clinical recommendations

Neuroendocrine bronchial and thymic tumors: ESMO Clinical Recommendation for diagnosis, treatment and follow-up

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incidence
The annual incidence of typical and atypical bronchial carcinoid tumors has been reported to be 0.6/100 000 and the overall age-adjusted incidence of thymic carcinoids 0.01/100 000/year. Both bronchial and thymic carcinoids might be part of multiple endocrine neoplasia type I syndrome (MEN-I).

diagnosis
The diagnosis is made by histological examination of tumor tissue assisted by immunohistochemical detection of neuroendocrine markers.

The lung neuroendocrine tumors can be divided by histopathology into:

- Typical carcinoid (TC) with highly organized carcinoid architecture and rare mitoses.
- Atypical carcinoid (AC), which shows greater mitotic activity, <10/10HPF and exhibits focal and discrete necrosis.
- Large cell neuroendocrine carcinoma (LCNEC), which may be difficult to differ from atypical carcinoid; it has grater mitotic activity, >10/HPF and necroses are more widespread and confluent.
- Small-cell lung carcinoma (SCLC), which is the most poorly differentiated neuroendocrine tumor of the lung and recognized as a classical ‘oat-cell’ carcinoma. The mitotic activity is very high, >80/10HPF and necrosis is widespread.

Both typical and atypical carcinoids may express the neuroendocrine markers by immunohistochemistry (chromogranin A, synaptophysin and neuron-specific enolase), whereas large-cell carcinoma and small-cell lung carcinoma weakly or rarely express these markers. Thymic neuroendocrine tumors can show a continuous spectrum of differentiation from typical, well-differentiated carcinoid to small-cell neuroendocrine carcinoma type.

staging and risk assessment
There is no specific TNM staging for neuroendocrine bronchial and thymic tumors. The TNM staging should be carried out according to criteria for other lung tumors.

Conventional X-ray of the chest may suggest the diagnosis but CT and bronchoscopy, eventually assisted by endoscopic ultrasonography with biopsies, are the best procedures to detect bronchial neuroendocrine tumors [III, B]. Since 80% of typical bronchial carcinoids express somatostatin receptors, somatostatin receptor scintigraphy may be informative [III, B]. For thymic carcinoids contrast enhanced CT or MRI is recommended to detect the tumor and metastases. Somatostatin receptor scintigraphy is an additional option.

The biochemical findings are dependent on the histological type of bronchial neuroendocrine tumor. The TC presents increased plasma levels of chromogranin A [III, B]. When hormone-related symptoms are present, plasma ACTH, GHRH, IGF-I, urine cortisol, 5-HIAA or histamine metabolites may be elevated [III, B]. The biochemical profile for thymic carcinoid is usually similar to that of bronchial carcinoid.

TC are indolent tumors with a low rate of recurrence. Metastases after adequate resection are rare (7%). Five-year survival rates have been found to be 80%, whereas AC show a 5-year survival rate of 60%. Both LCNEC and SCLC have bad prognosis with 5-year survival rates of <10%. Thymic carcinoids have a 5-year survival rate of 60% for localized tumors, 50% for regional and 29% for distant metastases, and 80% for all stages.

treatment plan
localized tumors
Conservative surgery is the primary treatment for all localized neuroendocrine tumors, both of the lung and the thymus, with 5-year survival rates of 80–100%. Local external irradiation is...
an option for localized disease [III, B], especially if surgery can not be performed.

**metastatic and recurrent disease**

Cytotoxic treatment, combined with surgical resections when possible, has been the standard for metastatic lung and thymic carcinoids. For low-proliferating tumors, treatment with somatostatin analogs and α-interferons might be an option for functional tumors with severe clinical symptoms [III, B]. In non-functional tumors the use of somatostatin analogs is still controversial. Tumor-targeted radioactive treatment is on option in patients with tumors that present a high content of somatostatin receptors [III, B].

**follow-up**

Patients should be followed at 3-month intervals during treatment with cytotoxic agents or biological treatment. After primary surgery patients with TC and AC should be followed at least yearly up to 10 years [III, C]. Biochemical markers, such as chromogranin A, should be determined every 3–6 months and CT or MRI once a year. Metastatic or recurrent disease should be followed more often, with imaging evaluation at least every 6 months.

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

**literature**