Curr. Treat. Options in Oncol. (2019) 20: 70
DOI 10.1007/s11864-019-0671-0

Neuroendocrine Cancers (JR Strosberg, Section Editor)

Carcinoid Syndrome: Updates and Review of Current Therapy

Kira Oleinikov, MD
Shani Avniel-Polak, PhD
David J. Gross, MD
Simona Grozinsky-Glasberg, MD[*]

Address
[*]Neuroendocrine Tumor Unit, ENETS Center of Excellence, Endocrinology and Metabolism Department, Division of Medicine, Hadassah-Hebrew University Medical Center, P.O.B. 1200091120, Jerusalem, Israel
Email: simonag@hadassah.org.il

Published online: 9 July 2019

This article is part of the Topical Collection on *Neuroendocrine Cancers*

Keywords Treatment · Neuroendocrine · Carcinoid syndrome

Opinion statement

Carcinoid syndrome (CS) is a complex disorder caused by functional neuroendocrine tumors (NETs). This debilitating disease is characterized by hyper-secretion of biologically active substances eliciting major hormonal symptoms burden and fibrotic changes that are often challenging for management. There have been a number of insights that have substantially advanced treatments since the introduction of somatostatin analogs (SSAs). Second-line treatments are needed in a substantial proportion of patients with advanced disease that have uncontrolled hormone secretion on the highest labeled doses of SSAs. International guidelines suggest several available options including dose escalation of SSAs, interferon alpha, everolimus, radionuclide therapy, liver-directed therapies, and the novel tryptophan hydroxylase 1 inhibitor, telotristat ethyl. The clear preference of one second-line therapy over the other is not stated since their relative and long-term efficacy are largely unknown, and standardized approach of hormonal response assessment is lacking in the literature. In the clinical setting, the treatment of CS is guided in conjunction with patients' performance status, tumor origin, grade, stage, and growth rate, with regard to both anti-hormonal, as well as anti-proliferative effect. There is an unmet need for further well-designed randomized placebo-controlled and head-to-head studies that systematically assess CS symptom control and biochemical response following a specific intervention.

Introduction

Carcinoid syndrome (CS) is the most frequent of the hormonal syndromes described in association with neuroendocrine tumors (NETs) [1]. The CS comprises a constellation of hormonal symptoms manifested by abdominal pain, increased bowel movements, episodic facial flushing, bronchoconstriction, venous telangiectasia, niacin deficiency–related symptoms, and long-term complications, such as mesenteric fibrosis and carcinoid heart disease (CHD) [1–5].

The recent US epidemiological study reported an estimated CS prevalence of 19% in a population of 9512 patients with NET diagnosis. The data analysis demonstrated a clear CS association with female gender, non-Hispanic white race, advanced tumor stage, lower grade, and tumor origin [4•].

Over 40 humoral substances were identified as being potentially involved in pathogenesis of CS. The main mediator appears to be serotonin (5-HT), which is considered the primary marker associated with the syndrome, as well as histamine, prostaglandins, and tachykinins [6, 7].

The symptomatic occurrence of CS is predominantly associated with NETs of the small intestine origin in the setting of extensive liver metastases, as the secreted vasoactive substances have to bypass liver inactivation and directly enter the systemic circulation. In smaller percentages, CS may present in lung carcinoids, NETs of pancreatic and ovarian origin, and in metastatic small bowel NETs with extrahepatic disease [4, 5].

Serotonin is thought to be particularly important in mediating diarrhea in carcinoid syndrome, through its effect on gut motility and secretion [8–10]. In CS patients, chronic diarrhea occurs with a frequency of 60–80% and has a major detrimental impact on the general health status, along with emotional and social well-being [11–13]. Chronic secretory diarrhea in CS patients may lead to dehydration, renal insufficiency, electrolyte imbalances, and malabsorption, as a consequence of absorptive and secretory imbalance in the gut [11]. A recent study of 2822 CS patients demonstrated that patients with diarrhea had almost a 2-fold higher risk of disease-related hospitalizations that was reflected in 1.5-fold higher total healthcare spending [13].

Elevated serotonin levels are implicated in the pathogenesis of fibrotic complications in the mesentery as well as cardiac valves [14–17, 18••]. Patients with carcinoid heart disease (CHD) have higher urinary excretion rates of 5-HIAA and higher plasma levels of neurokinin A, activin A, substance P, atrial natriuretic peptide, N-terminal pro-brain natriuretic peptide, chromogranin A, and connective tissue growth factor (CTGF) than patients without CHD, although the individual substance contribution in pathogenesis of fibrosis remains unclear [14, 19].

In many patients, the treatment of CS is challenging owing to the difficult control of carcinoid syndrome symptoms in parallel with tumor progression. The development of multiple treatment options assists in optimizing the personalized therapy in CS patient population, with regard to the patient's performance status, tumor grade, stage, and primary location.

The use of somatostatin analogs as the first-line treatment is recommended by international guidelines [20, 21]. Second-line options include SSA dose increase, interferon alpha (IFN-α), locoregional therapy, everolimus, telotristat ethyl, or peptide receptor radionuclide therapy (PRRT) using radiolabeled SSAs, without a clear consensus regarding sequencing of the available options [20, 21]. This absence of agreement results from mostly non-standardized approach in evaluating the symptomatic response rates throughout retrospective and prospective studies (Fig. 1).

Treatment

Nutrition and lifestyle

- Nutritional status should be routinely assessed and malnutrition should be addressed accordingly.
- Supplementation of common deficiencies may be required including pancreatic enzymes, vitamins B3 (niacin), B12, and fat-soluble vitamins.

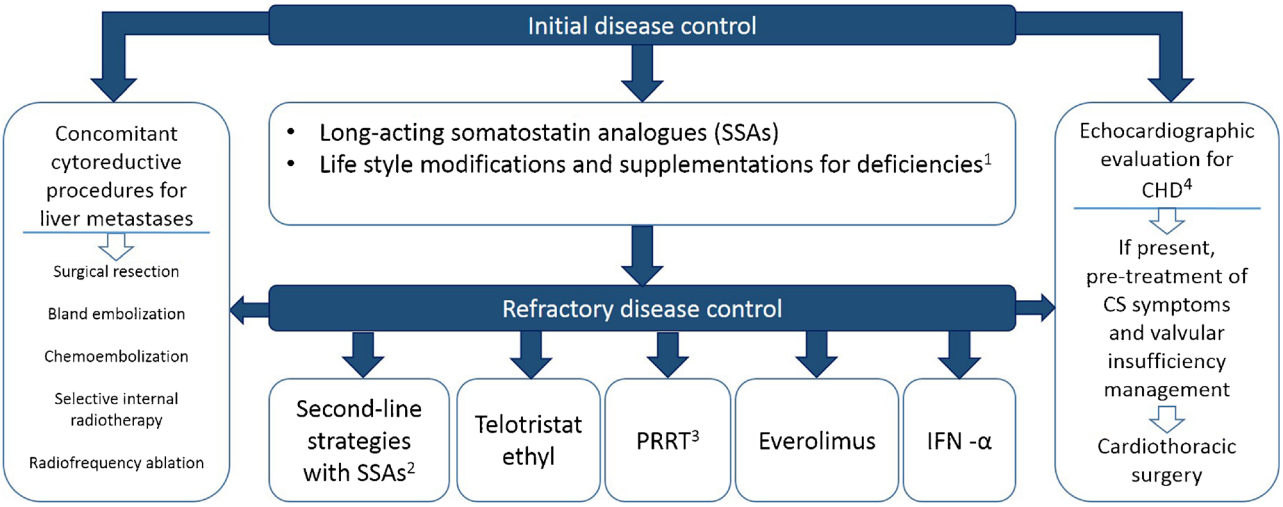

Fig. 1. Carcinoid syndrome management proposed algorithm. [1]See the "Nutrition and lifestyle" section; [2]increase in SSAs dose, decreased injection interval, and switching to the alternative SSA; [3]peptide receptor radionuclide therapy; [4]carcinoid heart disease.

- Alcohol, spicy food, tryptophan rich food, and physical exertion may exacerbate the symptoms of CS.

Malnutrition has been reported in 14 to 25% of gastrointestinal NET patients reaching rates up to 40% in association with extensive and/or progressive disease, under somatostatin analog therapy and with exocrine pancreas insufficiency [22, 23]. Regular screening of nutritional status and interventions is required [24].

For patients experiencing provoked episodes of flushing and diarrhea, lifestyle adjustments should include avoiding alcohol, spicy foods, and strenuous exercise. In CS, the diarrhea is secretory and usually is not responsive to food restrictions. Assessment of diarrhea in CS patients requires consideration of a broader differential diagnosis including steatorrhea due to exocrine pancreatic insufficiency caused by SSAs therapy, bacterial overgrowth, and postoperative malabsorption [25–27].

Tryptophan is the common precursor of serotonin and niacin. In CS patients, the majority of tryptophan is metabolized to serotonin and may lead to niacin (vitamin B3) deficiency in 28–45% of patients [28]. Niacin deficiency can result in pellagra, manifested as dermatitis, diarrhea, and dementia. Regular screening for deficiencies and appropriate supplementation should include niacin, vitamin B12 in patients after resection of the terminal ileum and in patients with long-term SSAs therapy or PPI therapy, and pancreatic enzyme and fat-soluble vitamins supplementation in patients with long-term SSAs therapy [29].

Pharmacologic treatment

Somatostatin analogs (SSAs)

- Somatostatin analogs (SSAs) provide substantial symptom relief in CS patients and are recommended as first-line treatment.

- All approved analog formulations seem to offer similar efficacy and are usually well tolerated.
- Loss of hormonal symptom response to standard SSA doses can occur due to tachyphylaxis and/or tumor progression and may respond to SSA dose escalation or require additional second-line therapy.

Somatostatin is a cyclic peptide acting as a neuromodulator in the brain and a paracrine hormone in the gastrointestinal (GI) tract. It exerts predominately inhibitory effects on endocrine and exocrine function of the GI tract and has an anti-proliferative effect by binding and activating its G protein-coupled receptors (somatostatin receptors 1 to 5 (SSTR 1–5)) [30].

Somatostatin anti-tumor action is mediated through various mechanisms, either directly inducing cell cycle arrest and apoptosis in special instances by binding predominantly to SSTR subtype 2 expressed on the tumor cells, or indirectly affecting tumor proliferation by inhibition of angiogenesis and immunomodulation [31].

For several decades, since the first introduction of SSAs, their therapeutic effect has been extensively studied and is considered the first-line treatment in nonresectable and/or metastatic disease [21, 22, 32].

The short-acting analog octreotide may be administered subcutaneously at a dose of 50–500 mcg three times a day, whereas the long-acting formulations include octreotide long-acting release (LAR), an intramuscular injection at a dose of 30 mg every 28 days, and lanreotide autogel, a deep subcutaneous injection at a dose of 120 mg every 28 days [33].

These preparations are usually well tolerated with the most frequently occurring side effects being pain at the site of injection, nausea, abdominal cramps, diarrhea, and less frequently glucose intolerance, cholelithiasis, and bradycardia [32–36].

The anti-proliferative effect of these drugs was clearly demonstrated in double-blind placebo-controlled trials. [32–36].

A recent meta-analysis summarized the treatment of CS patients with both analogs, reporting achievement of CS symptom control in 66–70% of patients and a decrease in 5-HIAA levels in 45–46% of CS patients [37•].

Both, short- and long-acting analogs seem to offer similar efficacy in terms of CS symptom control, although they have not been tested in head-to-head trials to date.

Despite the clear efficacy of SSAs, loss of response can occur after prolonged use. Downregulation of SSTRs on tumor cell surface and development of antibodies to SSAs have been hypothesized to underlie tachyphylaxis, namely time-dependent treatment resistance to SSAs.

Several studies explored dose escalation, decreased injection interval, and switching to the alternative SSA, as a second-line treatment after usual dosages of SSAs, and reported favorable results in terms of clinical, biochemical, and tumor response. Overall, these interventions resulted in decreased bowel movements frequency in 72% of patients and reduced flushing in 84% of subjects. The biochemical response reported in these studies was 29% [37•, 38–41].

Pasireotide, a SSA with affinity to SSTR subtypes 1, 2, 3, and 5, was tested in patients with NETs in an attempt to overcome resistance to SSAs therapy. However, a randomized phase III study of pasireotide LAR versus high-dose (40 mg) octreotide LAR in patients with advanced GEP-NETs failed to show

superiority of pasireotide LAR in comparison with first-generation SSAs at maximum approved doses [42].

Interferon alpha

- Interferon alpha has a well-described anti-hormonal, as well as anti-proliferative activity in CS patients.
- The safety profile of this drug limits its widespread use.
- It may be considered in patients with CS refractory to SSAs.

The anti-secretory effects of interferon alpha (IFN-α) in CS patients as well as its anti-proliferative efficacy were well described [43–47]. It has cytostatic, cytotoxic, anti-angiogenic, and immunomodulatory effect by inducing cell cycle arrest, apoptosis, decreasing the expression of VEGF mRNA, and activating T lymphocytes [30]. The recommended dose of IFN-α is 3–9 MU subcutaneously every other day. Slow release formulation of 80–100 mg PEGylated IFN-α is given subcutaneously once a week.

However, low tolerability of the drug due to its side effects (e.g., flu-like symptoms, chronic fatigue, liver and bone marrow toxicity) has limited its use [42]. In several single-arm prospective series, the reported response rates of IFN-α monotherapy varied widely between 0–90% for clinical and 50–80% for biochemical control [44–47]. A multicenter randomized controlled study in 39 CS patients combining IFN-α with SSAs did not demonstrate a significant beneficial effect vs SSAs given alone [43].

Serotonin synthesis inhibitor-telotristat ethyl

- Oral inhibitor of serotonin synthesis-telotristat ethyl was recently approved in symptomatic, CS-related diarrhea refractory to SSAs therapy.
- The drug efficacy was demonstrated in phase 3 studies by reducing bowel movement frequency, with response rates of 40–44%.
- As expected, flushing is usually not responsive to this therapy.

Serotonin (5-hydroxytryptophan) is considered the main contributor to the clinical symptoms of CS [6, 7]. It is formed from tryptophan in a rate-limiting process controlled by the enzyme tryptophan hydroxylase (TPH). TPH is found in two isoforms: TPH1 distributed peripherally, particularly in GI system, while TPH2 is active in the brain, as a neurotransmitter [48–50]. Para-chlorophenylalanine, a non-selective inhibitor of TPH, was evaluated in the past as a treatment for carcinoid syndrome, but its use was halted due to increased frequency of depression in patients, presumably due to reduction in brain serotonin [51].

The oral TPH inhibitor telotristat ethyl was shown to have equivalent affinity to both isoenzymes; however, it does not cross blood-brain barrier thus decreasing the risk of CNS adverse events related to TPH2 inhibition [52]. Telotristat ethyl is metabolized to its active metabolite, telotristat, by carboxylesterases. Compared with the telotristat ethyl, telotristat has an inhibitory potency of about 28- and 34-fold greater for TPH1 and TPH2, respectively. Following oral administration of telotristat ethyl at a dosage of 500 mg three times daily, the peak plasma concentrations of telotristat ethyl and telotristat are

achieved within 0.5–2 h and within 1.5–3 h, respectively. Most common side effects are mild abdominal pain and nausea, possibly related to slowing of the gastric motility [53, 54].

Telotristat ethyl was evaluated in double-blind randomized phase 3 clinical trials (TELESTAR and TELECAST) designed for patients with either 4 or more stools per day or less than 4 stools per day on SSA therapy, aiming to explore the efficacy and safety of the drug in patients with uncontrolled CS. A reduction in bowel movement was shown in 40–44% of patients treated with telotristat ethyl, compared with 0–20% of patients treated with placebo. In patients with four or more stools per day, placebo reduced daily stool frequency by 0.9, whereas telotristat ethyl 250 mg tid or 500 mg tid reduced daily stool frequency by 1.7 and 2.1, respectively. As expected from the known actions of serotonin, flushing was not significantly reduced [55, 56••].

Mammalian (mechanistic) target of rapamycin (mTOR) inhibitor-everolimus

- Everolimus combined with SSAs for functionally active NET is routinely used in clinical practice as anti-tumor agent, although it is not approved for specifically hormonal control.

The abnormal activation of the serine/threonine protein kinase named mTOR upregulates several cellular processes such as cell growth, proliferation, and survival in many cancers including NETs. The inhibition of mTOR by rapamycin and its analogs such as everolimus was shown to have an anti-proliferative effect and lead to the approval of everolimus in treatment of NETs of pancreatic, lung, and intestinal origin [57, 58].

Of note, the combination of everolimus and SSAs is often used in patients with progressive NETs and seems to have a synergistic effect. However, the side effects of everolimus, such as stomatitis, rash, diarrhea, fatigue, weight loss, hyperglycemia, and pneumonitis, may be challenging, with around 60% of patients requiring dose reduction and up to 19% requiring therapy withdrawal [59].

A double-blind, placebo-controlled phase III trial RADIANT-2 assessed everolimus 10 mg daily in combination with long-acting octreotide 30 mg q28d in advanced NET patients and a history of symptomatic carcinoid syndrome with a progression-free survival as a primary end point. A significant reduction in u5HIAA ($p < 0.0001$) was observed in the everolimus arm compared with the placebo arm (both with concurrent administration of long-acting octreotide 30 mg q28d) although the control of symptoms associated with carcinoid syndrome was not assessed [60].

Peptide receptor radionuclide therapy (PRRT)

- PRRT with radiolabeled SSAs is registered for progressive small intestine NETs.
- Several sub-analyses in CS patients within the prospective series demonstrated the beneficial impact on hormonal symptoms, presumably due to treatment cytoreductive effect.

PRRT in NET patients with progressive disease relies on overexpression of somatostatin receptors by neuroendocrine tumors. The available radionuclide

options include 90Yttrium (90Y) or 177Lutetium (177Lu) labeled SSAs [61]. This targeted radiation treatment yields an objective radiological response in up to 20–30% of NET patients [62, 63].

The randomized prospective phase 3 trial NETTER-1 demonstrated that 177Lu-Dotatate therapy markedly prolongs progression-free survival compared with high-dose octreotide alone, in patients with metastatic and progressing small intestinal NET [64••]. In addition, the same study reported a significant quality-of-life benefit in ^{177}Lu-Dotatate arm compared with octreotide [65].

PRRT is usually well tolerated, with self-limiting acute side effects of nausea and vomiting (attributed mainly to amino acid infusions performed concurrently with PRRT). Transient bone marrow suppression occurring 2–6 weeks after treatment (rarely Grade 3 or 4 neutropenia (1%), thrombocytopenia (2%), or lymphopenia (9%)), myelodysplastic syndrome (MDS) and leukemia (< 5%) and renal function deterioration are rarely reported. The potential exacerbation of hormonal syndromes leading to carcinoid crisis during/after PRRT (1%), although rare, must be acknowledged; therefore, the patients with CS must be carefully selected, prepared, and monitored [63].

A meta-analysis of 156 patients with CS-specific outcomes treated with either 177Lu-DOTATATE or 90Y-DOTATOC from four prospective phase 2, single-center studies demonstrated a symptomatic improvement in 74% of 47 patients suffering from diarrhea or 64% of 56 patients with flushing, although, the overall biochemical response was observed in only 17% of 177 patients with available data [37•].

Liver-directed therapies

- Liver-directed interventions can result in tumor volume reduction, aiming for both tumor and hormonal production control.
- Good-quality data on this approach is lacking, as no randomized, prospective studies are available.

Extensive data in the literature supports the notion that the clinical picture of CS becomes evident when excessive amounts of the tumor-secreted mediators reach the systemic circulation. In most cases, this is enabled by the presence of liver metastases that circumvent the hepatic inactivation of bioactive substances released into the portal circulation. Multiple liver-directed interventions have been assessed including surgical resection, radiofrequency ablation, selective internal radiotherapy, bland embolization, and chemoembolization. However, most studies are single institution retrospective series characterized by poor-quality data [66].

While many studies evaluated radiologic response and progression-free survival, multiple series also included symptomatic and/or biochemical response. In addition, the assessment of clinical and biochemical CS response rate of the cytoreductive strategies is difficult, as the majority of patients received simultaneous SSAs therapy [67–76].

In case of potentially resectable liver metastases, surgery may provide long-term disease-free survival as well as symptomatic relieve from CS. However, patients with CS often present with extensive liver involvement, which is rarely amenable for complete surgical removal. The value of R2 surgical debulking remains controversial, as the evidence from randomized, controlled studies is

absent. In support of this approach, small retrospective series report a clinical benefit in terms of symptom relief in the case of successful surgical debulking, although potential patient selection bias may complicate the interpretation of the results [67–70].

Trans arterial liver embolization, with or without chemotherapy, is often considered for CS patients with inoperable liver metastases [71–75]. The role of radiofrequency ablation (either with the ablation alone or as an adjunct to surgery) in low volume liver disease to allow maximal debulking is yet to be established [69–70]. For highly selected young patients with liver-only metastases and resected primary tumor, liver transplantation may be an option, given the reported recurrence-free survival of 20–30% at 5 years [77].

Special points

Carcinoid crisis prevention and treatment

- Carcinoid crisis is associated with a high mortality rate, usually elicited by direct tumor manipulation during invasive procedures in CS patients.
- Current recommendation for crisis prevention includes prophylaxis with peri-procedural octreotide infusion.

Carcinoid crisis is a potential life-threatening condition usually manifested by hemodynamic instability with predominant hypotension, tachycardia, flushing, arrhythmias, and bronchoconstriction that is presumably elicited by the release of biologically active substances. The potential risk of carcinoid crisis is increased in CS patients undergoing invasive procedures (e.g., surgery, embolotherapies), as well as, radionuclide therapy [78, 79]. While it is still debated whether peri and intraoperative octreotide infusion prevents carcinoid crisis, it is generally recommended for patients with CS undergoing invasive procedures [80–82]. One recommendation on perioperative prevention of carcinoid crisis is IV octreotide infused at a rate of 150 to 500 μg/h, 12 h pre-operatively, continuously throughout the procedure and post-operatively until stable. 100- to 200-μg boluses of IV octreotide can be administered and repeated as needed, if any manifestations of carcinoid crisis occur during the procedure. Despite prophylactic measures, carcinoid crisis is not entirely preventable and requires prompt recognition intraoperatively and aggressive treatment. A recent prospective study suggests that the etiology of hypotension is consistent with distributive shock responsive to treatment with intravenous fluids and vasopressors, and that expeditious management decreases the rate of carcinoid crisis–associated complications [83•].

Compliance with Ethical Standards

Conflict of Interest

Kira Oleinikov, Shani Avniel-Polak, David J. Gross, and Simona Grozinsky-Glasberg declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Jensen RT, Norton JA, Oberg K. In: Feldman M, Friedman LS, Brandt LJ, editors. Neuroendocrine tumors in Sleisenger and Fordtran's gastrointestinal and liver diseases, edn tenth. Philadelphia: Elsevier Saunders; 2016. p. 501–41.
2. Boutzios G, Kaltsas G. Clinical syndromes related to gastrointestinal neuroendocrine neoplasms. Front Horm Res. 2015;44:40–57.
3. Van Der Lely AJ, Herder WW. Carcinoid syndrome: diagnosis and medical management. Arq Bras Endocrinol Metabol. 2005;49(5):850–60.
4.• Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18:525–34. Recent extensive study on the frequency and epidiomology of carcinoid syndrome.
A population-based analysis focusing on epidemiology, clinical characteristics and survival of carcinoid syndrome patients.
5. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017.
6. Druce M, Rockall A, Grossman AB. Fibrosis and carcinoid syndrome: from causation to future therapy. Nat Rev Endocrinol. 2009;5(5):276.
7. Ardill JE, Armstrong L, Smye M, et al. Neuroendocrine tumours of the small bowel: interpretation of raised circulating chromogranin A, urinary 5 hydroxy indole acetic acid and circulating neurokinin A. QJM. 2016;109:111–5.
8. Tohmola N, Itkonen O, Sane T, et al. Analytical and preanalytical validation of a new mass spectrometric serum 5-hydroxyindoleacetic acid assay as neuroendocrine tumor marker. Clin Chim Acta. 2014;428:38–43.
9. Adaway JE, Dobson R, Walsh J, et al. Serum and plasma 5-hydroxyindoleacetic acid as an alternative to 24-h urine 5-hydroxyindoleacetic acid measurement. Ann Clin Biochem. 2016;53:554–60.
10. Tellez MR, Mamikunian G, O'Dorisio TM, et al. A single fasting plasma 5-HIAA value correlates with 24-hour urinary 5-HIAA values and other biomarkers in midgut neuroendocrine tumors (NETs). Pancreas. 2013;42:405–10.
11. Chuang CC, Bhurke S, Chen SY, Brulais S, Gabriel S. Clinical characteristics, treatment patterns, and economic burden in patients treated for neuroendocrine tumors in the United States: a retrospective cohort study. J Med Econ. 2015;18(2):126–36.
12. Fröjd C, Larsson G, Lampic C, Von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. Health Qual Life Outcomes. 2007;5(1):18.
13. Broder MS, Chang E, Romanus D, Cherepanov D, Neary MP. Healthcare and economic impact of diarrhea in patients with carcinoid syndrome. World Journal of Gastroenterol. 2016;22(6):2118.
14. Modlin IM, Bodei L, Kidd M. Neuroendocrine tumor biomarkers: from monoanalytes to transcripts and algorithms. Best Pract Res Clin Endocrinol Metabol. 2016;30(1):59–77.
15. Laval VR, Pavel M, Steffen IG, Baur AD, Dilz LM, Fischer C, et al. Mesenteric fibrosis in midgut neuroendocrine tumors: functionality and radiological features. Neuroendocrinology. 2018;106(2):139–47.
16. Laskaratos FM, Rombouts K, Caplin M, Toumpanakis C, Thirlwell C, Mandair D. Neuroendocrine tumors and fibrosis: an unsolved mystery? Cancer. 2017;123(24):4770–90.
17. Grozinsky-Glasberg S, Grossman AB, Gross DJ. Carcinoid heart disease: from pathophysiology to treatment—'Something in the Way It Moves'. Neuroendocrinology. 2015;101:263–73.
18.•• Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. J Am Coll Cardiol. 2017;69(10):1288–304.
A multidisciplinary consensus statement on management of carcinoid heart disease based on an evidence-based review of the published data and on the expert opinion.
19. Dobson R, Burgess MI, Banks M, Pritchard DM, Vora J, Valle JW, et al. The association of a panel of biomarkers with the presence and severity of carcinoid heart disease: a cross-sectional study. PLoS One. 2013;8(9):e73679.
20. Pavel M, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology. 2016;103(2):172–85.
21. Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon J, Heaney AP, et al. The North American Neuroendocrine Society (NANETS) consensus guidelines

for surveillance and medical management of midgut neuroendocrine tumors. Pancreas. 2017;46(6):707.
22. Dimitriadis GK, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer. 2016;23(9):R423–36.
23. Qureshi SA, Burch N, Druce M, Hattersley JG, Khan S, Gopalakrishnan K, et al. Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study. BMJ Open. 2016;6(5):e010765.
24. Maasberg S, Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C, et al. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasia. Neuroendocrinology. 2017;104(1):11–25.
25. Jin XF, Spampatti MP, Spitzweg C, Auernhammer CJ. Supportive therapy in gastroenteropancreatic neuroendocrine tumors: often forgotten but important. Rev Endocr Metab Disord. 2018;1:1–4.
26. Clement DS, Tesselaar ME, van Leerdam ME, Srirajaskanthan R, Ramage JK. Nutritional and vitamin status in patients with neuroendocrine neoplasms. World J Gastroenterol. 2019;25(10):1171.
27. Altieri B, Barrea L, Modica R, Muscogiuri G, Savastano S, Colao A, et al. Nutrition and neuroendocrine tumors: an update of the literature. Rev Endocr Metabol Disord. 2018;19(2):159–67.
28. Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EG, Kema IP, Walenkamp AM. Niacin (Vitamin B3) supplementation in patients with serotonin-producing neuroendocrine tumor. Neuroendocrinology. 2016;103(5):489–94.
29. Barrea L, Altieri B, Muscogiuri G, Laudisio D, Annunziata G, Colao A, et al. Impact of nutritional status on gastroenteropancreatic neuroendocrine tumors (GEP-NET) aggressiveness. Nutrients. 2018;10(12):1854.
30. Alonso-Gordoa T, Capdevila J, Grande E. GEP–NETs UPDATE: Biotherapy for neuroendocrine tumours. Eur J Endocrinol. 2015;172(1):R31–46.
31. Bousquet C, Lasfargues C, Chalabi M, Billah SM, Susini C, Vezzosi D, et al. Current scientific rationale for the use of somatostatin analogs and mTOR inhibitors in neuroendocrine tumor therapy. J Clin Endocrinol Metab. 2012;97(3):727–37.
32. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33.
33. Pavel M, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: systemic therapy-biotherapy and novel targeted agents. Neuroendocrinology. 2017;105(3):266–80.
34. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, 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(28):4656–63.
35. Arnold R, Wittenberg M, Rinke A, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, Mueller HH, PROMID Study Group. 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 (PROMID): results on long-term survival.
36. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016;23(3):191.
37.• Hofland J, Martínez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019;1
A literature review and meta-analysis regarding pharmacological therapies in CS, focusing on treatment efficacy in terms of symptomatic and biochemical response.
38. Strosberg JR, Benson AB, Huynh L, Duh MS, Goldman J, Sahai V, et al. Clinical benefits of above-standard dose of octreotide LAR in patients with neuroendocrine tumors for control of carcinoid syndrome symptoms: a multicenter retrospective chart review study. Oncologist. 2014;19(9):930–6.
39. Al-Efraij K, Aljama MA, Kennecke HF. Association of dose escalation of octreotide long-acting release on clinical symptoms and tumor markers and response among patients with neuroendocrine tumors. Cancer Med. 2015;4(6):864–70.
40. Ferolla P, Faggiano A, Grimaldi F, Ferone D, Scarpelli G, Ramundo V, et al. Shortened interval of long-acting octreotide administration is effective in patients with well-differentiated neuroendocrine carcinomas in progression on standard doses. J Endocrinol Investig. 2012;35(3):326–31.
41. O'Toole D, Ducreux M, Bommelaer G, Wemeau JL, Bouché O, Catus F, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer. 2000;88(4):770–6.
42. Wolin EM, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Dev Ther. 2015;9:5075.
43. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion. 2000;62:92.
44. Arnold R, Rinke A, Klose KJ, Müller HH, Wied M, Zamzow K, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. Clin Gastroenterol Hepatol. 2005;3(8):761–71.
45. Veenhof CH, de Wit R, Taal BG, Dirix LY, Wagstaff J, Hensen A, et al. A dose-escalation study of recombinant

interferon-alpha in patients with a metastatic carcinoid tumour. Eur J Cancer. 1992;28(1):75–8.
46. Di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors: a study by the Italian Trials in Medical Oncology Group. Cancer. 1996;77(2):402–8.
47. Nobin A, Lindblom A, Marnsson B, Sundberg M. Interferon treatment in patients with malignant carcinoids. Acta Oncol. 1989;28(3):445–9.
48. McKinney J, Knappskog PM, Haavik J. Different properties of the central and peripheral forms of human tryptophan hydroxylase. J Neurochem. 2005;92(2):311–20.
49. Amireault P, Sibon D, Côté F. Life without peripheral serotonin: insights from tryptophan hydroxylase 1 knockout mice reveal the existence of paracrine/autocrine serotonergic networks. ACS Chem Neurosci. 2012;4(1):64–71.
50. Heredia DJ, Gershon MD, Koh SD, Corrigan RD, Okamoto T, Smith TK. Important role of mucosal serotonin in colonic propulsion and peristaltic reflexes: in vitro analyses in mice lacking tryptophan hydroxylase 1. J Physiol. 2013;591(23):5939–57.
51. Engelman K, Lovenberg W, Sjoerdsma A. Inhibition of serotonin synthesis by para-chlorophenylalanine in patients with the carcinoid syndrome. N Engl J Med. 1967;277(21):1103–8.
52. Kulke MH, O'Dorisio T, Phan A, Bergsland E, Law L, Banks P, et al. Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. Endocr Relat Cancer. 2014;21(5):705–14.
53. European Medicines Agency. Xermelo, INN-Telotristat. Summary of product characteristics. Available from: https://www.ema.europa.eu/docs/en_GB/document./WC500237107.pdf. Accessed January, 2019.
54. Pavel M, Hörsch D, Caplin M, Ramage J, Seufferlein T, Valle J, et al. Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial. J Clin Endocrinol Metab. 2015;100(4):1511–9.
55. Kulke MH, Horsch D, Caplin ME, et al. Telotristat Ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2017;35:14–23.
56.•• Pavel M, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RR, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. Endocr Relat Cancer. 2018;25(3):309–22
A randomized, controlled phase 3 study, assessing safety and efficacy of telotristat ethyl in CS symptomatic patients.
57. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23.
58. Chan J, Kulke M. Targeting the mTOR signaling pathway in neuroendocrine tumors. Curr Treat Options in Oncol. 2014;15(3):365–79.
59. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low-to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol. 2008;26(26):4311.
60. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378(9808):2005–12.
61. Bergsma H, van Vliet EI, Teunissen JJ, Kam BL, de Herder WW, Peeters RP, et al. Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. Best Pract Res Clin Gastroenterol. 2012;26(6):867–81.
62. Brabander T, Teunissen JJ, Van Eijck CH, Franssen GJ, Feelders RA, de Herder WW, et al. Peptide receptor radionuclide therapy of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab. 2016;30(1):103–14.
63. Cives M, Strosberg J. Radionuclide therapy for neuroendocrine tumors. Curr Oncol Rep. 2017;19(2):9.
64.•• Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35
A randomized, controlled trial, evaluating the efficacy and safety of lutetium-177 (177Lu)-Dotatate in patients with advanced midgut NETs, who progressed under SSA treatment.
65. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177Lu-Dotatate in the phase III NETTER-1 trial. J Clin Oncol. 2018;36(25):2578.
66. Foster DS, Jensen R, Norton JA. Management of liver neuroendocrine tumors in 2018. JAMA Oncol. 2018;4(11):1605–6.
67. Grozinsky-Glasberg S, Kaltsas G, Kaltsatou M, Lev-Cohain N, Klimov A, Vergadis V, et al. Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. Endocrine. 2018;60(3):499–509.
68. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin. 2003;12(1):231–42.
69. Saxena A, Chua TC, Perera M, Chu F, Morris DL. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. Surg Oncol. 2012;21(3):e131–41.
70. Eriksson J, Stålberg P, Nilsson A, Krause J, Lundberg C, Skogseid B, et al. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. World J Surg. 2008;32(5):930–8.
71. Drougas JG, Anthony LB, Blair TK, Lopez RR, Wright JK Jr, Chapman WC, et al. Hepatic artery chemoembolization for management of patients with advanced metastatic carcinoid tumors. Am J Surg. 1998;175(5):408–12.

72. Strosberg JR, Choi J, Cantor AB, Kvols LK. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. Cancer Control. 2006;13(1):72–8.
73. Pericleous M, Caplin ME, Tsochatzis E, Yu D, Morgan-Rowe L, Toumpanakis C. Hepatic artery embolization in advanced neuroendocrine tumors: efficacy and long-term outcomes. Asia Pac J Clin Oncol. 2016;12(1):61–9.
74. Nazario J, Gupta S. Transarterial liver-directed therapies of neuroendocrine hepatic metastases. Semin Oncol. 2010;37(2):118–26 WB Saunders.
75. Pitt SC, Knuth J, Keily JM, McDermott JC, Weber SM, Chen H, et al. Hepatic neuroendocrine metastases: chemo-or bland embolization? J Gastrointest Surg. 2008;12(11):1951–60.
76. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, Rosemurgy AS, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol. 2006;13(4):572–81.
77. Fan ST, Le Treut YP, Mazzaferro V, Burroughs AK, Olausson M, Breitenstein S, et al. Liver transplantation for neuroendocrine tumour liver metastases. HPB. 2015;17(1):23–8.
78. Keskin O, Yalcin S. Carcinoid crisis in the intensive care unit. Oncol Crit Care. 2019:1–7.
79. Kwon DH, Paciorek A, Mulvey CK, Chan H, Fidelman N, Meng L, et al. Periprocedural management of patients undergoing liver resection or embolotherapy for neuroendocrine tumor metastases. Pancreas. 2019;48(4):496–503.
80. Woltering EA, Wright AE, Stevens MA, Wang YZ, Boudreaux JP, Mamikunian G, et al. Development of effective prophylaxis against intraoperative carcinoid crisis. J Clin Anesth. 2016;32:189–93.
81. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. Surgery. 2016;159(1):358–67.
82. Massimino K, Harrskog O, Pommier S, Pommier R. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. J Surg Oncol. 2013;107(8):842–6.
83.• Condron ME, Jameson NE, Limbach KE, Bingham AE, Sera VA, Anderson RB, et al. A prospective study of the pathophysiology of carcinoid crisis. Surgery. 2019;165(1):158–65

A prospective study on the pathophysiology of intraoperative carcinoid crisis.

Publisher's Note