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ORIGINAL ARTICLE

Carcinoid heart disease in patients with advanced small-intestinal neuroendocrine tumors and carcinoid syndrome: a retrospective experience from two European referral centers

L. Algeri[1,2], L. Falkman[3], F. Spada[1], S. Frassoni[4,5], V. Bagnardi[4], S. Boselli[6], D. Cardinale[7], M. Zanobini[8], J. Crona[3], L. Benini[1], D. Tamayo[6], C. Mazzon[6], L. Gervaso[1], C. A. Cella[1], M. G. Zampino[1], D. Ciardiello[1], A. Russo[2], G. Badalamenti[2], S. Welin[3] & N. Fazio[1]*

[1]Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology (IEO), IRCCS, Milan; [2]Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), Section of Medical Oncology, University of Palermo, Palermo, Italy; [3]Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden; Departments of [4]Statistics and Quantitative Methods; [5]Medicine and Surgery, University of Milano-Bicocca, Milan; [6]Data Management-Clinical Trial Office, Scientific Direction, European Institute of Oncology (IEO), IRCCS, Milan; [7]Cardioncology Unit, European Institute of Oncology (IEO), IRCCS, Milan; [8]Department of Cardiac Surgery, Centro Cardiologico Monzino, Milan, Italy

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Background: Up to 50% of patients with advanced small-intestinal neuroendocrine tumors (SI-NETs) and carcinoid syndrome (CS) develop carcinoid heart disease (CHD). However, the true frequency and prognostic markers for CHD in CS are lacking. We described the real-world management of patients in two NET referral centers in this clinical context and relationships between clinical features, including CHD and overall survival (OS).

Patients and methods: This is a retrospective analysis of patients with stage IV SI-NET and CS, treated at the European Institute of Oncology in Milan and Uppsala University in Sweden between 2015 and 2021. CHD was defined as at least one moderate right-sided heart valve defect. Median OS and cumulative incidence of CHD were estimated from the diagnosis of metastatic disease, and the association between clinical parameters with both OS and occurrence of CHD was evaluated.

Results: We included 165 patients, with 97% having low-intermediate-grade SI-NETs and 86% having synchronous liver metastases. Ninety-eight patients (59%) became refractory to full label dose of somatostatin analogues and 25% developed a CHD. At CHD diagnosis, baseline urine 5-hydroxyindoleacetic acid (24-h u5-HIAA) value and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) value were known in 76% of patients. Moderate-to-severe tricuspid insufficiency was the most common alteration of CHD. Prognosis was significantly impaired by CHD (multivariable hazard ratio for OS = 2.85, $P < 0.001$). The median OS from the CHD diagnosis was 4.5 years [95% confidence interval (CI) 2.1-7.2 years], and the 5-year survival rate was 34% (95% CI 13% to 57%).

Conclusions: In our study population of SI-NET patients with CS, more than half had a refractory carcinoid syndrome (RCS) and one-quarter developed a CHD, with a negative impact on OS. Therefore, it is recommended to screen and monitor patients with CS for CHD, ideally with a combination of u5-HIAA, NT-proBNP values, and echocardiography at CS baseline, preferably in NET referral centers.

Key words: neuroendocrine tumor, carcinoid syndrome, carcinoid heart disease, small intestinal

INTRODUCTION

Small-intestinal neuroendocrine tumors (SI-NETs) (particularly ileal) are the main subgroup of gastro-entero-pancreatic (GEP) NETs, with an incidence of up to 1.49/100 000 persons/year.[1] Advanced SI-NETs may be non-functioning (NF) or functioning (F) due to a clinical syndrome dependent on tumor hypersecretion of several bioactive molecules, mainly serotonin. Carcinoid syndrome (CS) is the most common hormone-related clinical syndrome to be associated to NETs, being characterized by secretory diarrhea and/or facial flushing, along with the

*Correspondence to: Dr Nicola Fazio, Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, Program in Digestive and Neuroendocrine Cancers, European Institute of Oncology, IEO, IRCCS, ENETS GEP NEN and lung NET Center of Excellence, EURACAN Domain G4 NET Center of Excellence, ItaNET-affiliated NET Center, Via Ripamonti 435, 20141 Milan, Italy. Tel: +390257489429; Fax: +390294379224

E-mail: nicola.fazio@ieo.it (N. Fazio).

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detection of increased levels of blood serotonin and/or its urine metabolite 5-hydroxyindolacetic acid (5-HIAA).[2] The incidence of CS is 1/100 000 persons/year, and its prevalence varies between 19% and 35%.[3] Patients with CS more likely have liver metastases from low/intermediate-grade SI-NETs.[2-4] Patients with advanced, low-, or intermediate-grade SI-NETs have a median overall survival (mOS) of 8-10 years[5] and CS seems to impair both survival[2] and lifestyle significantly, and to impact on health resources.[3,6]

A value of 5-HIAA in 24-h urine (24-h u5-HIAA) >50 μmol is consistent with the CS diagnosis,[2] and a higher 24-h u5-HIAA value (notably, >300 μmol/24 h) implies a twofold to threefold increase in risk of CHD occurrence/progression, having a significant negative prognostic relevance.[7] Currently, plasmatic 5-HIAA (p5-HIAA) assay is a promising method, having more stability than whole blood serotonin determination, with sensitivity and specificity of 89% and 97%, respectively, at a cut-off value of 118 nmol/l[8,9]; however, it is not routinely adopted yet.[10]

Due to both their antisecretory[11-14] and antiproliferative[11,15-17] activities, somatostatin analogues (SSAs) are the backbone of CS treatment. However, despite the use of full label dose of SSAs, in up to 30% of patients a refractory carcinoid syndrome (RCS) occurs. An increase in drug frequency,[18] step-up dosing,[19,20] and/or short-acting SSAs as rescue therapy[2] are useful strategies to achieve symptom control. However, in many cases further treatments with an anti-syndromic purpose are required, such as peptide receptor radionuclide therapy (PRRT),[21-23] telotristat ethyl (TE),[24-28] targeted therapy (TT),[29,30] and liver-directed therapies.[2,31-33]

Between 20% and 50% of patients with CS will develop carcinoid heart disease (CHD)[3] during their disease history with a detrimental effect on survival.[3] Patients with CHD have a 3-year OS rate of 31%, compared with 69% for those without CHD.[2,3] However, the overall prevalence is uncertain due to lack of consistent screening using transthoracic echocardiography (TTE).[34] Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) represents the most validated tool for CHD screening and follow-up, showing sensitivity and specificity of 92% and 91%, respectively, at a cut-off level of 235-260 pg/ml.[35] Furthermore, NT-proBNP levels are positively linked to CS aggressiveness, New York Heart Association functional class, and lastly, overall mortality.[2,36] CHD may be indolent or result in fast clinical deterioration, leading to end-stage right heart failure (RHF).[3] The tricuspid valve (TV) and pulmonary valve (PV) are the most common valves involved in CHD (90% and 69% of cases, respectively).[12] However, it is important to consider that left-sided heart valves may be affected in more than one-third of CHD patients. Valve replacing should be proposed to patients with severe cardiac valve damage and well-controlled systemic disease.[2]

On this basis, we aimed to describe the real-world management of patients with CS associated with metastatic SI-NET in two international NET referral centers and to study the relationship between clinical parameters and OS, and prognostic impact of CHD.

PATIENTS AND METHODS

Study design and population

Among patients with NET diagnosis presented at the multidisciplinary team (MDT) of the European Institute of Oncology (IEO) in Milan and Department of Endocrine Oncology of Uppsala University from 2015 to 2021, we retrospectively selected those with advanced SI-NETs and CS. These institutions are neuroendocrine neoplasms (NEN) Centers of Excellence (CoEs) certified by both European Neuroendocrine Tumor Society (ENETS) and European Reference Network for Rare adult Solid Cancer (EURACAN). Selection criteria for the study were: histological diagnosis of NET, any tumor grade, and history of CS defined as secretory diarrhea and/or skin flushing, with or without increased levels of urinary and/or plasmatic 5-HIAA. Isolated flushing episodes were considered as suggestive findings of CS after exclusion of alternative biological/clinical explanations; likewise, due to its non-specific nature, an isolated diarrhea episode was excluded if attributable to any condition other than CS. RCS was defined by recurring or persisting CS symptoms and/or increasing or persistently high u5-HIAA value despite the use of full label dose of SSA.[2] Baseline biochemical parameters were included only if they were assessed within 6 months from the CS and CHD diagnosis, respectively. 24-h u5-HIAA secretion was reported as 'normal levels' (10.4-46.8 μmol/24 h), 'high levels' (>50 μmol/24 h), 'very high levels' (>300 μmol/24 h), or 'not available' (N/A). We used an NT-proBNP cut-off level of 260 pg/ml as threshold for CHD diagnosis, as reported by the current ENETS guidelines.[7] For CHD diagnosis, echocardiography was carried out by trained cardiologists to rule out the presence of the right-sided valvular injury. CHD was defined as at least one moderate right-sided heart valve abnormality (either TV or PV regurgitation/stenosis). We described in detail the characteristics of all the valves affected, retrieving all information by dedicated templates which are commonly employed in our institutes, in accordance with the latest guidelines.[37] Baseline demographics and clinical features were collected from all patients at the time of NET diagnosis (obtained by biopsy of either primary or metastatic site), based on the 2019 World Health Organization (WHO) diagnostic criteria for GEP NENs.[38] Tumor stage was assessed according to the eighth edition of the American Joint Committee on Cancer/International Union against Cancer (Union Internationale Contre le Cancer) TNM (tumor—node—metastasis) classification.[39] We collected on electronic Case Report Form (eCRF) patient and tumor characteristics together with treatment patterns and sequencing. All retrieved data were pseudonymized. The study has been carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board or ethics committee at each center and by the Data Protection Officer at IEO Center (U-ID: 4035). All patients gave their informed consent for the research, as required by the institutional regulation for retrospective analyses in both CoEs.

Statistical analysis

Continuous data were reported as median and ranges or as median and interquartile ranges (IQR). Categorical data were reported as counts and percentages. The OS function was defined as the time from metastatic NET diagnosis until death or last contact, and was estimated using the Kaplan–Meier method. The association between patient, tumor, and treatment characteristics with OS was evaluated using univariable Cox proportional hazards regression models. The association between the occurrence of CHD and OS was evaluated using the time-dependent Cox regression model. Variables with $P < 0.1$ in univariable analysis were included in multivariable analysis. The cumulative incidence function (CIF) of CHD was estimated according to the method described by Kalbfleisch and Prentice,[40] considering death as a competing event. Univariable Fine and Gray regression models were used to assess the association between patient, tumor, and treatment characteristics with the development of CHD. The association between both PRRT and TE with the occurrence of CHD was evaluated using time-dependent Fine and Gray regression models. For patients with CHD, the OS from CHD diagnosis was also calculated. All reported P values were two-sided, with a P value < 0.05 considered as statistically significant. All analyses were carried out with the statistical software SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

In total 165 patients were included in the dataset—88 from the IEO Center and 77 from the Uppsala center (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103959).

One hundred and fifty-two patients (92%) had synchronous distant metastases, and the liver was the most common site. The median age of patients at metastatic NET diagnosis was 62 years (IQR 55-69 years), with a modest male prevalence (53%). Somatostatin receptor imaging was carried out in all the patients included and it was positive in almost all of them (95%). According to the 2019 WHO diagnostic criteria,[38] the majority of NETs were grade 2 (53%), and 3% were grade 3.

Regarding CS, most of the patients had both diarrhea and flushing (58%). The majority had a diagnosis of CS earlier than the diagnosis of metastatic SI-NET (40%). The 24-h u5-HIAA at CS presentation was available in just over two-thirds of patients. Of note, despite the presence of CS symptoms/signs, 31% of patients had normal u5-HIAA values (10.4-46.8 μmol/24 h). The NT-proBNP at CS presentation was available in 40% of patients, with >60% showing normal values (<260 pg/ml). Patient and tumor characteristics are reported in Table 1.

In 65% of patients, the primary tumor had been resected. Ninety-three percent of patients received an SSA (47% octreotide LAR and 53% lanreotide autogel) at full label dose as first-line therapy for syndrome control. Six percent of patients started SSAs at a lower dose. Only two patients did not receive any systemic treatment because they

Table 1. Demographic, clinical and pathological characteristics of the study population ($N = 165$)

Variables	Level	*n* (% or range)
Sex	Female	77 (46.7)
	Male	88 (53.3)
Distant metastases	Metachronous	13 (7.9)
	Synchronous	152 (92.1)
Age at metastatic NET diagnosis, median (IQR)	62 (55-69)	
Site of metastases		
Liver	No	14 (8.5)
	Yes	151 (91.5)
Extra-regional lymph nodes	No	36 (21.8)
	Yes	129 (78.2)
Small bowel as site of metastases	No	89 (53.9)
	Yes	76 (46.1)
Peritoneum	No	128 (77.6)
	Yes	37 (22.4)
Bone	No	133 (80.6)
	Yes	32 (19.4)
Lung	No	150 (90.9)
	Yes	15 (9.1)
Other	No	154 (93.3)
	Yes	11 (6.7)
SRI	Negative	8 (4.8)
	Positive	157 (95.2)
Tumor grade	G1	72 (43.6)
	G2	88 (53.3)
	G3	5 (3.0)
Cardiovascular comorbidities	No	58 (35.2)
	Yes	107 (64.8)
Months between metastatic NET and CS diagnosis, median (IQR) (min-max)	0 (−1.1 to 0.5) (−68 to 97)	
Metastatic NET and CS diagnosis	CS diagnosis before metastatic NET diagnosis	66 (40.0)
	CS and metastatic NET diagnosis on the same date	48 (29.1)
	CS diagnosis after metastatic NET diagnosis	51 (30.9)
Symptoms at CS diagnosis	Diarrhea alone	22 (13.3)
	Flushing alone	48 (29.1)
	Both	95 (57.6)
Baseline level of 24-h u5-HIAA at CS diagnosis	10.4-46.8 μmol/24 h	36 (30.5)
	>50 μmol/24 h	57 (48.3)
	>300 μmol/24 h	25 (21.2)
	Missing	47
Baseline level of NT-proBNP at CS diagnosis	<260 pg ml	42 (63.6)
	>260 pg ml	24 (36.4)
	Missing	99
CS and NET evolution	Stable CS and SD	37 (22.4)
	Stable CS and PD	30 (18.2)
	RCS and SD	36 (21.8)
	RCS and PD	62 (37.6)
Baseline level of 24-h u5-HIAA at CHD diagnosis[a]	10.4-46.8 μmol/24 h	3 (10)
	>50 μmol/24 h	13 (42)
	>300 μmol/24 h	15 (48)
	Missing	10
Baseline level NT-proBNP at CHD diagnosis[a]	<260 pg ml	9 (29)
	>260 pg ml	22 (71)
	Missing	10

24-h u5-HIAA, 5-hydroxyindoleacetic acid (urine); CHD, carcinoid heart disease; CS, carcinoid syndrome; G, grade; IQR, interquartile range; NET, neuroendocrine tumor; NT-proBNP, N-terminal pro B-type natriuretic peptide; PD, progression of disease; RCS, refractory carcinoid syndrome; SD, stable disease; SRI, somatostatin receptor imaging.

[a]Variable calculated only for the 41 patients with CHD.

underwent upfront radical resection of both primary and liver metastatic disease. Thirty-seven patients (22%) had a fully controlled disease (both clinically and radiologically) during first-line SSA. More than half of the patients (59%) developed an RCS (Table 1).

Focusing on this latter subgroup, because of uncontrolled CS-related symptoms, 91% of patients had an interval shortening in SSA administration and in 23% an addition of short-acting injections as 'rescue' therapy was carried out; step-up dosing and switching to the alternative SSA at full label dose were also adopted (5% and 8%, respectively). Dose escalation was applied to all the patients who did not previously receive full label doses of SSA. However, despite the optimization of SSA schedule/dose, 33% of patients required further systemic treatment for both syndrome and tumor growth control, mainly PRRT (13%). In 22% of patients TE was prescribed because of refractory CS-related diarrhea. In patients developing RCS without progression of disease (22%), further systemic treatments [PRRT, interferon (IFN)-α, temozolomide, and pasireotide] were added to SSA in 28% of cases. Only 5% of patients underwent locoregional treatments with anti-syndromic intent, mostly transarterial embolization.

A CHD occurred in 24.8% ($n = 41/165$) of patients and in 39% of them an RHF was the first sign. In CHD patients, a baseline 24-h u5-HIAA was available in 76% of cases, with a value >300 µmol/24 h in 48% of them. Similarly, baseline NT-proBNP was available in 76% of patients, with 71% presenting with >260 pg/ml (Table 1). In 83% of CHD patients, an echocardiogram had been carried out at CS diagnosis. The most common valve alteration was a moderate-to-severe TV insufficiency (TVI) (90%), followed by PV insufficiency (PVI) (32%). Interestingly, in 58% of patients left-sided valves were also involved. A heart surgery was carried out in 19 out of 41 CHD patients (46%).

With a median follow-up of 4.2 years (IQR 2.6-6.5 years), 33% of our patients died. Since the diagnosis of metastatic disease, the 1-year OS rate was 97.5% [95% confidence interval (CI) 93.4% to 99.0%] and 5-year OS rate was 69.2% (95% CI 60.0% to 76.7%). The mOS of the whole study population was 8.9 years (95% CI 6.7-11.8 years) (Figure 1A).

Focusing on the CHD subgroup, 46% died. The 1-year OS rate was 81.9% (95% CI 65.7% to 91.0%), and just one-third was alive at 5 years [5-year OS rate: 34.4% (95% CI 13.2% to 57.0%)]. The mOS of the CHD patients was 4.5 years (95% CI 2.1-7.2 years) (Figure 1B).

The CIF of CHD in the whole study population at 1, 3, 5, and 8 years were 15.3% (95% CI 10.2% to 21.2%), 17.9% (95% CI 12.4% to 24.2%), 24.3% (95% CI 17.5% to 31.7%), and 30.2% (95% CI 21.7% to 39.0%), respectively (Figure 2).

In the multivariable Cox regression analysis, age at metastatic NET diagnosis [hazard ratio (HR) 1.06, 95% CI 1.03-1.09, $P < 0.001$] and CHD occurrence (HR 2.85, 95% CI 1.57-5.20,

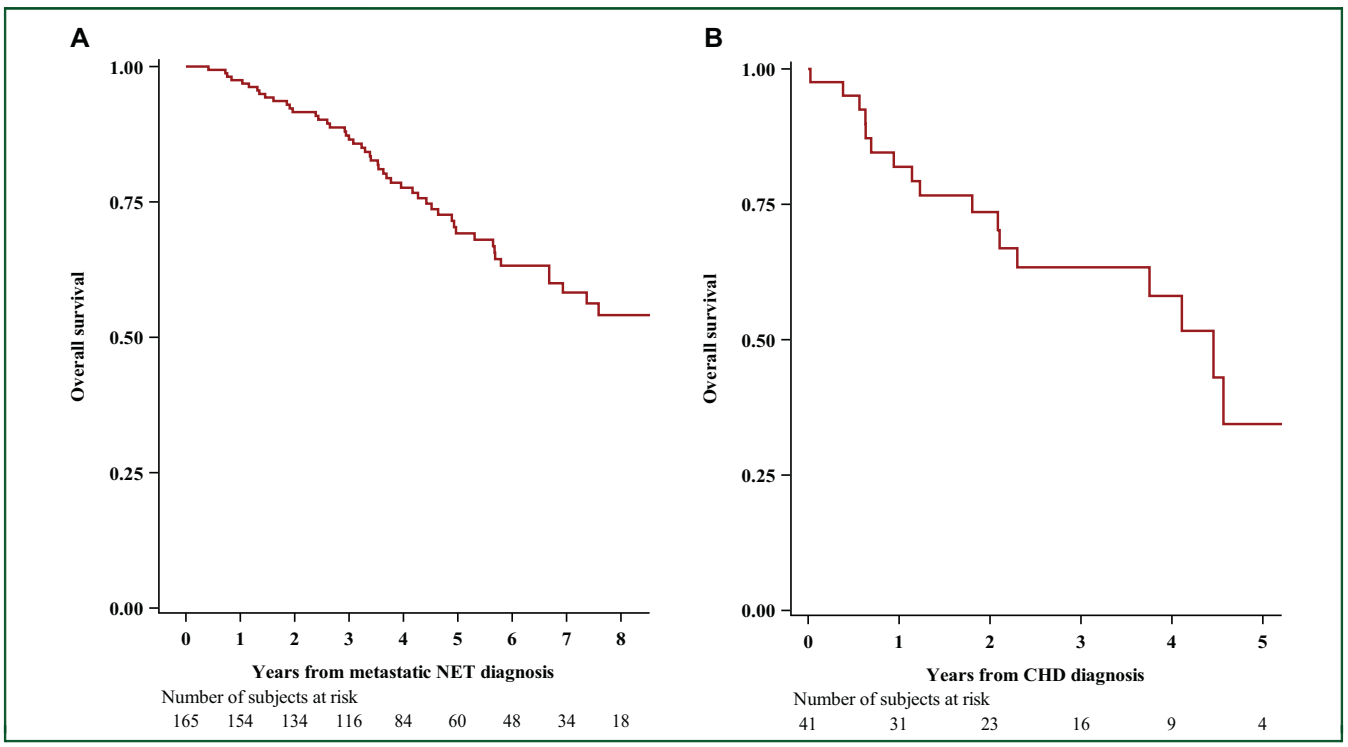

Figure 1. Overall survival in the whole study population ($N = 165$, A), and among patients with carcinoid heart disease ($N = 41$, B). (A) The OS function was defined as the time from metastatic NET diagnosis until death or last contact, and was estimated using the Kaplan–Meier method. With a median follow-up of 4.2 years (IQR 2.6-6.5 years), 33% of our patients died. Since the diagnosis of metastatic disease, the 1-year OS rate was 97.5% (95% CI 93.4% to 99.0%) and the 5-year OS rate was 69.2% (95% CI 60.0% to 76.7%). The median OS of the whole study population was 8.9 years (95% CI 6.7-11.8 years). (B) For patients with CHD, the OS from CHD diagnosis was also calculated. Forty-six percent of the CHD patients died. The 1-year OS rate was 81.9% (95% CI 65.7% to 91.0%), and just one-third was alive at 5 years [5-year OS rate: 34.4% (95% CI 13.2% to 57.0%)]. The median OS of the CHD patients was 4.5 years (95% CI 2.1-7.2 years).
CHD, carcinoid heart disease; CI, confidence interval; IQR, interquartile range; NET, neuroendocrine tumor; OS, overall survival.

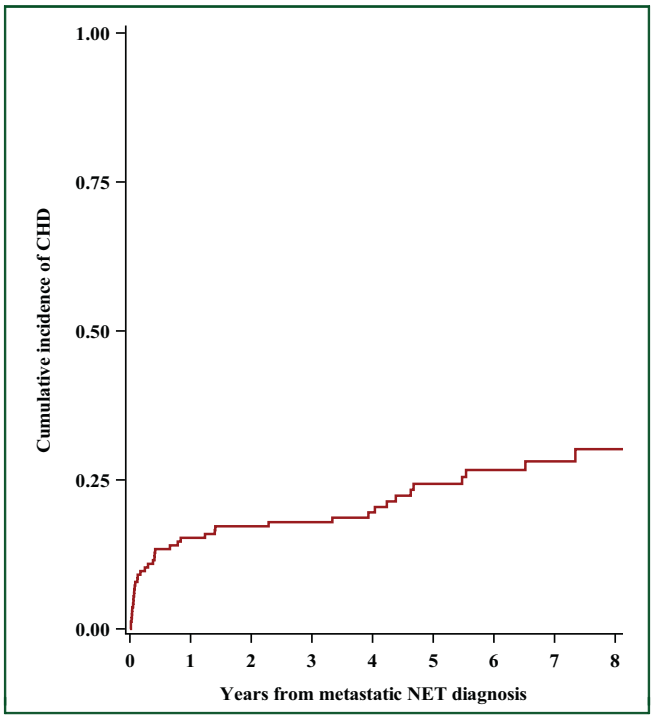

Figure 2. Cumulative incidence function of carcinoid heart disease ($N = 165$).
The CIF of carcinoid heart disease estimated according to method described by Kalbfleisch and Prentice, considering death as a competing event. The CIF of CHD in the whole study population at 1, 3, 5, and 8 years were 15.3% (95% CI 10.2% to 21.2%), 17.9% (95% CI 12.4% to 24.2%), 24.3% (95% CI 17.5% to 31.7%), and 30.2% (95% CI 21.7% to 39.0%), respectively.
CHD, carcinoid heart disease; CI, confidence interval; CIF, cumulative incidence function; NET, neuroendocrine tumor.

$P < 0.001$) were significantly associated with OS, as shown in Table 2.

We explored relationships between clinical features (synchronous metastases, CS-related symptoms burden, cardiovascular comorbidities, PRRT, and TE given as any line of systemic treatment, respectively) and development of CHD. In the univariable Fine and Gray regression analysis, TE was found to be associated with CHD occurrence (although not significantly: HR 3.51, 95% CI 0.94-13.1, $P = 0.061$), as shown in Table 3.

DISCUSSION

In our retrospective series on SI-NET patients with CS from two European ENETS and EURACAN CoE, a CHD was diagnosed in 24.8% of cases, which is consistent with literature.[2,3] Similarly to previous reports, we found a close relationship between CHD occurrence and risk of death. Our study population represents the clinical context at the highest risk of CS and, consequently, CHD.[41-43] In large series of patients with NET, those with metastatic low/intermediate SI-NETs with CS had 4.7 years of mOS compared with 7.1 years of those without CS.[3] The mOS of our entire population seems to be slightly better than that of historical reports,[2,3] maybe due to a selection bias. However, literature data concerning the true epidemiology of CS and CHD are controversial, being based on old-fashioned, retrospective, and heterogeneous studies including several primary sites and even NF-NETs.[2,3,41,43]

Although primary tumor resection may improve the quality of life in symptomatic patients for local mass effect, its efficacy in controlling CS and improving survival is still unclear.[44] The resected primary tumor did not correlate with OS according to our multivariable Cox regression.

Octreotide and lanreotide seemed to have similar clinical efficacy, although a direct comparison between them has not been carried out yet in prospective randomized trials.[2,45,46] Our data suggested that full label dose SSA does not control CS in more than half of the cases. Our 60% of patients developing an RCS is higher compared with up to 30% reported in the literature.[47] These findings suggest that CS does not represent a single entity but a complex spectrum of clinical patterns with an unpredictable behavior, as reported by others.[41] The optimal therapeutic sequencing for RCS has not been established, being based on local experiences, single-arm studies, or subgroup analyses of larger studies including mixed populations. Likewise, there is no biomarker suitable for guiding treatment selection for RCS patients in daily clinical practice.[48] Due to the aforementioned reasons, clinicians should take into consideration several aspects, such as patients' symptom burden, tumor growth status (stable or progressive), hepatic tumor load, and CHD occurrence/progression.[2] In our study, almost all RCS patients had a titration of the SSA therapy, mainly by increasing drug administration frequency[2,18] or adding on short-acting octreotide.[11,13,14] However, around half of them required further systemic and/or liver-directed therapies similarly to other reports.[2,24-26] In those showing both RCS and tumor progression, PRRT was the preferred choice again in line with other reports.[2,21-23] Although TE has been approved by international regulatory authorities[27,28] based on phase III studies,[25,26] its availability varies among countries due to different local approvals and might lead to health care disparities. Interestingly, all patients treated with TE in our study were from the Uppsala center as in Italy TE is not reimbursed yet. Moreover, our RCS patients treated with IFN-α were all from the Uppsala center, probably due to the higher historical experience with this drug in CS.[49] However, given the absence of strong recommendations to add IFN-α to SSA in CS patients, and/or to its supposed low tolerability, its use in NET patients is currently very limited.[2,50]

Patients with CHD have been reported to have significantly higher u5-HIAA compared with patients without CHD, and u5-HIAA peak level is a significant predictor of progressive CHD.[3,11,51] In our cohort, two-thirds of patients had a baseline assessment of 24-h u5-HIAA value at CHD diagnosis, and over -thirds of them had a value >50 μmol/24 h. Furthermore, NT-proBNP is considered the most useful adjunct marker to echocardiography in screening for and monitoring of CHD, as its median levels have been reported significantly higher in patients with than without CHD.[2] Baseline NT-proBNP values were available in around 75% of our CHD patients, and half of them had >260 pg/ml levels. It is important to note that diagnosis of CHD requires

Table 2. Association between patient, tumor, and treatment characteristics with overall survival ($N = 165$)

Variable	Level	*n*	Death	Univariable analysis			Multivariable analysis		
				HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	Female	77	22	Ref.	—	—			
	Male	88	32	0.87	0.50-1.51	0.61			
Age at metastatic NET diagnosis	+1 year			1.06	1.04-1.09	<0.001	1.06	1.03-1.09	<0.001
Synchronous metastases	No	13	3	Ref.	—	—			
	Yes	152	51	2.05	0.62-6.74	0.24			
Site of metastases	Liver + other sites	142	46	Ref.	—	—			
	Only other sites	14	4	0.79	0.28-2.20	0.64			
	Only liver	9	4	1.44	0.51-4.03	0.49			
Tumor grade	G1	72	21	Ref.	—	—			
	G2/G3	93	33	1.37	0.79-2.37	0.27			
Resected primary tumor	No	57	20	Ref.	—	—	Ref.	—	—
	Yes	108	34	0.53	0.30-0.93	0.028	0.95	0.52-1.76	0.88
CS and NET status	Stable CS and SD	37	13	Ref.	—	—			
	Stable CS and PD	30	10	0.60	0.26-1.38	0.23			
	RCS and SD	36	7	0.56	0.28-1.11	0.10			
	RCS and PD	62	24	0.42	0.17-1.06	0.068			
CHD (time-dependent variable)	No	124	35	Ref.	—	—	Ref.	—	—
	Yes	41	19	3.25	1.84-5.75	<0.001	2.85	1.57-5.20	<0.001

Only variables with $P < 0.1$ in the univariable analyses were included in the multivariable model.
CHD, carcinoid heart disease; CI, confidence interval; CS, carcinoid syndrome; G, grade; HR, hazard ratio; NET, neuroendocrine tumor; PD, progression of disease; RCS, refractory carcinoid syndrome; SD, stable disease.

specific training in echocardiography. This is relevant since the presence of moderate-to-severe CHD-related valvular defects can be asymptomatic for a long time. For instance, an increased right-to-left ventricular width ratio can indicate the presence of TVI or PVI and should be reported as a possible sign of CHD (after excluding pulmonary embolism).[2] In the vast majority of our patients with CHD, a moderate-to-severe TVI was detected, in line with literature data.[2,51,52] Therefore, it is strongly recommended to refer NET patients to high-volume centers with a NEN-dedicated MDT and preferably also a CHD-dedicated MDT.[2]

Treatment of CHD can be medical and/or surgical. None of the co-variables analyzed was significantly associated with CHD occurrence. However, whether the combination of lanreotide autogel plus TE might significantly impact on CHD occurrence/progression is currently under investigation (NCT04810091).[53]

Table 3. Association between patient, tumor and treatment characteristics with occurrence of carcinoid heart disease ($N = 165$)

Variable	Level	*n*	CHD	HR	95% CI	*P* value
Synchronous metastases	No	13	2	Ref.	—	—
	Yes	152	39	1.89	0.51-6.99	0.34
Symptoms at CS diagnosis	Diarrhea alone	22	4	Ref.	—	—
	Flushing alone	48	8	0.88	0.27-2.81	0.83
	Both	95	29	1.77	0.65-4.82	0.26
Cardiovascular comorbidities	No	58	13	Ref.	—	—
	Yes	107	28	1.23	0.64-2.34	0.53
PRRT (time-dependent variable)	No	91	32	Ref.	—	—
	Yes	74	9	1.25	0.48-3.26	0.65
Telotristat ethyl (time-dependent variable)	No	150	38	Ref.	—	—
	Yes	15	3	3.51	0.94-13.1	0.061

CHD, carcinoid heart disease; CI, confidence interval; CS, carcinoid syndrome; HR, hazard ratio; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy.

We are aware about the several limitations of our study. Foremost, we selected our study population without using a specific threshold of symptoms/signs unlike other studies[24,25] but based on clinical features suggestive for CS, similarly to the inclusion criteria of the RADIANT-2 study.[29] Secondly, a baseline biochemical assessment of 24-h u5-HIAA at CS presentation was not available in around a third of patients; albeit p5-HIAA measurement has not been standardized yet, it seems to be a reliable and feasible tool particularly for CS monitoring, so its use should be implemented in clinical practice.[8-10] Furthermore, given the lack of a systematic biochemical evaluation in our series, RCS was defined by a symptomatic progression during full label dose of SSA. Finally, one-third of our CS patients did not have a baseline echocardiogram, and in 60% of them NT-proBNP was missing, leading to a possible underestimation of CHD at the time of CS diagnosis. Although our cohort has a good homogeneity since it included patients managed in two international NEN referral centers, the retrospective design of the study exposed to clear limitations, mostly due to the heterogeneity of the baseline diagnostic approach to CS and even more CHD as patients could have been managed in various centers in the different time points of their clinical history.

Conclusions

Our retrospective study showed that CS is a variegate clinical entity, requiring a personalized and multimodal approach. Among our SI-NET patients with CS, those with CHD had a poorer prognosis. Urine 5-HIAA and NT-proBNP combined with echocardiogram can have a relevant role when carried out at CS baseline. Therefore, patients with

this condition should be referred as soon as possible to NET referral centers preferably with also a CHD task MDT. Our analysis generated solid hypotheses which should be specifically investigated with prospective homogeneous clinical studies.

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DISCLOSURE

The authors have declared no conflicts of interest.

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