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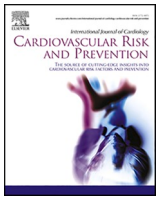

Screening for carcinoid heart disease: Trends and future Perspectives☆,☆☆

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ABSTRACT

Background: Screening for carcinoid heart disease (CHD), has historically lacked consensus expert guidelines. In 2017, the North American Neuroendocrine Tumor Society (NANETS) released expert recommendations for CHD screening among NET patients to improve CHD detection. The objective of this study is to evaluate CHD screening trends and utility of screening guidelines over more than two decades at a single tertiary care center.
Materials and methods: Patients with NETs referred for abdominal surgical evaluation at a single tertiary care center were included, 300 patients from 1999 to 2018 and 34 patients from 2021 to 2022. Lab values for the following NANETS-proposed criteria at any point during their treatments were recorded: NETs with liver metastasis, blood serotonin >5 times upper limit of normal (>1000 ng/mL), NT-ProBNP >260 pg/mL and clinical features suggestive of CHD.
Results: 85 % (285/334) of patients included in this study met one or more expert-recommended CHD screening criteria. However, 40 % (132/285) of patients meeting one or more criteria received CHD screening via echocardiogram at some point following NET diagnosis. While rates of screening for patients increased from the first decade to the second decade (32 % vs 40.6 %), the rates were much higher after guideline publication (70 %, 24/34). Furthermore, patients meeting multiple screening criteria were more likely to have evidence of structural valve disease.
Conclusions: Results of this study suggest that utilization of these four expert-recommended screening criteria have greatly increased rates of CHD screening via echocardiogram and could assist in improving early CHD detection, especially for patients meeting multiple criteria.

1. Background

Carcinoid syndrome, an endocrine disorder resulting from the release of vasoactive substances into the blood, develops in up to half of patients with neuroendocrine tumors (NETs) [1]. Among the substances released by these tumors, serotonin is generally considered the most relevant to carcinoid syndrome pathophysiology. Along with profound effects on the gastrointestinal system and peripheral vasculature, exposure of heart valves to high levels of circulating serotonin results in valvular insufficiency and stenosis via mechanisms not yet completely understood [2]. This process of valvular damage resulting from NET-secreted serotonin is termed carcinoid heart disease (CHD). CHD develops to some degree in approximately 50 % of patients with carcinoid syndrome (and 15–25 % of all patients with NETs) and presents almost exclusively as diseased tricuspid and pulmonic valve [3]. Valve damage resulting from CHD is irreversible and results in a poor prognosis compared to carcinoid syndrome alone [4]. If undetected and untreated, CHD eventually results in cardiovascular system failure.

Along with the optimal management of the NET, timely identification of patients with CHD is necessary to direct the need for referrals to cardiac treatment teams [5]. Historically, there has been limited literature available to guide physicians for which patients with NET

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diagnoses should be screened for CHD. Over the past decades, a lack of standardized guidelines for screening (via echocardiography) and follow-up have resulted in untreated tricuspid and pulmonary valve disease, leading to significant morbidity and mortality among patients. In 2017, expert guidelines were published outlining four objective criteria that, when present, should qualify patients to be screened for CHD: presence of liver metastasis, serotonin level greater than five times the upper limit of normal, NT-ProBNP level above 260 ng/mL, and clinical features suggestive of CHD (including peripheral edema, chest pain, shortness of breath, and ascites) [3]. With the implementation of these criteria, Strosberg and colleagues of the North American Neuroendocrine Tumor Society aimed to improve early detection of CHD, thereby improving the number of patients that could be successfully managed medically and optimizing postoperative outcomes for patients that did need surgical valve replacement.

The purpose of this study is to evaluate CHD screening trends over two decades at a single tertiary care center, compare screening trends before and after the implementation of screening guidelines, and to identify how the implementation of these screening guidelines might improve detection and referral rates for patients with CHD. Additionally, we hope to identify the validity of each criterion for CHD detection.

2. Methods

334 patients with neuroendocrine tumors that were treated at a single tertiary care center were identified for inclusion in this study – 300 patients included between January 1999 and January 2018 prior to expert recommendation, while 34 patients included between July 2021 and July 2022 after expert recommendations. Patient data were collected using in-hospital electronic medical records. Following CHD screening criteria outlined by expert recommendations, the presence (or absence) of those criteria at any point during treatment of their NETs were recorded for each patient [3].

1. Midgut NET with liver metastasis.
2. Serotonin level greater than 5 times the upper level of normal (>1000 ng/mL).
3. NT-ProBNP level >260 ng/ml.
4. Clinical features suggestive of CHD (edema, chest pain, shortness of breath, ascites).

CHD-specific screening was defined as patients who received at least one echocardiogram at any point after NET diagnosis. Results from patient echocardiograms were recorded based on existing healthcare provider interpretation. Echocardiography interpretation reports generated by staff cardiologists at the time of patient treatment were assessed for degree of valve insufficiency noted and the presence of structural changes to tricuspid or pulmonic valves (leaflet thickening with or without restriction).

Following IRB approval, collected patient data were de-identified and stored on secure institutional network servers. Descriptive statistics were generated to find the number of patients that received echocardiograms, interpreted to have right-sided valvular disease, and received referrals to cardiology, cardiothoracic surgery, or both. These data were stratified based on the individual CHD screening criteria, total number (out of four maximum) criteria met, and year of diagnosis and treatment.

3. Results

Demographic criteria for the study population can be found in Table 1. In total 334 patients included in this study, 132 (40 %) received echocardiograms, while 285 patients (85 %) were indicated for CHD screening by meeting one or more expert suggested CHD screening criteria. Among the 132 patients that received screening echocardiograms, 14 (11 %) were found to have structural changes (valve leaflet thickening or restriction) of the tricuspid or pulmonic valves consistent with CHD.

Table 1
Demographics.

DEMOGRAPHICS			
	1999–2008	2009–2018	2021–2022
Total Patients	162	138	34
Sex			
Male	87	62	19
Female	75	76	15
Age			
Mean	71	70	63
Median	72	75	63
Range	25–100	17–97	21–92
Primary Tumor Location			
Stomach	1	1	0
Pancreas	40	30	0
Small Intestine	113	93	29
Large Intestine	3	1	0
Appendix	2	0	3
Mesentery	6	2	2
Unknown	7	1	0

In the pre-guidelines cohort (300 patients), 162 total patients were evaluated and treated over the first decade of data collection (January 1999–December 2008), 52 (32 %) of whom received CHD screening via echocardiograms. 138 patients were evaluated over the second decade of the study (January 2009–January 2018), and 56 received echocardiograms (40.6 %). Among the 11 patients in this cohort with evidence of structural valve changes, 4 were detected in the first decade of data collection, compared to 7 detected over the second decade. Further extrapolation of data comparisons between the first and second decade of the study can be found in Table 2.

Among the post-guidelines patient cohort (July 2021–July 2022), 28 of 34 patients (82 %) met one or more recommended CHD screening criteria. 24 of 28 of patients (86 %) in the post-guidelines group meeting recommendations for CHD screening received an echocardiogram. Among the 24 patients screened, 3 (13 %) were found to have structural valve changes. Further extrapolation of these data are also included in Table 2.

Among individual criteria met, patients with elevated NT-ProBNP had the highest rates of structural valve changes present on echocardiography among screened patients (7/27, 25.9 %). Patients with elevated NT-proBNP also had higher rates of moderate and severe valvular insufficiency than those with other criteria. Further extrapolation of these data are also included in Table 3.

Table 2
Screening and disease data dependent of decade of screening.

	1999–2008	2009–2018	2021–2022
Total	162	138	34
Echo	52 (32.1 %)	56 (40.6 %)	24 (70.6 %)
Met 0 Criteria			
Total	27	15	7
Echo	2 (7.4 %)	3 (20 %)	0 (0 %)
Met 1 Criteria			
Total	47	44	7
Echo	14 (29.8 %)	13 (29.5 %)	7 (100 %)
Met 2 Criteria			
Total	50	42	8
Echo	14 (28 %)	16 (38.1 %)	7 (87.5 %)
Met 3 Criteria			
Total	32	34	8
Echo	17 (53.1 %)	22 (64.7 %)	7 (87.5 %)
Met 4 Criteria			
Total	6	3	4
Echo	5 (83.3 %)	2 (66.7 %)	3 (75 %)
Structural Valve Disease Detected			
	4 (2.5 %)	7 (5.1 %)	3 (8.9 %)

Table 3
Screening and disease data dependent on individual CHD screening criteria met.

Screening Criteria	# of patients	Received echo	Mild (TV/PV/both)	Moderate (TV/PV/both)	Severe (TV/PV/both)	Structural Changes
Liver Mets	264	109 (41.3 %)	21/1/5	13/1/5	3/0/6	13 (11.9 %)
⬆ *Serotonin*	139	67 (48.2 %)	6/2/3	9/0/3	1/0/2	13 (19.4 %)
⬆ *NT-ProBNP*	37	27 (73 %)	8/0/0	5/0/1	1/0/4	7 (25.9 %)
Clinical Symptoms	132	80 (60.6 %)	14/1/3	7/1/2	3/0/5	11 (13.8 %)

Mild = Mild valve regurgitation.
Moderate = Moderate valve regurgitation.
Severe = Severe valve regurgiation

For total number of criteria met by each patient, there was an increase in structural valve changes present with the increase in number of criteria met for each patient. Ten of thirteen patients (76.9 %) meeting all four suggested CHD screening criteria received echocardiograms, all of whom were found to have mild or greater right-sided valvular insufficiency and four of which had structural valve changes present (Table 4).

4. Discussion

In our study we evaluated screening trends for CHD among NET patients at a tertiary care center before and after the establishment of expert-recommended CHD screening criteria. As hypothesized, this review found a significant discrepancy between actual versus criteria-suggested CHD screening rates by echocardiograms – 85 % of patients in this cohort fit criteria to receive a screening echocardiogram, compared with 40 % of patients that received an echocardiogram. While the incidence of CHD in this cohort is beyond the scope of this retrospective study, 14 patients were found to have structural changes of right-sided heart valves consistent with CHD (4.2 % of the cohort, 10.6 % of screened patients). This is somewhat lower than expected when compared to recent literature estimates of 15–25 % CHD incidence among NET patients [1,6] but likely explained by a combination of this study's imperfect definition of patients with CHD. Given the progressive and irreversible nature of CHD, the noninvasive nature of screening via echocardiography, and the danger of performing non-cardiac surgery on patients with severe CHD, we believe that implementation of these guidelines can assist clinicians in detecting CHD among patients presenting with NETs.

Screening trends did indeed improve from the first decade (1999–2008) to the second decade (2009–2018) of data collection over this study, with an 8.5 % increase in rates of echocardiograms from the first to second decade. Three additional patients with structural valve disease were detected over the second decade of data collection despite fewer total number of patients. Along with higher rates of CHD screening, improved physician awareness for CHD and improvements in echocardiogram quality were additional likely contributors to increased rates of structural valve disease detection. Comparison of screening trends several years following the publication of CHD screening guidelines versus pre-guideline data further supports CHD screening guideline use. Compared to a pre-guideline screening rate of 36 % (108/300), over 70 % (24/34) of patients from the post-guideline group received echocardiograms, resulting in a structural valve disease detection rate of over double that of the pre-guideline group (8.9 % vs 3.7 % respectively).

Table 4
Screening and disease data dependent on total number of CHD screening criteria met.

Criteria met	# of patients	Received echo	Mild (TV/PV/both)	Moderate (TV/PV/both)	Severe (TV/PV/both)	Structural Changes
0	49	5 (10.2 %)	3/0/0	2/0/0	0/0/0	0
1	98	34 (34.7 %)	10/1/2	2/0/0	0/0/1	1 (2.9 %)
2	100	37 (37 %)	7/0/3	4/0/1	1/0/1	2 (5.4 %)
3	74	46 (62.2 %)	3/1/1	7/0/3	2/0/3	7 (15.2 %)
4	13	10 (76.9 %)	2/0/1	2/0/2	0/0/3	4 (40 %)

Mild = Mild valve regurgitation.
Moderate = Moderate valve regurgitation.
Severe = Severe valve regurgitation.

While giving every patient that meets a single CHD screening criteria an echocardiogram may not be completely practical, our review identified a few trends that may be useful to clinicians when using these criteria. First, NT-ProBNP appears to be the most specific standalone criteria for identifying patients at higher risk for CHD. This has been hypothesized in previous literature to be due to the direct relation of NT-ProBNP to overworked myocardial tissue compensating for inefficient circulation [2]. Previous work has suggested NT-proBNP as a reasonable test for CHD screening and that circulating levels may be positively correlated with severity of disease [7]. However, it is important to note that very few patients in our cohort (37/334, 11.1 %) had an elevated NT-ProBNP. This is because NT-ProBNP use has been streamlined only recently in patients with NETs, and the majority of this data group is over the past 2 decades. Kim et al. have more recently demonstrated an 86 % sensitivity and 90 % specificity for age-stratified cutoff points of NT-proBNP for the diagnosis of heart failure, which may be a more accurate tool to suggest the need for an echocardiogram [8]. Second, the presence of liver metastasis among this population was the single criteria with the lowest percent prevalence of structural valve changes of the four. Although it did capture all but a single patient with structural valve disease (13/14, 93 %) included in the study, it does represent an important physiological factor for the development of CHD and should certainly be considered by physicians, but it is likely lower predictive value for patients with structural valve disease caused by CHD is important to keep in mind [9]. Third, a strong trend of increased CHD risk was found for patients in our cohort that met a greater number of screening criteria. In general, patients that met multiple criteria developed more severe valve disease and were at higher risk for both tricuspid and pulmonary valve involvement. We suggest that echocardiography and cardiac care referral be more strongly considered for patients meeting multiple criteria, especially for those that meet all 4. Lastly, there were five patients in our cohort that did not meet any of the four CHD screening criteria, all of whom received an echocardiogram that displayed right-sided valve disease. Notably, all five of these patients did not have NT-proBNP levels checked at any time during their care, so it cannot definitively be said that these patients truly did not meet any CHD screening criteria. Two patients were screened due to presence of severe carcinoid syndrome symptoms accompanied by elevated serotonin (but not exceeding 5x the upper limit of normal), and three patients were screened due to cardiac disease history prior to NET diagnosis. These five patients serve as a helpful reminder that any set of screening criteria are not perfect, and healthcare providers should not disregard the importance of clinical judgement when considering CHD screening among carcinoid syndrome patients.

There are several limitations to this study, most of which are inherent

to a retrospective cohort study such as this one. As a retrospective chart review, the dependability of data collected for analysis is reliant on accurate clinical documentation and record recovery, of which no study is immune to possible error despite diligent and careful review. As mentioned previously, this study's definition of patients with CHD was limited to echocardiography results alone, some of which reported suboptimal visualization of the tricuspid or pulmonary valves. Given the large number of echocardiograms required for this review, individual echocardiogram interpretations were taken from results documented in the medical records rather than direct examination of the images by our research team. Given most CHD cases present with right-sided valve disease, we chose to consider CHD only as patients with structural changes of the tricuspid or pulmonary valves. While accounting for a very small percentage, it is possible for CHD to present as isolated left valve disease, which would have been missed in this study.

Future research is needed to continue improvements in CHD screening among NET patients. While we anticipate that the use of these four criteria will increase the screening of CHD, future work should be done looking at cohorts that have been screened strictly according to these criteria. There is also a large gap in knowledge regarding what direction clinicians should take after an initial echocardiogram is returned as normal. If a patient's NET is effectively managed, risk of future valve damage is decreased. But with continued exposure to circulating serotonin, it is unclear when screening should be repeated, and for patients with an initial positive echocardiogram, what interval echocardiograms should be repeated.

5. Conclusion

Our review suggests that utilization of these screening guidelines (including serotonin level, NT-ProBNP, presence of liver metastasis, and clinical symptoms) would help standardize screening and possibly increase the detection of CHD, especially for patients who meet multiple criteria. We support the use of these recommendations to guide screening efforts and referrals to cardiology and cardiothoracic surgery.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

CRediT authorship contribution statement

Bryan Mouser: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **James R. Howe:** Writing – review & editing, Validation, Project administration, Conceptualization. **Olivia Atari:** Writing – review & editing, Software, Investigation, Data curation, Conceptualization. **Joseph S. Dillon:** Writing – review & editing, Validation. **Chandrikha Chandrasekharan:** Writing – review & editing, Validation. **Kalpaj R. Parekh:** Writing – review & editing, Validation, Methodology, Conceptualization. **Mohammad A. Bashir:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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