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REVIEW

Carcinoid Heart Disease – A 2022 Retrospective

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Abstract: *We aim to introduce a 2022 update on CHD (carcinoid heart disease) considering a multidisciplinary perspective. This is a narrative mini-review. We searched English, full-length papers (PubMed). Inclusion criteria: original articles regardless of the level of statistical significance. We identified 44 papers and manually selected those with CHD, as follows: 8 original studies, 1 case series (N=9 patients), 16 case reports (N=1 patient/paper), and a total of 1,030 patients on published studies. The most remarkable results are the longest period of enrolment of 3-4 decades; CHD ratio among carcinoid syndrome of 37%; 30-day mortality post-cardiac surgery of 12%; median survival in CHD from 1.3 to 3.9 years (more than 2 years if valve intervention is provided); most useful prognostic markers: 5HIIA, NT-pro-BNP, but, potentially, chromogranin A. The specific protective role of somatostatin analogs against developing CHD is yet to be determined. CHD in the absence of carcinoid syndrome/liver metastasis may be related to ovarian NEN (neuroendocrine neoplasia) with a better outcome if prompt intervention. Remarkably, 3 guidelines are released regarding CHD on behalf of ENETS (European Neuroendocrine Tumor Society), and ESC (European Society of Cardiology). CHD still represents a most challenging entity situated at the crossroads of surgery, cardiology, oncology, endocrinology, and gastroenterology.*

Keywords: *carcinoid heart disease, neuroendocrine, serotonin, neuroendocrine neoplasia, carcinoid syndrome, 5HIIA, valve, tricuspid, echocardiography*

INTRODUCTION

The complex field of neuroendocrine neoplasia (NEN), a rare condition with an annual incidence of 2 to 5.1 cases per 100,000 individuals, represents one of the most spectacular domains with massive recent progress from a multidisciplinary perspective [1,2]. The two main direct cardiac complications of NENs' evolution are either heart metastasis or carcinoid heart disease (CHD), also, recently named carcinoid valvular heart disease [3,4]. Primary cardiac NENs are mostly uncommon [5]. While myocardial and pericardial NENs' spreading is unusual (representing less than 1-3% of NENs-related metastases), CHD represents the hallmark of a very severe disease, typically embracing a very poor outcome [6,7]. The advances in cardiac surgery and interventional once-cardiology which have been registered within the latest years improved the overall CHD prognostic, as recently seen in other cardiac surgical procedures [8,9].

CHD is related to hormonally active NENs that increase overall morbidity and mortality; nevertheless, valve intervention might associate with numerous benefits, but carriers of such interventions display additional risks, including the need for post-operative pacing or connected infectious risks [10,11]. The statistical confirmation that the surgical approach to CHD improves survival is currently based on observational data rather than controlled studies [12].

The pathogenesis of CHD is still poorly understood. However, the presence of CHD is closely correlated with abnormal levels of biomarkers (blood and urinary neuroendocrine markers, also, named vasoactive substances which are more than 40 types, despite not testing all of them in daily practice), especially serotonin, and its urinary metabolite 5-HIIA (5-hydroxy-indole acetic acid), but, also, chromogranin A, neuron-specific enolase, etc. which serve as diagnostic tools and prognostic markers as well as part of the surveillance protocols [13-15]. Novel biomarkers like those based on mRNA

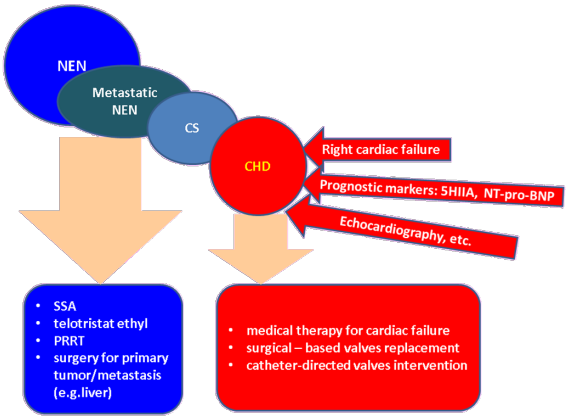
transcript are currently under development for daily practice implementation [13]. Cardiac imaging is essential for recognizing CHD, from traditional ultrasound to advanced techniques such as speckle-tracking echocardiography, 68 DOTA peptide PET-CT (Positronic Emission Tomography – Computed Tomography) scans, and cardiac magnetic resonance or CT [12,16-18].

CHD almost exclusively targets the right cardiac side with consecutive heart failure, but in the early stages, the complication might be underdiagnosed [19]. The left side of the heart is usually not affected (unless abnormal intra-cardiac shunts) because the fact that the main contributor of CHD, namely serotonin (5-hydroxytryptamine), but, also, histamine, bradykinins, and tachykinins, are enzymatically inactivated into pulmonary bloodstream [19]. Remarkably, in 2018 three cases of quadruple valve replacement were reported in addition to the prior four concerning CHD, which represents exceptional situations in NEN-CHD pointing out that the left heart side may be affected, as well [20].

Usually, at the moment when CHD is identified, the patients already have clinically manifested NEN in terms of traditional carcinoid syndrome (flush, diarrhea, wheezing, loss of appetite and malnutrition, non-specific abdominal pain or cramps, hypotension, telangiectasia, edema, etc.) that is presented in correlation with liver metastases, grossly affecting 30-40% of all NENs [21]. Most patients with CHD are aged between 50 and 70 years (males being slightly more affected than females), and present chronic fatigue and dyspnea, independent of carcinoid syndrome (but may be initially misdiagnosed as carcinoid syndrome or even carcinoid crisis) [19]. The most frequent type of NEN causing CHD is gut-derivate (noting that the small intestine is the most frequent NEN up to 65-67% followed by lung NEN of 25%) and approximately one out of five or two cases (depending on the studied population) is prove to develop CHD which finally influence the prognostic even more than the primary tumor growth itself (in some cases) [12,22]. One meta-analysis from 2021 (including 9 studies, N=416 adults with NEN, mean age of 63 years, 53% males) showed that 75% of CHD – related NENs originate from the small intestine and colon, and 98% of them have synchronous hepatic metastases. Tricuspid regurgitation was confirmed in 97% of individuals of different severities, respective 72% concerning pulmonary valve, while right heart failure was identified in 48% of all cases. After having a valve replacement (99% of tricuspid, and 59% of pulmonary valve), a 30-day mortality of 9% was identified (with a median post-surgery survival of 3 years) which points out an acceptable safety profile of valves intervention in CHD [23].

Overall, the multidisciplinary management of CHD includes cardiologic therapy for heart failure, the control of serotonin excess by using high doses of somatostatin analogs such as octreotide or lanreotide (and/or telotristat ethyl) that act on tumor growth as well, peptide receptor radionuclide therapy in addition to surgery for primary tumor and metastases, especially at the liver site (if feasible) to reduce the tumor burden, and, finally, surgical – based valves replacement or catheter-directed valves intervention in selected patients, depending on various criteria that take into consideration the underlying NEN, the heart status, and the access to cardiac surgery or interventional cardiology [24-28]. Globally, patients with carcinoid syndrome (thus metastatic NENs) and CHD have a more severe prognostic when compare to those without CHD, knowing that NEN individuals with clinically manifested carcinoid syndrome have a more severe prognostic versus those carcinoid free [28,29]. Valve intervention in CHD improves long-term outcomes despite the current peri-operatory mortality rate being considered at 10-20% [29]. Of note, there is no specific medication for CHD other than the medical approach for the originating tumor and associated hormonal panel (NEN's management), on one hand, and cardiologic therapy for heart failure in addition to interventional procedures targeting the affected valves [28-30] (Figure 1).

Figure 1: Sneak peek – carcinoid valvular heart disease



NEN = neuroendocrine neoplasia; CS = carcinoid syndrome; CHD = cardiac heart disease; 5HIIA = 5-hydroxyindoleacetic acid; NT-pro-BNP = NT-pro-brain natriuretic peptide; SSA = somatostatin analogues; PRRT = peptide receptor radionuclide therapy

MATERIALS AND METHODS

Aim

Our purpose is to introduce a 2022 update on CHD considering a multidisciplinary perspective.

Method

This is a narrative mini-review of literature. We searched English, full-length papers published in 2022 concerning journals indexed in PubMed (by using the terms "carcinoid

heart disease"). Inclusion criteria are represented by original articles particularly/specifically addressing CHD (in vivo) regardless of the level of statistical significance (original studies or case reports/series). Exclusion criteria: papers considering heart metastasis in NENs or primary cardiac NENs.

According to mentioned methodology, we identified 44 papers in 2022, and manually selected those with CHD, as follows: 8 original studies, 1 case series (N=9 patients), 16 case reports (N=1 patient/paper), a total of 1,030 patients on published studies, in addition to 8 reviews, 3 guidelines (one with duplicate). We excluded 3 articles concerning non-CHD, one in vitro study, and 3 papers regarding withdrawal (Figure 2).

CLINICAL STUDIES PUBLISHED IN 2022 CONCERNING CHD (accessed via PubMed)

We identified 8 original studies in 2022 (Table 1). A multicenter, retrospective study on 275 patients analyzed the clinical presentation and the outcome in NENs, confirming that more than one-third of the individuals with carcinoid syndrome are affected by CHD. All the patients had carcinoid syndrome (mean age of 57 years, aged between 21 and 84 years; metastatic disease was found in 94.6% of cases). CHD was identified in 37.3% of them (N=104) by using echocardiography, with the tricuspid valve being the most affected cardiac site, single or in combination with other valves. CHD correlated with a poor prognostic in individuals with carcinoid syndrome (similarly, male sex was found to be a risk factor); median survival in the studied population was of 9 years) [31].

Figure 2: The articles included according to the methodology of research

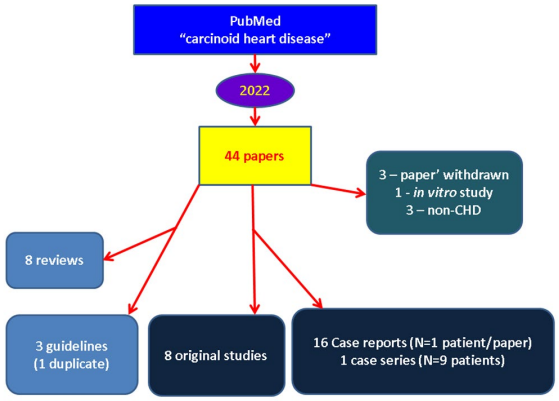


Table 1: Original studies published in 2022 considering carcinoid heart disease

First author/ Reference number	Type of Study	Number of patients	Results
Bergsten J [32]	retrospective (1986 - 2019)	60	30-day mortality (after cardiac surgery)=12% median post-operatory survival = 2.2 years
Levy S [34]	retrospective (1984 - 2021)	84	median survival since CHD diagnostic varying from 1.3 to 3.9 years
Levy S (bis) [35]	validation (case-control) study (1984 - 2021)	114	NT-pro-BNP has the best predictive value for CHD
Kostiainen I [36]	cross-sectional cohort study	65	low rate of CHD (5%) highly sensitive value of echocardiography (not BNP)
Shah HA [33]	retrospective study (2010 - 2019)	17	a 35% decline rate of 5-HIIA in association with liver function improvement
Macfie R [39]	retrospective study (2001 - 2021)	282	overall survival is lower in CHD *versus* non-CHD (N1=40 *versus* N2=242, p<0.001) valve replacement improves survival in CHD + inoperable liver metastasis
Konsek-Komorowska SJ [38]	retrospective study	108	chromogranin A inversely correlates with overall survival (p<0.05) in patients with carcinoid syndrome overall survival is lower in CHD *versus* non-CHD + carcinoid syndrome (67.22 versus 73 months)
Fijalkowski R [31]	retrospective study	275	prevalence of CHD 37.3% among patients with carcinoid syndrome overall survival is lower in CHD *versus* non-CHD

Abbreviations: CHD=cardiac heart disease; BNP=brain natriuretic peptide; N=number of patients

Bergsten J. et al. studied 60 patients (between 1986 and 2019, a total of 3 decades) with a median age of 64 years with CHD and cardiac surgery (N1=42 persons underwent both tricuspid and pulmonary valve replacement; N2=18 individuals had only tricuspid valve replacement with/without pulmonary valvotomy). The procedures (which exclusively used bioprosthetic valves) associated a 30-day mortality of 12%; and a median post-operatory survival of 2.2 years (a maximum of 21 years; statistically significantly higher in N1 versus N2, respective of 3 versus 0.9 years, p=0.02). A most useful tool of prognostic was echocardiography, either as a pre-operatory assessment (but with the limitation of underestimating

pulmonary involvement) or post-operatory surveillance. Additional poor prognostic markers are high pre-surgery levels of 5-HIIA and NT-pro-BNP (NT-pro-brain natriuretic peptide). Overall, the double valve is superior to single tricuspid replacement [32]. Moreover, a retrospective UK study (between 2010 and 2019) on 17 patients with CHD who became candidates for valve replacement surgery had a single valve procedure (3/17) versus double valve (13/17), respective triple valve (1/17). Post-operatory, a 35% decline of 5-HIIA witnesses the improvement of general status in association with hepatic function recovery which suggests an indirect benefit of cardiac surgery [33].

Levy S. et al. introduced a cohort study on 84 patients with CHD (58% males) followed for 4 decades (between 1984 and 2021) at Netherlands Cancer Institute; the median age of NEN confirmation was of 62.3 years with a consecutive CHD diagnostic after a median of 1.1 years and an associated median survival varying from 1.3 to 3.9 years (considering the patients who were most recently admitted when valve replacement surgery was more often applied). Prognostic markers are NT-proBNP (positively correlated with tricuspid regurgitation), respective to the implementation of valve replacement surgical procedures (which increases the survival rate) [34]. The same researchers conducted a validation (case-control) study on CHD – associated biomarkers. 114 individuals (N1 with CHD versus N2 without CHD) showed similar age (median age of N1 – 57.9 years, respective of N2 – 59.7 years, p=0.29). Among studied assessments like circulating serotonin, activin A, sST2 (soluble suppression of tumorigenicity 2), CTGF (connective tissue growth factor), and NT-pro-BNP had the best predictive value for CHD in individuals with high serotonin [35].

As opposed to these results, we mention a cross-sectional cohort study on 65 patients with small intestinal NETs (neuroendocrine tumors) (45% with carcinoid syndrome and 5% with CHD). The results showed that both categories had a statistically significant increase in hepatic tumor load, serum levels of chromogranin A, and urinary 5HIIA when compare to the patients without carcinoid syndrome ($p<0.005$). However, the authors identified a lower rate of CHD (5%) than expected in persons with carcinoid syndrome (30-50% – according to data from the literature). Moreover, they did not confirm the predictive value of proBNP but identified the highly sensitive value of echocardiography in subjects with elevated chromogranin A and 5HIIA [36].

Another classical biomarker in NENs is chromogranin A, very sensitive, but less specific [37]. A retrospective study focusing on blood chromogranin A values (N=108 patients with carcinoid syndrome; N'=84 individuals were followed-up and 27 of them complicated with CHD) showed that its increased levels inversely correlate with overall survival ($p<0.05$) in patients with carcinoid syndrome. Also, the presence of CHD is statistically significantly associated with a reduced overall survival (67.22 versus 73 months in patients with carcinoid syndrome but CHD-free) [38].

Some authors consider the protective effect of somatostatin analogs like octreotide for CHD, but a large study on 282 patients with carcinoid syndrome (between 2001 and 2021) did not sustain this observation. Overall survival was lower in patients with CHD versus non-CHD (N1=40 versus N2=242, $p<0.001$). Considering the patients with inoperable hepatic metastasis, the survival rate was lower in patients without undergoing valve replacement when compared to the individuals with CHD and cardiac surgery or the individuals CHD-free [39]. Similarly, we mention a case series of 9 subjects with NEN who followed for 39 months; initially, the patients were CHD-free and started therapy with somatostatin analogs (median time from NEN diagnostic to therapy initiation of one month; median time from starting the medical treatment to CHD confirmation of 23 months) [40]. As far as we currently know, we cannot predict that using somatostatin analogs is a protection factor against CHD, but, of course, this medication has a proven effect in controlling the hormonal and tumor burden [41].

INTERESTING CASE REPORTS

We identified according to our methodology 16 case reports (a total of 16 patients with CHD). We mention the case of a 70-year-old female with torrential tricuspid regurgitation due to CHD regarding an ovarian teratoma with neuroendocrine differentiation. The subject had a heterotopic tricuspid valve replacement with a stable disease within the following 6 months. Mostly particular, the patient did not experience carcinoid syndrome, and neither imaging assays proved any metastatic NEN (including hepatic) after gynecological surgery [42]. Similarly, another case of a large insular primary ovarian NEN was reported on a 40-year-old female admitted for virilization syndrome in association with unexpected CHD – related heart failure; the panel of increased neuroendocrine markers improved after gynecological intervention, but CHD aggravated even in the absence of liver metastasis requiring valve replacement within 6 years [43]. This scenario is extremely unlikely among the typical evolution of NENs, neither ovarian NEN is recognized as a common source of serotonin over-production. However, ovarian carcinoid tumors are among the rarest forms of CHD in the absence of carcinoid syndrome and/or liver metastases, thus their early removal massively improves the survival rate and does not follow within the general frame concerning the very poor outcome in CHD-NENs [44-46].

adequate diagnostic/recognition when she was identified with CHD and had cardiac surgery. The identification of primary NEN was after the intervention for CHD [47]. This case brings out at least two atypical aspects: CHD in young adults, as prior mentioned, which is rather atypical unless a clear genetic background is present, and CHD diagnostic before confirmation of primary NEN [48]. Generally, one-third of NENs remain with unknown primary sources [49]. Theoretically, younger patients with CHD and NEN might have a better post-cardiac surgery prognostic, but further statistical evidence is needed.

A 44-year-old male with neurofibromatosis type 1 had a 6-year history of gastric NET with hepatic metastasis. He was admitted for sensory neuronopathy and a meningocele. After glucocorticoid treatment was empirically initiated, additional decompressive laminectomy was done, but the patient soon developed CHD with a fatal outcome within 3 months (due to pneumonia) [50]. Of note, currently, we do not know the potential role of glucocorticoids (probably recommended for incidental co-morbidities) in aggravating CHD. Moreover, there are no consistent data to point out that individuals with genetic syndromes underlying NEN have a higher risk of developing CHD [51].

As consideration amid the recent COVID-19 pandemic, we mention one case of a 55-year-old male who delayed the presentation and was admitted for severe CHD which was confirmed synchronously with a high serotonin-producing primary NEN [52]. Another case brings out the particular aspects of cardio-oncology practice following valve replacement in subjects with CHD [53]. This is the case of a 58-year-old female who experienced a carcinoid crisis peri-operatory [54]. Another aspect concerns the post-surgery risks, for instance, a 77-year-old woman was offered a successful ablation therapy for recurrent atrial flutter developed after the surgical procedure of replacing the tricuspid valve [55]. Moreover, another case of an 81-year-old male introduces the idea of consecutive interventions in CHD considering the right side of the heart (severe pulmonary regurgitation was successfully approached by trans-catheter implantation 4 years after initial surgery for tricuspid) [56].

DISCUSSIONS

Pathogenic traits of CHD

Hedinger syndrome, tricuspid insufficiency in addition to pulmonary stenosis due to CHD still represents a challenging condition nowadays [57]. CHD is a progressive condition in subjects with carcinoid syndrome where the right side of the heart is transformed in terms of fibrosis, degeneration, inflammation, desmoplastic reactions causing valvar dam-age (stenosis or regurgitation), and cardiac insufficiency [58,59]. The formation of plaque-like deposits (myo-proliferative plaques) on endocardial areas of the valves and subvalvular system impairs the blood flow dynamics [60-62]. Similarly to CHD, mesenteric fibrosis might develop in individuals with carcinoid syndrome [60]. Common pathogenic factors are described like TGF-β (Transforming growth factor beta) or PDGF (platelet-derived growth factor), etc [60].

The clinical approach of CDD

The main predictors of CHD are an advanced stage of NEN with high levels of circulating serotonin but mostly increased 24-hour urinary 5HIIA in addition to the presence of carcinoid syndrome and other clinical features [63-65]. Other collateral elements may involve particular cardiac anatomy, for instance, patent foramen ovale is reported in half of the individuals with CHS (twice more frequently than in the general population) which causes a right-to-left shunting [66,67]. Intra-cardiac shunt explains the left heart involvement in CHD as one case was published in 2022 with four valves involvement [68,67].

Since initially, CHD is subclinical or completely asymptomatic, a strategy of periodic check-ups is necessary, including performing differential diagnostics with other complications of NENs [60,63,69]. Cardiac imaging represents a strong point in CHD management. Ultrasound is useful for serial evaluations and early assessment; CT exams might show various elements like early contrast opacification of inferior cave vein as an indicator of tricuspid regurgitation; modern imaging procedures like 68Ga-DOTATATE PET are helpful for adequate positive diagnostic, especially for cases with a low index of suspicion, when a differentiation with myocardial metastasis or non-NEN incidental conditions is needed [70-72]. One case from 2022 introduced 203Pb-VMT-α-NET Scintigraphy as a new alternative to PET/CT [73].

Full blown picture of heart valve disease – associated clinical manifestations and related cardiovascular and pulmonary complications of NENs including carcinoid crisis represents a sign of advanced disease and prompt multi-disciplinary intervention is required [74,75]. The overall experience with cardiac surgery for CHD is limited when compared to many of the non-CHD causes, thus there are still some areas of open discussion like predictors of successful intervention, the timing of the procedure, criteria of candidates selection, the type replacement (single or double valve) [76-79].

Key messages on behalf of highly specialized medical and surgical societies

In 2022 three papers of major importance were released concerning CHD. European Neuroendocrine Tumor Society (ENETS) published excellent “guidance” regarding carcinoid

syndrome and CHD. We mention a few major aspects: NT-proBNP remains the most important marker of CHD at the first-ever diagnostic (in patients who experience high serotonin status with or without clinical manifestation like carcinoid syndrome) and during follow-up. A cutoff value of 260 pg/mL indicates further investigations with echocardiography. In terms of ultrasound, the transthoracic approach is indicated, stress echocardiography might not bring additional information; while inadequate ultrasound data (including the evaluation of pulmonary vein damage) or planning for cardiac surgery may require supplementary imaging procedures like cardiac CT or magnetic resonance. Once identified, CHD requires serial NT-proBNP assays and cardiac ultrasound every 6 to 12 months, noting that sudden progress might occur anytime. Surgery (bioprosthetic valves are advised) should be done in severe CHD with more than 1 year of expected post-surgery survival; some specific criteria are recommended considering the adequate timing of intervention which should not be delayed. Double valve (tricuspid and pulmonary) replacement is better than a single one. Minimally invasive procedures are not yet studied enough [80]. Additionally, ENETS introduced a "synoptic" concerning the major role of echocardiography in CHD [81]. A collaboration of ESC (European Society of Cardiology) with other societies provided a guideline on cardio-oncology, also, addressing CHD. We mention some aspects, such as, for instance, echocardiography is recommended in patients with clinical evidence of CHD, carcinoid syndrome, and high BNP followed by a check-up every 3 to 6 months (level IB). BNP is assessed at baseline and every 6 months (level IB). A specific preparation is required considering the surgical/interventional risk of triggering a carcinoid crisis. Valve replacement, as in the ENETS guide-line, is recommended in patients with an expected survival of more than 1 year after intervention if they have symptomatic CHD or asymptomatic CHD (tricuspid or pulmonary) but with progressive dysfunction (level IC, respective IIaC) or severe mitral and/or aortic involvement in symptomatic cases (level IC) [82,83].

CONCLUSIONS

CHD represents a most challenging entity situated at the crossroads of surgery, cardiology, oncology, endocrinology, and gastroenterology. Until a few years ago, CHD was synonymous with a very severe form of NEN/carcinoid syndrome, with an expected poor outcome and limited resources. Recent cardio-oncology progress in addition to multiple shaped interventions for NEN allows a new level of approach in CHD to the benefit of the patients. However, many aspects are still open issues even in 2022.

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Authors' contribution
Conceptualization, CEN, and MC; methodology, CEN, and MC; software, MC; validation, CEN, MC, AER, and AC; formal analysis, AC; investigation, AER, and AC; resources, AER, and AC; data curation, AC; writing—original draft preparation, CEN, MC, and AC; writing—review and editing, CEN, MC, AER, and AC; visualization, CEN, and MC; supervision, CEN; project administration, CEN, and AC.
All authors have read and agreed to the published version of the manuscript.

List of Abbreviations
5-HIIA = 5-hydroxyindoleacetic acid
NEN = neuroendocrine neoplasia
CHD = carcinoid heart disease
NT-pro-BNP = NT-pro-brain natriuretic peptide
PET-CT = Positronic Emission Tomography – Computed Tomography
TGF = Transforming Growth Factor
PDGF = platelet-derived growth factor
NET = neuroendocrine tumor
NEN = neuroendocrine neoplasia
sST2 = soluble suppression of tumorigenicity 2
CTGF = Connective Tissue Growth Factor
ENETS=European Neuroendocrine Tumor Society
ESC=European Society of Cardiology

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