Neuroendocrine gastroenteropancreatic tumors: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Neuroendocrine gastroenteropancreatic (GEP) tumors constitute a heterogeneous group of tumors with location of the primary tumors in the gastric mucosa, pancreas, small and large intestine. The crude incidence is ~3.0 cases/100,000/year. The largest group are small intestinal neuroendocrine tumors (midgut carcinoids) with an incidence rate of 2.4/100,000/year. The incidence in autopsy series is significantly higher at 8.4/100,000/year. Neuroendocrine GEP tumors can appear at all ages, with the highest incidence from the fifth decade onwards. Exception is the carcinoid of the appendix, which occurs with the highest incidence below 30 years of age. Patients with multiple endocrine neoplasia, type I (MEN-I) or von Hippel–Lindau’s disease (vHL), may have a clinical onset 15 years earlier than patients with the sporadic type of neuroendocrine tumor.

diagnosis

Patients with clinical symptoms suggesting a neuroendocrine GEP tumor should be referred to a center with particular interest and knowledge in these diseases. The histopathological diagnosis is either performed on tissue samples obtained by open surgery, or by core needle biopsy from metastatic sites. The family of neuroendocrine GEP tumors constitutes a heterogeneous group, but all share common immunohistochemical features (immunoreactivity for the so-called ‘pan-neuroendocrine’ markers) including at least chromogranin A, synaptophysin and neuron-specific enolase (NSE). The proliferation potential should be evaluated with staining for the proliferation marker Ki-67 (MIB1) and expressed as percentage. Depending on clinical symptoms, specific hormonal markers can be searched in the tissue sample, and circulating markers determined in the serum.

staging and risk assessment

There is no specific TNM staging for neuroendocrine GEP tumors. They should be staged according to the organ from which they arise.

Neuroendocrine GEP tumors should be further characterized both by biopsy sample analysis and by determination of specific tumor markers in the plasma (depending on the associated clinical syndrome). Dynamic stimulation tests may be required in specific cases (fasting test for insulinomas; secretin test for gastrinomas, etc.). Determination of non-specific markers such as chromogranin A, NSE, urinary 5-HIIA and serotonin are of clinical value in many neuroendocrine GEP tumors including apparently non-functioning tumors [II, B]. Preoperative staging procedures should include whenever possible somatostatin receptor scintigraphy (Octreoscan) [II, B], although it is not equally sensitive for all neuroendocrine GEP tumors. This technique should always be completed with CT or MRI (depending on the tumour location) which offers, when positive, a more precise anatomical definition. ¹⁸FDG-PET can be useful for staging in less differentiated neuroendocrine GEP tumors.

Patients with endocrine pancreatic tumors often present with metastatic disease except for insulin-producing tumors, which are benign in 80% of cases [II, A]. Depending on size, hormonally inactive tumors are frequently non-metastatic at first diagnosis. The largest group of neuroendocrine GEP tumors are the so-called midgut carcinoids or classical carcinoids. About 40% of these present with a carcinoid syndrome including flushing, diarrhea and endocardial fibrosis. The 5-year survival rate for patients with endocrine pancreatic tumor is estimated to be 60–100% for localized disease, 40% for regional, 29% for metastatic and 80% for all stages. Similarly, for classical midgut carcinoids the 5-year survival rate has been reported to be 60% for all stages.

treatment plan

localized tumors

Surgery is the primary treatment for localized tumors and might be curative giving 5-year survival rates of 80–100% [II, A].

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metastatic and recurrent disease

Even in metastatic disease, surgery plays an important role in reducing tumor mass and can be performed before or concomitantly with medical treatment. Other means of cytoreductive procedures are important, such as radiofrequency ablation, laser therapy and embolization of liver metastases [III, B].

Cytotoxic treatment has been the standard for endocrine pancreatic tumors, but is of limited value for the treatment of low proliferating neuroendocrine GEP tumors. Biological treatment, such as somatostatin analogs and α-interferons has proved effective in control of associated clinical syndromes related to hormone production and release (carcinoid syndrome, gastrinoma, glucagonoma etc.). Their use in non-functioning tumors is still not widely accepted [IV, B]. Tumor-targeted radioactive treatment is an option in patients with tumors that present a high grade of uptake of In111-pentaoctreotide (Octreoscan) scintigraphy.

follow-up

Patients should be followed at 3-month intervals during treatment with cytotoxic agents or biological therapy. Patients undergoing curative surgery should be followed every 3–6 months for >5 years. Examination should include specific or non-specific biochemical markers depending on the associated (or on the lack of) clinical syndrome. Imaging is based on CT or MRI every 6 months. The role of Octreoscan in the follow-up is under evaluation.

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