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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETS)

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Abstract Gastroenteropancreatic neuroendocrine tumours (GEP NETs) represent a heterogenous family of tumours with growing incidence and challenging clinical management. Unlike other solid tumours, they have the ability to secrete different peptides and neuramines that cause distinct clinical syndromes. However, many are clinically silent until advanced disease. This guideline aims to provide practical recommendations for the diagnosis and treatment of GEP NETs. Most recent histological and staging classifications, as well as available therapeutic approaches, such as surgery, locoregional therapy, peptide receptor radionuclide therapy (PRRT) and hormonal or systemic therapy, are discussed in this manuscript, including some recent relevant achievements with novel targeted agents. Clinical presentation (with or without hormonal syndrome), histological tumour features (including proliferation index (Ki-67) and the presence or not of somatostatin receptors), tumour stage, and location of primary tumour and distant metastasis are all key issues that shall be taken into consideration to properly design and integrate the most adequate therapeutic strategy.

Keywords Guidelines · Neuroendocrine tumours · Enteropancreatic · Diagnosis · Therapy

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Introduction

Neuroendocrine tumours (NETs) comprise a heterogeneous family of neoplasms with a wide and complex spectrum of clinical behaviour. The incidence of NETs ranges from 2.5 to 5 cases per 100,000 in Caucasian populations and has substantially increased over the last decades, probably due in part to improved diagnostic techniques and clinical awareness. Moreover, the prevalence of these tumours is rather high due to their relatively long survival, ranging from 35% to 60% at 5 years for patients with advanced disease. In fact, gastroenteropancreatic NETs are the second most prevalent tumours derived from the digestive tract after colorectal carcinoma [1–3]. Age at diagnosis is generally younger than for carcinomas (5th decade) and they may arise sporadically or as a result of hereditary predisposition syndromes such as multiple endocrine neoplasia type 1 (MEN-1) or Von Hippel-Lindau's disease (VHL). Clinical onset in patients with genetic predisposition may occur 15 years earlier.

Diagnosis and staging

Diagnosis

NETs originate in a great diversity of tissues and are characterised by their ability to produce different peptides that cause distinct hormonal syndromes (Table 1). Based

Table 1 Clinical features of GEP-NETs

Tumour	Hormone	Islet cell type	Clinical syndrome
Carcinoid	Serotonin		Flushing, diarrhoea, bronchospasm, tricuspid insufficiency, pulmonary valve stenosis
Gastrinoma	Gastrin	γ	Zollinger-Ellison syndrome: recurrent peptic ulcer, diarrhoea/esteatorrhoea
Insulinoma	Insulin	β	Hypoglycaemia, catecholamine excess
Glucagonoma	Glucagon	α	Diabetes mellitus, migratory necrolytic erythema, panhypoaminoaciduria, thromboembolism, weight loss
VIPoma	VIP	δ	Verner-Morrison syndrome (WDHA): watery diarrhoea, hypokalaemia, achlorhydria, metabolic acidosis, hyperglycaemia, hypercalcaemia, flushing
Somatostatinoma	Somatostatin	δ	Diabetes mellitus, diarrhoea/steatorrhoea, hypochlorhydria, weight loss, gall bladder disease
PPoma	PP	PP cells	Hepatomegaly, abdominal pain, occasional watery diarrhoea

on this, NETs are broadly subdivided into "functional" or "nonfunctional" tumours (with or without a clinical syndrome). Most NETs arise from the gut or bronchopulmonary system and these endocrine tumours are commonly called carcinoid tumours. Carcinoid is also a generic term for a characteristic syndrome that results from the intermittent release of bioactive amines into the systemic circulation that occurs in some patients with NETs.

The most frequent functionally active NETs are, besides carcinoids, insulinoma, gastrinoma, vasoactive intestinal polypeptidoma (VIPoma) and glucagonoma. Nonfunctional tumours are often clinically silent until late advanced disease. Although these neoplasms are generally more indolent than carcinomas, they often have unpredictable biological behaviour and are on occasion associated with a very aggressive clinical course.

In order to appropriately diagnose and stage gastroenteropancreatic neuroendocrine tumour (GEP NETs) the following procedures are recommended:

- Medical history and physical examination.
- Laboratory tests, including liver and renal function tests.
- General hormonal markers: chromogranin A.
- Specific hormonal markers: urinary 5-HIAA (carcinoid syndrome); gastrin±secretin test (gastrinomas); insulin/glucose ratio, proinsulin, C peptide (insulinomas), glucagon, VIP and others depending upon clinical symptoms.
- Tumour specimen or biopsy: the histopathological report shall provide the WHO classification and TNM staging [4–6]. Immunohistochemical staining should always include Ki-67 (% of positive cells assessed in 2000 tumour cells in areas of highest nuclear labelling) and general neuroendocrine markers (chromogranin A, synaptophysin and neuron-specific enolase). Specific markers should only be tested if clinically indicated (insulin, glucagon, etc.).
- Somatostatin receptor scintigraphy (octreoscan).
- Dynamic CT scan of the abdomen.
- Chest X-ray. A thoracic CT scan may be considered in poorly differentiated tumours, colon primaries or those in whom surgery of liver metastasis is being considered.
- Genetic counselling in hereditary predisposition syndromes (MEN-1, VHL).

Depending upon clinical presentation and primary tumour site, the following procedures may be also considered:

- Oral endoscopy, enteroscopy, capsule endoscopy, endoscopic ultrasound, colonoscopy.
- FDG-PET (poorly differentiated NET metastasis of unknown primary; no use in low-grade tumours).
- Echocardiogram (carcinoid syndrome).
- Brain CT scan or bone scan (only if bone pain, neurological symptoms,…).

Staging

Recent international efforts are helping to improve the prognostic classification of this type of tumour and to better tailor therapeutic strategies in these patients. There are three major classifications in current clinical use: (1) the WHO classification [4], (2) the European NET Society (ENETS) TNM and grading system (proposed in 2006–2007; at that time no International Union Against Cancer (UICC) TNM classification specific for NETs existed) [5, 6] and (3) the UICC TNM system (7th edition, 2010) [7] (Tables 2 and 3). A unified worldwide TNM classification is under development.

Therapy

Surgery

Surgery is the only potentially curative therapeutic strategy in localised disease. Radical oncological surgery is indicated except for small carcinoids (<2 cm) of the stomach, appendix or rectum, in which more conservative surgical or endoscopic resections may be appropriate due to their low malignant potential. Small pancreatic insulinomas also have a very good prognosis (90% are benign tumours) and tumour enucleation is generally sufficient [3]. No adjuvant therapy is recommended in completely resected, well dif-

Table 2 TNM classification of NETs

GI tract:
– Carcinoid: separate staging by site
– Small cell/large cell: stage as carcinoma
Pancreas: stage as carcinoma
Lung: stage as carcinoma
Skin: separate classification for Merkel cell carcinoma

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ferentiated localised NETs. Adjuvant chemotherapy with platinum and etoposide may be considered in poorly differentiated tumours.

Surgery also plays a major role in advance disease. Surgery of metastasic disease is recommended if complete resection is feasible. Major cytoreductive therapy with palliative purposes may be considered even if R0 is not achievable in patients with extensive liver metastasis and hormonal syndrome refractory to medical therapy. Some advocate that this procedure may also extend survival and could therefore be considered in non-functioning tumours. However, data in this regard are not robust and need formal validation. Prophylactic cholecystectomy to prevent colelitiasis is recommended in patients undergoing surgery if treatment with somatostatin analogues is anticipated. Surgery of the primary tumour may be performed in selected patients to avoid obstruction due to the neoplasm or to the fibrotic reaction commonly associated with small-bowel carcinoids. Perioperative prophylactic therapy with somatostatin analogues is indicated in functional tumours to prevent carcinoid crisis.

Interventional radiology

In patients who are not suitable candidates for surgery, regional control of liver metastases may be achieved by different ablative techniques such as radiofrequency ablation, laser ablation and cryotherapy, among others [3]. Reduction of tumour burden often leads to a reduction of hormone secretion and, consequently, an improvement in symptom control. Other locoregional approaches include embolisation of the hepatic artery by particles or cytotoxic agents (chemoembolisation). These therapeutic strategies are based on the fact that, unlike normal hepatocytes, NET liver metastases are preferentially supplied by arterial rather than portal blood. They are generally employed with palliative purposes in patients with slow growing functional tumours refractory to medical therapy, but may also be useful to reduce tumour burden and control tumour progression in non-functioning tumours. Doxorubicin, streptozocin, mitomycin and fluorouracil are commonly used agents in this context, although randomised studies that properly evaluate the benefit-risk ratio of chemoembolisation with that of mechanical embolisation are lacking. Clinical responses have been reported in up to 80% of the patients and radiological responses in about 50%. Common adverse events include pain, fever or elevation of liver enzymes. Severe complications occur in 10% of cases and

Table 3 TNM staging for gastrointestinal NETs

Appendix	Stomach
T1 ≤2 cm	Tis <0.5 mm confined to mucosa
T2 >2–4 cm; caecum	T1 Lamina propria or submucosa & ≤1 cm
T3 >4 cm; ileum	T2 Muscularis propria or >1 cm
T4 Perforates peritoneum; other organs, structures	T3 Subserosa
	T4 Perforates serosa; adjacent structures
Small intestine	**Large intestine**
T1 Lamina propria/submucosa and ≤1 cm	T1 Lamina propria or submucosa or ≤2 cm; T1a ≤1 cm; T1b 1–2 cm
T2 Muscularis propria or >1 cm	T2 Muscularis propria or >2 cm
T3 Jejunal, ileal: subserosa. Ampullary, duodenal: pancreas or retroperitoneum	T3 Subserosa or pericolorectal tissues
T4 Perforates serosa; adjacent structures	T4 Perforates serosa; adjacent structures

Carcinoid: appendix			Carcinoid: other GI sites		
Stage I	T1	N0	Stage I	T1	N0
Stage II	T2, T3	N0	Stage IIA	T2	N0
Stage III	T4	N0	Stage IIB	T3	N0
	Any T	N1	Stage IIIA	T4	N0
Stage IV	Any T Any N	M1	Stage IIIB	Any T	N1
			Stage IV	Any T	Any M M1

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include acute liver or renal failure, liver abscess, cholecystitis or carcinoid crisis. Embolisation is contraindicated in patients with portal-vein thrombosis, liver insufficiency, biliary obstruction or prior Whipple procedure.

Systemic therapy

Patients with advanced disease have limited therapeutic options. Indeed, NETs exhibit low susceptibility to conventional cytotoxic therapy. Long-acting somatostatin analogues currently provide the best treatment to achieve symptomatic relief and some limited data suggest they may also retard disease progression. Symptomatic therapy in functional NETs may also include other specific drugs according to the hormone or peptide secreted in excess by the tumour, such as proton pump inhibitors in gastrinomas, diazoxide or glucagon in insulinomas, insulin or other pancreatic hormones in somatostatinomas, etc. Other means of achieving disease control include peptide-receptor radionuclide therapy. However availability and lack of controlled trials limit its widespread use. Recently, two new targeted agents, sunitinib and everolimus, have demonstrated for the first time a clinically relevant antiproliferative effect in well differentiated NETs of pancreatic origin. Everolimus may also prolong disease progression in non-pancreatic NETs. However, the magnitude of this effect is more limited. A number of other targeted agents are currently in clinical development and may add to the treatment armamentarium in the near future. A therapeutic algorithm is proposed in Figures 1 and 2 [8].

Somatostatin analogues and interferon

Somatostatin analogues remain the most effective drugs for symptom control in functional GEP NETs. Indeed, 70–80% of patients experience resolution of diarrhoea or flushing, and about 40% achieve biochemical response, although tumour regression is rare. More recently, a randomised double-blind placebo-controlled trial conducted in 85 patients with well differentiated metastatic midgut NETs showed that patients treated with octreotide LAR (30 mg every 28 days) had a significantly longer time to tumour progression (14.3 months) than patients treated with placebo (6 months) [HR: 0.34; 95% CI 0.20–0.59; $p<0.001$]. The greatest effect was observed in patients with low hepatic tumour load and resected primary tumour [9]. Data were not yet ready for overall survival analysis. The most convenient formulations are currently lanreotide autogel (60, 90 or 120 mg) and long-acting octreotide (10, 20 or 30 mg). Adverse effects are mild and manageable, and include malabsorption, endocrine disturbances (hypothyroidism, hypoglycaemia or, more commonly, hyperglycaemia), pain and erythema at the site of injection, hypersensitivity reactions and cholelithiasis upon long-term use [3, 8].

Interferon is also effective in terms of symptomatic control of the hormonal syndrome, but its use is limited by substantial adverse effects (alopecia, anorexia, fatigue, depression, weight loss, fever, a flu-like syndrome and myelosuppression). Although some small randomised trials have shown a trend towards an improved disease progression or overall survival when interferon was added to somatostatin analogues, this benefit was not consistently observed in all trials or did not reach statistical significance [3, 8]. For this reason it is generally indicated after failure of other therapies.

Peptide-receptor radionuclide therapy

Patients with advanced disease and a positive octreoscan may be considered for peptide receptor radionuclide therapy (PRRT). The optimal radionuclide is still to be determined, but treatment with 90Yttrium octreotide (90Y-DOTATOC), 90Y-lanreotide and Lu177-DOTA octreotate has been reported to achieve not only tumour stabilisation but also tumour regression (objective partial responses) in up to 30% of GEP NETs [10]. However, experience is limited to single-institution selected series and randomised controlled trials are lacking. In addition, the non-availability of this therapeutic strategy in most countries further limits its widespread use. The appropriate timing of this therapeutic intervention or the relative long-term benefit-risk ratio compared to other treatment options are key questions that remain unanswered. Alternatively, 131Iodine-metaiodiobenzylguanidine (MIBG) therapy may be considered in advanced tumours with a positive MIBG scan (20–50% of NETs).

Chemotherapy

Conventional cytotoxic therapy is considered the first treatment option for poorly differentiated or rapidly progressive advanced GEP NETs, the combination of cisplatin and etoposide being the most widely used chemotherapy regimen. Well differentiated tumours, particularly those of enteric or non-pancreatic origin, have a more indolent clinical course and are less responsive to chemotherapy. Indeed, radiological, biochemical and clinical responses are far more frequently observed in pancreatic NETs and, therefore, chemotherapy may be considered in this context as an early therapeutic intervention for advanced disease. In contrast, in GI NETs this treatment option is generally reserved for patients with tumours refractory or progressive to other therapeutic strategies (somatostatin analogues, interferon, locoregional treatment,…) and may soon be replaced by new emergent targeted agents. A combination of streptozotocin with doxorubicin or 5-fluorouracil is commonly employed, with response rates of 8–20% reported in recent series [3, 8, 11]. These combination schedules showed improved response rates and/or survival compared to single-agent therapy in some old classical randomised clinical trials. However, the antitumour efficacy of these agents against placebo or best supportive care

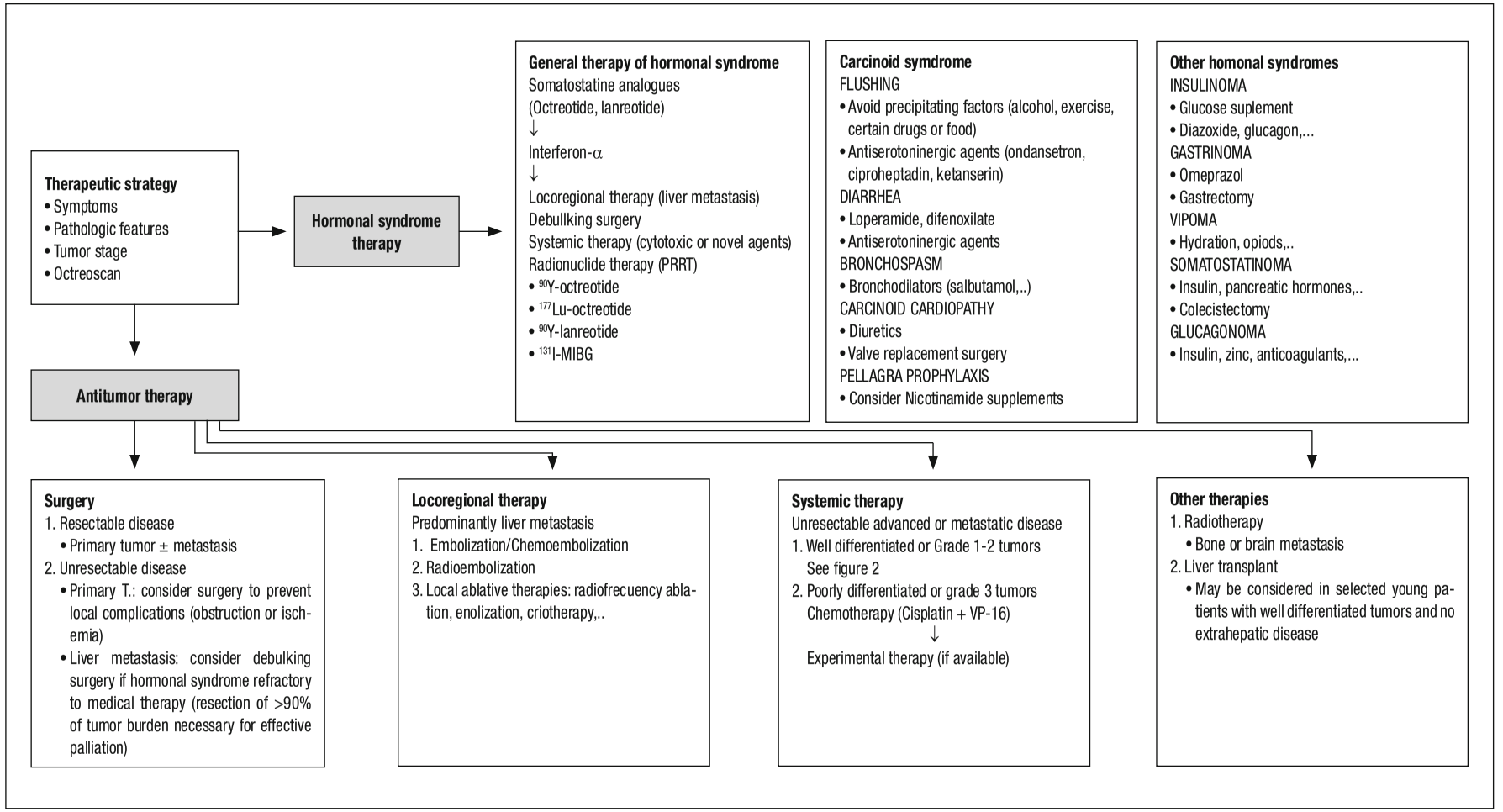

Fig. 1 Therapeutic algorithm in GEP NETs

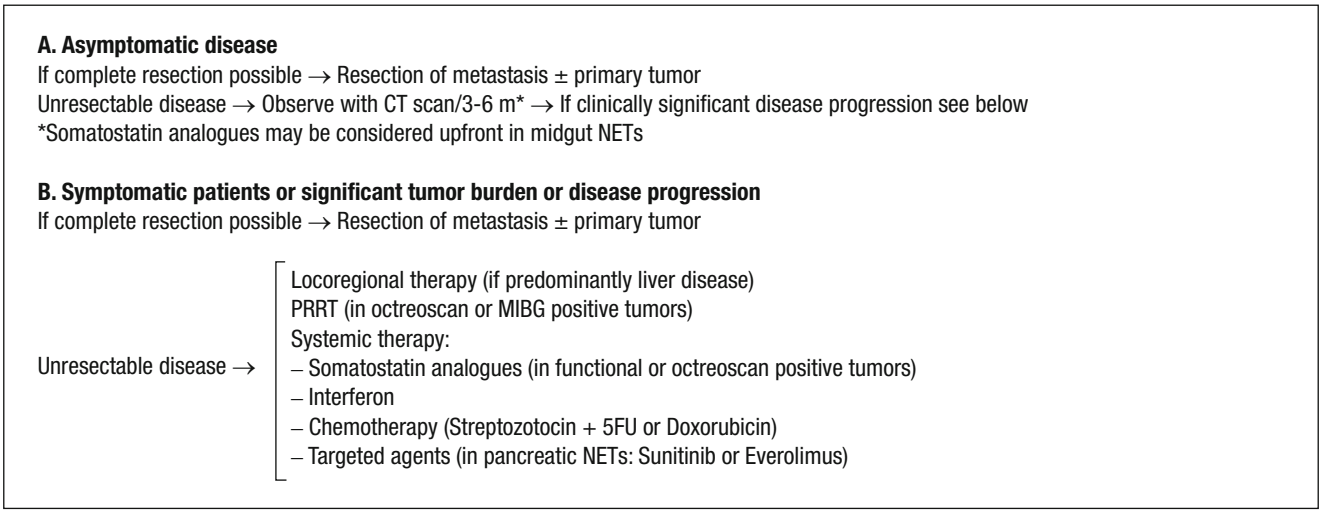

Fig. 2 Management of advanced/metastatic low- or intermediate-grade GEP NETs

has never been adequately evaluated in controlled trials. Other active drugs include dacarbazine or temozolomide.

Novel targeted agents

Several recent adequately powered randomised trials have for the first time demonstrated that there are agents able to positively impact the outcome of this disease, in particular angiogenesis and mTOR inhibitors. Sunitinib, a tyrosine kinase inhibitor that targets, among others, VEGFR, PDGFR and c-kit, was evaluated in a randomised placebo-controlled trial in patients with progressive well differentiated pancreatic NETs not suitable for curative surgery [12]. Crossover of placebo patients to sunitinib at disease progression was not initially permitted. About two thirds of patients had received prior chemotherapy and 20–22% were receiving concomitant somatostatin analogues. This study aimed to include 340 patients but was prematurely closed with 171 patients due to the excess of deaths observed in the placebo arm. At that point, patients who had progressed on the placebo arm became candidates for open-label sunitinib therapy. Although objective responses were only observed in 9% of treated patients, progression-free survival was significantly superior in patients treated with sunitinib vs. those receiving placebo (11.4 vs. 5.5 months; HR 0.42; p=0.001), as well as overall survival (HR 0.41, p=0.02). Toxicity was manageable, the main severe adverse events being neutropenia, hypertension and hand-foot syndrome. Based on these results the European Medicines Agency has recently granted approval for the use of sunitinib in this disease. On the other hand, mTOR inhibitors are also emerging as new effective drugs for NETs. Two large phase III trials were reported in 2010. The first one, the RADIANT-3 study, was conducted in 410 patients with progressive advanced low- or intermediate-grade pancreatic NETs who were randomly assigned to everolimus or placebo with a double-blind crossover study design [13]. Fifty percent of patients had received prior chemotherapy. Again, objective responses were low (5%), but patients treated with everolimus had a significantly longer progression-free survival than those treated with placebo (11.4 vs. 5.4 months, HR 0.34, p<0.0001). No impact was observed on survival, but this may be explained by the fact that 73% of patients on placebo crossed over to everolimus at disease progression. The safety profile of everolimus was acceptable, with mucositis, infections and pulmonary events as the major severe adverse events. The second large study, RADIANT-2, included 429 patients with low- or intermediate-grade advanced NETs with a history of carcinoid syndrome (the great majority of non-pancreatic origin). These patients were randomly allocated to receive octreotide LAR with placebo or with everolimus, with cross-over to everolimus allowed at disease progression for placebo allocated patients [14]. Median progression-free survival evaluated by local investigators was 12 months versus 8.6 months for everolimus versus placebo treated patients, respectively (HR 0.78, 95% CI [0.62-0.98] $P_{unilateral}$=0.036), although this benefit was of borderline statistical significance by blinded central review (HR 0.77; 95% CI [0.59 -1.00] $P_{unilateral}$=0.026). Similar to what was observed in the prior study, a high proportion of patients on the placebo arm crossed over to everolimus at disease progression (58%) and no differences were observed in overall survival among study arms. Based on these data, everolimus is currently being evaluated by regulatory authorities for potential marketing authorisation in this disease. Another agent in advanced clinical evaluation is bevacizumab, which is currently being tested in a randomised trial against PEG-interferon in carcinoid tumours, the results of which are eagerly awaited in the near future.

In conclusion, sunitinib and everolimus (the latter pending marketing authorisation) are new treatment options

in patients with low- or intermediate-grade pancreatic NETs in whom disease progression has been documented. Whether these agents should be employed before or after chemotherapy failure is a matter of debate. The efficacy of both agents seems similar, although no formal head-to-head comparisons exist or are expected to be performed in the near future. Regarding the use of everolimus in non-pancreatic functional NETs, while a final decision from the regulatory authorities is awaited, no firm recommendations can be made yet, as the reported benefit is of lower magnitude and further analysis of data is currently ongoing. Efforts to provide predictive biomarkers to help select subgroups of patients that are more likely to benefit from each individual drug are certainly warranted.

Follow-up

Follow-up recommendations are based on expert opinion as there is no solid evidence to support the type and frequency of performance of specific procedures. Patients with localised disease who have undergone complete resection are recommended to be followed every 6–12 months for at least 5 years in order to detect potentially resectable recurrences. General or specific markers may be tested depending on whether the tumour presented a hormonal syndrome or not. Imaging procedures (CT scan or MRI) shall be performed every 6 months. The role of octreoscan in follow-up is currently being evaluated.

Conflict of interest Rocío García-Carbonero: advisory board for Pfizer and Novartis and research funds from Ipsen. Ramón Salazar: advisory board for Pfizer, Ipsen and Novartis and research funds from Novartis. Isabel Sevilla: advisory board for Pfizer, Novartis, Ipsen and Keocyt. Dolores Isla: no conflict of interest to declare

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