Effect of hormone secretory syndromes on neuroendocrine tumor prognosis

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Abstract

The treatment of hormone hypersecretory syndromes caused by neuroendocrine tumors (NETs) can be a major challenge. NETs originating from the small intestine often secrete serotonin causing flushing, diarrhea and valve fibrosis, leading to dehydration or heart failure in severe cases. NETs from the pancreas can secrete a wider variety of hormones, like insulin, glucagon and gastrin leading to distinct clinical syndromes. Historically mortality in patients with functioning NETs was high due to the complications caused by the hypersecretion of hormones. This has been reduced with several drugs: proton-pump inhibitors decrease acid secretion caused by gastrinomas. Somatostatin analogs can inhibit the secretion of multiple hormones and these are now the cornerstone for treating patients with a gastroenteropancreatic NET. However, peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs and everolimus can also decrease symptoms of hypersecretion and increase progression-free survival. Several factors affect the survival in patients with a functioning NET. Complications of hypersecretion negatively impact survival; however, secretion of hormones is also often a sign of a well-differentiated NET and due to the symptoms, functioning NETs can be detected in an earlier stage suggesting a positive effect on prognosis. The effect on survival is also dependent on the type of hormone being secreted. This review aims to study the effect of hormone secretion on the prognosis of NETs with the contemporary treatments options available today.

Key Words

- ▶ neuroendocrine tumor
- ▶ hormone secretion
- ▶ prognosis
- ▶ carcinoid syndrome

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Introduction

Neuroendocrine tumor (NETs) are often best known for causing hypersecretory syndromes, through the hormones they secrete, which is mainly determined by the cell of origin (Kaltsas *et al.* 2004). More than 15 individual neuroendocrine cell types have been identified, and they all secrete different hormones, causing different kinds of syndromes (Kidd *et al.* 2015). These syndromes of hormone excess are diagnosed when the clinical

presentation fits a certain syndrome, and this is confirmed by demonstrating that corresponding hormone levels are elevated (Kaltsas *et al.* 2004). When patients present without a specific syndrome or without elevated hormone levels, they are diagnosed with a non-functioning, or non-syndromic, NET. Small intestinal NETs almost exclusively secrete serotonin, and when metastasized causing the carcinoid syndrome with symptoms of flushing, diarrhea

Table 1 Overview of the most common neuroendocrine tumor syndromes: origin and incidence.

Hormone	Cell	Location	Tumor	Incidence (per million)
Serotonin	EC	Stomach, pancreas, duodenum, small intestine, colon, appendix, rectum	Carcinoid	0.2–0.6
Insulin	B	Pancreas	Insulinoma	1–3
Gastrin	G	Duodenum	Gastrinoma	0.5–2
Glucagon	a	Pancreas	Glucagonoma	0.02–0.06
VIP	VIP	Pancreas, sympathetic ganglia	VIPoma	0.05–0.2
ACTH	Various	Lung, adrenals, thyroid, pancreas	ACTHoma	Rare
PTH	Various	Lung, pancreas	PTH-like-oma	Rare
Somatostatin	D	Pancreas, stomach, duodenum, colon, rectum, appendix	Somatostatinoma	Rare

and carcinoid heart disease. Pancreatic NETs show a much larger variation in hormonal secretion and are capable to secrete insulin, glucagon, gastrin and other hormones (Table 1). Arising from different neuroendocrine cell types and causing different symptomology, survival differs between these syndromes as well. Strong predictors of survival are the grade, based on the Ki67-index, and the WHO/ENETS staging (Klimstra *et al.* 2010). The biomarkers chromogranin A and neuron-specific enolase are predictors of survival as well. Serum chromogranin A is a marker for tumor burden, and elevated serum chromogranin A is associated with a shorter survival (Arnold *et al.* 2008, Han *et al.* 2015). Neuron-specific enolase was long thought to be a predictive biomarker not only in poorly differentiated NET and small cell carcinomas but also in low-grade NETs, an elevated serum neuron-specific enolase is a negative predictor of survival (van Adrichem *et al.* 2015). The influence of hormone hypersecretion on survival in patients with NETs remains unclear.

Historically, the slow growth of NETs often resulted in survival not being limited by tumor burden but by complications caused by the hypersecretion of hormones (Thorson *et al.* 1954). However, many steps have been made in treatment of these patients mainly with the discovery of somatostatin and the subsequent development of octreotide, allowing the inhibition of hormone secretion and thus reduction of clinical symptoms and morbidity (Kvols *et al.* 1986). Long-acting somatostatin analogs can now be administered only once a month vs three times daily for octreotide subcutaneously, once more improving quality of life for patients (Rinke *et al.* 2009, Caplin *et al.* 2014). Also peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs and tumor-targeted therapy (everolimus and sunitinib) are now available for the treatment of metastatic NETs (Kwekkeboom *et al.* 2008, Raymond *et al.* 2011, Yao *et al.* 2016). Also, simply decreasing acid secretion with PPIs

in gastrinoma patients strongly reduces the incidence of peptic ulcer disease (Hirschowitz *et al.* 2005). It is without question that before all these contemporary options were available, patients with a hypersecreting NET had a worse prognosis, due to the complications of hormone hypersecretion. On the other hand, hormone secretion is often a sign of a well-differentiated NET with, theoretically, a better survival (Wang *et al.* 2011). Also symptoms caused by the secreting NET could allow for detection of the NET in an earlier stage. In this review, we will study available literature, questioning the influence of hormonal secretion on NET prognosis in the current era, focusing on NETs originating from the pancreas and the gut.

Serotonin and the carcinoid syndrome

The histological diagnosis of a 'Karzinoid' was first described early in the twentieth century and the first cases of carcinoid syndrome were described from 1927 onward (Oberndorfer 1907, Postma 1927, Cassidy 1930). Patients presented with diarrhea and flushing and post-mortem examination revealed tumors in the ileum, liver metastases and tricuspid valve stenosis, but the link connecting these findings remained unknown (Cassidy 1931, Scholte 1931). In the 1950s, several discoveries were made, significantly advancing the knowledge of the carcinoid syndrome. Serotonin was identified by Page and in a case series published in 1954, Thorson and coworkers linked flushing, diarrhea and right-sided heart failure to carcinoids in the small intestine and identified serotonin secretion as a possible cause of the syndrome (Page 1954, Thorson *et al.* 1954). Survival varied from over ten years when patients first complained of abdominal pain or flushing, to weeks when presenting with heart failure.

Nowadays the carcinoid syndrome is a well-known entity. Text books clearly describe the symptomatology of flushing, diarrhea, bronchospasm and eventually

valvular heart disease, but this typical presentation is rare (Pape *et al.* 2008). It is a clinical diagnosis, made when these symptoms are present and when there is evidence for increased serotonin secretion. Serotonin levels can be measured in several ways, but excretion of 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA), the degradation product of serotonin, is most validated in diagnosis and follow-up of NETs (O'Toole *et al.* 2009). In the near future, plasma 5-HIAA will probably play a more prominent role (Tellez *et al.* 2013). Occasionally, NETs from organs like the lung, ovaries and pancreas can cause the carcinoid syndrome, but it is most frequently associated with NETs from the embryological midgut and so our knowledge on the carcinoid syndrome is mainly based on these tumors. The midgut NETs arise from enterochromaffin cells in the intestine and when the tumor is limited to the abdomen (ENETS Stage I–IIIb), secreted serotonin is efficiently metabolized in the liver and therefore localized disease rarely causes symptoms. But liver, bone and retroperitoneal or distant node metastases as well as lung and ovary primaries directly secrete serotonin and other mediators into the systemic circulation, and this causes the carcinoid syndrome (Grozinsky-Glasberg *et al.* 2015). This factor is of great importance because this influences incidence of carcinoid syndrome in different centers and it confounds the influence of the carcinoid syndrome on prognosis.

In epidemiological studies, incidence of midgut NETs varies between regions. Current incidence is estimated to be around 0.3–1.1 cases annually per 100,000 persons and seems to be increasing in recent years (Modlin *et al.* 2003, Yao *et al.* 2008, Ellis *et al.* 2010, Landerholm *et al.* 2010). Whether this is due to a true increase in incidence or to increased imaging procedures or both remains to be elucidated. The incidence of the carcinoid syndrome in these patients is highly dependent on the selected population. In nationwide surveys or cancer registries, 3–19% of patients with a small intestinal NET have the carcinoid syndrome, but incidence has been reported as high as 71% in specialized centers, treating more patients with advanced disease (Bax *et al.* 1996, Janson *et al.* 1997, Soga 2003, Niederle *et al.* 2010, Halperin *et al.* 2017).

When surgery, chemotherapy and radiotherapy were the only options for the treatment of metastatic small intestinal NETs, the prognosis was mediocre and overall 5-year survival rate was approximately 50–60% for all stages combined (Barclay & Schapira 1983, Zollinger 1986). Also patients with a functioning NET had a shorter median survival. In a study by Norheim and coworkers in 1987, median survival from the time of histologic

diagnosis was 14 years but 8 years from the time of onset of the carcinoid syndrome (Norheim *et al.* 1987). With new options for treatment becoming available for patients with a NET in the past two decades, there has been a large improvement in the quality of life and prognosis.

Patients with the carcinoid syndrome almost exclusively have extensive disease but curative surgery should still be the first option to consider. Unfortunately, this is not feasible in many patients and palliative therapy should be started to control symptoms and tumor growth (Pavel *et al.* 2016). This is best achieved with a somatostatin analog (SSA). The first studies with these drugs revealed significant reduction of symptoms by reducing serotonin secretion, measured with 24-h urinary 5-HIAA excretion (Modlin *et al.* 2010). Subsequently, this was confirmed in randomized controlled trials. Two well-known, landmark trials have shown that SSAs increase progression-free survival (PFS). Lanreotide was found to increase PFS in patients with non-functioning neuroendocrine tumors (gastrinomas were included) (Caplin *et al.* 2014). In the PROMID trial, median PFS increased from 6.0 months with placebo to 14.3 months when treated with octreotide LAR and in this study 36% of patients had the carcinoid syndrome at baseline (Rinke *et al.* 2009). Treatment effect was equal in patients with a functioning or non-functioning tumor and while PFS was shorter in patients with a functioning tumor, this did not reach significance (HR 1.38; 95% CI: 0.81–2.37). Second-line options include peptide receptor radionuclide therapy (PRRT) and everolimus (van der Zwan *et al.* 2015). PRRT with ¹⁷⁷Lu-DOTAtate resulted in a longer PFS in patients with midgut NETs. After 20 months, 65.2% of these patients were without tumor progression (RECIST) as compared to 10.8% in the control group using a doubled dose (60mg) of octreotide LAR every 4 weeks in the NETTER-1-study (HR for progression 0.21; 95% CI: 0.13–0.33) (Strosberg *et al.* 2017). Furthermore, PRRT can reduce symptoms (pain, fatigue and carcinoid-related symptoms) in selected patients (Kam *et al.* 2012, Seregini *et al.* 2013). Everolimus is specifically tested in patients with the carcinoid syndrome, but no direct comparison was made with non-functioning tumors, as these were studied in a different trial (Pavel *et al.* 2011, Yao *et al.* 2016). Compared to octreotide LAR alone, treatment with everolimus resulted in a larger reduction of urinary 5-HIAA excretion in the RADIANT-2 trial, but the effects on symptoms of carcinoid syndrome or quality of life were not studied (Pavel *et al.* 2011). With all these contemporary medical options, 5 year survival for stage IV midgut NETs has been described as being 54% to as

Table 2 Overall survival and peri-operative mortality in surgical series on carcinoid heart disease.

	Overall survival	Peri-operative mortality	Number of patients
Robiolio <i>et al.</i> (1995)	5 year: 25%	62.5% (<1995)	8
Moller <i>et al.</i> (2005)	Median survival: 2.6 years	25% (1981–1989)	12
		9% (1995–2000)	43
Mokhles <i>et al.</i> (2012)	5 year: 43%	5.7% (1993–2010)	19
Bhattacharyya <i>et al.</i> (2010)	2 year: 44%	18% (2006–2010)	22
Connolly <i>et al.</i> (2015)	5 year: 35%	20% (<1990)	10
		16.4% (1990–1999)	61
		7.2% (2000–2009)	97
		3.7% (2010–2012)	27
Edwards <i>et al.</i> (2016)	2 year: 69%	13% (2005–2015)	32

Peri-operative mortality: mortality rate the first 30 days after surgery for carcinoid heart disease.

high as 84.8% (Quaadvlieg *et al.* 2001, Yao *et al.* 2008, Jann *et al.* 2011).

Treatment of carcinoid heart disease has also vastly improved. In the nineties over a quarter of patients died of carcinoid heart disease, and this was almost 50% of disease-related death (Makridis *et al.* 1997). There is strong evidence that serotonin plays an important role, so reduction of secretion with SSAs and telotristate could potentially reduce the risk of developing carcinoid heart disease, but no studies, with these drugs, show the effect on the incidence of carcinoid heart disease or overall survival due to the slow progressive character of NETs (Pavel *et al.* 2015). Also increasing experience in valve replacement surgery in patients with carcinoid heart disease has resulted in a sharp reduction of peri-operative mortality to approximately 4–10% with an overall survival approaching that of non-syndromic patients (Table 2). However, this might be biased by selecting patients for surgery in an earlier stage. Regular screening on carcinoid heart disease and optimal timing of cardiac valve replacement are important factors that determine the ultimate outcome.

Altogether treatment of the carcinoid syndrome has clearly advanced and with that, its influence on prognosis is diminishing. Historically symptomatic patients, on average, have a shorter survival. Simply looking at the urinary 24-h 5-HIAA excretion indeed shows that patients with elevated excretion have a shorter survival (Turner *et al.*

2006, Formica *et al.* 2007, van der Horst-Schrivers *et al.* 2007). But after correction for metastases (ENETS Stage IV) and tumor burden (with chromogranin A), urinary 5-HIAA excretion is no longer a predictor for survival (Janson *et al.* 1997, Zandee *et al.* 2016). Few studies have purely compared survival of functional and non-functional midgut NETs. Often urinary 5-HIAA excretion is used as marker for the carcinoid syndrome, but this does not always correlate with the clinical symptoms, which are used to define carcinoid syndrome (Zuetenhorst *et al.* 2004). Only limited number of studies have been published on the effect of carcinoid syndrome on survival (on the basis of clinical symptoms) (Table 3). Halperin and coworkers and Janson and coworkers demonstrated a shorter survival for functional NETs (HR 1.10 and HR 2.9) in a respective cohort-study (SEER database) and a center-based study (Janson *et al.* 1997, Halperin *et al.* 2017). However, after correction for liver burden and other biomarkers by Janson and coworkers, survival no longer differs between patients with and without carcinoid syndrome. Halperin and coworkers could not correct for tumor burden, due to the limitations in the data collection. In contrast to these studies, two other studies did not demonstrate a significant influence of carcinoid syndrome on survival (Formica *et al.* 2007, Jann *et al.* 2011).

Much less is known of the influence of carcinoid syndrome in pancreas NETs because this is a rare phenomenon, occurring in about only 1% of pNETs (Modlin *et al.* 2005, Soga 2005, Bilimoria *et al.* 2007,

Table 3 Overall survival in patients with carcinoid syndrome vs non-functional midgut NET.

	Hazard ratio (95% CI)	2-year survival	5-year survival	10-year survival	
Survival in carcinoid syndrome (functional vs non-functional)					
Jann <i>et al.</i> (2011)		96.9% vs 97.6%	85.6% vs 93.7%	64.2% vs 79.7%	NS
Janson <i>et al.</i> (1997)	2.9 (1.4–6.0)				NS in multivariate
Formica <i>et al.</i> (2007)	1.18 (0.7–1.9)				NS
Halperin <i>et al.</i> (2017)	1.10 (1.02–1.20)				No correction for tumor burden

NS: not significant.

La Rosa *et al.* 2011). However, its influence on survival seems to mimic that of the midgut NETs. Serotonin secretion has a negative influence on survival, but it occurs mainly in patients with metastasized disease and bulky tumors. After correcting for this fact, serotonin secretion no longer influenced survival (Zandee *et al.* 2017).

It is clear that the mortality of the carcinoid syndrome is decreasing due to reduction of serotonin secretion with potent drugs and improved valve surgery. At the same time, survival has increased for both functional and non-functional NETs, due to the anti-proliferative effect of SSAs, tumor-targeted therapy and PRRT. Unfortunately mortality for patients with the carcinoid syndrome remains relatively high, but this is probably due to extensive tumor load and not due to the effects of serotonin secretion.

Pancreatic neuroendocrine tumors

Neuroendocrine tumors originating from the pancreas can produce a wide variety of hormones like insulin and glucagon. Currently, it is not recommended to screen for hormone secretion unless symptoms fit a certain functioning tumor syndrome (Falconi *et al.* 2016). Unlike the carcinoid syndrome in patients with midgut tumors, pNETs do not need to metastasize before symptoms arise.

For example, 90% of insulinomas are smaller than 4 cm and limited to the pancreas at diagnosis (Mehrabani *et al.* 2014). Non-functioning pNETs mostly present either with an incidentaloma or with abdominal pain, and it is suggested that thereby these patients present more frequently with advanced disease (Cheema *et al.* 2012, Crippa *et al.* 2014).

In many studies, comparing survival of non-functioning pNETs with their functional counterpart, functional pNETs are described as a group with no sub-selection for the type of hormone. Therefore, we will first discuss these studies, followed by a focus on the prevalent syndromes.

After diagnosis of a pNET according to guidelines, curative surgery is the first consideration (Falconi *et al.* 2016). A small number of studies are published on observation only, for non-functioning pNETs smaller than 2 cm. Results are promising, but no long-term data is available yet (Sadot *et al.* 2016). Due to the symptomatology of functioning pNETs observation is often not preferred except for selected patients with a gastrinoma. Only Cubilla and coworkers report a worse prognosis for patients with functional tumors but values for significance are not reported (Cubilla & Hajdu 1975). Most surgical series show a better prognosis for patients with a functional tumor, but after correction for other

Table 4 Reported 5-year survival, comparing functional and non-functional pancreatic neuroendocrine tumors.

	5-year survival (%)			Number of patients	Functioning (insulinoma %)	Remarks
	Functional (%)	Non-functional (%)	P value			
Surgical series						
Phan <i>et al.</i> (1998)	77	52	0.025	125	64 (55)	Surgical, <i>P</i> =0.14 in metastatic NET
Sarmiento <i>et al.</i> (2002)	100	70	0.08	29	9 (33.3)	Surgical
Jarufe <i>et al.</i> (2005)	82.5	55.0	0.41	44	24 (66.6)	Surgical curative (50% ≥ Stage IIIb)
Vagefi <i>et al.</i> (2007)	89	78	0.16	168	70 (33.3)	Surgical
Bilimoria <i>et al.</i> (2008)	67.7	60.0	<0.001	3851	619 (20.7)	Surgical series all stages, <i>P</i> =0.03 in multivariate
Gao <i>et al.</i> (2010)	77	74	0.225	112	47 (60.0)	Surgical treatment all stages
Partelli <i>et al.</i> (2015)	71	57	0.148	166	15 (26.7)	Surgery stage IV, including palliative and no resection
Cohort studies						
Wang <i>et al.</i> (2011)	96.8	71.6	0.008	93	39 (71.7)	DSS, all stages, center based Not significant in multivariate
Martin-Perez <i>et al.</i> (2013)	83.6	73.4	0.185	483	171 (44.4)	Population based
Chu <i>et al.</i> (2002)	48	30	0.27	55	21 (28.5)	All stages
Halfdanarson <i>et al.</i> (2008)	47.6	31.3	<0.001	1483	137 (27.0)	All stages, SEER database <i>P</i> =0.004 in multivariate

factors like stage, often no significant difference is found (Table 4 and 5). Phan and coworkers have reported a higher probability of survival for functional pNETs, but at baseline, patients with non-functional NETs had, on average, a larger primary tumor and more often metastatic disease. A subgroup analysis in malignant NETs (node or hepatic metastases) showed no significant difference in survival for functionality. Only Bilimoria and coworkers report a significant difference in uni- and multivariate analyses between functional and non-functional pNETs in patients undergoing pancreatic surgery, including metastasized pNETs (Bilimoria *et al.* 2008). In the subgroup analysis of this study, a better prognosis for gastrinomas is reported (HR 0.52, 95% CI: 0.30–0.92), while other syndromes did not have a significant longer survival. Several center-wide or cohort studies report a better survival for functional tumors (Ekeblad *et al.* 2008, Halfdanarson *et al.* 2008, Wang *et al.* 2011, Yang *et al.* 2015). Including all stages of disease and all types of treatment, functional tumors have a better prognosis; however, in multivariate analyses, only Halfdanarson and coworkers report higher survival rates for functional NETs (HR 0.71; 95% CI: 0.57–0.89). Wang and coworkers have studied 93 pNET patients and reported a higher five-year survival in functioning NETs. However, at baseline, the non-functioning NETs were significantly more poorly differentiated and were also more often metastasized to lymph nodes. Ekeblad and coworkers and Yang and coworkers also reported higher survival probabilities in functional NETs, but in multivariate analyses, correcting for stage and differentiation, this was no longer significant. So in this broad spectrum, patients with a functional pNET have a better prognosis than their non-functioning counterparts; however, this is often biased by stage and differentiation. Correction for these factors almost always results in comparable prognosis for functional and non-functional pNETs, so once again, the difference in prognosis between functioning and

non-functioning NETs is probably explained by tumor burden and differentiation and not by hormone secretion.

Insulinomas

The first patient with the typical presentation of an insulinoma was described in 1927 by Wilder (Wilder *et al.* 1927). This patient turned out to have a malignant insulinoma with liver metastases. Insulinomas present mainly with hypoglycemia resulting in episodes of confusion, loss of consciousness, sweating or dizziness and body weight increases (Stefanini *et al.* 1974, Fajans & Vinik 1989). The diagnosis of an insulinoma is based on Whipple's triad: neuroglycopenia with a proven hypoglycemia and elevated circulating insulin levels with resolving of symptoms after normoglycemia is established (Whipple 1938, de Herder *et al.* 2006, Cryer *et al.* 2009). Some patients suffer from convulsions or abnormal behavior resulting in long neurological or psychiatric treatment before the insulinoma is diagnosed. These disabling symptoms might bear an advantage: almost 90% of patients present with localized disease with tumors smaller than 5 cm restricted to the pancreas. Prognosis is excellent in these patients. Overall survival and curation rates are often near 100% after enucleation or (partial) pancreatectomy, higher than most series on non-functioning pNETs (Tsutsumi *et al.* 2013, Mehrabi *et al.* 2014).

Once metastasized, insulinomas form a unique clinical challenge. With its recurrent hypoglycemia, it causes major comorbidity and, if uncontrolled, mortality as well. In this often palliative setting, symptom control is the major treatment goal in these patients. Diazoxide is often used to prevent hypoglycemia by reducing insulin secretion through its effect on ATP-sensitive potassium channels (Altszuler *et al.* 1977). Fluid retention and hirsutism are the most common side effects (Gill *et al.* 1997). If the insulinoma expresses somatostatin receptors

Table 5 Reported survival (either hazard ratio or median survival) comparing functional and non-functional pancreatic neuroendocrine tumors.

	Hazard ratio for functioning pNET (95% CI)	Median survival (functional vs non-functional)	P value	
Cubilla and Hajdu (1975)		2.8 years vs 4.3 years	NA	P value not reported
Venkatesh <i>et al.</i> (1990)		45.2 vs 40.4 months	>0.2	Surgical
Hochwald <i>et al.</i> (2002)		152 vs 110 months	0.61	Surgical
Panzuto <i>et al.</i> (2005)	0.9 (0.38–2.15)		0.8	
Ekeblad <i>et al.</i> (2008)	0.63 (0.48–0.83)		0.004	Not significant in multivariate analysis
Yang <i>et al.</i> (2015)		80.2 months vs 45.3 months	0.005	Not significant in multivariate analysis

lanreotide or octreotide LAR can potentially reduce insulin secretion as well. However, if somatostatin receptor-expression is low, these drugs can also increase the number of hypoglycemia by decreasing glucagon secretion, more than they decrease insulin secretion. A short clinical trial with short-acting octreotide is, therefore, recommended when starting with somatostatin analogs (de Herder *et al.* 2011).

PRRT with radiolabeled somatostatin has also been reported to be effective in reducing hypoglycemia in patients with metastatic insulinoma. Treatment results in long-lasting euglycemia and can stabilize tumor growth (van Schaik *et al.* 2011). Other effective options for metastasized insulinoma include chemotherapy (streptozotocin and 5-fluorouracil) or everolimus (Moertel *et al.* 1980, Kulke *et al.* 2009, Bernard *et al.* 2013).

As metastasized insulinomas are rare, no large series are available on prognosis. The few series with more than 10 patients report a median survival of approximately 2–3 years, but survival of over 30 years has been described in single patients (Danforth *et al.* 1984, Hirshberg *et al.* 2005, Starke *et al.* 2005). All these series have been published before PRRT or tumor-targeting therapy was available and thereby probably underestimate current prognosis as for example van Schaik and coworkers report a median progression-free survival of 27 months in five patients after treatment with PRRT, which is a vast improvement compared to these historical cohorts. Median survival of metastatic non-functioning pNET in the period before 2005 is 2–3 years as well (Solorzano *et al.* 2001, Wang *et al.* 2011, Yang *et al.* 2014).

So it seems that insulinomas have a better prognosis than non-functioning pNETs when resectable, but metastatic disease has not been reported to have a better survival. It remains unclear if the better prognosis of insulinomas is due to the early detection because of hypoglycemia or whether this is related to a more indolent course of disease caused by other factors like different genetic mutations in line with evidence in non-functioning pNETs (Sadanandam *et al.* 2015).

Gastrinoma

Gastrin secreted in large amounts by a gastrinoma causes severe peptic ulcer disease through acid hypersecretion and is known as the Zollinger–Ellison Syndrome (ZES) (Zollinger & Ellison 1955). ZES is diagnosed when an inappropriate high gastrin is demonstrated, but the diagnosis is challenging because of proton-pump inhibitors (PPIs) being widely used nowadays (Falconi *et al.* 2016).

Discontinuing PPIs can aid the diagnostic process, but in patients with ZES, peptic complications can rapidly arise, so this should only be done cautiously (Poitras *et al.* 2012). Gastrinomas are most often localized in the duodenum or the pancreas (gastrinoma triangle), but are not always found with pre-operative imaging. Fortunately, this does not influence the outcome and should not withhold patients from surgery (Alexander *et al.* 1998, Norton *et al.* 2012). A sharp decrease in peptic complications in ZES has been established since the introduction of PPIs leading to a discussion if surgery is indicated for ZES (Hirschowitz *et al.* 2005, Wilcox *et al.* 2011). Treatment strategy is also highly dependent on the presence or absence of the multiple endocrine neoplasia 1 (MEN-1) syndrome. Several studies have shown the benefit of surgical resection for sporadic gastrinoma. A large amount of patients have lymph node metastases at the time of first resection, so removal of peritumoral nodes is advised (Norton *et al.* 2012, Giovinazzo *et al.* 2013). This results in curation of approximately half of patients after surgery and an excellent 10-year survival of over 90% in patients with a localized gastrinoma, higher than non-functional pNETs (Thompson *et al.* 1988, Weber *et al.* 1995, Bilimoria *et al.* 2008, Norton *et al.* 2012). For MEN-1-associated gastrinomas, only medical treatment with PPIs can be started in most cases. Due to the multifocal nature of gastrinomas in MEN-1, curation rates are much lower in MEN-1 patients, but on the other hand, prognosis is better, also justifying an observational strategy (Weber *et al.* 1995, Jensen *et al.* 2012). Although local lymph node metastases do not seem to influence prognosis too much, survival does decrease once liver metastases occur. Then 5-year survival decreases to 30–46% with 10-year survival of 16–30% (Weber *et al.* 1995, Yu *et al.* 1999). This seems to be slightly better in MEN-1 with reported 15-year survival of over 50%. Mainly when diffuse liver metastases are diagnosed survival is significantly reduced in MEN-1 (Yu *et al.* 1999). Then palliative treatment should be considered in the form of SSAs, PRRT with radiolabeled somatostatin analogs or sometimes debulking, always in combination with a PPI. PRRT with radiolabeled somatostatin resulted in a partial response in 45% of patients with a gastrinoma, but time to progression was shorter than that in non-functioning pNETs (Kwekkeboom *et al.* 2008, Grozinsky-Glasberg *et al.* 2011).

So while 60% of gastrinomas are classified as being malignant because of peritumoral lymph node metastases, this is not reflected in survival. Even with only 50% cure after local resection, survival is high in the absence of liver

metastases, and in surgical cases, survival is higher than that for patients with non-functional pNETs.

Glucagonoma

Patients with a glucagonoma usually present with diabetes mellitus and typical skin lesions named necrolytic migratory erythema. Other clinical features include glossitis, anemia, weight loss and venous thrombosis (Soga & Yakuwa 1999a). First described in 1966 by McGavran, current incidence is estimated to be 0.02–0.06 per million (McGavran et al. 1966, Vinik & Moattari 1989, Yao et al. 2007). Tumors are localized in the pancreatic body or tail in 80% of patients and more than half of patients present with liver metastases (Soga & Yakuwa 1999a). In line with the other pNETs, surgery should be considered for localized glucagonoma. It is of importance to correct diabetes mellitus and mineral deficiencies in the often cachectic patients. SSAs can be administered pre-operatively to aid in this process and simultaneously low-molecular-weight heparins should be administered for prevention of thrombosis (Kaltsas et al. 2004). Radical resection of the glucagonoma can result in long-lasting remission in 80–100% of patients (Soga & Yakuwa 1999a, Chu et al. 2003).

In patients with metastatic glucagonoma treatment with SSAs results in weight increase and reduction of skin lesions (Kindmark et al. 2007, Eldor et al. 2011). Small numbers of patients have been treated with PRRT with radiolabeled somatostatin. The largest series of patients has been described by Soga and coworkers. Describing 407 cases of glucagonoma, they report a 10-year survival of 100% in localized disease (not including peri-operative mortality) and 51% in case of metastatic glucagonoma (Soga & Yakuwa 1999a). Other smaller series report 5-year survival of 70% for all stages of glucagonoma combined (Chu et al. 2003, Kindmark et al. 2007, Eldor et al. 2011). No direct comparison between non-functioning pNETs and glucagonomas are available.

VIPoma

The syndrome caused by hypersecretion of vasoactive intestinal peptide (VIP) is known under multiple synonyms, namely VIPoma, Verner–Morrison syndrome, pancreatic cholera or Watery diarrhea hypokalemia achlorhydria (WDHA) syndrome. Currently VIPoma syndrome is mostly used in literature, but supplied with all these names one already knows a lot about VIPomas.

First described by Verner and Morrison in 1958, hardly all patients present with diarrhea, sometimes so severe it causes hypokalemia and metabolic acidosis through bicarbonate depletion (Verner & Morrison 1958). The primary tumor is localized in the pancreas in 81% of patients, and these tumors behave more malignant than the approximately 20% neurogenic tumors (Soga & Yakuwa 1999b). As one of the rarest syndromes in pNETs (estimated incidence of 0.1–0.6 per million) few large series on epidemiology and survival are available. Once again, localized disease has an excellent prognosis when resection is feasible (5 year survival 94%), but 5-year survival declines to 60% in the presence of liver metastases (Soga & Yakuwa 1999b). No direct comparison with non-functioning NETs is available once more, but survival seems to be grossly similar as metastatic non-functioning pNETs. If curative surgery is no longer an option treatment with SSAs can dramatically reduce stool volumes. Reduction of tumor volume, either through debulking, embolization, PRRT or radiofrequency ablation have all successfully been used in individual cases (Peng et al. 2004, Moug et al. 2006, Kwekkeboom et al. 2008).

ACTH

Ectopic ACTH secretion (EAS) is a type of Cushing's syndrome (CS), a severe endocrine disorder associated with severe morbidity and high mortality risk (Lacroix et al. 2015). In 1963, EAS was identified as a cause of CS when Liddle described a case of CS caused by a malignancy secreting ACTH (Liddle et al. 1963). It is now known to cause approximately 10–20% of CS and it is associated with pulmonary NET (small-cell lung carcinoma and carcinoid), pNET, pheochromocytoma and medullary thyroid carcinoma (Ilias et al. 2005). Typical signs and symptoms are muscle weakness, hypokalemia, body weight changes, truncal obesity, full moon face, hypertension and diabetes (Lacroix et al. 2015). EAS can often present with an aggressive form of CS, with urinary free cortisol more than 10 times elevated. EAS patients are thereby at risk of heart failure, opportunistic infection, bowel perforation and pancreatitis (Ilias et al. 2005, Isidori et al. 2006, Kamp et al. 2016). As soon as EAS is diagnosed, control of hypercortisolism should have high priority. Options include ketoconazole, metyrapone and also laparoscopic biadrenalectomy should certainly be considered in severe cases (van der Pas et al. 2012, Reincke et al. 2015). Resection of localized disease will of course cure EAS but

should be performed preferably when hypercortisolism is controlled to prevent complications.

Due to the complications of hypercortisolism mortality is high at presentation, but thereafter, it is mainly influenced by stage and type of tumor. EAS associated with small-cell lung cancer and medullary thyroid carcinoma have the worst prognosis while occult tumors and NETs have a better prognosis (five-year survival 60–80%) (Ilias *et al.* 2005). Kamp and coworkers demonstrated a worse prognosis during the first 5 years of treatment of EAS patients vs other NETs, but over the entire follow-up no significant difference was found (Kamp *et al.* 2016). At baseline, EAS patient had stage IV disease in significantly higher percentage but number of patients was too small to correct for stage. It does however affirm that aggressive treatment of hypercortisolism is essential, because of its high mortality rate, but when this is done successfully, survival is limited by tumor burden comparable to non-functioning pNETs.

Conclusion

Every hormone hypersecretory syndrome associated with NETs presents with its own clinical challenge varying from hypoglycemia to heart failure and from opportunistic infections to diarrhea. This influences prognosis in a number of ways. On the one hand, symptoms allow for detection in earlier stages but the effects of hypersecretion can increase mortality. Survival in localized functioning NETs has always been high, but survival in metastatic disease is now also increasing, mainly due to the introduction of SSAs and PRRT with radiolabeled somatostatin which both reduce secretion and tumor growth, but also targeted therapy with everolimus and sunitinib, increases PFS.

Contemporary studies in midgut NETs show no significant difference in survival between patients with the carcinoid syndrome and those without, probably as a result of SSAs and other new therapies. The worse prognosis often reported in patients with the carcinoid syndrome is probably a reflection of tumor burden and not due to the serotonin secretion.

In pNETs multiple hormonal syndromes have been described. In studies comparing functioning pNETs as a whole, they often have a better survival than the non-functional pNETs, but correction for stage and differentiation often corrects for this fact, probably explaining the difference in survival.

For individual syndromes, excellent prognosis has been reported when a radical resection is possible and then survival is better than non-functional pNETs. Mainly insulinomas and gastrinomas seem to have a better survival than non-functioning pNETs, but this comparison can only be made by comparing different populations, which makes this conclusion limited. The overall survival in patients with the other functional pNET syndromes is shorter and conclusions are difficult to make as stage and grade differ and reported numbers are often too low to reach significance. But overall, the arsenal of drugs currently available has limited mortality associated with hypersecretion and NET mortality is now mainly caused by tumor burden and no longer by hypersecretion.

Declaration of interest

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