Check for updates

Society for Endocrinology

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

Received 9 April 2025
Accepted 4 November 2025
Available online 13 November 2025
Version of Record published 2 December 2025

RESEARCH

Exploring the carcinoid crisis: insights from a cancer-specific centre

Maribel del Olmo-García[1,2], Grace Kong[3,4], HuiLi Wong[4,5], Michael Michael[4,5], Hilmy Ismail[6], Wing Fai Nip[3], Leeanne Pasanen[3] and Cherie Chiang[7,8]

[1]Department of Endocrinology and Nutrition, University and Polytechnic Hospital La Fe, Valencia, Spain
[2]Department of Medicine, University of Valencia, Valencia, Spain
[3]Department of Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia
[4]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[5]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[6]Department of Anaesthetics, Peter MacCallum Cancer Centre, Melbourne, Australia
[7]Department of Internal Medicine, Peter MacCallum Cancer Centre, Parkville, Australia
[8]Department of Diabetes and Endocrinology, Melbourne Health, University of Melbourne, Parkville, Australia

Correspondence should be addressed to M del Olmo-García: maribeldelolmo@gmail.com

This paper forms part of the special collection Women in Neuroendocrine Tumour Science. The Guest Editors were Maribel del Olmo-García and Krystallenia Alexandraki.

M del Olmo-García was not involved with the review or editorial process for this paper

G Kong is a member of the *Endocrine Oncology* Editorial Board and was not involved with the review or editorial process for this paper

Abstract

Objective: To assess the prevalence, pre-procedure biomarkers, and management of carcinoid crisis (CC) in a cancer-specific hospital.

Design: Retrospective observational study of subjects with carcinoid syndrome (CS) undergoing invasive procedures or systemic therapies over 5 years.

Methods: Electronic haemodynamic parameters and patient records were extracted. CC incidence was assessed using strict (SBP <80 mmHg, >10 min) or broad criteria (severe hypotension, hypertension, arrhythmias, >1 min).

Results: 48 patients with CS underwent 71 procedures (35 invasive procedures, 36 systemic therapies). CC did not occur during systemic therapies. Prophylactic octreotide infusion was used in 63% of invasive procedures. CC occurred in 43% of procedures as defined by broad criteria and in 20% as defined by strict criteria. Compared to those without CC, patients with strictly defined CC had higher chromogranin A ($P < 0.001$), higher 5-HIAA ($P = 0.03$), higher BNP ($P = 0.03$), longer hospital stay ($P < 0.001$), and higher postoperative complications ($P < 0.001$). Lower intraoperative mean arterial pressure (MAP) correlated with postoperative complications ($\rho = -0.55$, $P = 0.004$) and longer hospital stay ($\rho = -0.62$, $P = 0.001$). All subjects with strictly defined CC were treated with more than one drug; however, there were five patients with broadly defined CC who did not require treatment for transient haemodynamic instability.

Conclusions: Pre-operative biomarker assessment is essential to triage CS patients at risk of CC and thereafter trigger a risk-based management pathway. Prolonged intraoperative hypotension correlated best with postoperative outcomes, and is a better definition for CC in our cohort.

Keywords: carcinoid; carcinoid crisis; neuroendocrine tumour; somatostatin analogues

Published by Bioscientifica Ltd.
https://eo.bioscientifica.com
© 2025 the author(s)

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Downloaded from Journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

Introduction

Neuroendocrine neoplasms are uncommon tumours that originate from neuroendocrine cells, which are distributed throughout the body and play a vital role in the endocrine and nervous system. These neuroendocrine tumours (NETs) typically arise from gastroenteropancreatic origins, and less frequently from the bronchopulmonary or thymus (Perren *et al.* 2017). Up to 30% of NETs are functional, secreting peptide hormones with associated syndromic manifestations. The most common functional syndrome is the carcinoid syndrome (CS), found in up to 20% of NETs, with manifestations of diarrhoea, flushing, labile blood pressure, and bronchospasm. CS typically manifests in NETs that originate in the midgut, including the small intestine, appendix, and right colon, with less frequent occurrences in NETs originating in the foregut, such as the respiratory system, thymus, stomach, and duodenum. Surgical or radiological manipulation of tumours can trigger massive release of serotonin and vasoactive peptides, resulting in potentially fatal carcinoid crisis (CC), characterised by prolonged haemodynamic instability (hypotension, hypertension, tachycardia, cardiac arrhythmias, and shock) and may include symptoms such as flushing, diarrhoea, bronchoconstriction (wheezing, hypoxia, and respiratory failure), and cardiac arrest (Kaltsas *et al.* 2017). A markedly elevated 24 h urine 5-hydroxyindoleacetic acid (5-HIAA) of greater than 300 μmol/day is associated with a two- to three-fold increased risk of cardiac carcinoid disease, which in itself is a risk factor for CC (Grozinsky-Glasberg *et al.* 2022). Individuals experiencing a crisis face heightened risks of postoperative complications such as acute renal injury, myocardial infarction, stroke, and hepatic dysfunction, with associated prolonged hospital admission (Kinney *et al.* 2001).

Since CS is the most common functional NET, the risk assessment and prevention of CC remain a significant concern, particularly before tumour manipulation, peptide receptor radionuclide therapy (PRRT), locoregional therapies, and other invasive procedures (Tapia Rico *et al.* 2018, Bardasi *et al.* 2022). Treatment for both CC and CS often relies on somatostatin analogues (SSA). Patients identified as high risk for CC may receive prophylactic perioperative infusions of octreotide or preoperative treatment with long-acting SSA, although the evidence supporting this practice is limited and has been challenged (Wonn *et al.* 2022). In cases where intraoperative standard resuscitative measures fail to achieve haemodynamic stability, bolus injections of octreotide are administered (Seymour & Sawh 2013). However, evidence-based efficacy remains unclear due to the lack of consensus in the definition of CC, and the identification of individuals and procedures which infer the greatest risk. Furthermore, there is uncertainty about whether the underlying pathophysiology of carcinoid crisis mimics that of carcinoid syndrome (Condron *et al.* 2019).

In this retrospective single-centre study, we aim to evaluate the prevalence, exacerbating triggers, characteristics, and outcomes of carcinoid crisis in patients with CS. By analysing the pre-procedure clinical risk and subsequent outcomes of this cohort, we seek to provide insights into the optimal definition, risk stratification, and management of CC.

Material and methods

Study design

This retrospective study was conducted and approved by the institutional review board at Peter MacCallum Cancer Center (QA/104507/PMCC), a cancer-specific hospital in Australia and a NET Centre of Excellence certified by the European NET Society (ENETS). Patients diagnosed with NETs and CS who underwent invasive procedures or systemic therapies between January 2019 and December 2023 were extracted from the electronic medical record (EMR) using International Classification of Diseases (ICD) codes specific to NETs and carcinoid syndrome. Subjects were included if i) NET was confirmed on histology, ii) had clinical diagnosis of carcinoid syndrome based on symptoms (flushing, diarrhoea, bronchospasm) and/or elevated 5-HIAA, and iii) underwent invasive procedures or intravenous systemic therapies (e.g. surgery, biopsy, endoscopy, PRRT, chemotherapy). Not all patients had available 5-HIAA measurements, as this test was not routinely ordered or accessible at all times. In some cases, carcinoid syndrome was confirmed based on clinical features and elevated chromogranin A levels. Subjects were excluded if there was lack of documented follow-up at Peter MacCallum Cancer Center.

Data collection included patient demographics and tumour characteristics (primary site, metastatic sites, and biochemical hormone status), clinical presentation of carcinoid syndrome, type of invasive procedure, American Society of Anesthesiologists Classification (ASA) (Doyle *et al.* 2025), as well as preoperative, intraoperative, and postoperative management of CS. Intraoperative vital signs (blood pressure and heart rate) were recorded automatically during surgery in a minute-by-minute registry and uploaded into the electronic medical record (EMR) (Fig. 1).

Definition of carcinoid crisis

Due to the lack of international consensus on the definition of carcinoid crisis, two sets of criteria were applied to the study cohort:

(i) Strictly defined carcinoid crisis required prolonged hypotension (systolic blood pressure <80 mmHg) for greater than 10 min, not attributed to acute blood loss (Massimino *et al.* 2013, Woltering *et al.* 2016, Kinney *et al.* 2018).

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

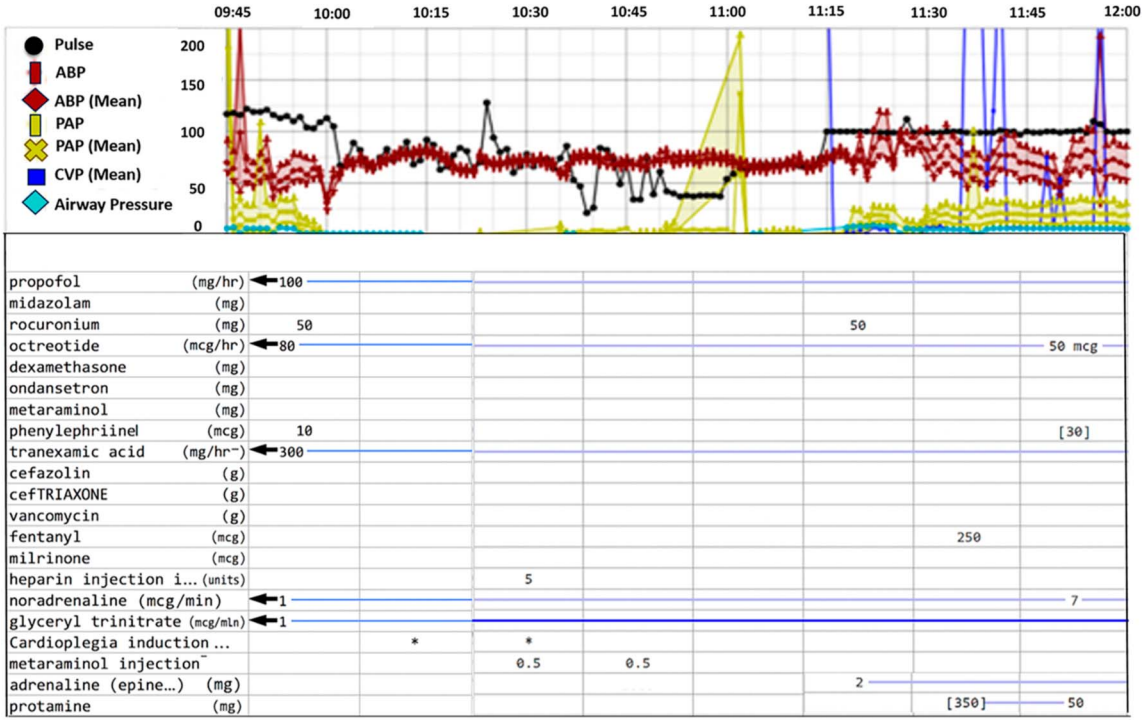


Figure 1

Example of intra-operative electronic record of a subject with carcinoid crisis.

(ii) Broadly defined carcinoid crisis was based on the presence of one or more of the following criteria during or immediately following a procedure for greater than 1 min (Condron *et al.* 2016, Xu *et al.* 2022).
(iii) Severe hypotension (systolic blood pressure <80 mmHg).
(iv) Severe hypertension (systolic blood pressure >180 mmHg).
(v) Heart rate >120 beats per minute.
(vi) CC documented by the anaesthetist during surgery due to haemodynamic instability or the presence of other symptoms that could not be explained by other causes (e.g. blood loss).

Statistical analysis

The incidence of carcinoid crisis was calculated and expressed as a percentage of the total number of procedures. CC groups are i) no CC, ii) strictly defined CC only, iii) broadly defined CC only (strictly defined CC excluded), and iv) all CC (strict and broadly defined CC). Comparative analysis was performed using chi-square test for categorical variables and Student's *t*-test or Mann–Whitney U test for continuous variables.

One-way ANOVA was used to assess differences among the means of the CC groups in the following variables: duration of invasive procedure, chromogranin A (CGA) concentration, brain natriuretic peptide (BNP) concentration, 5-HIAA concentration, and length of hospital stay. Following significant ANOVA results, Tukey's honest significant difference (HSD) test was used for post-hoc pairwise comparisons to identify specific group differences. To compare the means of two independent groups for the number and duration of carcinoid crisis, an independent sample *t*-test was conducted. In addition, the chi-square test for independence was applied to explore the association between patient groups and the occurrence of postoperative complications. An exploratory analysis was performed to assess the relationship between the lowest intraoperative mean arterial pressure (MAP) and postoperative outcomes (complications and length of stay) using Spearman's rank correlation. Receiver operating characteristic (ROC) analyses were conducted to assess the discriminatory capacity of pre-procedure chromogranin A (CgA) for predicting strictly defined carcinoid crisis. The area under the curve (AUC), optimal cut-off according to the Youden index, sensitivity, and specificity were calculated. Statistical significance was defined as a *P*-value <0.05, and data are presented as mean ± standard deviation (SD) unless specified. All statistical analyses were carried out using SPSS version 26.0 (IBM SPSS Statistics, IBM Corp, USA) and R software version 4.0.3 (https://www.r-project.org/).

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

Table 1 Demographic and NET characteristics of the patients with CS.

Total number of patients	**48**
Males, *n* (%)	25 (52.1)
Age, years ± SD	58 ± 26.1
Primary tumour location, *n* (%)	
Small bowel	40 (83.3)
Unknown origin	5 (10.4)
Colon/rectum	2 (4.2)
Lung	1 (2.1)
Metastatic disease, *n* (%)	48 (100)
Liver	42 (87.5)
Nodal	27 (56.3)
Bone	6 (12.5)
Peritoneum	6 (12.5)
Pancreatic	3 (6.3)
Tumour differentiation, *n* (%)	
Well differentiated	46 (95.8)
Poorly differentiated	2 (4.2)
Histological grade, *n* (%)	
G1	23 (48.9)
G2	22 (46.7)
G3	3 (4.4)
Carcinoid heart disease, *n* (%)	20 (42.6)

Results

A total of 1,371 patients with NET had 555 procedures between January 2019 and December 2023 at Peter MacCallum Cancer Centre. Of these, 48 patients were diagnosed with CS and underwent a total of 71 procedures. Demographic and NET characteristics of the patients are presented in Table 1. The majority of patients had small bowel primary with liver metastasis. 94% of the CS subjects had grade 1 or 2 NETs. There was a high prevalence of carcinoid heart disease. The characteristics of the 71 procedures (49% invasive, 51% systemic therapies) are summarised in Table 2.

Table 2 Procedure types and systemic therapies performed in patients with carcinoid syndrome.

Total procedures	**71**
Invasive procedures, *n* (%)	35 (49.3)
Surgery, *n* (%)	22 (30.9)
Laparotomy, *n* (%)	10 (14)
Heart valve replacement, *n* (%)	8 (11.3)
Laparoscopic cholecystectomy, *n* (%)	4 (5.6)
Colonoscopy, *n* (%)	5 (7)
Biopsy, *n* (%)	2 (2.8)
TACE, *n* (%)	2 (2.8)
Others, *n* (%)	4 (5.6)
Systemic therapies, *n* (%)*	36 (50.7)
PRRT	34 (47.9)
Chemotherapy	2 (2.8)

*Systemic therapies (PRRT and chemotherapy) are shown separately as they do not involve anaesthesia and carry a different carcinoid crisis risk profile.

The SSA standard dose regimen (Lanreotide Autogel 120 mg 4 weekly or Octreotide LAR 30 mg 4 weekly) was the most frequently prescribed (n = 12) in patients before invasive procedures. Six patients required higher dose or more frequent injections to control CS symptoms. Due to SSA intolerance, dose was reduced in one patient and ceased entirely in two patients. One patient required telotristat to control flushing and diarrhoea. Fourteen patients did not require SSA as CS resolved after initial PRRT.

Of the biochemical markers evaluated within 6 months pre-procedure in the entire cohort, 32 patients (67%) had a documented 5-HIAA test (556 ± 782 mcmol/day, reference interval <50 mcmol/day), 100% of subjects had chromogranin A performed (4,630 ± 9,458 μg/L, reference interval 27–94 μg/L), and 67% had BNP testing (81 ± 106 ng/L, reference interval <100 ng/L).

No octreotide infusion was used during systemic therapies (PRRT or chemotherapy), and no subject experienced carcinoid crisis by either definition up to 48 h post-treatment. As these therapies differ from anaesthetic procedures, they are reported separately in Table 2. Prophylactic octreotide infusion was used in 22 out of 35 invasive procedures. CC occurred in 43% (15/35) of procedures as defined by broad criteria and in 20% (7/35) as defined by strict criteria.

Biochemical parameters before invasive procedures in the strictly defined CC cohort revealed elevated chromogranin A (P = 0.016 vs no CC, P = 0.02 vs broadly defined CC), elevated 5-HIAA (P = 0.025 vs no CC, P = 0.047 vs broadly defined CC), and elevated BNP (P = 0.029 vs no CC) (Table 3). No difference in biochemical parameters was found in the broadly defined CC and no CC groups. Exploratory univariable analyses were performed to identify factors associated with strictly defined carcinoid crisis. Higher pre-procedure CgA (P = 0.016), 5-HIAA (P = 0.025), and BNP (P = 0.029) levels, the presence of carcinoid heart disease, and undergoing cardiac valve surgery were associated with severe CC. Given the small number of events (n = 7), no multivariable regression was performed. Pre-procedure CgA demonstrated good discriminatory performance for predicting strictly defined carcinoid crisis (AUC = 0.82, 95% CI: 0.70–0.95, P = 0.002). A threshold of approximately 7,000 μg/L yielded a sensitivity of 86% and specificity of 74%. All patients who experienced severe CC had CgA levels above this value.

ASA scores were all greater than 2 in the strictly defined CC cohort, indicative of severe disease processes. Compared to the broadly defined CC cohort, procedures were significantly longer, with longer total duration of CC in those with strictly defined CC (all heart valve surgeries). The total number of individual CC episodes was not different. Hospital length of stay was more than four-fold longer in strictly defined CC compared to the other two groups (P < 0.001), with significantly higher postoperative complications (χ^2 = 22.105, P < 0.001).

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-10574721] | Hospital Universitario La Fe user on 05 November 2026

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Table 3 Characteristics of patients and invasive procedures grouped by CC definition.

Classification	No carcinoid crisis	Strictly defined carcinoid crisis	Broadly defined carcinoid crisis	All carcinoid crisis
No. of subjects	13	7	15	22
Age, years	57 (25)	62 (27)	59 (26)	61 (26.5)
Males, *n* (%)	7 (53.8)	4 (57.1)	8 (53.3)	12 (54.5)
Invasive procedures	Colonoscopy (4) Laparotomy (2) Laparoscopic cholecystectomy (2) Embolization (2) Bone marrow biopsy (1) High dose RT (1) Endoscopic cholangiopancreatography (1)	Cardiac valve replacement (7)	Laparotomy (4) Endoscopic cholangiopancreatography (3) Laparoscopic cholecystectomy (2) Colonoscopy (2) Cardiac valve replacement (1) Nephrectomy (1) Transanal surgery (1) Left inguinal surgery (1)	Cardiac valve replacement (8) Laparotomy (4) Endoscopic cholangiopancreatography (3) Laparoscopic cholecystectomy (2) Colonoscopy (2) Nephrectomy (1) Transanal surgery (1) Left inguinal surgery (1)
Procedure duration (SD) (minutes)	114.6 (34.7)	399.4 (133.5)†	142.8 (17.9)	228.3 (11.7)
Use of prophylactic octreotide infusion no. (%)	9 (69)	6 (86)	8 (53)	14 (64)
Number of CC episodes during invasive procedure (SD)	n/a	3.1 (0.8)	4.1 (1.3)	3.8 (0.9)
Total duration of CC (minutes) median (IQR)	n/a	70.9 (18.4)	16.3 (0.1)	33.6 (5.6)
Treatment for CC during procedure (number of subjects)				
Octreotide bolus	n/a	3	6	9
Metaraminol	n/a	2	7	9
Noradrenaline	n/a	7	2	9
Adrenaline	n/a	4	0	4
Ephedrine	n/a	0	1	1
Phenylephrine	n/a	2	5	7
Glucocorticoids	n/a	1	3	4
Esmolol	n/a	0	1	1
No treatment	n/a	0	5	5
Biochemical status before procedure				
5-HIAA mcmol/day (SD)	168 (27) (*n* = 10)	750 (56)*,†,‡ (*n* = 6)	70 (28) (*n* = 13)	373 (21) (*n* = 19)
Chromogranin A μg/L (SD)	2,334.1 (1,072) (*n* = 13)	11,286.8 (3,006.6)*,†,‡ (*n* = 7)	2,155 (28.2) (*n* = 15)	5,378.4 (516.8) (*n* = 22)
BNP ng/L (SD)	71.4 (6.2) (*n* = 9)	212 (55)† (*n* = 7)	93.7 (9.9) (*n* = 12)	129.3 (3.4) (*n* = 19)
Outcome post procedure				
Hospitalization days (SD)	3.8 (1.6)	14.7 (6.9)*	3.5 (1.6)	8.9 (1.0)
30 days mortality	0	1	0	1
Complications	0	2 (severe bleeding)	0	2

n/a, not applicable.

*P < 0.01 between the three groups. †P = 0.01 compared to no CC. ‡P < 0.01 compared to broadly defined CC.

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

Exploratory analysis revealed a significant inverse correlation between intraoperative MAP and postoperative outcomes. Lower MAP values were associated with longer hospital stay (ρ = −0.62, P = 0.001) and higher incidence of postoperative complications (ρ = −0.55, P = 0.004).

The use of prophylactic octreotide infusion did not differ between the three groups. Carcinoid crisis occurred in 9 of 22 procedures (41%) with prophylactic octreotide infusion and in 6 of 13 procedures (46%) without infusion by the broad definition (P = 0.77).

Using the strict definition, CC occurred in 4 of 22 procedures (18%) with prophylaxis and 3 of 13 (23%) without (P = 0.68). These findings indicate no statistically significant difference between the groups. The treatment for established CC differed between the strictly and broadly defined groups. Potent vasoactive drugs such as noradrenaline and adrenaline were used more frequently in strictly defined CC. Octreotide and metaraminol were used more frequently in broadly defined CC. All subjects with strictly defined CC were treated with more than one drug; however, there were five patients with broadly defined CC who did not require treatment for transient haemodynamic instability.

Based on the exploratory associations observed between procedure type, biochemical markers, and clinical features, we developed a conceptual framework to stratify perioperative risk for carcinoid crisis (Fig. 2). The algorithm integrates three main domains identified in our cohort: i) procedure-related risk (high for cardiac valve surgery, intermediate for major abdominal surgery, and low for endoscopic or minor procedures); ii) tumour and secretory burden, reflected by markedly elevated chromogranin A (>7,000 μg/L), high 5-HIAA, or extensive liver metastases; and iii) hormonal and cardiac control, including the presence of carcinoid heart disease, elevated BNP, or uncontrolled symptoms. Combining these domains allows clinicians to classify patients as low, intermediate, or high risk and to guide decisions regarding peri-operative octreotide prophylaxis.

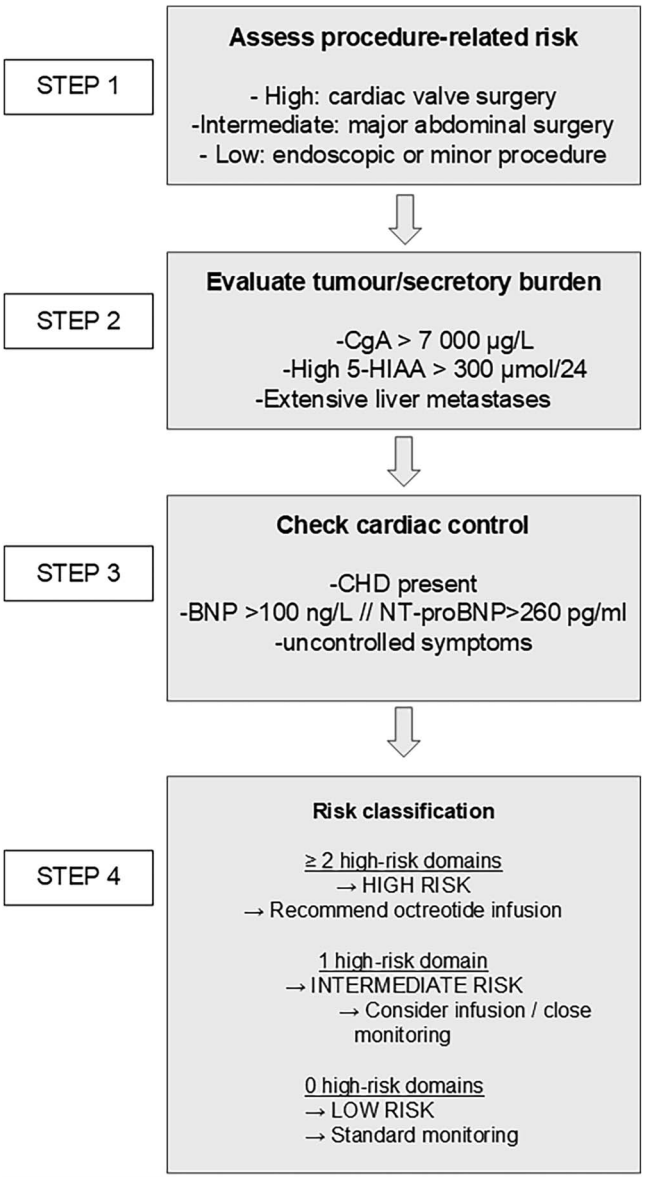


Figure 2

Proposed perioperative risk algorithm for patients with carcinoid syndrome. The framework integrates three domains: (1) procedure-related risk, (2) tumour and secretory burden (CgA >7,000 μg/L, high 5-HIAA, extensive liver metastases), and (3) hormonal/cardiac control (BNP/NT-proBNP elevation, carcinoid heart disease, uncontrolled symptoms), to stratify patients into low-, intermediate-, and high-risk categories and guide the use of prophylactic octreotide infusion. This algorithm is exploratory and intended for hypothesis generation and future validation.

Discussion

The evidence surrounding the efficacy of prophylactic octreotide infusion to improve peri-procedure outcome in subjects with CS has been limited, partly due to the lack of consensus for defining carcinoid crisis (Bardasi *et al.* 2022). This uncertainty leads to differential practice among anaesthetists in optimisation of SSA pre-procedures and can result in unnecessary delays. In this comprehensive analysis of CS subjects' haemodynamic status during procedures, we retrospectively applied broad and strict CC definitions to evaluate the subsequent prevalence, patient characteristics, and outcomes in CC.

Although PRRT and chemotherapy were analysed separately, their inclusion provides additional context as carcinoid crises have been occasionally reported after systemic therapies. Carcinoid crisis has been reported in CS subjects undergoing treatment with PRRT (de Keizer *et al.* 2008). We did not find CC, even

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Endocrine Oncology (2025) **5** e250034
https://doi.org/10.1530/EO-25-0034

by broad definitions, among our 34 subjects undergoing multiple PRRT cycles despite the lack of prophylactic octreotide infusions and PRRT administered 3–4 weeks after routine SSA injection. This may be due to internal stringent processes to identify patients who are at high risks of CC, protocols to optimise peptide control of CS pre-PRRT, and planned critical care service review following PRRT in high-risk subjects. PRRT-induced CC was reported in a case series from two Australian centres; only one out of the seven patients required acute haemodynamic support (Tapia Rico *et al.* 2018). Due to possible interference of unlabelled SSA competing with PRRT, our findings are supportive of close haemodynamic surveillance in high tumour load patients undergoing PRRT without prophylactic octreotide infusion, but with optimisation of medical therapy and clinical status through multidisciplinary care before PRRT.

With invasive procedures, the prevalence of CC in this cohort varied significantly depending on the definition used and the type of procedures performed. When employing the broad definition, the prevalence of all CC was 63% in our cohort. However, when using the stringent criteria, only considering prolonged hypotension, the prevalence dropped to 20%. A recent systematic review reported a pooled (n = 943 procedures across eight studies) incidence of 19% for CC in patients undergoing surgery for midgut neuroendocrine tumours and/or liver metastasis (Xu *et al.* 2022). This review primarily used the stringent definition, focussing on hypotension as the main criterion for CC. However, the inconsistency in definitions across different studies substantially influenced the reported incidence of CC. For example, Kinney *et al.* reported 0% incidence of CC in 196 procedures (Kinney *et al.* 2018), while Fouche *et al.* reported 55.6% incidence of suspected CC in 81 procedures (Fouché *et al.* 2018). Some studies focused solely on hypotension, while others included a broader range of symptoms such as flushing, bronchospasm, and arrhythmias. This variation makes direct comparison challenging but underscores the need for a standardised definition.

All of our strictly defined CC (prolonged hypotension) episodes occurred exclusively during cardiac valve replacement surgery, despite the majority receiving prophylactic octreotide infusions. These patients had higher pre-operative risk by virtue of their carcinoid heart disease: higher ASA score, BNP, chromogranin A, and urine HIAA concentrations. Our exploratory analysis identified several variables associated with severe CC, including high CgA, elevated 5-HIAA and BNP levels, presence of carcinoid heart disease, and cardiac valve surgery. These parameters are consistent with previous reports linking tumour burden and secretory activity with intra-operative haemodynamic instability. Although limited by sample size, these findings suggest that a combination of biochemical and procedural factors can help stratify risk before surgery. Chromogranin A (CgA) seems a promising predictor of severe carcinoid crisis. High CgA levels likely reflect increased tumour and secretory burden, predisposing to haemodynamic instability during major procedures. In our exploratory ROC analysis, a pre-procedure CgA threshold of around 7,000 μg/L showed good sensitivity and specificity for identifying patients who subsequently developed severe CC. Although this cut-off requires validation in larger cohorts, markedly elevated CgA levels should prompt careful optimisation and multidisciplinary planning before elective surgery, particularly cardiac valve replacement.

Although CC has been reported in abdominal laparoscopy and laparotomy (Massimino *et al.* 2013, Condron *et al.* 2016), we did not find any strictly defined CC in the 11 abdominal surgeries performed in our cohort. This might be due to our institution's policy to proactively look for and surgically treat carcinoid heart disease before abdominal surgery, such as liver resection, in order to avoid massive bleeding from portal hypertension. In a multi-centre review of 276 patients with CS, 16% had carcinoid heart disease, which was found to be a poor prognostic indicator (Fijalkowski *et al.* 2022). Earlier cardiac surgical intervention offers survival benefit, alleviates symptoms from right-sided heart failure, and has been advocated by multiple studies (Oleinikov *et al.* 2021). Late surgical intervention in New York Heart Association class III or IV CHD subjects, however, can still confer a survival benefit (Connolly *et al.* 2015). The authors noted high doses of octreotide were required in the 195 subjects who underwent CHD surgery; specific incidence rates of carcinoid crisis were not detailed in this study, highlighting the need for further research with clear definitions of CC.

Our data suggest that using severe, prolonged hypotension as the primary criterion for defining CC might be the most appropriate approach due to several compelling reasons. Our findings indicate that crises characterised by severe hypotension (systolic blood pressure <80 mmHg for more than 10 min) always required vasopressor/octreotide bolus intervention and were associated with post-operative complication and prolonged hospital stay. The need for these powerful vasoactive agents underscores the critical nature of hypotensive crises compared to other types of haemodynamic instability. Broadly defined CC with shorter duration of haemodynamic instability, on the other hand, was common and found in 43% of invasive procedures. Up to one-third of these broadly defined CC episodes resolved without any pharmaceutical intervention and therefore do not warrant the 'crisis' label.

High tumour or secretory burden indicated by urine 5-HIAA and chromogranin A concentrations are known predictors of CC (Bardasi *et al.* 2022). Similarly, elevated levels of these biomarkers in our study were significantly associated with prolonged CC and inpatient stay, highlighting the importance of pre-operative

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

assessment (Oberg *et al.* 2017). By utilising these biomarkers, clinicians can more effectively stratify patients based on their risk profiles and tailor their perioperative management strategies to mitigate the potential for severe complications, thereby improving overall patient outcomes.

Preoperative octreotide infusion was employed to mitigate the risk of carcinoid crisis during invasive procedures in the majority of our cohort. Despite prophylactic octreotide infusion being used in most invasive procedures, we did not observe a statistically significant reduction in CC incidence. This aligns with previous reports suggesting that perioperative octreotide may not completely prevent haemodynamic instability but could still attenuate its severity in selected patients. Larger prospective studies are needed to clarify the optimal prophylactic strategy. The recent literature questioned the efficacy of octreotide since CC rate did not increase compared to historical control without prophylactic octreotide infusion (Wonn *et al.* 2022). A meta-analysis included multiple studies and found no consistent evidence supporting the efficacy of preoperative octreotide infusion in preventing intra-operative CC (Xu *et al.* 2022). Despite these findings, major guidelines continue to recommend the use of preoperative octreotide. The North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS) guidelines both advocate for the administration of octreotide to reduce the risk of CC during surgical and invasive procedures (Kaltsas *et al.* 2017). This discrepancy between clinical practice guidelines and emerging evidence highlights the need for further research to clarify the role of octreotide in managing CS. A major barrier, as we already highlighted, is the lack of consistent definition of CC. The single CC-related mortality in our cohort was a subject who suffered a crisis during CHD surgery without prophylactic octreotide cover. A risk assessment incorporating a rubric of the procedure-related risk, the patient's disease load, and peptide control can assist the decision of prophylactic octreotide infusion. This will mandate usage in CHD surgeries while reducing usage in low-risk patients undergoing minor procedures, such as endoscopies. Based on our findings and previous reports, we propose a pragmatic framework for perioperative risk assessment in patients with carcinoid syndrome.

The model integrates three domains: i) procedural risk (high for cardiac valve surgery, intermediate for major abdominal surgery, low for endoscopic or minor procedures); ii) disease and secretory burden (CgA >7,000 μg/L, elevated 5-HIAA, extensive liver metastases); and iii) hormonal and cardiac control (presence of carcinoid heart disease, elevated BNP, uncontrolled symptoms). Combining these factors can help stratify patients into low-, intermediate-, and high-risk categories and guide the decision on perioperative octreotide use. While this rubric is exploratory and not yet validated, it provides a clinically meaningful starting point for structured risk evaluation.

Our study has several limitations that should be acknowledged. First, it is a retrospective analysis, which inherently carries biases and potential omissions. However, with the intra-operative haemodynamic parameters and medications fully interfaced into the electronic medical record (Fig. 1), CC diagnosis was based on minute-by-minute blood pressure electronic record rather than paper record by the anaesthetists. This data extraction strategy should reduce observer bias and under-reporting of broadly defined CC. Second, this study reflects the practice of a large oncological hospital, which is a high-volume ENETs Centre of Excellence with expertise in CS and CC management. This may limit the generalisability of our findings to other settings with different patient demographics and clinical practices. All the strictly defined CC occurred during CHD surgery; therefore, our findings might not apply to CC in the setting of other procedures. A further limitation is that 5-HIAA was available in only two-thirds of the cohort, reflecting changes in institutional testing availability and the retrospective nature of data collection.

Based on our data and supporting the literature, defining carcinoid crisis (CC) primarily by the presence of severe hypotension is likely the most clinically meaningful approach. Our study provides valuable insights into the management of carcinoid crisis and highlights areas for future research, especially regarding the definitions and preventive strategies for this condition. Further prospective studies are necessary to validate our findings and enhance their applicability across different clinical settings.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

Funding

M d O-G was supported by the ENETS Preceptorship Programme 2023.

References

Bardasi C, Benatti S, Luppi G, *et al.* 2022 Carcinoid crisis: a misunderstood and unrecognized oncological emergency. *Cancers* **14** 3. (https://doi.org/10.3390/cancers14030662)

Condron ME, Jameson NE, Limbach KE, *et al.* 2019 A prospective study of the pathophysiology of carcinoid crisis. *Surgery* **165** 158–165. (https://doi.org/10.1016/j.surg.2018.04.093)

Condron ME, Pommier SJ & Pommier RF 2016 Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery* **159** 358–365. (https://doi.org/10.1016/j.surg.2015.05.036)

Downloaded from journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026

Connolly HM, Schaff HV, Abel MD, *et al.* 2015 Early and late outcomes of surgical treatment in carcinoid heart disease. *J Am Coll Cardiol* **66** 2189–2196. (https://doi.org/10.1016/j.jacc.2015.09.014)

de Keizer B, van Aken MO, Feelders RA, *et al.* 2008 Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. *Eur J Nucl Med Mol Imag* **35** 749–755. (https://doi.org/10.1007/s00259-007-0691-z)

Doyle DJ, Hendrix JM & Garmon EH 2025 American Society of Anesthesiologists classification. In *StatPearls*. Treasure Island, FL, USA: StatPearls Publishing. (https://www.ncbi.nlm.nih.gov/books/NBK441940/)

Fijalkowski R, Reher D, Rinke A, *et al.* 2022 Clinical features and prognosis of patients with carcinoid syndrome and carcinoid heart disease: a retrospective multicentric study of 276 patients. *Neuroendocrinology* **112** 547–554. (https://doi.org/10.1159/000518651)

Fouché M, Bouffard Y, Le Goff MC, *et al.* 2018 Intraoperative carcinoid syndrome during small-bowel neuroendocrine tumour surgery. *Endocr Connections* **7** 1245–1250. (https://doi.org/10.1530/ec-18-0324)

Grozinsky-Glasberg S, Davar J, Hofland J, *et al*. 2022 European Neuroendocrine Tumor Society (ENETS) 2022 Guidance paper for carcinoid syndrome and carcinoid heart disease. *J Neuroendo* **34** e13146. (https://doi.org/10.1111/jne.13146)

Kaltsas G, Caplin M, Davies P, *et al.* 2017 ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pre- and perioperative therapy in patients with neuroendocrine tumors. *Neuroendocrinology* **105** 245–254. (https://doi.org/10.1159/000461583)

Kinney MA, Warner ME, Nagorney DM, *et al.* 2001 Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth* **87** 447–452. (https://doi.org/10.1093/bja/87.3.447)

Kinney MAO, Nagorney DM, Clark DF, *et al.* 2018 Partial hepatic resections for metastatic neuroendocrine tumors: perioperative outcomes. *J Clin Anesth* **51** 93–96. (https://doi.org/10.1016/j.jclinane.2018.08.005)

Massimino K, Harrskog O, Pommier S, *et al.* 2013 Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. *J Surg Oncol* **107** 842–846. (https://doi.org/10.1002/jso.23323)

Oberg K, Couvelard A, Delle Fave G, *et al.* 2017 ENETS consensus guidelines for standard of care in neuroendocrine tumours: biochemical markers. *Neuroendocrinology* **105** 201–211. (https://doi.org/10.1159/000472254)

Oleinikov K, Korach A, Planer D, *et al.* 2021 Update in carcinoid heart disease – the heart of the matter. *Rev Endocr Metab Disord* **22** 553–561. (https://doi.org/10.1007/s11154-020-09624-y)

Perren A, Couvelard A, Scoazec JY, *et al.* 2017 ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. *Neuroendocrinology* **105** 196–200. (https://doi.org/10.1159/000457956)

Seymour N & Sawh SC 2013 Mega-dose intravenous octreotide for the treatment of carcinoid crisis: a systematic review. *Can J Anaesth* **60** 492–499. (https://doi.org/10.1007/s12630-012-9879-1)

Tapia Rico G, Li M, Pavlakis N, *et al.* 2018 Prevention and management of carcinoid crises in patients with high-risk neuroendocrine tumours undergoing peptide receptor radionuclide therapy (PRRT): literature review and case series from two Australian tertiary medical institutions. *Cancer Treat Rev* **66** 1–6. (https://doi.org/10.1016/j.ctrv.2018.03.002)

Woltering EA, Wright AE, Stevens MA, *et al.* 2016 Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth* **32** 189–193. (https://doi.org/10.1016/j.jclinane.2016.03.008)

Wonn SM, Ratzlaff AN, Pommier SJ, *et al.* 2022 A prospective study of carcinoid crisis with no perioperative octreotide. *Surgery* **171** 88–93. (https://doi.org/10.1016/j.surg.2021.03.063)

Xu A, Suz P, Reljic T, *et al.* 2022 Perioperative carcinoid crisis: a systematic review and meta-analysis. *Cancers* **14** 2966. (https://doi.org/10.3390/cancers14122966)

Downloaded from Journals.bioscientifica.com/eo/article-pdf/doi/10.1530/EO-25-0034/507810/eo-25-0034.pdf by [CU-1057472] | Hospital Universitario La Fe user on 05 November 2026