Annals of Oncology 23 (Supplement 7): vii120–vii123, 2012
doi:10.1093/annonc/mds267

Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Neuroendocrine tumors (NETs) of the lung comprise a heterogeneous population of tumors ranging from well-differentiated bronchial NETs to highly malignant and poorly differentiated small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC). The incidence of pulmonary NETs is low, although reported to have increased over the past 30 years [1, 2]. This is mainly due to improved detection methods and diagnostic protocols. Of all NETs ∼25% are located in the respiratory tract. Typical carcinoids (TCs) comprise ∼1%–2% and atypical carcinoids (ACs) only 0.1%–0.2% of pulmonary neoplasms. According to the surveillance, epidemiology and end results program (SEER) database from 2003, the combined incidence has been 1.57/100 000 inhabitants [3]. SCLC is the most common bronchial NET reported to account for 15%–20% of invasive lung cancers. LCNEC comprise 1.6%–3% of resectable lung cancers. The prevalence of thymic NET is ∼3% of the total number of NETs at all sites. In the last SEER database, a reported incidence of thymic NETs is 0.02/100 000 population per year [4]. They constitute ∼5% of all thymic tumors. Both bronchial and thymic NETs may be part of multiple endocrine neoplasia type 1 syndrome (MEN-1, 5%–15%). The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years. This review is restricted to typical/atypical NETs and thymic NETs.

diagnosis

NETs of the lung and thymus should be referred to a center with particular interest in and knowledge of the disease for careful evaluation and treatment. NETs of the lung include the low-grade TC, intermediate-grade AC, the high-grade LCNEC and SCLC. The incidence of SCLC has been declining the last 35 years in the western world, maybe due to decreasing smoking habits [5]. Mixed tumors are found in <5% of patients and are more frequently found in the peripheral areas of the lung. They consist of a combination of SCLC and LCNEC, but also mixtures of either SCLC or LCNEC with adenocarcinomas and/or squamous cell carcinoma. About 70% of all bronchial NETs are located in the major bronchi and the remainder in the periphery of the lungs. They occur more frequently (60%) in the right than in the left lung, and particularly in the middle lobe [6]. The cell of origin for bronchial NETs have been suggested to be pulmonary neuroendocrine cells (PNECs) that usually exist as solitary cells, but sometimes aggregate to form small nodules termed neuroepithelial bodies (NEBs), which are located within the ciliated epithelium. PNECs express serotonin and neuron-specific enolase (NSE) and also gastrin-releasing peptide (GRP) [7]. In adults, NEBs have been described to respond to hypoxia by the secretion of serotonin, thereby inducing local vasoconstriction to decrease the bloodstream in poorly ventilated areas of the lung and thereby, direct the blood toward better ventilated areas. Diffuse idiopathic PNEC hyperplasia is a rare preneoplastic condition comprising a generalized proliferation of PNECs predominantly in women and non-smokers [7]. Up to 90% of patients with central bronchial NETs are symptomatic, presenting with hemoptysis, cough, recurrent pulmonary infection, fever, chest discomfort and unilateral wheezing, while peripheral carcinoids are incidentally discovered in most of the cases [6]. The carcinoid syndrome is very rare in patients with bronchial NETs. Nevertheless, a carcinoid crisis may occasionally occur in previously asymptomatic patients following bronchoscopic biopsy laser disobliteration, surgical manipulation or peptide receptors radiotherapy (PRRT). AC syndrome may cause life-threatening bronchostenosis and should be promptly recognized and treated. In about 2% of

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†Approved by the ESMO Guidelines Working Group: August 2007, last update July 2012. This publication supersedes the previously published version—Ann Oncol 2010; 21 (Suppl. 5): v220–v222.

patients with Cushing's syndrome, the cause is ectopic adeno-cortic trophic hormone (ACTH) production from either bronchial or thymic NETs [5, 6].

SCLC derives from normal bronchial epithelial cells expressing neuroendocrine characteristics. Alternatively, a common pulmonary stem cell may exist giving rise to both neuroendocrine stem cells and SCLC cells [7].

The World Health Organization (WHO) classification of bronchial NETs combined architectural growth patterns of tumor cells (organoid growth versus small-cell diffuse growth) with the mitotic index and the presence of necrosis (Table 1) [8, 9].

The identification of the neuroendocrine phenotype and the correct NET classification necessarily include the evaluation of specific neuroendocrine markers. Among these chromogranin A and synaptophysin expression are the most reliable stains (Table 2). Other markers helpful to define a neuroendocrine phenotype include PGP 9.5, NSE and CD56. Transcription factors driving neuroendocrine cell differentiation during human development have been described in bronchial NETs. These include human achaete-scute homolog 1 whose expression has been reported in high-grade bronchial NETs. In addition, the proliferation index as detected by Ki-67 immunostaining is also an extremely useful tool to better classify a bronchial NET although actually not included in the WHO classification criteria [7, 10].

Most thymic NET cases are completely asymptomatic and imaging performance for other reasons generally incidentally discovers thymic NETs. Not infrequently distant metastases are present at the time of diagnosis. Clinical symptoms usually occur at a later stage of the disease, such as chest discomfort, superior vena cava syndrome, dyspnea and cough. Thymic NETs are frequently associated with hormonal hyper-secretion such as ACTH secretion giving rise to Cushing's syndrome and growth hormone releasing hormone (GHRH) hyper-secretion with ectopic acromegaly [10]. The tumor seems to have a predilection for men (man to female ratio 3:1). A characteristic feature of these tumors is the presence of nests of tumor cells that are detached from the surrounding stroma and contain areas of necrosis. The tumors often show architectural features of neuroendocrine differentiation with positive immunohistochemistry for chromogranin A, synaptophysin and CD56. They can be divided into low, intermediate and high-grade tumors. Low-grade tumors present <10 mitoses/10 high power field (HPF), intermediate tumors 10-20 mitoses/HPF and high grade tumors <10 20 mitoses/10 HPF. The tumors may be associated with MEN-1 in 4%–8% of the cases. Nearly all cases associated with MEN-1 are male patients and smokers [9].

Table 1. Classification of bronchial NET

Histological type	Necrosis	Mitotic count
TC	absent	<2/10 HPF
AC	present focal	2–9/10 HPF
LCNEC	present (extensive)	>9/10 HPF
SCLC	present (extensive)	>50/10 HPF

TC: typical carcinoid; AC: atypical carcinoid; LCNEC: large-cell neuroendocrine carcinoma; SCLC: small-cell carcinoma.

Table 2. Diagnosis bronchial NET

Clinical symptoms bronchial NET
- Hemoptysis, cough, recurrent pulmonary infections, wheezing
- Carcinoid syndrome, Cushing's syndrome } Rare

Clinical symptoms thymic NET
- Chest discomfort, superior vena cava syndrome, stridor, Cushing's syndrome, acromegaly

Pathology
- Histopathology
- Immunohistochemistry (chromogranin A, synaptophysin, CD56, Ki-67)

Biochemistry (specific)
- p-Chromogranin A, p-NSE, u-5HIAA, [[a]u-cortisol, p-ACTH, p-GHRH, IGF-1]

Imaging
- Multislice CT scan
- ^{111}In-DTPA-scintigraphy: (Octreoscan®)

PET: ^{68}Ga-DOTATATE, FDG

Bronchoscopy

Genetic screening
- MEN-1 genetic screening when suspected

[a]Clinical symptoms suggesting Cushing's syndrome alt acromegaly.
NSE, neuron-specific enolase; 5HIAA, 5-hydroxy indol acetic acid.

staging and risk assessment

A tumor–node–metastasis (TNM) staging is recommended for bronchial NETs and is included in the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM staging system (Table 3). TNM staging of thymic NETs follows the general rules for tumors of the thymus. Biochemical evaluation for both bronchial and thymic NETs include plasma chromogranin A, plasma-NSE, and in selected cases dU-5-hydroxy indol acetic acid with clinical symptoms of carcinoid syndrome and urine cortisol with Cushing's disease, plasma ACTH and those with signs of acromegaly, plasma GHRH and insulin growth factor (IGF)-I (III, A) [10]. Conventional X-ray of the chest may suggest a diagnosis of both bronchial and thymic NETs, but computed tomography (CT) scan is the recommended investigation. Bronchoscopy, if necessary with additional endoscopic ultrasonography with biopsies, is the best procedure to detect central bronchial NETs (III, A). Since 80% of typical bronchial carcinoids express somatostatin receptors, somatostatin receptor scintigraphy may be informative as well as ^{68}Gallium-DOTATATE/TOC (DOTA0, D-Phe1, 8tyr3] Octreotate) positron emission tomography (PET) scanning (III, B) [11, 12]. For more aggressive bronchial NETs such as LCNEC and SCLC, fluoro deoxy glucose (FDG) PET is more informative than somatostatin receptor scintigraphy (III, B) [13, 14]. For thymic NETs contrast enhanced CT or magnetic resonance imaging (MRI) is recommended to detect tumor metastases. Somatostatin receptor scintigraphy may be used for these tumors as well as PET scanning with ^{68}Gallium-DOTATATE (III, B). Bronchial NETs sometimes present with AC syndrome related to the secretion of histamine metabolites. The biochemical profile for thymic NETs

Table 3. AJCC staging for lung tumor NETs

Primary tumor (T)	
TX	Primary tumor cannot be assessed or tumor was proved 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 (i.e. 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 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 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

is usually similar to the bronchial NETs. A core biopsy is preferred from relevant lesion; Cushing's syndrome is present in about one-third of the patients, particularly in patients with MEN-1 associated thymic NET [10].

TCs exhibit a good prognosis with a 5-year survival of 87%–90%. However, distant metastases from TCs may occur many years even after radical resection of the primary tumor. A 15-year follow-up is therefore recommended. ACs are regarded as intermediate in grade and are associated with poor prognosis and a 5-year survival of 44%–78%. The LCNEC is associated with a 5-year survival rate of 15%–57% and finally the 5-year survival rate for SCLC is ∼5% [6, 10].

The prognosis for patients with primary thymic NETs remains poor. This is due to the aggressive nature of tumor with a high incidence of recurrence following surgery. Low-grade thymic NETs present a 5-year survival of 50% and a10-year survival of 9%, whereas high-grade thymic NETs have a 5-year survival of nearly 0% [10].

management of localized disease

The main therapy for bronchial NETs is surgical resection. The surgical approach is dependent on the size, location and tissue type. Bronchoscopic laser excision of intraluminal typical bronchial NETs should be considered a suboptimal treatment and reserved for inoperable patients or performed as pre-operative disobliterating procedure. The surgical techniques of choice are lobectomy or sleeve resection (III, A). Pneumonectomy should be avoided except in selected cases. Systemic nodal dissection should be performed since lymphonodal metastases may be present in up to 25% of cases in TC and >50% in AC [15, 16]. Thymic NETs should whenever feasible be subjected to radical surgical resection (III, A). Unfortunately, the percentage of recurrence remained remarkably high, higher than in bronchial NET counterparts and a protracted follow-up should always be performed also in patients radically operated.

management of advanced/metastatic disease

Cytotoxic treatment combined with surgical resection when indicated has been the standard for metastatic bronchial and thymicNETs, although the available chemotherapy regimens demonstrate a rather poor effect (III, A) [17, 18]. Chemotherapy for SCLC, which is a chemosensitive but not curable cancer, is discussed in the appropriate guidelines. For low proliferating tumors treatment with somatostatin analogs and alpha interferon might be an option for functional tumors with clinical symptoms (III, B). Treatment with these agents has resulted in partial remission (PR) in 5%–10% but stable disease (SD) in 30%–50% and symptomatic improvement in

40%–60% of cases. Treatment with novel agents, such as tyrosine kinase inhibitors (e.g. sunitinib) and the mTOR-inhibitor everolimus, have been reported in very small series or in the subgroup analysis of larger studies not designed specifically for lung NET with mainly stabilization of the disease (objective response rates 5%–10%; III, B). In non-functioning tumors, the use of somatostatin analogs is still controversial, but after the PROMID study indicating antitumor efficacy by octreotide long acting release (LAR) in small intestinal NETs, it is now widely accepted also for non-functioning tumors of other origins (III, B). Peptide receptor radiotherapy is an option in patients with tumors that present a high content of somatostatin receptors (III, B). Available chemotherapy regimens for TC and AC include a combination of streptozotocin plus 5-fluoro-uracil/doxorubicin. Temozolomide alone or in combination with capecitabine and sometimes bevacizumab has demonstrated clinical benefit (III, B). A combination of cisplatinum and etoposide is mainly used in high proliferating tumors (III, B). In general chemotherapy, results are discouraging except for temozolomide alone or in combination with capecitabine (III, B). No randomized trials have been performed that could guide the treatment. However, the RADIANT-2 trial, which was a randomized trial between everolimus (10 mg) and placebo in NET tumor patients, included 44 of the 429 patients with bronchial NETs. A clear benefit of everolimus compared with placebo was noted (II, A). Symptomatic metastatic disease confined to the liver may be treated with embolization, radiofrequency ablation (RFA) and radio-embolization of liver metastases. External local irradiation of brain and bone metastases might be beneficial. In thymic NETs chemotherapy using cisplatinum-based regimens has been of value. However, temozolomide-based treatment is also reported to give some benefit (III, B) [18, 19]. All treatment series are very small. Somatostatin analogs can be used to control the Cushing's syndrome related to thymic and bronchial NETs. PRRT is promising in thymic NETs but more studies are needed [20].

response evaluation and follow-up

After primary surgery patients with TC and AC should be followed at least yearly up to 15 years (III, B) to detect surgically manageable recurrences. Biochemical markers, such as chromogranin A and NSE, should be determined every 3–6 months (in cases with elevated values at baseline), and CT should be performed once a year in atypical and every 2 or 3 years in typical. Patients with metastatic or recurrent disease should be followed during treatment with cytotoxic or biological agents more often, at 3–6-month intervals with imaging, preferably by CT and biological markers to assess possible benefits of the treatment administered [21].

conflict of interest

Prof. Öberg has reported: speakers' bureau and advisory board membership: Ipsen, Novartis, Pfizer. Prof. Rougier has reported: honoraria from Sanofi Aventis, Amgen, Keocyte, Merck Serono, Pfizer, Roche and Lilly; advisory board for Sanofi Aventis and Keocyte.

The other authors have reported no potential conflicts of interest.

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