

# Management of neuroendocrine tumours

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## Introduction

Neuroendocrine (NE) tumours of the gastrointestinal tract and pancreas constitute about 2% of all malignant tumours. They include a number of different tumours, derived from cells of the diffuse NE cell system [1]. The largest group of NE tumours are the so-called carcinoids, with an incidence of about 2.5/100 000 [2], which by tradition have been divided into foregut, midgut and hindgut tumours. This old classification is based on the embryonic origin of the different tumours, where the foregut primaries have been located in the lung, thymus, gastric mucosa; the midgut with primary tumours in the ileum, caecum and proximal colon; and the hindgut with the primaries in the distal colon and rectum. This old classification is now about to be abandoned, and a more tumour-based classification has emerged. The new World Health Organization (WHO) classification now indicates five subtypes [3]:

- 1 well-differentiated endocrine tumour
- 2 well-differentiated endocrine carcinoma
- 3 poorly differentiated endocrine carcinoma
- 4 mixed exocrine and endocrine carcinomas
- 5 tumour-like lesions.

This classification can be used for all types of NE tumour; not only for carcinoids.

A classical midgut carcinoid will, in the new terminology, be classified as a *well-differentiated endocrine carcinoma of the ileum*, whereas a benign insulin-producing tumour of the pancreas will be a *well-differentiated endocrine tumour of the pancreas*. The differentiation between different tumour types is based on histomorphology, tumour size and the presence or absence of local invasion and/or metastases. This new classification of NE tumours is a step forward, although the former classification of carcinoid tumours into foregut, midgut and hindgut remains clinically available and is still used in many clinical studies. It will take some time for the new classification to be generally accepted.

NE tumours exhibit substantial differences in terms of genotype and phenotype. Foregut carcinoids mainly located in the lung but also endocrine pancreatic tumours, frequently show loss of 11q, which represent a characteristic genetic alteration in these tumours. Both typical and atypical carcinoids of the lung show loss of heterozygosity at 11q13, harbouring the multiple endocrine neoplasia type 1 (MEN-1) gene. Atypical carcinoids also show loss of heterozygosity at 3p14–p21.3.

Recent studies have shown that carcinoid tumours of the lung and the gastrointestinal tract may develop via different molecular pathways. Inactivation of one of several tumour suppressor genes on chromosome 18 may be important for the biological behaviour of gastrointestinal tumours. Familial midgut carcinoids are rare but bronchial carcinoids as well as endocrine pancreatic tumours and gastric carcinoids may be part of a MEN-1 syndrome [4, 5].

## Clinical presentation

The different NE tumours may be divided into functioning and non-functioning tumours. Functioning tumours present clinically with symptoms related to overproduction of hormones and amines such as midgut carcinoids with carcinoid syndrome, gastrinoma with Zollinger–Ellison's syndrome, insulinoma with hypoglycaemic symptoms, glucagonoma with glucagonoma syndrome and VIPoma with watery diarrhoea–hypokalaemia–achlorhydria (WDHA) syndrome.

Non-functioning tumours produce and secrete peptides that do not cause any distinct clinical symptom. The majority of endocrine pancreatic tumours is non-functioning tumours (40–45%).

The classical carcinoid syndrome includes flushing (80%), diarrhoea (70%), abdominal pain (40%), valvular heart disease (30–40%), telangiectasia (25%), wheezing (15%) and pellagra-like skin lesions (5%).

The flushing observed in patients with classical carcinoid syndrome has usually a pink to red colour and involves the face or upper trunk. It lasts for a few minutes and may be triggered by alcohol, physical exercise, mental stress and tyramine-containing foods such as chocolates, walnuts and bananas.

The atypical carcinoid syndrome that is seen in bronchial carcinoids has a purple rather than pink colour with telangiectasias, hypertrophy of the skin of the face, headache, lacrimation, hypotension, cutaneous edema and bronchoconstriction.

Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50–70% of patients with a carcinoid syndrome. Haemodynamically significant heart disease is seen in about 5–10% of patients [6, 9, 10].

Zollinger–Ellison's syndrome is related to a gastrin-producing tumour located either in the pancreas (45–50%) or in the duodenum (35–55%). These tumours produce gastrin,

which stimulates high acid output with recurrent gastritis and gastric ulcers. Nowadays with the use of proton-pump inhibitors severe ulcer disease is very rare.

Insulinoma or hypoglycaemic syndrome is characterized by neuroglycopenia, particularly in the morning or after exercise, blurred vision and sometimes even psychosis. Secondary to low blood glucose the patient might develop palpitations and sweating.

WDHA syndrome or VIPoma syndrome is characterized by severe secretory diarrhoea up to 10–15 l/day, hypercalcaemia, hypokalaemia, achlorhydria, flushing and diabetic glucose tolerance.

Glucagonoma syndrome is very often present with typical necrolytic migratory erythema but also anaemia and thrombosis. About 50% of the patients also show mild diabetes mellitus [6–8].

Non-functioning tumours of the intestine present with large abdominal masses, bleeding from the gastrointestinal tract and/or intestinal obstruction. Non-functioning endocrine pancreatic tumours become very large until they cause abdominal discomfort, pain and liver enlargement. Sometimes they also cause jaundice [8].

## Biochemical diagnosis of NE tumours

Since the majority of NE tumours secretes peptides and amines, these can be used as markers both for diagnosis and monitoring of therapy.

The most important tumour marker is chromogranin A, which is a glycoprotein stored in the secretory granules of tumour cells and is released together with other peptides and amines. The level of chromogranin A is increased in 70–90% of all NE tumours. The sensitivity and specificity are approximately 92% and 96%, respectively.

Another marker is pancreatic polypeptide, which is increased in 50–60% of patients with endocrine pancreatic tumours and a somewhat lower number in carcinoid of the gastrointestinal tract. The specificity and sensitivity is lower for this marker.

Another tumour marker is human chorionic gonadotropin (HCG)  $\alpha$ -subunit, which is particularly useful to determine the malignant potential of a NE tumour.

A specific marker for patients with a carcinoid syndrome is the 24 h urinary level of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin with a sensitivity of 73% and specificity of 100%. The urine should be collected under dietary restrictions, excluding bananas, chocolate, tea, coffee, walnuts and pecan.

Patients with foregut carcinoid tumours rarely secrete serotonin but may release adrenocorticotrophic hormone (ACTH), growth hormone releasing hormone (GHRH) or histamine [11–14].

Serum gastrin together with measurement of the basal and stimulated acid output are the best diagnostic tools for gastrinoma. Sometimes a secretin infusion test measuring gastrin is

For the diagnosis of an insulin-producing tumour, measurement of fasting serum insulin and blood glucose might be sufficient, but sensitivity can be improved by analysing proinsulin and C-peptide as well. Sometimes 24–72 h fasting is necessary to diagnose an insulinoma.

VIPoma is demonstrated by measuring plasma vasoactive intestinal peptide (VIP), which is significantly elevated in most patients.

Plasma glucagon is elevated in most patients with a glucagonoma.

Non-functioning tumours may present with a high chromogranin A level as well as pancreatic polypeptide and HCG- $\alpha$  subunit [7, 8].

## Imaging of NE tumours

A unique feature of NE tumour cells is the expression of peptide hormone receptors on their surface. These receptors may be targets for both diagnosis and therapeutic procedures.

The majority of NE tumour cells expresses somatostatin receptors particularly receptor subtypes 2 and 5. They are the basis for somatostatin receptor scintigraphy (Octreoscan). This procedure is actually the most important staging procedure for NE tumours since 55–95% of these tumours express somatostatin receptors. Somatostatin receptor scintigraphy has a diagnostic accuracy of 83% and a positive predictive value of 100%. It has a higher sensitivity than I-131-metaiodobenzylguanidine (MIBG) scanning

Undifferentiated anaplastic NE tumours with a high proliferation capacity lack somatostatin receptors and may give a negative somatostatin receptor scintigraphy. These tumours can be diagnosed by positron emission tomography (PET) scanning with [ $^{18}$ F]-2-deoxy-2-fluoro-D-glucose (18-FDG).

Another PET tracer with high sensitivity for well-differentiated hormone-producing NE tumours is C11-5HTP, with very high sensitivity and specificity. Tumours with a size of 2 mm can be visualized by this method.

Besides imaging by radionuclides, computed tomography (CT) scan or magnetic resonance imaging (MRI) as well as ultrasonography should always be performed to visualize the precise location and size of the lesion for evaluation during treatment. Most recently a combined PET–CT camera has been developed, which makes a computerized fusion image of both methods.

For endocrine tumours of the pancreatic head, endoscopic ultrasonography is particularly useful. Other localization procedures are bronchoscopy, gastroscopy and colonoscopy [7, 8, 15–18].

## Treatment of NE tumours

### Surgery

The clinical management of metastatic NE tumours requires a multi-modal approach including surgery and other means of

Surgery remains the treatment of choice and is the only approach that can achieve a complete cure in patients with NE tumours. In cases of metastases, surgery has been used to improve hormone-mediated symptoms, quality of life and survival in certain groups of patients, as well as to reduce tumour bulk and prevent further local and systemic effects. Surgical resection of primary tumours as well as lymph nodes and liver metastases can improve survival. In addition, surgery can also be employed after medical treatment to achieve substantial tumour reduction in an attempt to maximize the disease-free interval. Surgery and thermal ablation (radiofrequency treatment) are new promising methods for treatment of liver metastases. Significant clinical improvement and reduction in tumour size have been reported.

Liver transplantation has been suggested in selected patients without residual extrahepatic manifestations. However, long-term results are not that encouraging at the moment and liver transplantation should be reserved for a very few patients, where other means of therapy cannot control the disease [7, 19, 20].

### Embolization and chemoembolization

A significant number of patients have liver metastases at diagnosis. Therefore treatment aimed at reducing the tumour bulk in the liver may significantly improve quality of life and survival. Such procedures include embolization of liver metastasis with or without concomitant cytotoxic agents (chemoembolization). Chemoembolization is embolization combined with intra-arterial administration of chemotherapy.

By chemoembolization, the concentration of chemotherapeutic drugs may reach a higher local concentration and their action may be more effective due to the cellular tumour

ischaemia. Contraindications for liver embolization include complete portal vein obstruction and hepatic insufficiency.

If liver metastases are the only site of metastasis, embolization may be the first-line treatment in patients with NE tumours poorly responsive to biological treatment or systemic cytotoxic treatment.

Chemoembolization gives symptomatic improvement in 75–100%, biochemical responses in 57–90% and significant tumour reduction in 35–80% of patients with NE tumours. The response duration is between 8 and 40 months.

Side effects are usually mild and transient nausea, vomiting, abdominal pain, mild fever and raised liver enzymes. Patients with extensive disease may suffer necrosis of the tumour with carcinoid crises. Other rare but important complications are acute renal failure (hepato-renal syndrome), peptic ulcer bleeding and necrosis of the gall bladder [21, 22].

### Radiotherapy

External radiotherapy has limited value in the treatment of NE tumours. It is reserved mainly for treatment of brain metastases and pain related to bone metastases.

Tumour-targeted radiolabelled somatostatin analogues have been used during the past few years with some encouraging results. The various compounds used are <sup>111</sup>indium-DTPA-octreotide, <sup>90</sup>yttrium-DOTA-octreotide, <sup>90</sup>yttrium-DOTATOC and MAURITIUS, all giving a symptomatic improvement in 40% of the patients, biochemical responses in 24–30% and significant tumour reduction in 5–10%.

To overcome the limitation of administering radiotherapy to non-octreotide avid lesions and lack of uptake due to tumour heterogeneity, several other isotopes such as <sup>177</sup>lutetium and <sup>186</sup>rethium are being examined. <sup>177</sup>Lu-DOTA-octreotate

**Table 1.** Cytotoxic therapy for carcinoid tumours

Drug	Regimen	Number of patients	Overall response (%)	Median duration (months)
<b>Single agents</b>				
Doxorubicin	60 mg/m <sup>2</sup> every 3–4 weeks	81	21	6
5-Fluorouracil	500 mg/m <sup>2</sup> /day ×5 every 5 weeks	30	17–26	3
Streptozotocin	500–1500 mg/m <sup>2</sup> /day ×5 every 3–5 weeks	14	0–17	2
Dacarbazine	250 mg/m <sup>2</sup> /day ×5 every 4–5 weeks	15	13	4.5
Cisplatin	45–90 mg/m <sup>2</sup> every 3–4 weeks	16	6	4.5
<b>Combinations</b>				
Streptozotocin	500 mg/m <sup>2</sup> /day ×5 every 3–6 weeks	175	7–33	3–7
+5-Fluorouracil	400 mg/m <sup>2</sup> /day ×5 every 3–6 weeks			
Streptozotocin	1000 mg/m <sup>2</sup> /week ×4	10	40	5
+Doxorubicin	25 mg/m <sup>2</sup> /week then every 2 weeks			
Streptozotocin	500 mg/m <sup>2</sup> /day every 6 weeks	24	39	6.5
+Cyclophosphamide	100 mg/m <sup>2</sup> once every 3 weeks			
Etoposide	130 mg/m <sup>2</sup> /day ×3	13	0	–
+Cisplatin	45 mg/m <sup>2</sup> /day on day 2 and 3.			

shows a high tumour uptake with a very good ratio of tumour to kidney uptake. This isotope has recently been administered to 80 patients with a variety of progressive NE tumours and 49% showed a partial response [23–25].

### Medical treatment

Medical treatment of NE tumours includes treatment with both chemotherapy and biological agents, such as somatostatin analogues and interferon (IFN)- $\alpha$ .

### Chemotherapy

Chemotherapy has been considered the gold standard for treatment of most NE tumours. However, its use is usually reported in a limited number of patients and with variable criteria for assessment of antitumour response.

Cytotoxic treatment is predominantly used in patients with tumours with a high proliferative capacity shown by a proliferation index of >10–15% measured by the antibody Ki67 and with a large tumour burden. Patients with a classical midgut carcinoid with a low proliferating capacity (Ki67 usually <2%) do not benefit from cytotoxic treatment.

The most common chemotherapy for the treatment of endocrine pancreatic tumours is a combination of streptozotocin plus 5-fluorouracil or doxorubicin. Response rates are between 40% and 70%. In classical midgut carcinoids the same combination induces responses of short duration in <10%.

**Table 2.** Chemotherapy of endocrine pancreatic tumours

	No. of patients	Objective response (%)	Duration (months)
Streptozotocin + 5-fluorouracil	170	45–63	18–36
Streptozotocin + doxorubicin	50	40–69	12–24
Cisplatin + etoposide	14	50	9
Dacarbazine	11	9	6
Paclitaxel	15	7	5

For anaplastic tumours with a high proliferative capacity (Ki67 >15%) combinations of cisplatin and etoposide have been useful with a response rate of 67% and a tendency to prolonged survival [26, 27]. Newer cytotoxic agents such as paclitaxel and gemcitabine have not been of substantial value. Results of phase II studies with different chemotherapeutic regimens are shown in Tables 1 and 2.

### Somatostatin analogues

The rationale for the clinical use of somatostatin analogues is based on the identification of high-affinity somatostatin receptors in 80–90% of NE tumours. Regular octreotide at a subcutaneous daily dose of 200–450  $\mu$ g is associated with a median 60% symptomatic, 70% biochemical and 8% tumour response. A limited number of patients has been reported with partial tumour regression during treatment with somatostatin analogues and very few cases have shown complete tumour regression. However, a high number of patients reached disease stabilization.

Slow release formulations of octreotide (Sandostatin LAR®) and somatuline (Somatuline Autogel®) have been effective with a monthly dose of 20–30 mg octreotide or 60–120 mg somatuline. In clinical practice the patient is treated subcutaneously with immediate release octreotide 100  $\mu$ g 2–3 times/day for at least 3–4 days to see whether the patient can tolerate somatostatin analogue treatment. Thereafter, a long-acting formulation of octreotide 20 mg or somatuline 90 mg is given intramuscularly every 4 weeks. The immediate release formulation of octreotide is continued during the first 2 weeks to prevent symptoms until the long-acting formulation of the drug reaches a steady state concentration. If symptoms return before the next administration, the interval can be shortened to 2 or 3 weeks. The patient should also have a supply of immediate release octreotide for particular situations.

When a patient develops resistance to a somatostatin analogue, which may occur after 9–12 months of treatment, dose escalation may be tried with doses up to 60 mg for octreotide or 150 mg of somatuline.

**Table 3.** NE tumours: somatostatin analogue therapy (summary of several trials)

Response	Standard dose (100–1500 $\mu$ g/day) (%)	High dose (>3000 $\mu$ g/day) (%)	Slow release (20–30 mg/day every 2–4 weeks) (%)
Symptomatic	64 (146/228)	42 (11/26)	63 (76/119)
Biochemical			
Complete response	11 (6/54)	3 (1/33)	3 (3/119)
Partial response	55 (116/211)	72 (24/83)	64 (76/119)
Stable disease	34 (72/211)	21 (7/33)	18 (21/119)
Progressive disease	11 (23/211)	3 (1/33)	15 (19/119)
Tumour			
Complete response	–	2 (1/53)	–
Partial response	5 (7/131)	11 (6/53)	3 (4/119)
Stable disease	38 (50/131)	47 (25/53)	79 (94/119)

If a patient becomes resistant to somatostatin analogue treatment, IFN- $\alpha$  might be an alternative to up-regulate the number of somatostatin receptors type 2 or to give a period of rest to somatostatin receptors. Somatostatin analogue therapy can be re-instituted after 2–3 months, by using either the immediate release or the long-acting formulation.

SOM230 is a new somatostatin analogue that has a prolonged half-life, ( $\sim 24$  h) and exerts a more potent inhibitory effect than the compounds currently available, as it binds with much higher affinity to somatostatin receptors 1, 2, 3 and 5. The introduction of SOM230 into clinical practice will address a long-standing question as to whether somatostatin receptor subtypes 1 and 3, which mediate antitumour effects (cell cycle inhibition and induction of apoptosis) will be clinically beneficial in NE tumours [28–31]. Results of trials with somatostatin analogues are given in Table 3.

### Interferons

Interferons are compounds known to exert a combination of effects directed to several groups of tumours and are considered as biological response modifiers as they interact with other soluble or cell-associated regulatory factors. The recommended dose of IFN- $\alpha$  is 3–9 MU subcutaneously every other day, or slow release formulation pegylated IFN- $\alpha$  80–100  $\mu\text{g}$  subcutaneously once a week. The dose should be titrated individually and the leucocyte count may be used as guidance: a leucocyte count of  $<3.0 \times 10^9/\text{l}$  indicates an optimal IFN- $\alpha$  dose.

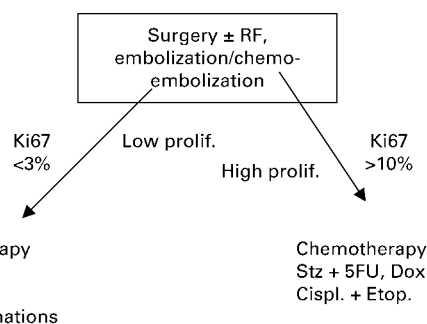
Several studies in patients with carcinoid tumours have reported a median symptomatic and biochemical response rate of 40–70%, biochemical responses in 40–60% and significant tumour reduction in 10–12% (Table 4). Disease stabilization is noted in a further 35% of the patients. Flu-like symptoms are almost universal with interferon treatment but are usually short lasting. Chronic fatigue and mild depression may develop in  $\sim 50\%$  of patients. Autoimmune reactions appear in  $\sim 15\%$  of patients [27, 32, 33].

**Table 4.** Therapy with IFN- $\alpha$  in patients with midgut carcinoids

Number of patients	Biochemical response (%)	Subjective response (%)	Tumour value response (%)
29 <sup>a</sup>	PR 53 (13/25)	72 (32/29)	PR 10 (3/29)
	SD 36 (9/25)		SD 86 (25/29)
27 <sup>b</sup>	PR 39 (9/23)	65	PR 20 (4/20)
16	PR 16 (1/6)	80 (4/5)	PR 0 (0/16)
	SD 50 (3/6)		SD 66 (10/15)
14	PR 44 (4/9)	55	PR 0 (0/16)
13	PR 8 (1/13)	50	PR 8 (1/13)
	SD 31 (4/13)		SD 77 (10/13)

<sup>a</sup>Natural leucocyte IFN- $\alpha$ , 6 MU subcutaneously  $\times 8$  weeks.

<sup>b</sup>High-dose IFN- $\alpha$  2a 24 MU/m<sup>2</sup> subcutaneously  $\times 8$  weeks.



### Progression

#### Tumour-targeted radiotherapy:

<sup>177</sup>Lu-DOTA-octreotate  
<sup>90</sup>Y-DOTA-octreotide

#### Experimental protocols:

Gleevec  
Rapamycin  
Iressa  
Cetuximab

SMS=Somatostatin, RF=radiofrequencyablation, 5FU=5-fluorouracil, Stz=Streptozotocin, Dox=Doxorubicin, Cispl=Cisplatinum, Etop=Etoposide

**Figure 1.** Algorithm of NE tumours.

### Combination of IFN and somatostatin analogue

The value of combining IFN- $\alpha$  with somatostatin analogues has been discussed during the past few years. Early non-randomized studies indicated a beneficial effect of the combination, with significant antitumour and biochemical responses in patients resistant to either IFN or a somatostatin analogue alone [34, 35].

Recent randomized trials have not supported this early observation, but these studies have several flaws. One of these studies included a low number of patients and the statistical analyses were not performed correctly [36]. The combination of IFN- $\alpha$  and a somatostatin analogue showed a non-significant trend to improved survival. The other study included different types of NE tumours with different tumour biology and it was not easy to evaluate the combination therapy [37].

The tolerance of IFN- $\alpha$  is improved by use of a concomitant somatostatin analogue and experimental data indicate an up-regulation of the somatostatin receptor type 2 by IFN- $\alpha$ . Therefore the combination of IFN- $\alpha$  with a somatostatin analogue should be evaluated in randomized studies in pre-defined patient populations. Current concepts in therapy are summarized in Figure 1.

### New compounds

Inhibition of intracellular signal transduction by tyrosine kinase receptors may be a new target in the treatment of NE tumours. Many NE tumours express platelet-derived growth factor- $\alpha$  and - $\beta$  receptor subtypes and ligands, and also vascular endothelial growth factor and epidermal growth



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