

Neuroendocrine Tumors of the Lung

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Bronchial carcinoids belong to the infrequent pulmonary neoplasias. They distinguish themselves through neuroendocrine differentiation of the cells and relatively indolent clinical behavior. Previously, they were numbered among the bronchial adenomas. However, due to their potential for metastasis, they are currently considered to be malignant neoplasias. Like neuroendocrine tumors in other parts of the body, bronchial carcinoids also originate in neuroendocrine cells diffusely distributed in the body.

In terms of frequency, neuroendocrine tumors of the lung are second most common following those of the gastrointestinal tract (Table 1).

Neuroendocrine tumors of the lung usually appear sporadically, although up to 15% occur within the context of MEN I syndrome.

Bronchial neuroendocrine tumors account for approximately 1-2% of all lung tumors occurring in adulthood. In children, they belong to the most frequent malignant lung diseases. They typically first appear in late adolescence. The global rate of incidence is between 0.2 to 2 cases per 100,000 individuals in the population per year. In most study series, women are more often affected than men. The increasing incidence in the past decades is less a result of a rise in frequency than due to the better image-rendering diagnostic tools and more differentiated pathological diagnostics which currently also detect many asymptomatic tumors. The average age at which diagnosis of a neuroendocrine tumor is made is 45 years. A connection between neuroendocrine tumors and nicotine consumption has not been demonstrated. Although seldom, large numbers of carcinoids do occur in families. Patients with autosomal-dominant syndrome of multiple endocrine neoplasia type I (MEN I) show a high incidence of malignant endocrine neoplasias. However, hereditary pulmonary neuroendocrine tumors were also described which are not associated with MEN syndrome. Histologically, bronchial carcinoids are part of a spectrum of endocrine tumors of the lung which distinguish

themselves clearly through different biological behavior. On one end of the spectrum are the typical carcinoids. These are highly-differentiated, slow growing, and seldom metastasize. At the other end are the poorly-differentiated neuroendocrine carcinomas. Biologically, the large cell neuroendocrine carcinoma resembles the small cell bronchial carcinoma (SCLC) with highly aggressive behavior, rapid growth, and early metastasis.

WHO Classification

Neuroendocrine tumors of the lung were the subject of considerable controversy in the past. Multiple, in part unclear and confusing classification systems resulted from this. The recent, generally accepted WHO classification system dates from 2004. According to it, neuroendocrine tumors of the lung are categorized according to a clinical-pathological spectrum which ranges from diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) all the way to poorly-differentiated small cell bronchial carcinoma and the large cell neuroendocrine tumors (Table 2).

TNM Classification

The staging of pulmonary carcinoids is equivalent to that for lung tumors. Typical carcinoids are usually diagnosed during stage I, while the atypical carcinoids are mostly in UICC stage II or III at time of diagnosis.

Clinical Features

The majority of the tumors (80%) occur in the proximal air passages. Complaints are usually caused by stenosis of the air passages as a consequence of the tumor mass. As a result, patients suffer coughing, rhonchus, dyspnea, or recurring infections caused by retention pneumonia in the same lung segment or pulmonary lobe. In addition, due to the typical hypervascularization of the tumors, bleeding with hemoptyses can occur. Occasionally chest pain occurs. Usually, diagnosis is made very late. Patients are frequently treated symptomatically

Table 1 Pulmonary Carcinoids

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| • 1-2 % of all lung tumors |
| • 25% of all carcinoids |
| • 80-90 % typical carcinoids |
| • 10-20% atypical carcinoids |
| • 70-80% proximal, 20-30% peripheral |
| • 61% on right side, primarily in middle lobe |

over a long period of time or in the case of recidivate infections treated with various antibiotics. In contrast to this, patients with peripheral pulmonary carcinoids (20%) are asymptomatic. These tumors are often discovered by chance in chest x-rays.

Peptide Production and Paraneoplastic Syndrome

Unlike carcinoids originating in the primitive midgut, carcinoids of the primitive foregut, to which pulmonary carcinoids also belong, generally have a lower level of serotonin and therefore usually do not cause a carcinoid syndrome. The reason for this is that neuroendocrine tumors of the foregut often have a deficiency of aromatic amino acid decarboxylases and cannot produce serotonin and its metabolites by themselves. Although they synthesize a large variety of other peptides and hormones within the cell (gastrin-releasing peptide, 5-hydroxytryptophan and chromogranins), bronchial carcinoids only occasionally secrete bioactive amines. The result of this is that the hormone level in the plasma or urine is very low and the neuroendocrine tumors can hardly be discovered this way. Only a small portion of patients clinically develop a paraneoplastic syndrome caused by peptide secretion. Carcinoid syndromes are very seldom associated with a tumor size larger than 5 cm. However, carcinoid syndrome appears in patients with pulmonary carcinoid and liver metastases in more than 80% of cases.

Diagnostics

1. *Laboratory.* Determination of chromogranin A (CgA) in serum as a broad-spectrum marker for neuroendocrine tumors is a relatively sensitive procedure. As a component of the membrane of the secretory granules of neuroendocrine cells, CgA is co-secreted with peptide and polypeptide hormones within the context of hypersecretion.

Increased blood levels of Chromogranin A are present with almost all metastatic NETs and are suitable as progress parameters. Neuron-specific enolase (NSE) can be pathologically increased with neuroendocrine tumors.

2. *Chest X-ray.* 75% of patients with a bronchial carcinoid have a suspicious chest x-ray. Most masses are round to oval in shape, 2-5 cm on average, and hilar or perihilar. Cavitation is rare. Pleural involvement is unusual, but can be associated with post-obstructive pneumonia.

3. *CT Scan.* Most neuroendocrine neoplasias present as isodense tumors in CT images. Between 5 and 20% of the typical bronchial carcinoids are associated with hilar or mediastinal adenopathies (Figures 1a and 1b).

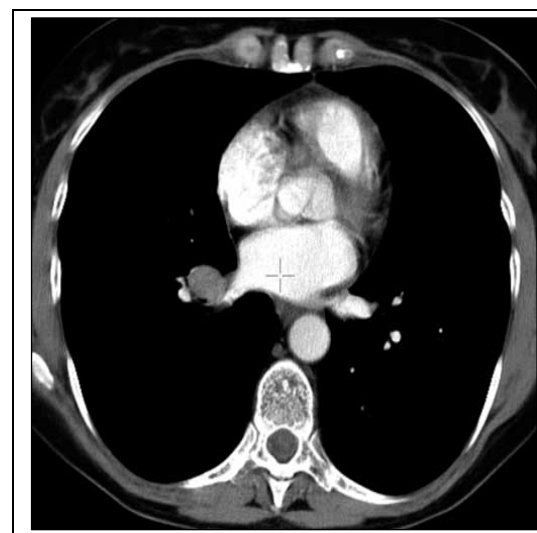


Figure 1a: Central position, pulmonary carcinoid with regular borders

4. *Bronchoscopy, Endosonography and Biopsy.* Approximately three-fourths of bronchial carcinoids are central and accessible for biopsy.

Bronchoscopically, a typical pink to red vascularized structure with intact bronchial epithelium is seen. Carcinoids are generally broad-based on the bronchus, but can also be polypoid (Figure 2a). A cytological brush biopsy is more sensitive than sputum cytology. The diagnostic value is low however, because the mostly intact bronchial epithelium encases the tumor. Pre-operative diagnosis of a typical carcinoid through biopsy does not always make sense. Since the carcinoids are heavily

vascularized, a biopsy can lead to heavy bleeding (Figure 2b). Life-threatening complications due to hemorrhaging are rare, however. The application of diluted epinephrin prior to and following biopsy decreases the risk of bleeding. In the case of a macroscopically definitive finding and clear indication for surgery, there is no change in the therapeutic approach as a result of a biopsy making it unnecessary to perform one. Endobronchial sonography can be used to exclude invasions of the bronchial wall in the

Table 2: 2004 WHO Criteria for Diagnosis of Neuroendocrine Tumors

Tumor Type	Criteria
Typical carcinoid tumors	Carcinoid morphology and <2 mitoses/2mm ² (10 HPFs), no necrosis and >0.5 cm
Atypical carcinoid tumors	Carcinoid morphology with 2-10 mitoses/2mm ² (10 HPFs) or necrosis (often punctual)
Large cell neuroendocrine carcinomas	Neuroendocrine morphology (organoid structures with trabecular, rosette-like or palisade-like structures)
	High mitosis rate >10/2mm ² (10 HPFs), mean 70/2 mm ² ;
	Necrosis (often large regions);
	Cytological characteristics of NSCLC: large cells, small ratio of cell nucleus to cytoplasm, some tumors show fine nuclear chromatin and missing nucleoli, belong however to the NSCLC due to their cell size and abundant cytoplasm.
	Positive immunohistochemical marking for one or more NE markers (other than NSE) and/or neuroendocrine granules under electron emission microscopy
Small cell neuroendocrine carcinomas	Small cells (normally smaller than 3 lymphocytes;
	Little cytoplasm;
	Nuclei: fine, granular chromatin, no or dull nucleoli
	High mitosis rate : >11 mitoses /2mm ² (10 HPFs), mean 80/2 mm ² (10HPFs); and
	Often necroses, very frequently large zones

HPF: high- power field; **NSCLC:** non-small cell lung carcinoma; **NE:** neuroendocrine

sub-millimeter range before or after endobronchial resection. Endosonographically-

guided puncture of enlarged lymph nodes can also be meaningful for determining disease stage.

Pre-operative endoscopic resection of the endoluminal tumor is recommended if an exact estimation of tumor expansion is only possible through this, or it would influence the extent of surgical resection, or if poststenotic pneumonia is present.



Figure 1b: Carcinoid in the interbronchus

5. *Octreotide Scintigraphy.* Up to 40% to 80% of neuroendocrine tumors show somatostatin receptors that bind radioactively labeled somatostatin analogs ($^{111}\text{Indium}$ -labeled octreotide or pentatreotide) and can be imaged using a gamma camera. Indium–octreotide scintigraphy is suitable for detection of tumors <1.5 cm. It is of very significant value in diagnosing the primary and the metastases of neuroendocrine tumors, but is, however, not specific for these tumor entities, because meningiomas, astrocytomas, non-small cell bronchial carcinoma and mamma carcinomas can also possess somatostatin receptors. Sensitivity for this procedure varies (80- 90%) since the various neuroendocrine tumors show a different percentage of somatostatin receptors. In the case of inoperable or metastatic pulmonary carcinoids, octreotide scintigraphy can be helpful in evaluating the probability of response to radioreceptor therapy.

6. *Somatostatin Receptor PET.* Somatostatin receptor $^{68}\text{Gallium}$ -DOTATOC or DOTANOC positron emission tomography (PET) is currently the most sensitive imaging procedure for detecting neuroendocrine tumors due to its very high sensitivity and the extremely high

tumor contrast. The length of time for the procedure is a maximum of three hours, while octreotide scintigraphy stretches out over two days. With $^{68}\text{Gallium}$ -DOTANOC receptor PET, the detection of tumors <1 cm is possible. A further advantage is the substantially lower radiation exposure.

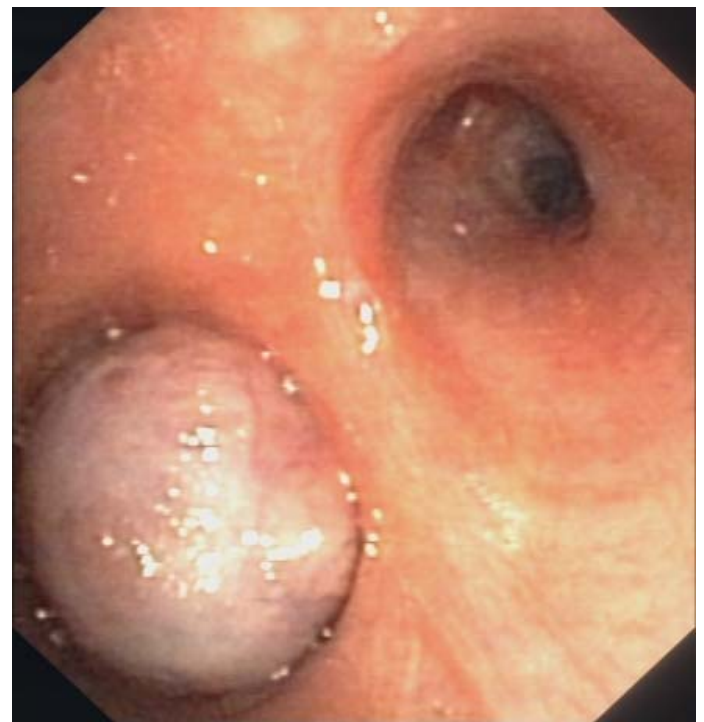


Figure 2a: Typical centrally located, heavily vascularized pulmonary carcinoid

Therapy

Surgical resection of the tumor is the therapy of choice if the overall condition of the patient allows for it. Goal is block resection with complete removal of the neuroendocrine tumor with retention of the most functional lung tissue possible. Complete mediastinal lymph node resection should be performed to the extent possible. In selected cases, an alternative is offered by bronchoscopic resection using a high-frequency loop, argon beamer or Nd-YAG laser, in particular in combination with cryotherapy, if no metastases in the mediastinal lymph nodes and no invasion of the bronchial wall exist. In a study, Laurent Bertoletti et al evaluated 18 patients with pulmonary neuroendocrine tumors in the lung who were treated with endobronchial mechanical resection and cryotherapy. Only in one patient could a recidivate tumor be observed after seven years. Cryotherapy is not associated

with long-term complications like bronchial stenoses and presents itself as a gentle, tissue-sparing therapy option with good prognosis. This therapy combination is very promising since neuroendocrine tumors react very sensitively to cold and at the same time cryotherapy does not destroy cartilage tissue of the tracheobronchial tree. These therapy options are suitable for multi-morbid and functionally inoperable patients who cannot be expected to undergo surgical resection.

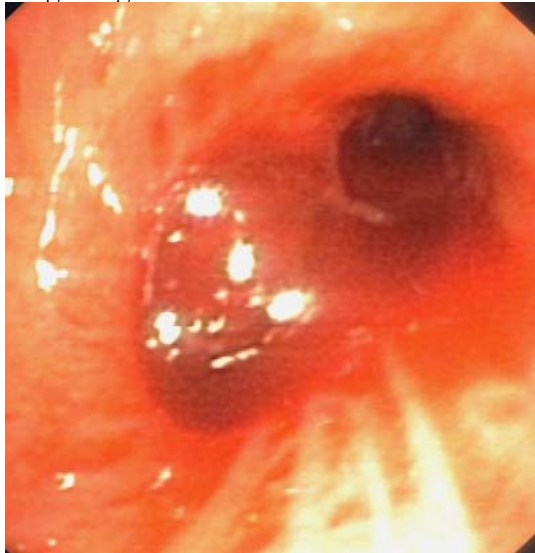


Figure 2b: Heavy bleeding following tissue sampling

Adjuvant Therapy

Adjuvant therapy is not indicated following complete resection. In cases of poorly-differentiated neuroendocrine tumors and mediastinal lymph node involvement (N2), adjuvant therapy in the form of chemotherapy, radiotherapy, or a combination of both is advised. There are, however, no prospective studies documenting the success of adjuvant therapies in patients with bronchial carcinoids (typical or atypical); in addition, there is only very little experience on the part of individual institutions. Although carcinoids have proven to be relatively radio-resistant, radiotherapy makes sense as a palliative measure for locally advanced, non-resectable primary tumors. Furthermore, it is recommended that this patient group receive a combination of radio and chemotherapy in a form similar to that for patients with SCLC. However in comparison, the response rate is better in patients with SCLC.

Chemotherapy

Patients with metastatic neuroendocrine tumors of the lung are often treated with a chemotherapy protocol similar to that for SCLC (e.g. cisplatin in combination with etoposide or paclitaxel). Chemotherapies based on streptozotocin are also recommended, but show a limited efficacy.

Biotherapy

The effectiveness of α -interferon and octreotide on pulmonary carcinoids is very limited since only few patients show stable disease progression while receiving them. The value lays primarily in improving symptoms in the case of classic carcinoid syndrome.

Radioreceptor Therapy

In the case of an inoperable, metastatic, somatostatin receptor-positive neuroendocrine tumor of the lung, peptide receptor radionuclide therapy with octreotate-coupled ^{90}Y tritium (DOTATOC or DOTATATE) leads to a response and symptom improvement in more than half of patients.

Prognosis

Typical bronchial carcinoids have a good prognosis; only 1-2% of the carcinoids recidivate. The five-year survival rate is between 75 and 100%. Incomplete resection is associated with a significantly worse prognosis. Atypical carcinoids have a great tendency to metastasize. The five-year survival rate varies between 30 and 65%. The prognosis becomes worse with positive nodal status in the case of atypical carcinoids, however not in terms of the typical carcinoids.

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