adults with pancreatic NET.[24]

For treatment decisions, the NCCN panel recommends that histologic grading systems be used as a general guide combined with clinical judgment.[17] Current consensus supports surgery as the treatment of choice and the only curative option for localized, resectable TC and AC.[6,17] Resection of the primary tumor is not indicated in the setting of unresectable metastases if the primary site is relatively stable.[17] Adjuvant therapy has not been comprehensively studied in relation to lung NET, and its implementation is still in dispute. The NCCN Small Cell Lung Cancer guidelines, which also include information for lung carcinoids, recommend the use of adjuvant chemotherapy with or without radiation therapy for patients with stage II/III AC,[19] whereas the ENETS limits this recommendation to a consideration in patients with AC with positive lymph nodes.[6] The North American Neuroendocrine Tumor Society guidelines note a lack of evidence to support effective implementation of adjuvant chemotherapy and/or radiation for the treatment of lung NETs.[9]

For patients with unresectable or metastatic tumors, there is a lack of consensus among the guidelines with regard to recommended first-line and subsequent treatment regimens (Table 2).[6,17,19,25] Systemic therapy options for advanced/metastatic NET include somatostatin analogues (octreotide and lanreotide), targeted therapy (everolimus), interferon, chemotherapy (eg, temozolomide-based), and peptide receptor radionuclide therapy (for NET-expressing somatostatin receptors [SSTR]).[6,17-19] Management of advanced TC and AC according to the most recent ENETS guidelines takes into consideration the pathologic features (mitotic count, Ki-67), SSTR expression, and growth rate (slowly or actively progressive) (Table 3).[6,25] These guidelines were published just prior to the approval of everolimus for lung NETs in the United States, and they recommend everolimus as a first-line therapy in metastatic, progressive lung NETs based on RADIANT-4 data, due to the absence of approved drugs.[25] For TC with strong SSTR expression on imaging, somatostatin analogues may be considered as first-line therapy. Although comprehensive data on somatostatin analogues in patients with lung NET are currently lacking, the clinical response of TC is expected to be similar to low-grade gastroenteropancreatic NETs.[25] Guideline updates based on the recent approval of everolimus in progressive, well-differentiated, nonfunctional NETs of lung and GI origin are anticipated.

The NCCN NET guidelines recommend cytotoxic chemotherapy for patients with progressive metastases only when no other treatment options are available.[17] In contrast, the NCCN Small Cell Lung Cancer guidelines suggest cisplatin and etoposide as the preferred regimen for advanced AC tumors.[19] The ENETS guidelines recommend systemic chemotherapy under certain conditions; that is, when Ki-67 is in the upper range for AC (Ki-67 > 15%), in rapidly progressive disease (progression according to Response

TABLE 2] Lack of Consensus Among Recent Guidelines for Antiproliferative Systemic Treatment Recommendations for Advanced, Unresectable Lung Carcinoids

Guideline	First-line Treatment	Other Treatment Recommendations
NCCN NET (2016)[17]	SSA	• For clinically significant progressive disease: ◦ Consider everolimus (category 3) and interferon alfa-2b (category 3) ◦ Consider cytotoxic chemotherapy (category 3) if no other options are feasible
NCCN SCLC (2016)[19]	CIS + ETOP (AC only)	• No substantial evidence for a preferred regimen in TC • Treatment options for TC/AC include sunitinib (not included in other guidelines)
ENETS (2015/2016)[6,25]	SSA or EVE	• SSA for TC/AC (preferably Ki-67 < 10%), slow-growing, with strong SSTR expression • EVE recommended for progressive metastatic tumors when SSA are not an option • Chemotherapy is a consideration for aggressive AC (Ki-67 > 15%), generally after failure to improve with other therapies • PRRT is an option for progressive tumors with strong, homogeneous SSTR expression across lesions

SSA refers to octreotide long-acting release or lanreotide autogel/depot formulations. AC = atypical carcinoids; CIS = cisplatin; ENETS = European Neuroendocrine Tumor Society; ETOP = etoposide; EVE = everolimus; NCCN = National Comprehensive Cancer Network; PRRT = peptide receptor radionuclide therapy; SCLC = small cell lung cancer; SSA = somatostatin analogues; SSTR = somatostatin receptor; TC = typical carcinoids. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Systemic Therapy Options for Advanced, Unresectable Lung Carcinoids Based on ENETS Guidelines (2015/2016)[6,25]

Therapy Option	Level of Recommendation	Pathology	Ki-67	SSTR Expression	Growth Rate (RECIST)
Octreotide or lanreotide	Considered as first-line therapy	TC or AC	Preferably Ki-67 < 10%	Strongly positive	Slow
Everolimus	Recommended as first-line therapy	TC or AC	Not specified	Positive or negative	Progressive
Chemotherapy	Considered generally after failure of other therapies	AC	Ki-67 > 15%	Negative	Aggressive (progression within 3-6 mo)
PRRT	Considered as an option	TC or AC	Not specified	Strongly positive; homogeneous expression across lesions	Progressive

RECIST = Response Evaluation Criteria in Solid Tumors. See Table 2 legend for expansion of other abbreviations.

Evaluation Criteria in Solid Tumors in 3-6 months), and/or after failure of other therapies or in SSTR-negative disease.[25] Several cytotoxic drug combinations have been investigated in metastatic lung carcinoids; however, this research has only yielded minor activity for AC in particular, and a recommended standard therapy has yet to be determined.[9,12,26] In general, most clinical evidence is based on small, retrospective, single-institution studies,[18] and further prospective clinical investigations are needed via large randomized controlled trials that include a substantial number of patients with lung NETs.

The efficacy of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy in the treatment of advanced midgut NET has been reported in the randomized Phase III NETTER-1 study.[27] However, no prospective Phase III evidence is available for lung TC/AC. A Phase II study in 34 patients with progressive, metastatic TC/AC showed antitumor activity with ^{177}Lu-DOTATATE, both in terms of the disease control rate (62%), which comprised a large proportion of patients with stable disease (47%), and median PFS (18.5 months).[28] An apparent difference in disease control rate was evident between TC and AC, with rates of 80% and 47%, respectively. Further prospective Phase III data are warranted.

Promising systemic therapies in advanced lung carcinoids that are currently in open or ongoing trials include lanreotide (SPINET, NCT02683941), and everolimus and/or pasireotide long-acting release (LUNA, NCT01563354). The lanreotide Phase III trial will investigate whether lanreotide prolongs PFS compared with placebo in TC and AC, which have previously been reported in patients with gastroenteropancreatic NET.[29] The Phase II LUNA trial is investigating everolimus and pasireotide long-acting release, alone or in combination, in adults with advanced TC or AC of the lung and thymus. The primary outcome measure is the proportion of patients who are progression free at 9 months, with an expected study completion date of October 2016.

As is evident by the limited clinical information available regarding lung NETs, specifically well- and intermediate-differentiated TC and AC, debate and controversy in classification, diagnostic methods, and appropriate treatment regimens still exist. The impact on prognosis of early diagnosis combined with a suitable treatment regimen can be substantial and clearly indicates the need for increased awareness and investigation in lung NETs. Along with this research, lung NET guidelines require regular updating as clinical data become available, ensuring that patients and clinicians have the most clinically relevant information. Treatment options available for patients with lung NETs have previously been limited. RADIANT-4 was the first Phase III prospective trial involving a large subgroup of patients with lung NETs, and it reported unequivocal evidence of everolimus efficacy in lung carcinoids, which led to its recent approval in the United States as the first treatment for advanced, progressive, nonfunctional lung NET. Additional adequately powered and active comparator or placebo-controlled clinical trials are required to examine efficacy in this specific patient group. Currently, several drugs are being investigated as therapy options that may provide clinical evidence of their efficacy in lung NETs. However, it is important to note that issues surrounding classification, diagnosis,

and treatment of lung NETs need to be addressed, along with increasing the awareness among thoracic specialists who are frequently on the frontline of diagnosis and who care for patients with this rare type of lung cancer.

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