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
patients with Cushing’s syndrome, the cause is ectopic adeno-corticotropic 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.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Necrosis</th>
<th>Mitotic count</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>absent</td>
<td>&lt;2/10 HPF</td>
</tr>
<tr>
<td>AC</td>
<td>present</td>
<td>2–9/10 HPF</td>
</tr>
<tr>
<td>LCNEC</td>
<td>present (extensive)</td>
<td>&gt;9/10 HPF</td>
</tr>
<tr>
<td>SCLC</td>
<td>present (extensive)</td>
<td>&gt;50/10 HPF</td>
</tr>
</tbody>
</table>

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

**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 68Gallium-DOTATATE/TOC (DOTA0, D-Phe1, 8tyr3) Octreotide) positron emission tomography (PET) scanning (III, B) [11, 12]. For more aggressive bronchial NETs such as LCNEC and SCLC, fluorodeoxy 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 68Gallium-DOTATATE (III, B). Bronchial NETs sometimes present with AC syndrome related to the secretion of histamine metabolites. The biochemical profile for thymic NETs...
 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
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.

references

5. Travis WD. Lung tumors with neuroendocrine differentiation. Eur J Cancer 2009; 45(Suppl. 1): 251–266.