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REVIEW ARTICLE

AIMN, ITANET, SIE joint position paper for the recognition, prevention and management of NET carcinoid syndrome and crises during peptide receptor radionuclide therapy

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Abstract

Purpose Carcinoid syndrome (CS) is the most frequent neuroendocrine tumor (NET)-related syndrome with variable presentations related to hormonal discharge and long-term complications, such as carcinoid heart disease (CHD). Carcinoid crisis (CC) is an acute and serious CS complication, due to a massive release of vasoactive hormones and biologically active substances, which may occur during stressogenic procedures such as peptide receptor radionuclide therapy (PRRT). CC is an emergency and life-threatening condition that needs to be prevented, promptly recognized, and managed. The purpose of this joint Italian multidisciplinary position paper is to support the involved personnel in delivering [177Lu]Lu-based PRRT to syndromic NET patients, focusing on CC management.

Methods The literature evidence regarding CS, CHD, and CC during/after PRRT and the knowledge of 22 Italian NET experts in Anesthesiology, Endocrinology, Gastroenterology, Nuclear Medicine, Oncology, and Surgery involved in PRRT were the basis for the present document.

Results The expert panel expressed several recommendations regarding: 1) CC high-risk patients identification; 2) CC prevention, including considerations of the behavioral and nutritional status, and somatostatin analogue therapy; 3) how to implement PRRT premedication in CC high-risk patients; 4) how to manage CC during PRRT, including post-PRRT monitoring, and radiation protection considerations.

Conclusion This practical guide summarizes the views and experience in CS, CHD, and CC in relation to PRRT of a joint NET-dedicated Italian multidisciplinary team. These recommendations should be taken into the context of Nuclear Medicine good practice and do not substitute any national and International legal or regulatory provisions.

Keywords Carcinoid heart disease · CC · CS · Lutetium · Neuroendocrine tumor · PRRT · RLT · RPT

Introduction

Carcinoid syndrome (CS) is the most common hormone-related clinical condition associated with neuroendocrine tumors (NETs). The estimated overall incidence of CS is 1 out of 100,000 persons per year, with an increasing incidence over the years mirroring the general increase in frequency of NETs, with a prevalence varying between 19 and 35% [1]. It is a multi-organ disease that is characterized by a constellation of symptoms related to hormonal secretion and long-term complications, such as mesenteric fibrosis and carcinoid heart disease (CHD) [2]. Over 40 circulating substances, such as serotonin, histamine, prostaglandins, and tachykinins, are considered in the pathogenesis of CS. Nevertheless, the specific role of the various potential mediators is still far from being clearly understood. In detail, as many of these substances are metabolized in the liver, in the presence of liver metastases, their metabolism is bypassed,

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leading to the development of CS that is, as a matter of fact, generally related to small bowel NETs with liver metastases [3]. However, in up to 13% of cases, CS can develop in patients without hepatic metastases, particularly in patients with NETs with primary sites in the ovary, testis, lung/bronchi, pancreas, or occasionally, with gastrointestinal (GI) NETs with extensive retroperitoneal metastases [1]. Serotonin has been proven to be the main involved mediator, and 5-hydroxy-indole-acetic acid (5-HIAA), its metabolite, is the most accurate biomarker for CS [4]; it is also responsible for diarrhea development, given its effects on gut motility and gastrointestinal secretion [3]. Increased serotonin levels are also implicated in the pathogenesis of fibrotic complications, both in the mesentery and in cardiac valves [5, 6]. This leads to possible intestinal obstruction and coronary heart disease (CHD). However, scarce data are available for other substances such as neurokinin A, substance P, atrial natriuretic peptide, N-terminal pro-brain natriuretic peptide (NT-proBNP), and chromogranin A (CgA). The exception is the connective tissue growth factor (CTGF), which likely acts downstream of serotonin and TGF-β. CTGF promotes fibroblast activation and extracellular matrix (ECM) deposition. To definitely link serotonin with CS is the clinical response to the treatment with specific serotonin inhibitors (i.e., telotristat ethyl), resulting in significant improvement of diarrhea [7].

On the other hand, serotonin is not involved in other CS manifestations such as flushing. In this setting, the main role seems to be played by tachykinins (including substance P, neurokinin A, and neuropeptide K), elevated in a significant proportion of CS patients and consistently increased during spontaneous and provoked flushes, especially after pentagastrin stimulation. Finally, evidence of histamine as a causative mediator of CS is sparse, and most results were contradictory or limited to specific subgroups [7].

Between 20–50% of patients with CS develop CHD [8], even if the overall prevalence is uncertain due to a lack of consistent screening using transthoracic echocardiography (TTE) [9]. CHD is a spectrum of cardiac features and occurs in patients with metastatic NET and CS. The presence of CHD is a major prognostic indicator, with reduced overall survival at 3 years of 31% in patients with CHD, compared to 69% in patients without CHD [8–10]. It is usually due to plaque-like fibrous deposits on right-sided heart valves and endocardial surfaces, inducing tricuspid valve regurgitation/stenosis, ultimately leading to right ventricular volume overload and life-threatening right heart failure [2]. However, the specific mechanism underlying the occurrence of CHD remains to be elucidated. It has been reported that circulating hormones determine an inflammatory status leading to supportive matrix, stromal, endothelial, and inflammatory cell hyperproduction that play a relevant role in the development of fibrotic complications crucial for tumor growth, invasion, and metastases onset [11].

Carcinoid crisis (CC) is the most serious acute complication of CS, resulting from the massive release of vasoactive hormones and other biologically active substances. The reported incidence of this life-threatening condition varies widely, largely depending on the definition applied: in a recent systematic review and meta-analysis, the pooled incidence of CC ranged from 10% (when hemodynamic instability lasting ≥ 10 min was required) to 31% (when no time limit was included in the definition), in patients with midgut NET and/or liver metastasis undergoing surgery [12]. It may occur during stressogenic procedures such as surgery, biopsy, embolization, but also peptide receptor radionuclide therapy (PRRT) [13, 14]. During the above-mentioned stressogenic conditions, changes in blood pressure (more often hypotension and shock), stupor, flushing, diarrhea, bronchospasm, hyperthermia, and cardiac arrhythmia can occur. CC is an emergency and life-threatening condition that needs to be promptly managed as it may lead to death [2].

This joint Italian multidisciplinary position document is based upon the current best practice and knowledge of experienced Centers and Italian Physicians involved in NET PRRT, aimed to assist the involved personnel in delivering PRRT to NET patients for the recognition, prevention, and management of CS, CHD, and CC. Specific syndromic entities (i.e., pheochromocytoma) are out of the scope of this article and will be assessed separately.

NET syndromic patients' diagnostic approach

The hallmark symptoms of CS in NET include episodic flushing (sudden, intense redness of the face, neck, or upper chest, often accompanied by warmth or a burning sensation), diarrhea (watery diarrhea can occur multiple times daily, leading to dehydration and electrolyte imbalances), and abdominal cramping. Other manifestations include wheezing and shortness of breath (due to serotonin-induced bronchoconstriction), and in more advanced stages, CHD, characterized by right-sided heart valve dysfunction with fatigue, peripheral edema, ascites, and jugular venous distension (due to valvular fibrosis, particularly of the tricuspid valve, leading to tricuspid regurgitation, pulmonary valve dysfunction, and reduced right ventricular function). Less common symptoms are pellagra-like skin changes due to niacin deficiency and hypotension or tachycardia during severe episodes [1–8].

The diagnosis of CS is based on clinical pathognomonic symptoms (chronic diarrhoea and/or flushing, bronchospasm, abdominal pain) in patients with known/suspected

NETs, coupled with biochemical evidences based on systemic elevated levels of serotonin or its metabolite 5-HIAA (usually measured on 24-h urinary samples with suggested cutoff > 50 µmol for CS; other measurement have been proposed but platelet serotonin suffers of saturation limits while serum/plasma 5-HIAA is not widely available) [2], whose elevated levels are strongly indicative of the syndrome. Differently, plasmatic CgA shows low specificity for NET diagnosis as well as for CS, as it can be elevated in many other conditions (e.g., renal failure, use of proton pump inhibitor—PPI).

CHD is diagnosed through a combination of physical examination findings, such as heart murmurs indicative of tricuspid or pulmonary valve regurgitation or stenosis, and the presence of right heart failure signs, such as peripheral edema and hepatomegaly. A careful cardiovascular exam, focused on detecting murmurs, should be conducted in all CS patients to assess for CHD. The NT-proBNP is useful in detecting cardiac dysfunction in CHD (cut-off level of 235–260 pg/mL or 31pmoL/L [2]), while urinary 5-HIAA concentrations > 300 µmol increase two- to three-fold the risk of CHD development/progression for CS [2], correlating with the severity of heart valve involvement [2]. Imaging plays a crucial role in localizing NETs and assessing the presence of distant metastasis. Cross-sectional imaging with contrast-enhanced computed tomography (ceCT) or magnetic resonance imaging (MRI) is commonly employed. However, functional imaging with somatostatin receptor-based techniques, particularly [^{68} Ga]Ga-DOTA-peptide positron emission tomography (PET)/CT, has become the standard for detecting and staging NETs [15]. CS patients can develop CHD, especially in the case of an increased right-to-left ventricular width ratio on ceCT (performed for conventional staging or restaging purposes), which can underscore the presence of tricuspid valve regurgitation (TR) or pulmonary valve regurgitation (PR) and should be reported as possible signs of CHD (after excluding pulmonary embolism). According to the ENETS guidance paper [2], CHD assessment is challenging and focuses on functional imaging of the left and right chambers of the heart. Indeed, TTE is the key investigation for CHD diagnosis and monitoring, ideally performed by an experienced professional in CHD using the ENETS CHD Task Force Echo synoptic score [16]. Echocardiograms should carefully assess valves (leaflet thickening, mobility, degree of regurgitation and stenosis), ventricular size, and function. TTE can also be performed in 3D mode or using a transesophageal approach and should include an 'agitated saline contrast study' to identify a patent foramen ovale (PFO); furthermore, in CHD patients without cardiac symptoms and an enlarging right ventricle (RV), consider performing exercise testing to evaluate the functional status. Cardiac MRI and cardiac CT (CCT) are useful additional modalities when TTE images are inadequate or in pre-operative planning; indeed, full CCT (requiring a high-pitch or high-volume CT scanner) has a valuable role in pre-operative planning, allowing excellent anatomical visualization of the pulmonary valve, assessment of coronary arteries, relationship of cardiac metastases (if present, concerning coronary arteries), and RV function assessment. During ceCT/MRI for CHD NET patients staging/restaging, the contrast flow rate must be lowered in case of severe cardiac impairment, being aware of the longer circulation period when timing contrast phases and interpreting the images. CHD can progress rapidly, and patients should have regular echocardiograms (and NT-proBNP dosage) at 6–12 months intervals for follow-up imaging.

Carcinoid crisis during/after PRRT: evidence from the literature

Literature evidence regarding carcinoid crisis during or after PRRT is scarce and mainly based on case reports. The first case was described in 2006 by Davì et al. in a 65-year-old male with heavily pre-treated and progressive well-differentiated atypical bronchial carcinoid with extensive liver metastases after the 2nd cycle of 2.6 GBq of [^{90}Y]Y-DOTATOC, coadministered with renal protection [17]. During the PRRT infusion, the authors describe intense flushing controlled by anti-H1 (promethazine 50 mg IM) and dexamethasone (4 mg intravenously—IV—in 100 ml of saline); due to symptoms persistence, he subsequently received octreotide (0.5 mg sc 2/die), dexamethasone (4 mg daily) and anti-H1 (oxatomide 30 mg 2/die) from the day after PRRT up to discharge. Despite anti-H1 prolonged therapy at home, the patient presented severe flushing, labial and periocular edema, diarrhea, and nausea with increased creatinine, blood urea nitrogen, CgA, 5HIAA, serotonin and hypokalemia; therefore, he received intense treatment with iv octreotide (50 µg/h), anti-H1 and anti-H2 (chlorpheniramine 10 mg and ranitidine 50 mg every 6 h) and corticosteroid (betamethasone 4 mg every 8 h) with clinical improvements. After 3 months, the biochemical markers improved, and PRRT was continued at a lower activity (1.6 GBq at the 3rd cycle), including pretreatment with anti-H1/H2, corticosteroids, and octreotide from the day after, with only transitory flushing after the infusion.

Yadav et al. described the case of a 60-year-old male with syndromic well-differentiated pulmonary carcinoid with several liver and peritoneal metastases (elevated 5HIAA), treated with somatostatin analogue (SSA) LAR (20 mg monthly), who underwent PRRT with [^{177}Lu]Lu-DOTANOC (7.4 GBq + renal protection) [18]. Carcinoid crisis

started within 24 h after the 1 st PRRT cycle with severe vomiting, nausea, diarrhea, shortness of breath, facial flushing, edema, peripheral cyanosis, and tachycardia (normal TTE and electrocardiogram—ECG). The initial treatment showed scarce response (octreotide 100 mg and hydrocortisone 100 mg IV 8 hourly, IV fluids, antiemetics, antacids) while the intensive treatment (octreotide 100 mg IV, 6 hourly) obtained symptomatic improvement after 3 days. The patient was then discharged with the following recommendations: octreotide 100 mg 8 hourly for 2 weeks, followed by SSA LAR 30 mg monthly.

Another carcinoid crisis was reported by Siow Ping et al. in a 62-years old male progressive well-differentiated typical carcinoid with multiple liver and bone metastases, operated and treated with SSA LAR 120 mg every 2 weeks with additional iv octreotide due to a previous crisis with severe flushing, diarrhea and hypotension (very high 5-HIAA and CgA values; no data for CHD which was however suspicious) [19]. After 1 month from SSA LAR suspension (refusing also octreotide), the patient underwent to [^{177}Lu] Lu-labelled PRRT (7.4 GBq) after premedication with serotonin receptor 3 antagonist (anti-5-HT3, granisetron 2 mg), IV dexamethasone 4 mg, and PPI. Nonetheless, he had a carcinoid crisis with flushing and diarrhea 7 h post-PRRT and renal protection, treated with IV octreotide 50 µg/hour; however, the authors described a clinical worsening with severe hypotension, tachycardia, intense diarrhea, and diffuse flushing. Immediate resuscitation was obtained by administering fluids, octreotide (100 µg/hour IV), SSA LAR (120 mg sc), ranitidine (50 mg IV), chlorpheniramine (10 mg IV), and hydrocortisone (50 mg IV). Octreotide was slowly tapered down by 25 µg each hour and then stopped 24 h after PRRT, with a prescribed discharge therapy including prednisolone (30 mg daily per os), chlorpheniramine (4 mg every 8 h for 3 days), and granisetron (1 mg per os in case of diarrhea).

Dhanani et al. described the case of a 58-year-old female with syndromic (abdominal pain, flushing, diarrhea), progressive small-intestine NET with mesenteric, liver, and bone metastases, operated and treated with SSA LAR 30 mg (very high CgA value) [20]. A TTE, 6 months before PRRT, showed a normal tricuspid valve with mild to moderate TR, mild aortic and mitral regurgitation (MR), considered non-specific at that time. She then underwent PRRT with [^{177}Lu] Lu-DOTATATE: after an initial reaction to aminoacid renal premedication (arginine and lysine) with nausea and vomit treated with iv dexamethasone 8 mg/metoclopramide 10 mg, the authors observed carcinoid crisis immediately after the 1 st PRRT cycle (8.1 GBq in 2 h infusion) with syncope, vomit, hypotension (95/40 mmHg), followed by a non-palpable pulse and unconscious state with resuscitation after one cycle of cardio-pulmonary resuscitation (CPR). She was then admitted to the emergency department, where her condition deteriorated into pulseless electrical activity. After orotracheal intubation and due to failed resuscitation efforts (6 cycles of CPR and 2 mg adrenaline IV), octreotide was administered (100 µg, 2 doses, two minutes apart) with immediate return of sinus rhythm (still hypertension). Octreotide infusion was maintained at 50 µg/h, and she was transferred to the intensive care unit (ICU) for invasive ventilation and standard post-cardiac arrest therapy, including targeted temperature management (samples showed very high 5-HIAA and CgA values). She was extubated the next day with no signs of organ failure, and the octreotide infusion was weaned off over the next 6 days. ICU TTE showed severe valve regurgitation (especially TR) with right ventricle dilatation (normal coronary angiogram), treated with mechanical replacement of the aortic, mitral, and tricuspid valves as well as the closure of a PFO. The histopathological examination of the valves confirmed carcinoid involvement.

Carcinoid crisis can also be fatal, with even a late onset [21]. A 51-year-old female with progressive, syndromic well-differentiated serotonin-secreting ileal NET (Ki67 3%) with liver metastases, first grade MR and TR at TTE (no timing data), operated and treated with SSA (controlling flush-symptoms), underwent PRRT with carcinoid crisis 4 days after the I cycle. She was admitted to the ICU due to impaired consciousness, progressive delirium, and increased inflammatory parameters (C-reactive protein 16 mg/dL, white blood cell 23.6 g/L) for suspected urosepsis from chronic II-grade hydronephrosis. The authors reported hypertensive blood pressure via a femoral artery catheter and hypotensive non-invasive determinations with the progression of liver and renal failure (oliguria), delirium, bloody diarrhea, and dermal livedo reticularis. A CT revealed massive and diffuse arterial vasoconstriction with infarction of the kidneys, liver, and spleen as a secondary low-input syndrome with multiorgan insufficiency. They also described steadily increased vascular resistance index (reduced cardiac input), myocardial necrosis markers, and NT-proBNP (1287 pg/ml, as progressive cardiac failure), CgA, catecholamine (excess of vasoactive amine), and 5-HIAA values (less evident than the others). Peripheral hydropic decompensation with extensive bilateral pleural effusions, oliguria, absence of hypotension, arterial hypoxemia, and ultimately the end-stage condition of the patient thwarted aggressive volume therapy; the intensive treatment was ineffective (octreotide increasing dose iv up to 500 µg/h, anti-histaminic cyproheptadine per os, nimodipine, phentolamine, and dobutamine) and the autopsy revealed progression of NET disease to several organs.

Moving to cohort studies, the Erasmus Group led by de Keizer et al. reported only a few carcinoid crises in the 1st cycle of 479 patients treated with [^{177}Lu]Lu-octreotate

PRRT (7.4 GBq) and concomitant renal protection [22]. All patients developing CC (2 bronchial, 1 small-intestine) had baseline increased biomarkers and were already syndromic (flushing, diarrhea, hypokalemia, and/or nausea) with extensive metastatic disease, liver metastases, and 2/3 also had skeletal metastases. Carcinoid crisis (immediate in 2, after 2 days in 1) treatment included high-dose octreotide, IV fluid replacement, and other supportive measures (corticosteroids, antiemetics, and/or loperamide) with full recovery in all cases. In all patients, additional precautions were taken before further PRRT, including SSA continuation, corticosteroids, prolonged observation, and reduction of PRRT dose; nonetheless, the 2/3 patients with previous immediate carcinoid crises developed another crisis.

Tapia Rico et al. reported the experience from 2 tertiary Australian centers, with 7/206 «high-risk» patients experiencing carcinoid crisis within 12 h after the 1st cycle of [^{177}Lu]Lu-octreotate (7.4 GBq) [23]. Patients were considered «high-risk» due to previous carcinoid crises, elevated baseline CgA (5/7), extensive liver metastasis (3/7), and CHD (1/7). SSA LAR was stopped 4 weeks before PRRT, and octreotide was started in 4/7; four patients continued SSA infusion during PRRT due to uncontrollable baseline symptoms and high tumour burden. Despite prophylaxis (histaminergic and serotonergic blockade, plus dexamethasone), patients experienced carcinoid crises following PRRT, with one requiring haemodynamic support. Crisis treatment varied from regular doses of sc octreotide to IV octreotide infusions (50–100 µg/100 µg/h) with improvements; however, 5/7 re-experienced carcinoid symptoms during the following PRRT cycles. In Table 1, we resumed the above-mentioned carcinoid crisis during/after PRRT.

Refractory syndromic patients treated with PRRT

According to ENETS guidance papers [2, 24], PRRT can be an option for refractory carcinoid syndrome, especially in cases of progressive metastatic disease. PRRT can also be considered in selected CHD patients after multidisciplinary meetings involving Cardiologists, Cardiac Surgeons, and Anesthesiologists. Also in this scenario, the evidence is scarce and discordant.

In a case report, Ramesh et al. described the case of a 30-year-old male with G2 small-intestine NET with liver and abdominal metastases, with severe flushing, diarrhea, and dyspnea uncontrolled by monthly SSA LAR [25]. TTE showed a severely dilated right atrium, severe tricuspid stenosis, moderate pulmonary stenosis, and severe TR, considered inoperable due to suboptimal cardiac function. PRRT was then considered to control carcinoid syndrome using a prolonged infusion timing for amino acids of 8 h (no other data are available). After 2 cycles of [^{177}Lu]Lu-DOTATATE, there was an impressive clinical improvement, confirmed after a total of 6 cycles (cumulative 37.4 GBq dose) by TTE, [^{68} Ga]Ga-DOTATATE PET/CT, and 5-HIAA reduction. The patient was then asymptomatic and was being considered for corrective cardiac surgery.

Zandee et al. retrospectively assessed the effect of up to 4 cycles of [^{177}Lu]Lu-DOTATATE PRRT in 22 stage IV non-progressive midgut NET with liver metastases and SSA-refractory carcinoid syndrome (median baseline 5-HIAA of 869 µmol/24 h) [26]. All patients were screened with a TTE, and 12/22 (55%) had CHD. Two patients underwent prior replacement of the tricuspid valve. Lanreotide and octreotide LAR were discontinued a minimum of 6 weeks before PRRT (3/22), while short-acting octreotide was discontinued a minimum of 24 h (18/22); SSA treatment was restarted at least 4 h after PRRT, and all patients were admitted for 1-night clinical observation. A mean improvement in diarrhea and flushing was observed in most cases, as well as a reduction in 5-HIAA values. However, there was a significant reduction in cognitive functioning, and 5 patients discontinued PRRT because of clinical progression (n = 2) or progression of heart failure (n = 3). The authors conclude that adequate screening and treatment for CHD before PRRT remains essential for this patient group. Otherwise, treating refractory CS with PRRT was safe in stable midgut NET.

Expert consensus recommendations for carcinoid crisis management in NET patients undergoing PRRT

Based on ENETS guidance paper [2] and available literature [17–22, 27, 28], specific recommendations for CC management in NET patients undergoing PRRT are provided as follows:

Carcinoid crisis prevention

CC must be prevented by adopting some measures to early identify and diagnose CS, starting therapy with SSAs in all patients with CS (or increasing the dose until the clinical and biochemical control of the syndrome), avoiding CS triggers as possible, and routinely assess 5-HIAA [29, 30]. Namely, to identify patients at risk for CC, it is of paramount importance during the PRRT enrollment visit to assess any potential risk factors listed in Table 2.

Effective management of NET patients necessitates a multidisciplinary approach, which is essential for enhancing care quality [31], especially for patients susceptible to

Table 1 Resume of carcinoid crisis events during/after PRRT described in the literature

Study	n and type of NET (CHD)	Radionuclide (cycle, dose)	Risk factors	PRRT premedication	CC Symptoms	Treatment	Evolution
Case report [17]	1 well-differentiated atypical bronchial carcinoid (no)	[^{90}Y] Y-DOTATOC (2nd, 2.6 GBq)	Extensive liver metastases	Renal protection	Persistent face and upper trunk flushing, severe ocular and labial edema, diarrhea, nausea	iv octreotide, Anti-H1/H2, steroids in saline	Clinical improvement and PRRT continuation*
Case report [18]	1 well-differentiated atypical bronchial carcinoid (no)	[^{177}Lu]Lu-DOTANOC (1st, 7.4 GBq)	Syndromic, extensive liver metastases, high 5-HIIA	Renal protection	Severe vomit, diarrhea, breath shortness, facial flushing, edema, peripheral cyanosis and tachycardia	iv octreotide	Clinical improvement
Case report [19]	1 well-differentiated typical bronchial carcinoid (no)	[^{177}Lu] Lu-DOTA-peptide (1st, 7.4 GBq)	Previous CC, high 5-HIAA and CgA	os anti-5-HT3, iv steroid, PPI, and renal protection	Severe hypotension, tachycardia, flushing, diarrhea	iv fluids, octreotide, anti-H1/H2, and steroid, sc SSA LAR	Clinical improvement
Case report [20]	1 small-intestine NET (yes)	[^{177}Lu]Lu-DOTATATE (1st, 8.1 GBq)	Syndromic, liver metastases, CHD	Renal protection	Syncope, vomit, hypotension, non-palpable pulse and unconscious state	CPR, iv adrenaline and octreotide**	Clinical improvement and PRRT continuation after CHD treatment
Case report [21]	1 serotonin-secerning G2 ileal NET (yes)	NA	Syndromic, CHD	NA	Impaired consciousness, delirium, oliguria, bloody diarrhea, dermal livedo reticularis, hypertension	iv massive fluids, and octreotide, os anti-histaminic, nimodipine, phentolamine, and dobutamine	Exitus
Cohort study [22]	2 bronchial carcinoid, 1 small-intestine NET (no)	[^{177}Lu] Lu-octreotate (1st, 7.4 GBq)	Syndromic, liver metastases, increased biomarkers	1/3 SSA, 3/3 renal protection	Mainly flushing, diarrhea, nausea, in 1 hypotension	high-dose octreotide, iv fluids, and other supportive measures***	Clinical improvement and PRRT continuation****
Cohort study [23]	NA (yes, 1/7)	[^{177}Lu] Lu-octreotate (1st, 7.4 GBq)	Previous CC, increased CgA (5/7), liver metastasis (3/7), CHD (1/7)	4/6 octreotide, 7/7 anti-histaminic, anti-serotonergic, dexamethasone	Flushing, diarrhea, profuse sweats and/or abdominal pain in 6/7, worsening flushing and bronchoconstriction in 1/7	sc to iv octreotide, hemodynamic support and vasopressors in 1/7	Clinical improvement and PRRT continuation*****

5-HIAA 5-hydroxy-indole-acetic acid; *anti-5-HT3* selective serotonin receptor (5-HT3) antagonists; *anti-H1/2* anti-histaminic; *CC* carcinoid crisis; *CHD* carcinoid heart disease; *CPR* cardio-pulmonary resuscitation, *NA* not available; *NET* neuroendocrine tumor; *PPI* proton-pump inhibitor; *PRRT* peptide receptor radionuclide therapy; *SSA LAR* somatostatin analogue long-acting release;

*lower activity PRRT with anti-H1/H2, corticosteroid and octreotide premedication with only transient flushing

**CHD was then treated with mechanical replacement of the aortic, mitral and tricuspid valves as well as closure of a patent foramen ovale (PFO)

***corticosteroids, metoclopramide, and/or loperamide

****despite precautions, 2/3 patients with previous immediate CC developed another crisis

*****5/7 re-experienced carcinoid symptoms during the following PRRT cycles

CS undergoing PRRT. It is strongly advised to hospitalize patients at risk for CC, ensuring (at least) 48 h monitoring at the 1 st cycle and observation post-PRRT administration (the Nuclear Medicine Physician can also consider halving the PRRT activity).

In all patients with CS, echocardiography should be performed at baseline and then periodically. NT-proBNP should be evaluated as a screening biomarker of CHD since it correlates with CHD severity [2]. Patients with CHD need to be carefully monitored. Periodical clinical, serum NT-proBNP, and echocardiographic assessment are the gold standard for monitoring CHD progression. In symptomatic CHD with variable degrees of right heart failure, medical treatments include diuretics such as loop/thiazides and aldosterone antagonists. In patients with symptomatic CHD, surgical valve replacement is the best option to prevent unpredictable worsening of heart function and cardiac decompensation because of CC onset [2]. Although not part of the typical clinical picture of CS, particular attention should be paid to patients with mesenteric fibrosis or peritoneal

Table 2 Carcinoid crisis risk factors

Carcinoid crisis risk factors
Syndromic patients, especially if scarcely controlled by SSA
History of previous carcinoid crisis
Presence and severity of CHD
Advanced age
Emotionally stressed patients
High tumor burden, especially in the liver
Increased 24 h urinary 5-HIAA concentrations
Use of sympathomimetic and beta-2 agonists

5-HIAA 5-hydroxy-indole-acetic acid; *CHD* carcinoid heart disease; *SSA* somatostatin analogue

disease who are candidates for PRRT. In this subgroup of patients, in fact, peritoneal lesions can have a modest PRRT response, and there is also a considerable risk (15–25%) of developing episodes of bowel obstruction due to fibrosis after transient peritoneal inflammation [32].

Behavioral and nutritional status assessment

It is advisable to correct any unsafe behavior before PRRT, avoiding strenuous physical effort, emotional stress, as well as bowel movements-stimulating liquids (alcohol, coffee) and spicy food. Despite few evidences, it is also advisable to limit the excessive intake of potential triggers such as tryptophan-rich foods (e.g., chocolate, eggplant, kiwi, nuts, pineapple, plums, tomato, and fruits in general, especially avocado, banana, and dried fruit), while maintaining a balanced and complete diet to ensure adequate nutritional status. We also advise assessing patients' nutritional status, aiming to identify and correct any discrepancies such as hydroelectrolytic (Na, K, Mg, P) and protein imbalances. It is also important to identify and correct any malnutrition (i.e., vitamin A, B3, B12, D, E, K) using vitamins and supplements such as niacin/nicotinamide by oral intake for hypo-B3, paying attention to any malabsorption to be corrected using, for example, pancreatic enzymes in case of pancreatic insufficiency symptoms with an initial minimum standard dose of 40,000–50,000 units of lipase with main meals, and half-dose (20,000–25,000 units) with snacks [33, 34].

Somatostatin analogue treatment

SSAs play a central role in the therapeutic strategy for CS. Clinical and biochemical control of the syndrome can be obtained with conventional doses of SSAs, commonly employed as long-acting formulations. In particular, long-acting release (LAR) octreotide 30 mg for intramuscular (IM) injection and lanreotide autogel 120 mg for deep subcutaneous (sc) injection can be administered every 28 days, in case of clinical and/or biochemical evidence of CS [2]. However, only partial or non-durable relief is obtained in many patients. In these cases, high-dose schedule treatment with SSAs is considered, either by reducing the administration interval (every 14–21 days), increasing the dose of long-acting SSAs, or by adding a rescue dose of short-acting s.c. octreotide (i.e., 100–500 µg bid or tid). Higher doses can be considered because SSAs must be adapted to patients' symptomatology with regard to diarrhea [35]. Cessation of SSA before PRRT (or [^{68} Ga]Ga-DOTA PET) is not recommended in uncontrolled CS/CHD patients (use rescue sc or IV octreotide or adjust date of [^{68} Ga]Ga-DOTA PET/PRRT to be at the end of SSA monthly administration) [36]. According to indications and the EMA-prescribing schedule, SSA LAR should not be administered < 4 weeks before the PRRT administration, while short-acting SSA should not be administered < 24 h before the PRRT administration. SSA can be resumed starting from 4 h after the PRRT injection [14]. When feasible, one should also evaluate tumor debulking strategies (surgery, ablation, radiotherapy, embolization) before PRRT. Additional considerations regarding specific cases depend on the main symptomatology.

Other preventive treatment

In accordance with ENETS guidance paper [2], the use of antihistamines can reduce flushing and bronchospasm, while corticosteroids can reduce bradykinin production [37]. Although dexamethasone can mitigate tumor inflammation and related complications, its use prior to PRRT warrants caution, as steroids may lower SSTR expression [38]. To minimize this risk, steroid administration can alternatively be considered after PRRT infusion.

As regards diarrhea, the first step is to evaluate the etiology (i.e., antibiotics, bile acids, pancreatic enzymes, niacin supplement), selecting the more appropriate treatment including antidiarroic (i.e., loperamide 4–16 mg orally daily or Codeine 10–90 mg orally daily), antiserotoninergics (cyproheptadine 4 mg every 8 h) and, in more serious cases, serotonin inhibitors (telotristat ethyl 250 mg every 8 h orally). Furthermore, in the case of anxious patients, consider benzodiazepines.

In patients with right heart failure, a reduction in salt and fluid intake, considering that thiazide or loop diuretics may improve symptoms (to be used cautiously due to possible paradoxical effect on cardiac output reduction). For highly suspicious CHD patients (NT-proBNP cut-off level of 235–260 pg/mL or 31pmoL/L [2]), a TTE within 3 months before PRRT is mandatory; if CHD is confirmed, then it is advisable to undergo a cardiac surgeon assessment. Cardiac valve surgery (valve replacement) has to be considered before PRRT. Indeed, cardiac surgery represents the most effective treatment option for advanced CHD to be performed in severe

symptomatic CHD patients (i.e., fatigue, dyspnea, edema, ascites) with an anticipated post-operative NET-related survival of at least 1 year [2]. Additionally, symptomatic medications may be used to manage respiratory symptoms.

PRRT premedication

In patients at risk for CC, the PRRT premedication, including the renal protection protocol (to be discussed with cardiologists), must be implemented as suggested in Table 3.

Furosemide is the most widely used drug for CHD treatment, which also foresees a more comprehensive pharmacological/cardiological framework including other therapeutic options (ACE inhibitors/sartans, beta-blockers in patients with preserved ejection fraction, mineralocorticoid agonists, antiarrhythmics, etc. [36]). We underscore the importance of having ready-to-use 100 µg octreotide syringes available in the administration room since CC may also potentially occur in non-at-risk patients. Finally, in severe CS, in order to prevent a CC, some medications should be avoided: histamine-releasers (i.e., atracurium, morphine, meperdine, succinylcholine, diclofenac, indomethacin, ketoprofen, thiopenthal), sympathomimetics (i.e., epinephrine/adrenaline, which has the potential to worsen the release of vasoactive peptides), anaesthesia or different cytolytic therapies (i.e., hepatic embolization) [2, 39].

Table 3 Premedication to be used in patients at risk for CC 1 h before/during PRRT administration

Pharmaceutics	Dosages
Corticosteroids	Dexamethasone 4–8 mg per os (after PRRT infusion)
Antiemetics	Ondansetron 4 mg per os Granisetron 1 mg per os
SSA	Octreotide 100–500 µg sc every 8 h or Octreotide 50–200 µg iv (octreotide iv infused at the starting dose of 50 µg iv increased to 100–200 µg iv if necessary, 12 h pre-PRRT and through PRRT and post-PRRT until the patient is stable) or Octreotide 100–200 µg sc every 8 h in the 7 days preceding PRRT until shortly before PRRT administration or even during, to be resumed 2–4 h after PRRT
Antihistaminic	Anti-H1 (chlorphenamine 10 mg IV in slow infusion) Anti-H2 (any active principle, as available)
Renal Protection	Reduce the flow rate by 1/3 (from 250 ml/h to 175 ml/h)*, reduce the total volume by 50–75% or Reduce the concentration (25 g of lysine or arginine instead of 50 g total, in max 1L of crystalloids instead of 2L) or Maintain normal premedication and administer furosemide 40 mg at the end*
Benzodiazepines	Depending on the degree of anxiety and the clinical characteristics of the patient, prefer those with short half-lives

CgA chromogranin A; *PRRT* peptide-receptor radionuclide therapy; *in case of CHD

Carcinoid crisis management during PRRT

Despite prevention and premedication, CC can still occur, representing a life-threatening condition. This context requires the immediate administration of an IV bolus of octreotide (100–500 µg), which can be repeated every five minutes until stabilization of the haemodynamic crisis. Subsequently, a maintaining dose of 50–100 µg/h has to be administered in continuous IV infusion. If severe hypotension occurs, vasoactive agents may be considered [2]. When a carcinoid crisis does occur, timely management is critical. Recent studies suggest that, besides octreotide, vasoactive agents are a helpful tool to manage hemodynamic instability, a condition reported in 57% of cases despite peri-procedural octreotide [40]. The early use of vasoactive agents seems to shorten crisis duration [41–44]. Based on the available data, the best sympathomimetics to use in this attempt are selective alpha1-agonists. Concomitant octreotide infusion is suggested to avoid the worsening of symptoms due to hormonal release.

In the CC eventuality, we suggest the following step-by-step protocol, schematically summarized in Fig. 1:

1. Stop PRRT administration.
2. Monitor vital signs parameters (blood pressure, heart rate, ECG). Alert ICU. In case the patient is unstable, consider possible transfer to the ICU. Consider hemodynamic instability as systolic blood pressure lower than 80 mmHg or higher than 180 mmHg, heart rate persistently higher than 120 beats per minute, or any dysfunction that, if sustained, would be expected to result in end-organ dysfunction (i.e., ventricular arrhythmias or bronchospasm causing desaturation) [42].
3. Start octreotide 100–500 µg iv in crystalloids solution, maintaining the infusion at 50–100 µg/h with a possible increase up to 500 µg/h. If necessary, administer boluses of 25 mL repeated at 5-min intervals. Once cardiorespiratory stability is achieved, slowly reduce the octreotide infusion by 25–50 µg/h based on tolerance and, when symptoms are controlled, convert to octreotide 100–200 µg sc (bridge therapy, with Endocrinological input) to then resume Octreotide long-acting release (LAR).
4. Consider using Hydrocortisone 100 mg or Methylprednisolone 1–2 mg/kg IV.

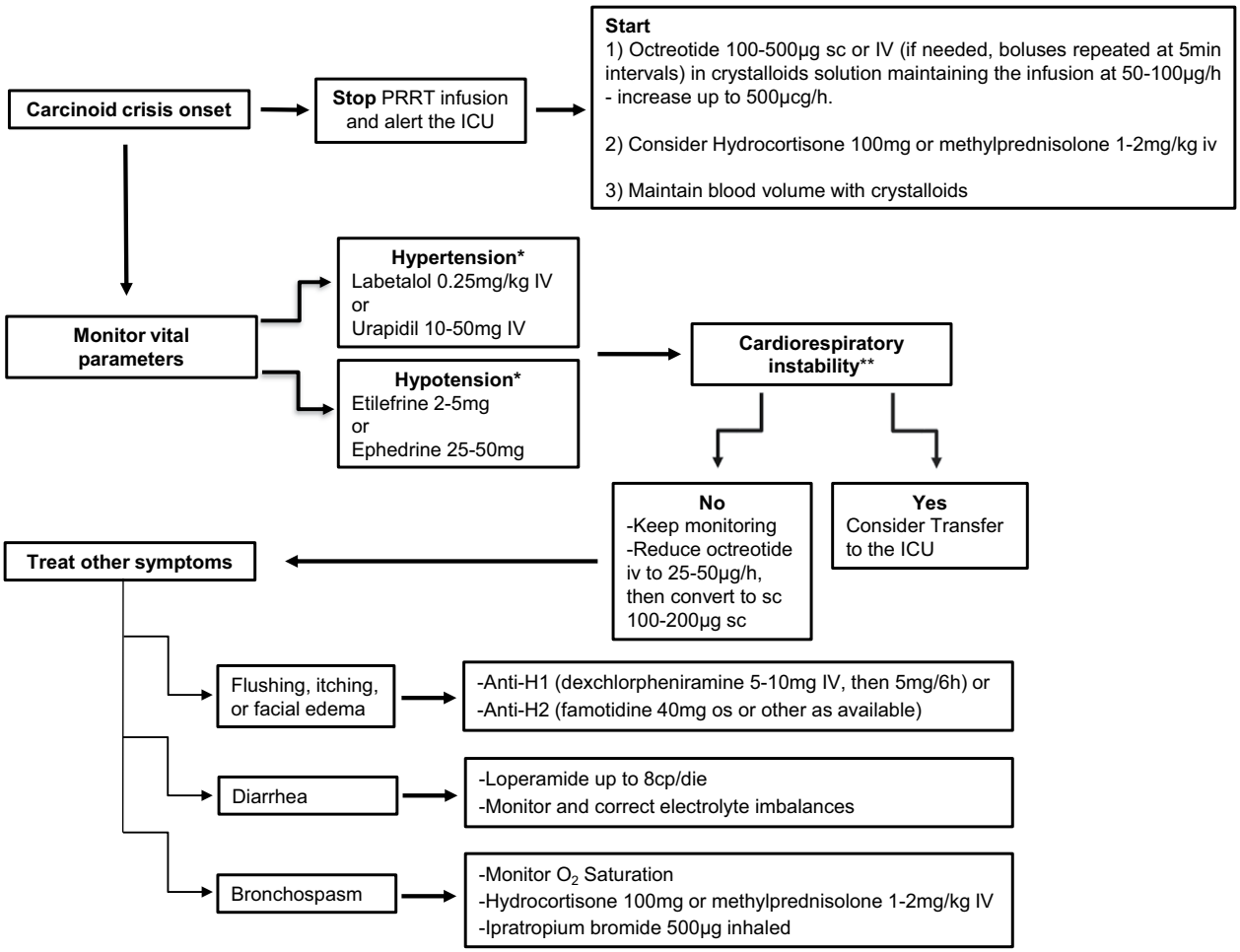

Fig. 1 Carcinoid crisis management (during PRRT) flowchart. *Dosage should be adjusted according to blood pressure response. **Systolic Blood Pressure < 80 mmHg or > 180 mmHg, heart rate persistently > 120 beats per minute, or any disfunction that if sustained would be expected to result in end-organ dysfunction

5. In case of hypotension, start intravenous fluids and consider inotropic agents (Etilefrine boluses 2–5 mg iv). Alternatively, use Ephedrine 25–50 mg boluses. Dosage should be adjusted according to blood pressure response.
6. In case of hypertension, use alpha- or beta-blockers: Labetalol 0.25 mg/kg IV in bolus, repeated every 10 min, and start infusion (200 mg in 250 mL crystalloids, 2 mg/h). If not controlled, consider Urapidil bolus 10–50 mg and then in infusion (200 mg in 500 mL crystalloids, 9 mg/h). Dosage should be adjusted according to blood pressure response.
7. Consider possible transfer to the ICU if cardiorespiratory stability is not achieved. Waiting for ICU transfer or the anesthesiologist's arrival, start ephedrine 25–50 mg bolus IV and maintain blood volume with 500 mL crystalloids in infusion.
8. Once the patient is stabilized, additional considerations can be made based on the main symptomatology upon resolution:

   – In case of flushing, itching, or facial edema, consider: Anti-H1 (chlorphenamine 5-10mg IV in slow infusion) or Anti-H2 (famotidine 40 mg os or other, as available);
   – In case of diarrhea, consider: monitor and correct any electrolyte imbalances, monitor creatinine, hemostasis, and transaminases;
   – In case of bronchospasm, consider: O2 support, anticholinergics (ipratropium bromide 500µg inhaled), corticosteroids (hydrocortisone 100 mg or methylprednisolone 1-2mg/kg IV).

Carcinoid crisis monitoring post-PRRT

After discharge (at least 48 h monitoring/observation post-PRRT administration), the patient should continue medications (i.e., antiemetics, corticosteroids, antihistamines, etc.) until symptom resolution, as well as the SSA (i.e., continue octreotide 100–200 µg sc every 8 h). Additional measures/precautions before any subsequent PRRT must be taken, considering the doses and timing of the various medications used to overcome the previous crisis (i.e., prolonged observation in the Hospital, continuation of SSA, etc.). Some authors also suggest halving the dose in the PRRT cycle after the CC; however, this is in the absence of significant evidence. In the case of CHD patients, a TTE and NT-proBNP dosage will be necessary every 6–12 months.

Radiation protection considerations

ICU admission must be anticipated and properly organized prior to initiating PRRT procedures. The Radiation Protection Expert should conduct specific assessments to evaluate the risk of contamination to surfaces and objects that may come into contact with the patient (i.e., hospital room, bathroom, bedding, food, and utensils). Staff must also be trained in managing patients who are radioactive. Upon the patient's discharge (or earlier if contamination is suspected), a surface contamination check must be performed, including room floors and associated bathrooms. In such cases, special waste storage procedures must be followed, and the use of toilet systems with filtration capabilities (not connected to standard sewage tanks) may be considered. These systems can retain significant amounts of 177Lu, reducing environmental radioactive release. Post-discharge, emergency or life-saving care must never be delayed. The patient should carry documentation indicating their radioactive status, enabling medical personnel to implement universal precautions against potential contamination. The Radiation Safety Office at the treatment site should be contacted as needed. In emergencies, patient isolation is not mandatory (though recommended), and waste should be handled as usual unless visibly contaminated. If hospitalization becomes necessary, the Radiation Protection Expert must be informed. A single room with a dedicated toilet is preferred, and close contact should be limited to less than 1 m for no more than 2 h per day [45].

Conclusion

This practical guide summarizes the views and experience in CS, CHD and CC in relation to PRRT of a joint NET-dedicated Italian Multidisciplinary Team including Anesthesiologists, Endocrinologists, Gastroenterologists, Nuclear Medicine Physicians, Oncologists, Surgeons, representing the National Association of Nuclear Medicine (AIMN), Italian Society of Endocrinology (SIE), and the Italian Association for Neuroendocrine Tumors (ITANET). These recommendations should be taken into the context of nuclear medicine good practice and do not substitute for national and international legal or regulatory provisions.

Abbreviations

5-HIAA	5-Hydroxy-indole-acetic acid
Anti-5-HT3	Serotonin receptor 3 antagonist
CC	Carcinoid crisis
CCT	Cardiac CT
ceCT	Contrast-enhanced computed tomography
CgA	Chromogranin A
CHD	Carcinoid heart disease
CPR	Cardio-pulmonary resuscitation
CS	Carcinoid syndrome
CTGF	Connective tissue growth factor
ECG	Electrocardiogram
GEP	Gastroenteropancreatic
GI	Gastrointestinal
H1/H2	Histamine-receptor 1/2
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
LAR	Long-acting release
NET	Neuroendocrine tumor
NT-proBNP	N-terminal pro-brain natriuretic peptide
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography/computed tomography
PFO	Patent foramen ovale
PPI	Proton pump inhibitor
PR	Pulmonary valve regurgitation
PRRT	Peptide receptor radionuclide therapy
RV	Right ventricle
SC	Subcutaneous
SSA	Somatostatin analogue
TR	Tricuspid valve regurgitation
TTE	Transthoracic echocardiography

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Declarations

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