clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v223–v227, 2010
doi:10.1093/annonc/mdq192

Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

K. Öberg[1], G. Åkerström[2], G. Rindi[3] & S. Jelic[4]
On behalf of the ESMO Guidelines Working Group*

[1]*Department of Endocrine Oncology, University Hospital, Uppsala, Sweden;* [2]*Department of Surgery, University Hospital, Uppsala, Sweden;* [3]*Institute of Pathology, U.C.S.C. Policlinico A. Gemelli, Rome, Italy;* [4]*Internal Medicine Service, Institute of Oncology and Radiology, Belgrade, Serbia*

incidence

Neuroendocrine gastroenteropancreatic tumours (GEP-NET) constitute a heterogeneous group of tumours with their origin in neuroendocrine cells of the embryological gut, most commonly with the primary lesion located in the gastric mucosa, the small and large intestine, the rectum or the pancreas. The crude incidence has significantly increased over the last year, from 3.0 cases/100 000/year to 5.25/100 000/year. The prevalence has recently been calculated as 35/100 000/year. The most recent analysis of the US SEER database indicates an incidence of 0.95/100 000 for small intestinal neuroendocrine tumours (so-called classical carcinoids), 0.86/100 000/year for rectal, 0.32/100 000/year for pancreatic and 0.30/100 000/year for gastric NETs. Neuroendocrine GEP tumours can appear at all ages, with the highest incidence from the fifth decade upwards. Exception is the carcinoid of the appendix, which occurs with the highest incidence at ~40 years of age. There is a slight overall higher incidence of NETs for males (5.35) compared with females (4.76). Patients with multiple endocrine neoplasia type 1 (MEN-I) or von Hippel–Lindau's disease (vHL), may have a clinical onset 15 years earlier than patients with the corresponding sporadic type of neuroendocrine tumour.

diagnosis

Patients with clinical symptoms suggesting a neuroendocrine GEP tumour should be referred to a centre with special interest in and knowledge of these diseases. The histopathological diagnosis is performed on tissue samples obtained either by endoscopic biopsy, open surgery or by core needle biopsy from metastatic sites. The family of neuroendocrine GEP tumours constitutes a heterogeneous group, but all share common histochemical features, with immunoreactivity for the so called 'pan-neuroendocrine' markers, including chromogranin A and synaptophysin. The proliferation potential should be evaluated by staining with the proliferation marker Ki-67 (MIB-I). Depending on clinical symptoms, specific hormonal markers can be searched for in the tissue sample, but it must be remembered that there is not always a correlation between tissue expression of hormones and amines and circulating levels. All patients should have an analysis of chromogranin A in plasma as a general tumour marker and depending on clinical symptoms, other markers should be analysed such as urinary 5HIAA for the carcinoid syndrome, gastrin for the Zollinger–Ellison syndrome and insulin/pro-insulin for the hypoglycaemic syndrome. Dynamic stimulation tests may be required in specific cases (fasting test for insulinomas; secretin test for gastrinomas, etc.).

staging and risk assessment

Neuroendocrine tumours arising at different anatomical sites of the digestive system represent tumour entities that differ in their biology and clinical presentation (Table 1). The WHO classification system was established in year 2000 (Table 2), dividing the tumours into well-differentiated endocrine tumour, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinoma and mixed exocrine and endocrine tumours. Recently the European Neuroendocrine Tumor Society has proposed a TNM staging and grading system for various types of GEP-NET (Tables 3–8). Pre-operative staging should whenever possible include somatostatin receptor scintigraphy (Octreoscan), although it is not equally sensitive for all GEP-NETs. This technique should always be complemented with CT or MRI (depending on the tumour location), which can generally provide more precise anatomical definition if positive. PET scanning with specific tracers, such as [^{11}C]5-HTP, [^{18}F]DOPA or

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: August 2007, last update December 2009. This publication supercedes the previously published version—Ann Oncol 2009; 20 (Suppl 4): iv150–iv153.

Conflict of interest: Professor Öberg and Professor Åkerström have reported no conflicts of interest; Professor Rindi has reported that he is a consultant for IPSEN Pharma and that he has been in the speakers' bureau and received a research grant from Novartis Pharma; Dr Jelic has reported no conflicts of interest.

Table 1. Classification of neuroendocrine GEP tumours (GEP-NETs) by site of origin and by hormonal activity

Intestinal neuroendocrine tumours (carcinoids, about two-thirds of GEP-NETs)
with carcinoid syndrome (30% of carcinoids)
without carcinoid syndrome (70% of carcinoids)
Pancreatic endocrine tumours (PETs) (about one-third of GEP-NETs)
Non-functioning (45%–60% of PETs)
Functioning (40%–55% of PETs)
Gastrinoma, excessive gastrin production, Zollinger–Ellison syndrome
Insulinoma, excessive insulin production, hypoglycaemia syndrome
Glucagonoma, excessive glucagon production, glucagonoma syndrome
VIPoma, excessive production of vasoactive intestinal peptide (VIP), watery diarrhoea, hypokalaemia–achlorhydria (WDHA) syndrome
PPoma, excessive pancreatic polypeptide (PP) production, (generally classified as non-functioning PETs)
Somatostatinoma, excessive somatostatin production
CRHoma, excessive corticotropin-releasing hormone (CRH) production
Calcitoninoma, excessive calcitonin production
GHRHoma, excessive growth hormone-releasing hormone (GHRH) production
Neurotensinoma, excessive neurotensin production
ACTHoma, excessive production of adrenocorticotropic hormone (ACTH)
GRFoma, excessive production of growth hormone-releasing factor (GRF)
Parathyroid hormone-related peptide tumour

Table 2. GEP-NET neoplasm: WHO classification

WHO 1	Well differentiated endocrine tumour
WHO 2	Well differentiated endocrine carcinoma
WHO 3	Poorly differentiated endocrine carcinoma
	Mixed exocrine-endocrine tumours
	Tumour-like lesions

[^{68}Ga]DOTA-octreotate can further optimize the staging of the disease. However, ^{18}FDG PET is only of value in poorly differentiated GEP-NET tumours. Endoscopy (gastroscopy, endoscopic ultrasonography, colonoscopy, etc.) is often of additional value.

Patients with endocrine pancreatic tumours, often present with metastatic disease, except for insulin-producing tumours, which are benign in 85% of cases [II, A]. The largest group of GEP-NETs, well-differentiated (neuro-)endocrine tumours of the small intestine (midgut carcinoids), present with the carcinoid syndrome in ~30%, including flushing, diarrhoea and endocardial fibrosis. The 5-year survival rate for patients with endocrine pancreatic tumours is estimated to be 60%–100% for localized disease, 40% for regional, 25% for metastatic and 80% for all stages. Similarly for 'classical' midgut carcinoids, the 5-year survival rate has been 60% for all stages.

Table 3. TNM classification for gastric endocrine tumours (European Neuroendocrine Tumour Society)

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	*In situ* tumour/dysplasia (<0.5 mm)
T1	Tumour invades lamina propria or submucosa and 1 cm
T2	Tumour invades muscularis propria or subserosa or >1 cm
T3	Tumour penetrates serosa
T4	Tumour invades adjacent structures
	For any T, add (m) for multiple tumours
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Table 4. TNM classification for endocrine tumours of the duodenum/ampulla/proximal jejunum (European Neuroendocrine Tumour Society)

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades lamina propria or submucosa and has a size <1 cm
T2	Tumour invades muscularis propria or size >1 cm[a]
T3	Tumour invades pancreas or retroperitoneum
T4	Tumour invades peritoneum or other organs
	For any T, add (m) for multiple tumours
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastases
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

[a]Tumour limited to the Ampulla of Vater for ganglyocitic paraganglioma.

Patients with high-grade poorly differentiated (neuro-) endocrine carcinomas present a median survival of only 10 months. In multivariate analyses of prognostic factors in GEP-NETs, pancreatic localization, poor degree of differentiation and distant metastases were negative prognostic factors [II, A].

treatment plan

localized disease

Surgery is the primary treatment for localized tumours and might be curative providing 5-year survival rates of 80%–100% in resectable cases. It is so far the only curative treatment [II, A].

Table 5. TNM classification for endocrine tumours of the pancreas (European Neuroendocrine Tumour Society)

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour limited to the pancreas and size <2 cm
T2	Tumour limited to the pancreas and size 2–4 cm
T3	Tumour limited to the pancreas and size >4 cm or invading duodenum or bile duct
T4	Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)
	For any T, add (m) for multiple tumours
N	Regional lymph nodes
NX	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastases
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Table 6. TNM classification for endocrine tumours of lower jejunum and ileum (European Neuroendocrine Tumor Society)

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades mucosa or submucosa and has a size <1 cm
T2	Tumour invades muscularis propria or size >1 cm
T3	Tumour invades subserosa
T4	Tumour invades peritoneum/other organs
	For any T add (m) for multiple tumours
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

treatment of extensive disease

The majority of patients present with metastatic disease. Even with metastatic disease, surgery plays an important role by reducing tumour masses (debulking, bypassing) and can be performed before or concomitantly with medical treatment. Resection of metastasis is a potential curative option when R0 resection is possible [III, B]. Other means of cytoreductive procedure are of importance, such as radiofrequency ablation (RF) and embolization/chemoembolization of liver metastases [III, B]. Liver transplantation can be considered in selected cases, young patients without documented spread outside the liver and resected primary tumour [III, B].

Table 7. TNM classification for endocrine tumours of colon and rectum (European Neuroendocrine Tumor Society)

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades mucosa or submucosa
	T1a size <1 cm
	T1b size 1–2 cm
T2	Tumour invades muscularis propria or size >2 cm
T3	Tumour invades subserosa, pericolic, perirectal fat
T4	Tumour directly invades other organs/structures and/or perforates visceral peritoneum
	For any T add (m) for multiple tumours
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Table 8. Gut endocrine tumours: tumour grading and classification: ENETS grading proposal

Grading proposal for foregut neuroendocrine tumours		
Grade	Mitotic count (10 HPF)[a]	Ki67 Index (5)[b]
G1	≤2	≤2
G2	2–20	3–20
G3	>20	>20

[a]10 HPF, high-power field = 2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.
[b]MIB1 antibody; percentage of 2000 tumour cells in areas of highest nuclear labelling.
Virchows Arch 2006; 449: 395–401.
Virchows Arch 2007; 451: 757–762.

Cytotoxic treatment has been of limited value for the treatment of low-proliferating GEP-NET tumours, such as the typical midgut carcinoids (response rates ∼10%–15%), but has been the standard of care for malignant endocrine pancreatic tumours (with response rates ∼30%–50%). Currently the following cytotoxic agents are applied: streptozotocin plus 5-flurouracil (5FU)/doxorubicin (response rates ∼30%), temozolomide alone or in combination with capecitabine (RR ∼35%–40%). Poorly differentiated tumours (WHO group 3) are mostly treated with cisplatinum/oxaliplatin plus etoposide (response rates ∼40%–60%) usually of short duration (Table 9).

Biological treatment, such as somatostatin analogues and α-interferons has proved effective in the control of associated clinical syndromes related to hormone production and release (carcinoid syndrome, VIPoma and glucagonoma syndrome). Their use in non-functioning tumours has been debated, but

Table 9. Chemotherapy.

Reference	Type of tumour	Regimen	No. of patients	Objective response	Response duration (months)	Median survival (months)
Moertel et al.	Pancreatic	STZ	42	36	17	16.5
		STZ + 5FU	42	63	17	26
Eriksson et al.	Pancreatic	STZ + 5FU or DOX	44	45	27.5	–
Moertel et al.	Pancreatic	STZ + DOX	36	69	18	26
		STZ + 5FU	33	45	14	18
Cheng and Saltz	Pancreatic	STZ + DOX	16	6	18	–
McCollum *et al.*	Pancreatic	STZ + DOX	16	6	3.9	20.2
Kouvaraki *et al.*	Pancreatic	STZ + DOX + 5FU	84	39	9.3	40
Moertel and Hanley	Carcinoids	5FU + cyclophosphamide	47	33	–	–
		STZ + 5FU	42	33	–	–
Engstrom *et al.*	Carcinoids	STZ + 5FU	80	22	8	16
		DOX	81	21	6.5	12
Bukowski *et al.*	Carcinoids	STZ + DOX + 5FU + cyclophosphamide	56	31	–	–
		STZ + 5FU + cyclophosphamide	9	22	–	10.8
Sun *et al.*	Carcinoids	DOX + 5FU	25	15.9	4.5	15.7
		STZ + 5FU	27	16	5.3	24.3
Moertel *et al.*	Poorly differentiated	Cisplatin + etoposide	18	67	8	19
Mitry *et al.*	Poorly differentiated	Cisplatin + etoposide	41	42	9	15
Fjallskog *et al.*	Poorly differentiated	Cisplatin + etoposide	36	47	9	–

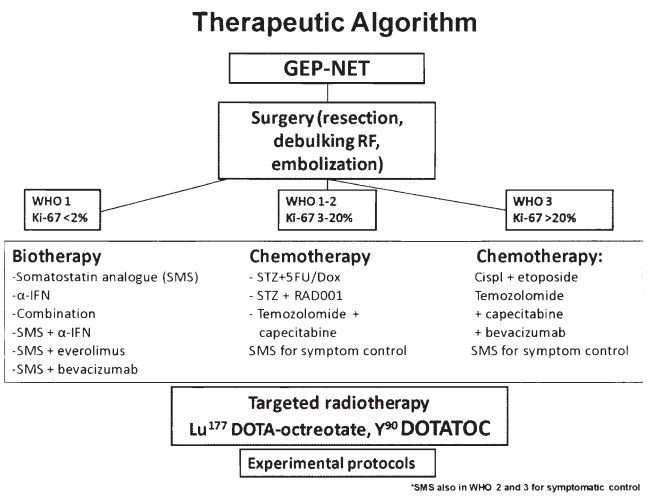

Figure 1. Therapeutic algorithm.

a recent study has indicated an antiproliferative effect by somatostatin analogues in both functioning and non-functioning tumours (the PROMID study) [II, B]. A combination of somatostatin analogues and α-interferons has been effective in patients with resistance to either drug. Furthermore, α-interferon up-regulates the numbers of somatostatin receptor type 2 [III, B].

Peptide receptor radiotherapy (PRRT) treatment is an option in patients who present with high-grade uptake on somatostatin receptor scintigraphy [III, B]. The precise role of PRRT has to be defined by future randomized trials and is usually applied as second-line therapy. Recently antiangiogenic agents (bevacizumab, sunitinib) and m-TOR inhibitors (RAD001, everolimus) have been applied in GEP-NETs with objective response rates of 10%–20%. A treatment algorithm is presented in Figure 1. This algorithm is based on the WHO classification and the ENETS guidelines for treatment of GI-NETs.

response evaluation

Response to current treatment should be evaluated by both biochemical markers and imaging. Chromogranin A is an important and stable marker that can be followed during long-term treatment, in both functioning and non-functioning tumours; CT scans or MRI are standards for treatment evaluation.

follow-up

Patients with malignant neuroendocrine tumours are usually followed at 3-month intervals during treatment with cytotoxic agents or biological therapy to evaluate the treatment response. The same is true for treatment with PRRT. Patients undergoing curative surgery should be followed every 3–6 months for >5 years. Biochemical testing is suggested every 3 months and imaging every 6 months.

notes

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

1. Yao JC, Hassan M, Phan A et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063–3072.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934–959.
3. Chandrasekharappa SC, Guru SC, Manickam P et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997; 276: 404–407.
4. Latif F, Tory K, Gnarra J et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 1993; 260: 1317–1320.
5. Solcia E, Klöppel G, Sobin LH. Histological Typing of Endocrine Tumours. World Health Organization Histological Classification of Tumours, 2nd edition. New York: Springer 2000 38–74.
6. Eriksson B, Oberg K, Stridsberg M. Tumor markers in neuroendocrine tumors. Digestion 2000; (62 Suppl 1): 33–38.
7. Rindi G, Klöppel G, Alhman H et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449: 395–401.
8. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab 2007; 21: 43–68.
9. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21: 69–85.
10. Panzuto F, Nasoni S, Falconi M et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocrine-Related Cancer 2005; 12: 1083–1092.
11. Sarmiento JM, Heywood G, Rubin J et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surgeons 2003; 197: 29–37.
12. Akerstrom G, Hellman P. Surgery on neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21: 87–109.
13. Toumpanakis C, Meyer T, Caplin ME. Cytotoxic treatment including embolization/chemoembolization for neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21: 131–144.
14. Öberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 2001; (12 Suppl 2): S111–S114.
15. Plöckinger U, Wiedenmann B. Neuroendocrine tumors: biotherapy. Best Pract Res Clin Endocrinol Metab 2007; 21: 145–162.
16. Rinke A, Müller H-H, Schade-Brittinger C et al. Placebo controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol 2009; 27: 4656–4663.
17. Van Essen M, Krenning EP, Kam BL et al. Peptide-receptor radionuclide therapy for endocrine tumors. Nat Rev Endocrinol 2009; 5: 382–393.
18. Yao JC. Neuroendocrine tumors. Molecular targeted therapy for carcinoid and islet-cell carcinoma. Best Pract Res Clin Endocrinol Metab 2007; 21: 163–172.
19. Klöppel G, Couvelard A, Perren A et al. ENETS guidelines for the standards of care in patients with neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology 2008 Dec 5.