Carcinoid Heart Disease:

Biochemical and Echocardiographic Assessment

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by

Dr Rebecca Dobson

MbChB (Hons) MRCP UK

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Declaration

I, Rebecca Dobson, confirm that the work presented in this thesis is my own. Where information has been derived from another source, I confirm that I have indicated this in my thesis.

Rebecca Dobson
July 2016

Table of Contents

	Page
Title page	**1**
Declaration	**2**
Table of contents	**3**
Acknowledgements	**4**
List of abbreviations	**5-6**
List of tables	**7-8**
List of figures	**9-10**
Publications pertaining to work contained within this thesis	**11-13**
Abstract	**14**
Chapter 1	
Introduction and aims	**15-49**
Chapter 2	
Methodology	**50-65**
Chapter 3	
Variation in Cardiac Screening And Management Of Carcinoid Heart Disease In The United Kingdom and Republic of Ireland	**65-78**
Chapter 4	
Validation of Biochemical Markers of Presence and Severity of Carcinoid Heart Disease Using Echocardiography	**79-95**
Chapter 5	
Determination of the Optimal Echocardiographic Scoring System to Quantify Carcinoid Heart Disease	**96-115**
Chapter 6	
Serial Surveillance of Carcinoid Heart Disease: Factors Associated with Echocardiographic Progression and Mortality	**116-131**
Chapter 7	
Discussion & conclusion	**132-139**
Appendix I Patient consent form	**140**
Appendix II Patient information sheet	**141-143**
Appendix III Title pages of publications	**144-147**
References	**148-164**

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List of Abbreviations

Akaike's information criterion	AIK
Area under the curve	AUC
Brain natriuretic peptide	BNP
British Society of Echocardiography	BSE
Carcinoid heart disease	CHD
Cardiac magnetic resonance imaging	CMR
Cardiovascular	CV
Chromogranin A	CgA
Chromogranin B	CgB
Chronic kidney disease	CKD
Continuous wave	CW
Computed tomography	CT
Electrocardiogram	ECG
European Neuroendocrine Tumor Society	ENETS
Five-hydroxyindoleacetic acid	5-HIAA
Gastrointestinal	GI
General Electric	GE
Killogram	KG
Left ventricle/ventricular	LV
Left ventricular outflow tract	LVOT
Likelihood ratio	LR
Litre	LT
Liquid chromatography/Mass spectrometry	LC/MS
Microgram	MCG
Millilitre	ML
Multi-disciplinary team	MDT
N-terminal-pro-brain natriuretic peptide	NT-proBNP
Nanogram	NG
Nanomole	NMOL
National Health Service	NHS
Neuroendocrine tumour	NET

Neurokinin A	NkA
North American Neuroendocrine Tumor Society	NANETS
New York Heart Association	NYHA
Odds Ratio	OR
Positron emission tomography	PET
Picogram	PG
Picomole	PMOL
Pulmonary regurgitation	PR
Pulmonary valve	PV
Pulsed wave	PW
Receiver operating characteristic	ROC
Response Evaluation Criteria in Solid Tumours	RECIST
Revolutions per minute	RPM
Right heart	RH
Right ventricle/ventricular	RV
Therapy	Tx
Three dimensional	3D
Trans-oesophageal echocardiogram	TOE
Transthoracic echocardiogram	TTE
Tricuspid regurgitation	TR
Two dimensional	2D
Single photon emission computed tomography	SPECT
Somatostatin analogue	SSA
United Kingdom	UK
United Kingdom and Ireland Neuroendocrine Tumour Society	UKINETS
United States of America	USA

List of Tables

Chapter 1

Table 1.1 Prevalence of carcinoid heart disease

Table 1.2 Comparison of imaging modalities for the assessment of carcinoid heart disease

Table 1.3 Echocardiographic scoring systems for carcinoid heart disease

Table 1.4 International guidelines for screening for carcinoid heart disease

Table 1.5 Surgical outcomes for valve replacement in carcinoid heart disease

Chapter 2

Table 2.1 Carcinoid heart disease scoring system

Table 2.2 Reference limits for RV and RVOT dimensions

Chapter 3

Table 3.1 Method of cardiac screening and cardiology involvement across each NET centre

Chapter 4

Table 4.1 Baseline characteristics of patients

Table 4.2 Diagnostic accuracy of NT-proBNP & plasma 5-HIAA

Chapter 5

Table 5.1 Characteristics of the patient population

Table 5.2a Echocardiographic characteristics of the right heart (morphology)

Table 5.2b Echocardiographic characteristics of the right heart (function)

Table 5.3 Echocardiographic characteristics of the left heart

Table 5.4 Comparison of the echocardiographic scores in the patient population

Table 5.5 Diagnostic accuracy of the scoring systems

Chapter 6

Table 6.1 Baseline characteristics of patients

Table 6.2 Multinomial logistic regression analysis

Table 6.3 Association of variables with progression of carcinoid heart disease

List of Figures

Chapter 1

Fig 1.1 Timeline of NETs

Fig 1.2 Carcinoid heart disease

Fig 1.3 Echocardiographic features of carcinoid heart disease

Fig 1.4 Cardiac MR images of carcinoid heart disease

Fig 1.5 Gallium-68-octreotide PET demonstrating avid focal uptake of tracer in the region of two masses (metastatic carcinoid tumour)

Chapter 2

Fig 2.1 Agreement plot (with 95% limits of agreement -1.19 to 1.30)

Chapter 3

Fig 3.1 Relative size of each centre according to the total number of NET patients managed per centre

Fig 3.2 Clinical criteria for carcinoid heart disease screening

Chapter 4

Fig 4.1 Consort flow diagram

Fig 4.2 Box plots demonstrating spread of results for all five biomarkers

Fig 4.3 Receiver operator characteristic curves for plasma 5HIAA and NTproBNP

Fig 4.4 Scatter diagram demonstrating correlations of NTproBNP and plasma 5HIAA with the echocardiographic score

Chapter 5

Fig 5.1 Distribution of scores for each scoring system for patients with and without carcinoid heart disease

Chapter 6

Fig 6.1 Consort flow diagram

Fig 6.2 Baseline 5HIAA and NTproBNP according to patient group

Fig 6.3 Effect of baseline carcinoid heart disease on survival

Publications Pertaining To Work Contained In This Thesis

Papers

1. Dobson R, Valle JW, Burgess MI, Poston G, Cuthbertson DJ. Variation in Cardiac Screening And Management Of Carcinoid Heart Disease In The United Kingdom and Republic of Ireland. Clin Oncol (R Coll Radiol) **2015;** 27(12):741-6

2. Adaway JE**, Dobson R**, Walsh J, Cuthbertson DJ, Monaghan PJ, Trainer P, Valle JW, Keevil BG. Serum and plasma 5-HIAA as an alternative to 24-hour urine 5-HIAA measurement. Ann Clin Biochem. **2016;** 53: 554-60

3. Dobson R, Burgess MI, Valle JW, Pritchard DM, Vora J, Wong C, Chadwick C, Keevil B, Adaway J, Hofmann U, Poston G, Cuthbertson DJ. Serial Surveillance of Carcinoid Heart Disease: Factors Associated with Echocardiographic Progression and Mortality. Br J Cancer **2014**; 111(9):1703-9

4. Dobson R, Burgess MI, Pritchard DM, Cuthbertson DJ. The Clinical Presentation and Management of Carcinoid Heart Disease. Int J Cardiol **2014**; 173(1): 29-32

5. Dobson R, Cuthbertson DJ, Jones J, Valle JW, Keevil B, Chadwick C, Poston GP, Burgess MI. Determination of the Optimal Echocardiographic Scoring System To Quantify Carcinoid Heart Disease. Neuroendocrinology **2014**; 99(2): 85-93

6. Dobson R, Burgess MI, Banks M, Pritchard D, Vora J, Valle J, Wong C, Chadwick C, George K, Keevil B, Adaway J, Ardill J, Anthony A, Hofmann U, Poston G, Cuthbertson DJ. The Association of a Panel of Biomarkers with the Presence and Severity of Carcinoid Heart Disease: A Cross-Sectional Study. PLoS One **2013** 8(9) e73679.

7. Dobson R, Cuthbertson DJ, Burgess, MI. The Optimal Use of Cardiac Imaging in the Quantification of Carcinoid Heart Disease. Endocr Relat Cancer **2013** 20 R247-R255.

8. Dobson R, Vinjamuri S, Hsuan J, Banks M, Terlizzo M, Wieshmann H, Daousi C, Poston GP, Cuthbertson DJ. Treatment of orbital metastases from a primary mid-gut neuroendocrine tumor with peptide-receptor radiolabelled-therapy (PRRT) using ^{177}Lutetium-DOTATATE. J Clin Oncol **2013**; 31 e272-e275

9. Dobson R, Burgess M, Wieshmann H, Cuthbertson DJ. A Full House of Metastatic Carcinoid Disease. BMJ Case Rep **2012** Jun 27; 006350

Oral Communications

Dobson R, Burgess M, Valle J, Poston G, Cuthbertson D. The Variability In Screening For Carcinoid Heart Disease in the United Kingdom and Republic of Ireland. UKI NETS **2013**

Dobson R, Burgess M, Valle J, Pritchard DM, Vora J, Keevil B, Adaway J, Hofmann U, Poston G & Cuthbertson D. Serial Assessment of Metastatic Neuroendocrine Tumours: Factors Associated With Progression of Carcinoid Heart Disease & Death. UKI NETS **2013**

Abstracts

Dobson R, Burgess M, Chadwick C, Pritchard M, Keevil B, Adaway J, Vora J, Hofmann U, Valle J, Ardill J, Poston G, Cuthbertson D. Comparison of the utility of biochemical markers in predicting the presence and severity of carcinoid heart disease. ENETS **2013**

Dobson R, Burgess M, Keevil B, Adaway J, Valle J, Poston G, Cuthbertson D. Plasma 5-hydroxyindoleacetic acid is a useful adjunct to NT-proBNP as a biomarker for carcinoid heart disease. UKI NETS **2012**

Adaway J, Keevil B, Monaghan P, Darby D, Valle J, Walsh J, **Dobson R**, Cuthbertson D. Plasma 5HIAA is a better marker of neuroendocrine tumours than urine 5HIAA? UKI NETS **2012**

Dobson R, Cuthbertson D, Burgess M. Which echocardiographic scoring system for carcinoid heart disease? Circ **2012**; 126: A11805

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Invited Lectures

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Carcinoid Heart Disease:
Biochemical and Echocardiographic Assessment

By Rebecca Dobson

Abstract

Introduction

Carcinoid heart disease is a para-neoplastic complication of neuroendocrine tumours, occurring in patients with carcinoid syndrome. Due perhaps to its rarity, there is conflicting evidence in the literature with regard to the optimum method of diagnosis and assessment of the condition. The aim of this thesis is to quantify the variation in clinical practice with regard to carcinoid heart disease and to identify the optimum biochemical and echocardiographic methods for the screening, diagnosis and assessment of progression of the condition.

Methods

Patients were prospectively recruited from specialist neuroendocrine clinics in the North of England and underwent evaluation of their symptoms, disease burden, biochemical markers, and transthoracic echocardiography.

Results

Wide variation in the screening and clinical management of carcinoid heart disease was identified. A total of 239 patients were recruited to the study and the prevalence of carcinoid heart disease was 21%. From a panel of biomarkers, N-terminal pro brain natriuretic peptide (NTproBNP) and plasma 5-hydroxyindoleacetic acid (5HIAA) were the most sensitive and specific biomarkers for the presence of carcinoid heart disease. All previously described echocardiographic scoring systems discriminated highly between those with/without carcinoid heart disease, with no single score performing significantly better than another. The complexity of the scoring systems varied considerably, with the simplest scoring system better suited for screening and the more complex systems most useful for pre-surgical assessment. A disease progression rate of 9% was demonstrated, with a further 22% of patients dying during the study. Plasma 5HIAA was the greatest predictor of disease progression and death.

Conclusion

There is considerable heterogeneity across the UK and Ireland in multiple aspects of screening and management of carcinoid heart disease. NTproBNP and plasma 5HIAA should be used to screen for the disease with transthoracic echocardiography reserved for those with elevated biomarkers. A simple echocardiographic scoring system should be used to screen for the disease, with the more complex scoring systems reserved for those patients with established disease. Biomarkers can also be used to predict risk of disease progression and death.

Chapter 1. Introduction

1.1 Introduction and Aims

1.2 Neuroendocrine Tumours

1.21 Medical management of NETs

1.22 Surgical management of NETs

1.3 Carcinoid Heart Disease

1.31 Pathophysiology

1.32 Prevalence

1.33 Clinical Presentation

1.34 Biomarkers

1.35 Imaging modalities for the assessment of carcinoid heart disease

- Echocardiography
- Cardiac computed tomography
- Cardiac magnetic resonance imaging
- Nuclear medical imaging

1.36 Echocardiographic scoring systems for carcinoid heart disease

1.37 Management of carcinoid heart disease

- Screening for carcinoid heart disease
- Medical management of carcinoid heart disease
- Surgical management of carcinoid heart disease

1.38 Progression of carcinoid heart disease

1.39 Prognosis of carcinoid heart disease

1.40 Future perspectives

1.1 Introduction and Aims

Neuroendocrine tumours (NETs) are rare, slow-growing malignancies that are usually located in the gastrointestinal system. They were first described by Langhans in 1867 (1), but it wasn't until 1907 that the term carcinoid was used to distinguish these neoplasms from adenocarcinomas (2). The tumours secrete substances such as serotonin, which lead to the carcinoid syndrome and are also responsible for the significant para-neoplastic complication of carcinoid heart disease.

The first case of carcinoid heart disease was documented by Biork *et al.* in 1952 (3). It is defined as "the presence of characteristic thickening, decreased excursion, and/or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation) in the absence of other causes" (4). Carcinoid heart disease is a relatively rare phenomenon and consequently there is a lack of clarity in the literature regarding how best to screen for and manage the condition.

The aims of this thesis are to:

- Explore the variation in screening and clinical management of patients with carcinoid heart disease.
- Determine the most sensitive and specific biochemical markers for the diagnosis of carcinoid heart disease.
- Elucidate the most appropriate echocardiographic scoring system for carcinoid heart disease.
- Examine the factors associated with both the progression of and death from carcinoid heart disease.

1.2 Neuroendocrine Tumours

Neuroendocrine, or carcinoid tumours are rare, slow-growing tumours, which most commonly arise from the enterochromaffin cells in the gastrointestinal tract. They can however arise anywhere within the body, with the bronchopulmonary system being the second most common site (5).

Carcinoid tumours are characterised by their ability to secrete a variety of vasoactive substances, including 5-hydroxytryptamine (serotonin), tachykinins, histamine and prostaglandins. These substances are in part or wholly responsible for both the carcinoid syndrome (facial flushing, diarrhoea and bronchospasm) (6) and carcinoid heart disease. Serotonin is a neurotransmitter capable of modulating neural activity, but it also plays a role in a variety of biological processes including bowel motility, cardiovascular function and bladder control (7). With regard to the heart, serotonin is involved in several different aspects of cardiac function. It plays a role in electrical conduction (complex regulation of the sinus node and atrioventricular node) and in heart valve closure (serotonin receptor activation on valve leaflets is thought to trigger mitosis, thereby increasing valve leaflet area and interfering with valve closure).

The incidence of NETs has significantly increased in recent years, with an age-adjusted incidence of 1 per 100,000 in 1973, and 5 per 100,000 in 2004 (8). This is likely to be due in part, to improvements in the diagnosis of the disease.

1.21 Medical Management of NETs

Over the past three decades numerous therapeutic advances have been made in the treatment of NETs (figure 1.1).

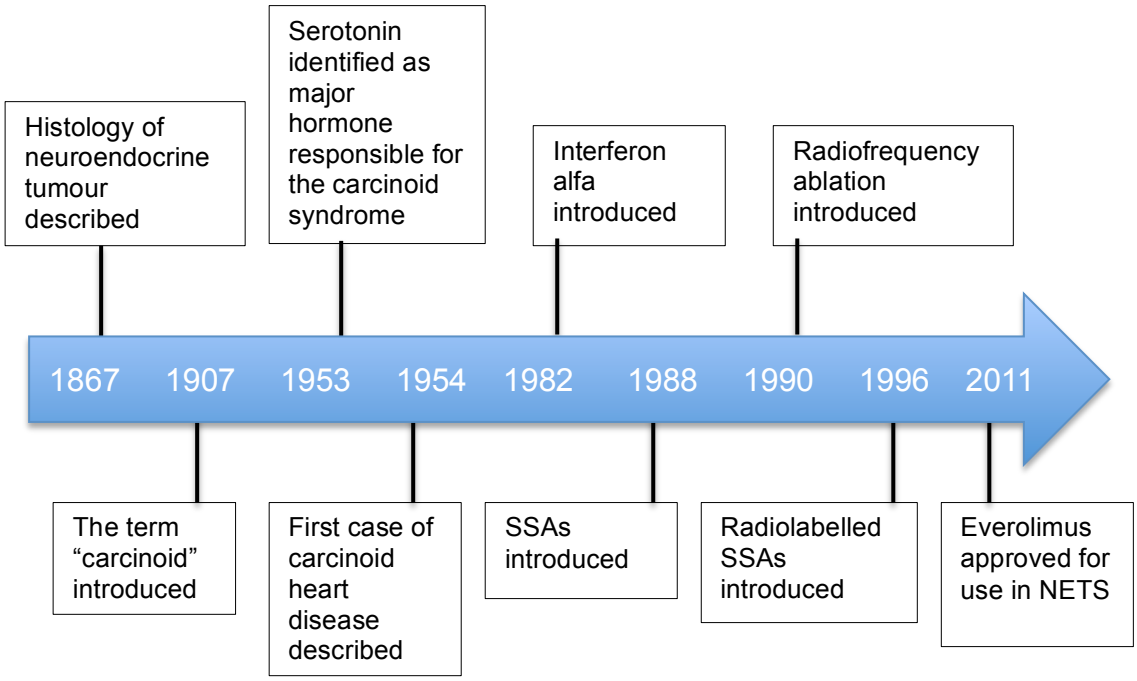


Figure 1.1 Timeline of NETs

In terms of medical therapy, somatostatin analogues (SSAs) are the mainstay of treatment for patients with carcinoid syndrome. Through their action on somatostatin receptors, they inhibit the secretion of a variety of peptides and amines including serotonin (9). This achieves both biochemical and symptomatic improvement in up to 70% of patients (10). Furthermore, following the landmark trials PROMID (11) and CLARINET (12), SSAs are now known to be beneficial in asymptomatic patients as they have an anti-proliferative effect, which can slow or prevent disease progression.

SSAs are commercially available as octreotide and lanreotide in both immediate release and long acting forms, and are manufactured by the pharmaceutical companies, *Ipsen* and *Novartis*. Long-acting formulations

of SSAs are used most commonly, with the short-acting preparations reserved for patients with refractory symptoms, the peri-operative period and for the management of carcinoid crisis (13). SSAs are usually well tolerated, with generalised abdominal pain the most frequently experienced side effect (10). Other adverse effects include injection site irritation, nausea, vomiting, and less frequently, hypothyroidism, cholecystitis and cholelithiasis. Acute pancreatitis, hepatitis and QT interval prolongation have been reported rarely.

Interferon alfa is also used in the treatment of NETs and there is limited evidence that it can induce disease stabilisation (14). The drug is used either as a sole agent or more commonly, in conjunction with SSAs to treat patients with refractory carcinoid syndrome (15). Symptomatic improvement with interferon alfa occurs in around 50% of patients, but its use is limited by side effects such as malaise, weight loss and fatigue (14).

In recent years the use of the cytotoxic agent everolimus has been investigated in patients with advanced NETs (16). The drug was associated with a significant biochemical improvement, with marked reductions in 5-hydroxyindoleacetic acid (5HIAA) noted when compared to placebo. Further research is required to assess symptom control with everolimus and it must be used with caution in those with carcinoid heart disease due to its propensity to cause oedema.

Peptide receptor radionuclide therapy is an established treatment for patients with inoperable or progressive disease and those with symptoms refractory to medical therapy (17). The two most commonly used radioisotopes are ^{177}Lutetium and ^{90}Ytrium, which are attached to a SSA via the chelating agent DOTA. This intervention is associated with tumour regression and symptomatic benefit in the vast majority of patients (18) but haematological and renal toxicity have been reported.

Pasireotide is a novel SSA, with a high binding affinity for somatostatin receptors one, two, three and five compared to octreotide and lanreotide

which have a high specificity for somatostatin receptor two only. The drug has had mixed results in recent phase II and III clinical trials, although patient numbers were small and more data are required before conclusions can be drawn (19,20).

Finally, in recent years a serotonin synthesis inhibitor has been developed, telotristat epitrate. This has recently completed a phase III clinical trial (yet to be published) but in phase II trials, has been associated with both significant biochemical and symptomatic improvement in patients with carcinoid syndrome not controlled with SSAs (21,22).

1.22 Surgical Management of NETs

Surgical resection of local-regional disease is the only potentially curative treatment for patients with midgut NETs (15). Other liver-directed therapies to reduce tumour load include chemo-embolisation and radio-frequency ablation. Trans-catheter embolisation reduces the burden of the NET, thereby also reducing hormone levels in patients with hepatic metastases (23).

1.3 Carcinoid Heart Disease

1.31 Pathophysiology

Carcinoid heart disease, also known as Hedinger Syndrome, was first described in 1954 (24). It is defined as “the presence of characteristic thickening, decreased excursion, and/or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation) in the absence of other causes” (4).

The mechanism of valve injury in carcinoid heart disease is not completely understood. Patients with carcinoid heart disease have higher circulating levels of serotonin compared to those without cardiac involvement, implying that serotonin released from the NET contributes to the development of the condition (25). The pathophysiology has been further inferred from human and animal studies with increased plasma concentrations of serotonin strongly implicated in several studies. Firstly, the specific serotonin re-uptake inhibitors fenfluramine and dexfenfluramine, used as appetite-suppressant drugs, and the ergot alkaloids, ergotamine and methysergide, used in the treatment of migraine, are known to cause valvular fibrosis (26). Secondly, in an *in vivo* rodent model of carcinoid syndrome in which there were significant increases in plasma serotonin, mice exhibited fibrotic cardiac valvular disease, which was abrogated by SSAs (27). Furthermore, high dose, long term oral administration of serotonin leading to valvular heart disease has been described in rabbits (28). Other mechanisms are also thought to contribute to the pathophysiology of the disease, with activin A (29) and connective tissue growth factor (30,31) both associated with the development of carcinoid heart disease.

Microscopically, the cardiac manifestations are characterised by plaques of fibrous tissue, which contain myofibroblasts within an extracellular matrix that consists mainly of collagen and a myxoid matrix, with an

absence of elastic fibres (32,33). Carcinoid plaques can be deposited anywhere in the heart, but have a predilection for the right side (85% of cases), particularly the tricuspid valve (figure 1.2). The septal and anterior tricuspid valve leaflets are most frequently affected, with the posterior leaflet often remaining relatively mobile (34). Interestingly, plaques tend to occur on the downstream side of valves, i.e. the ventricular aspect of the tricuspid valve and the pulmonary arterial aspect of the pulmonary valve (35). This plaque formation, and subsequent endocardial thickening results in retraction and fixation of the valve leaflets, which causes valvular regurgitation and/or stenosis and can ultimately lead to right heart dilatation and failure (figure 1.3).

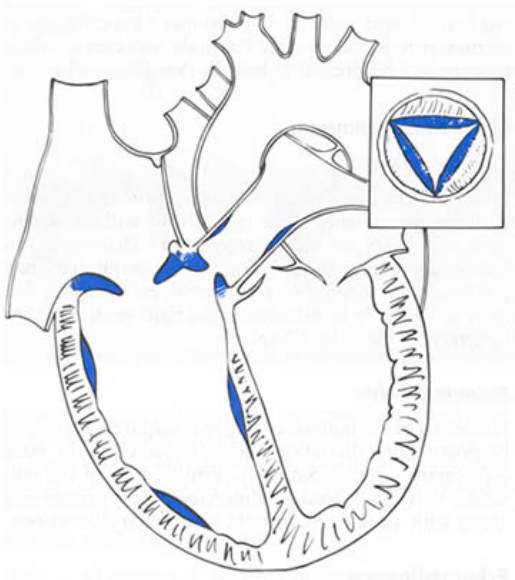


Figure 1.2 Carcinoid heart disease. Insert shows pulmonary stenosis. The leaflets of the tricuspid valve are thickened. Fibrous plaques are deposited on the lining of the right ventricle and pulmonary trunk (36).

Left-sided valve involvement has been reported in up to 15% of cases (37,38). Carcinoid heart disease affecting the mitral and aortic valves only, which then progressed to right-sided disease has also been described (39,40). In the majority of cases, the left heart is relatively protected, as the damaging substances secreted by the NET are inactivated by pulmonary monoamine oxidase activity (41). However patients with bronchial carcinoid, a patent foramen ovale or those with poorly controlled,

severe carcinoid syndrome that overwhelms the pulmonary degradative capacity may develop left sided lesions (42,43). Distinct from carcinoid heart disease, myocardial carcinoid metastases have also been described (44,45).

The majority of patients with cardiac involvement have hepatic metastases, which allow large quantities of secretory substances to reach the heart without inactivation by the liver. However, carcinoid heart disease has also been described in patients with ovarian primary tumours without hepatic metastases (46). The venous drainage of the ovary bypasses the portal circulation and therefore carcinoid heart disease can develop in the absence of hepatic involvement.

1.32 Prevalence

The prevalence of carcinoid heart disease varies in the literature (table 1.1), possibly due to differences in the clinical populations studied and advances in the treatment of NETs in recent years. Nevertheless, this complication affects a significant proportion of patients with metastatic neuroendocrine disease (47). As the management of carcinoid heart disease improves, patients are living longer with the condition and therefore it may have more of an impact on the patient in terms of both quality of life, and overall NET management.

Carcinoid heart disease is most common in patients with NETs of small bowel origin (72%) followed by lung, large bowel, pancreas, appendix and ovarian origin (48). In approximately one fifth of cases, the primary tumour site cannot be determined (42). The mean age at diagnosis of carcinoid heart disease is 59 years, and the condition is slightly more prevalent in males (60% of cases) (48).

Paper	Clinical setting	No of patients	Only patients with carcinoid syndrome included?	Proportion of patients with liver metastases	Proportion of patients taking SSAs	Prevalence of carcinoid heart disease
Pellikka *et al.*, 1993 (42)	Mayo Clinic, USA	125	Yes	Uncertain	57%	56%
Denney *et al.,* 1998 (49)	Vanderbilt University Medical Center, USA	23	Yes	70%	100%	35%
Westberg *et al.*, 2001 (50)	Sahlgrenska University Hospital, Sweden	52	Yes	Uncertain	Uncertain	77%
Zuetenhorst *et al.*, 2003 (51)	Netherlands Cancer Institute, Netherlands	37	No	92%	Uncertain	24%
Zeutenhorst *et al.*, 2004 (52)	Netherlands Cancer Institute, Netherlands	32	No	91%	Uncertain	28%
Bhattacharyya *et al.*, 2008 (53)	Royal Free Hospital, UK	200	Yes	95%	76%	19.5%
Bhattacharyya *et al.*, 2008 (54)	Royal Free Hospital, UK	150	Yes	97%	72%	20%
Korse *et al.*, 2009 (55)	Netherlands Cancer Institute, Netherlands	102	No	83%	Uncertain	67%
Mansencal *et al.,* 2010 (56)	Hôpital Ambroise Paré, France	80	Yes	100%	80%	33%
Bergestuen *et al.*, 2010 (29)	Oslo University Hospital, Norway	71	No	87%	45%	21%

SSAs somatostatin analogues

Table 1.1 Prevalence of carcinoid heart disease

1.33 Clinical Presentation

Patients with significant carcinoid heart disease will, on occasion, present with symptoms of right heart failure (dyspnoea, fatigue and ankle swelling) (57). However, it is important to note that a substantial proportion of patients with considerable cardiac involvement will have no cardiovascular signs or symptoms (34). In those with clinical signs, a raised jugular venous pressure with a prominent 'V' wave, ascites or pulsatile hepatomegaly may be present (58). The murmur of tricuspid regurgitation is pan-systolic and usually appreciated best at the left sternal edge. It classically increases in intensity during inspiration. Pulmonary regurgitation produces an early diastolic murmur and pulmonary stenosis a systolic murmur, heard best in the left second and third intercostal spaces. Clinical assessment including New York Heart Association (NYHA) classification and physical examination to identify cardiac murmurs or peripheral oedema is rarely sufficient, even with disease severe enough to warrant valve replacement (54).

Electrocardiographic (ECG) changes are non-specific but may include sinus tachycardia, right bundle branch block and P pulmonale in the inferior leads (59). A variety of arrhythmias have been associated with carcinoid heart disease including paroxysmal atrial tachycardia (59) and complete heart block (60). Other clinical presentations including constrictive pericarditis (61), restrictive cardiomyopathy (62) and ST segment elevation myocardial infarction secondary to coronary spasm (63) have all been described.

1.34 Biomarkers

Biochemical markers are useful surrogates for assessing the presence and progression of neuroendocrine disease. They have a role in the assessment of the response to treatment and may also serve as prognostic indicators (64). The measurement of biomarkers is non-

invasive, risk free and in most cases, relatively cheap when compared with imaging investigations.

Historically, well-established NET-specific biomarkers have been used in the assessment of carcinoid heart disease. However, in the late nineties N-terminal pro-brain natriuretic peptide (NTproBNP) was identified as a marker of left ventricular systolic dysfunction (65,66) and its value in the diagnosis and assessment of carcinoid heart disease was then recognised in 2008 (53).

5-Hydroxyindoleacetic Acid

As the development and progression of carcinoid heart disease is thought to be related to serotonin, it might be expected that plasma serotonin, or one of its metabolites, is a useful biochemical correlate of disease severity. Urinary levels of 5-Hydroxyindoleacetic acid (5HIAA), the main metabolite of serotonin, have been linked with the presence and progression of carcinoid heart disease (49,51) but its measurement is not without problems. Patients do not like to collect urine for 24 hours, and the result is affected by diet (foods containing tryptophans such as sesame seeds, milk and oats). More recently, a single measurement of plasma 5HIAA has been demonstrated to be proportional to urinary 5HIAA and has identical clinical correlation with other biomarkers used in the diagnosis and monitoring of NETs (67).

Chromogranin A

Chromogranin A (CgA) is present in the chromograffin granules of neuroendocrine cells and is used routinely as a biomarker in patients with NETs (68). The concentration of CgA has been associated with the prevalence of, and survival from, carcinoid heart disease (55). Korse *et al.* demonstrated a cut off 784 mcg/l with 73% sensitivity and 75% specificity for carcinoid heart disease (55). Its use in the monitoring of treatment of NETs is recommended in international consensus guidelines (69,70). However, CgA is commonly associated with false-positive results due to

high concentrations found with proton pump inhibitor therapy and in patients with renal impairment (71).

Chromogranin B

Chromogranin B (CgB), a calcium binding protein, is a regulator of cardiomyocyte signalling pathways that mediate hypertrophy and heart failure and is thought to be secreted from both the ventricles and the adrenal glands (68). It is also present in the secretory granules of neuroendocrine cells and therefore is a useful tumour marker in the assessment of neuroendocrine disease (72). CgB has the advantage over CgA of not being affected by proton pump inhibitor therapy or renal impairment (72).

Neurokinin A

Neurokinin A (NkA), a tachykinin which has effects on gastrointestinal motility, flushing and vasodilation is stored and secreted by midgut carcinoid tumours. It is used as a prognostic marker as it is a strong and independent predictor of premature death in these patients (73).

N-terminal Pro-Brain Natriuretic Peptide

NTproBNP is the most useful biomarker to date used in the diagnosis and assessment of carcinoid heart disease. NTproBNP is a neurohormone released mainly from the ventricles, but also from the atria in response to an increase in wall stress, as a result of volume and pressure overload (74). BNP is synthesised as pro-BNP, released into the circulation and cleaved into the physiologically active BNP and the inactive, stable degradation product NTproBNP.

NTproBNP has both diagnostic and prognostic significance for cardiac involvement (52,55). Bhattacharyya *et al.* and subsequently Korse *et al.* found similar cut-off levels of 260pg/ml and 280pg/ml for the detection of carcinoid heart disease in patients with carcinoid syndrome.

Bhattacharyya *et al.* demonstrated that NTproBNP is a sensitive and specific marker for the presence of carcinoid heart disease, and the authors advocated its use in the screening of the disease (53). This was corroborated in 2009 by Korse *et al.* who concluded that NTproBNP is helpful in the diagnosis of carcinoid heart disease, and also has a role in the timing of cardiac valve surgery (55).

Novel and Emerging Biomarkers

As fibrosis is an important feature of carcinoid heart disease, there has been interest in the role of growth factors with fibrogenic properties, such as Activin A and transforming growth factor-β. Bergestuen *et al.* found that Activin A was an independent predictor of carcinoid heart disease, and had an 87% sensitivity and 57% specificity for cardiac involvement (29).

Connective tissue growth factor is a matricellular protein that is up-regulated in many fibrotic diseases. Patients with mild or greater degrees of tricuspid regurgitation have raised levels of connective tissue growth factor and the biomarker is an independent predictor of right ventricular (RV) function in patients with NETs (30).

Galectin 3 is a novel marker of myocardial fibrosis, produced by macrophages and cardiac fibroblasts (75). It is associated with left ventricular remodelling and is a predictor of mortality in patients with severe chronic heart failure. Its value in the diagnosis or monitoring of carcinoid heart disease has not yet been evaluated.

1.35 Imaging Modalities for the Assessment of Carcinoid Heart Disease

Cardiac imaging plays a key role in the diagnosis and guidance of management of cardiac conditions. There are 4 main non-invasive imaging modalities in clinical use today; echocardiography, multi-sliced cardiac computed tomography (CT), cardiac magnetic resonance imaging

(CMR) and nuclear medicine imaging. Carcinoid heart disease is amenable to multi-modality assessment. Table 1.2 offers a comparison of the imaging modalities.

Echocardiography

Echocardiography is a relatively cheap, widely available and safe imaging modality using ultrasound, which is often the first line imaging technique for suspected structural heart disease. It was developed in 1954 by Edler and Hertz (76) and is now a fundamental part of daily clinical practice. An echo transducer performs the dual role of emitting and transducing ultrasound waves (>1.5MHz) using piezoelectric crystals, which convert electrical energy to ultrasound waves, and ultrasound back to electrical energy.

There are several different modes of echocardiography; two-dimensional (2D) imaging, M-mode imaging and Doppler ultrasound. Doppler information can be used in different ways; pulsed and continuous wave Doppler, colour flow mapping and tissue Doppler imaging. Each mode has a specific role in the assessment of cardiac structure and function.

2D imaging provides cross-sectional, real-time images of the heart. By manipulating the transducer, different “cuts” can be obtained so that the majority of areas of the heart can be assessed. M-mode imaging, the first available echo mode, uses a single ultrasound beam to calculate the distance of structures from the transducer. This mode has a high frame rate, and therefore excellent temporal resolution.

Doppler ultrasound is used to detect the velocity of blood flow through the heart (77). Pulsed wave (PW) Doppler uses pulses of ultrasound to analyse blood flow at a specific point. It has a high spatial resolution, but poor velocity resolution (78). Continuous wave (CW) Doppler, as its names suggests, uses continuous ultrasound waves to measure blood flow. It overcomes the velocity limitations of PW Doppler by sacrificing spatial resolution. It can therefore be used to measure high velocities, but

is unable to localise the flow along the ultrasound beam. Colour flow mapping is a pictorial representation of PW Doppler data acquired from a larger area. It is used to analyse direction and velocity of blood flow, with blue representing flow away from the probe, and red illustrating blood flow towards the probe. All of these techniques play a role in the assessment of carcinoid heart disease.

Echocardiography in the Assessment of Carcinoid Heart Disease

The consequences of carcinoid heart disease on valve morphology and function can be demonstrated relatively easily with 2D transthoracic echocardiography (figure 1.3). 2D imaging of each valve, in multiple views, is used to assess valve leaflet thickening, mobility and morphology. However 2D echocardiography has limited sensitivity and may miss single leaflet involvement or diffuse thickening of all valve leaflets without significant reduction in leaflet mobility or development of regurgitation, due to lower spatial resolution than other cardiac imaging modalities (79).

Valvular stenosis can be identified using PW and CW Doppler, with the cursor directed through each valve in multiple echocardiographic views. Significant regurgitation is easily identified using a combination of colour flow, CW and PW Doppler, and its consequences on right atrial and ventricular size and function can be assessed using 2D imaging, M Mode, colour and tissue Doppler Imaging.

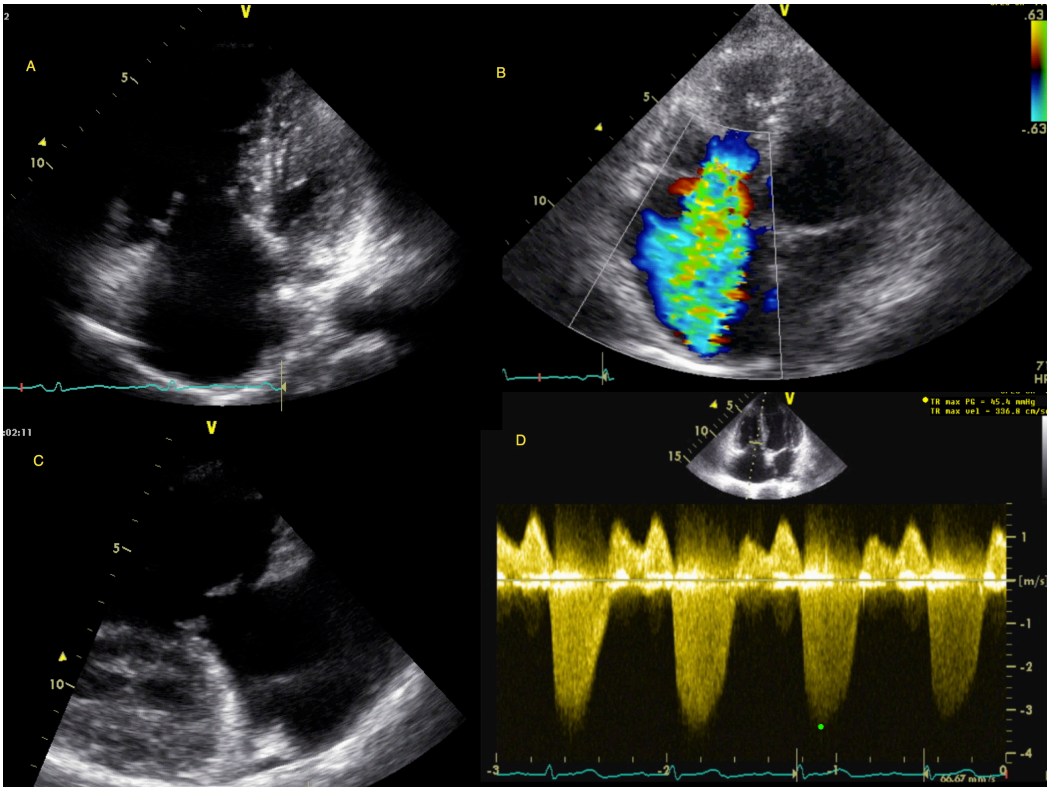
Imaging from the trans-oesophageal window allows accurate measurement of the thickness of the atrio-ventricular valve leaflets and the superficial wall layers of both atria (80) and is recommended in the latest European Neuroendocrine Tumor Society (ENETs) guidelines for patients in whom comprehensive evaluation of the right-sided heart valves is not possible via the trans-thoracic approach (13).

It has been suggested that contrast echocardiography should be performed in all patients with a diagnosis of carcinoid heart disease (81).

This is the modality of choice to determine the presence of intra-cardiac shunts and the patency of foramen ovale. Simultaneous venous injection of an agitated mixture of saline, blood and air and ultrasound recording of 2D images enables identification of any communication between the right and left heart.

Three-dimensional (3D) echocardiography, whilst being more time-consuming, can offer supplementary information. It enables an in-depth characterisation of valve pathology with an en-face view of the tricuspid valve, and has the ability to visualise all three leaflets simultaneously (82-84). 3D echocardiographic imaging is also able to demonstrate echogenic areas consistent with carcinoid deposits (85). Furthermore 3D imaging enables a comprehensive assessment of RV geometry, volumes and ejection fraction, which is not always possible with a 2D probe (82). The use of single-beat 3D echocardiography in RV volume quantification and RV functional assessment has recently been evaluated in a small population of patients with carcinoid heart disease (86). The authors demonstrated that, whilst not as sensitive as CMR, single-beat full-volume 3D echocardiography is more accurate than conventional 2D echocardiography in the assessment of patients with right heart pressure and volume overload.

Newer echocardiographic techniques, such as measurement of myocardial strain, are not used routinely in the assessment of carcinoid heart disease. However there is limited evidence that RV systolic function, as assessed by myocardial strain, is reduced in patients with neuroendocrine disease independently of valvular involvement (87). Mansencal *et al.* evaluated the prognostic utility of E/E' (ratio of early transmitral flow velocity to early diastolic mitral annulus velocity) in carcinoid heart disease (88). The authors demonstrated that E/E' ratio > eight was an independent marker of death, however this was a small study, with a limited explanation of the causative reasons for the association.



A – Apical four chamber view demonstrating severely thickened, retracted tricuspid valve with a severely dilated right atrium.

B – Colour flow across tricuspid valve illustrating severe tricuspid regurgitation with broad vena contracta.

C – Parasternal long axis view of thickened tricuspid valve.

D – Continuous wave Doppler across tricuspid valve; dense signal demonstrating severe tricuspid regurgitation.

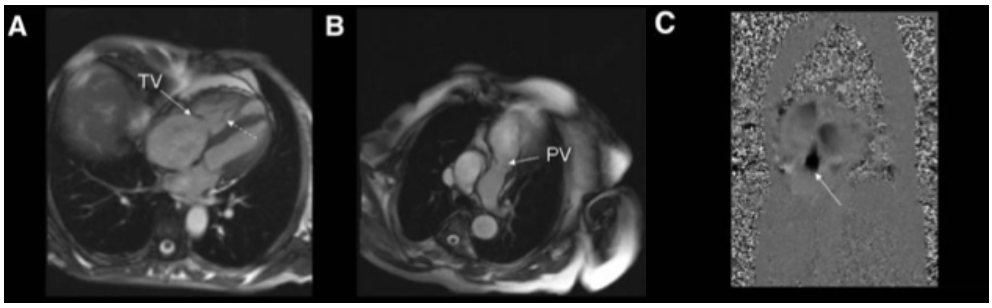
Figure 1.3 Echocardiographic features of carcinoid heart disease

Cardiac Computed Tomography

Imaging the heart using cardiac CT has been anticipated for many years, but has been limited by the poor spatial and temporal resolution of previous generations of CT scanners (89). However the introduction of multi-row detector CT has dramatically improved spatial resolution, enabling an in-depth assessment of the right heart chambers and valves, which are often difficult to assess using transthoracic echocardiography (90). One group has reported using routine staging CT (not cardiac CT) to calculate a right ventricle to left ventricle ratio, which can serve as an indirect marker of carcinoid heart disease in patients with functional NETs (91). However the clinical utility of this is uncertain and CT is not superior to transthoracic echocardiography with regard to quantification of haemodynamics (valvular regurgitation or pulmonary artery pressure) (92). The limited temporal resolution of cardiac CT can also limit appreciation of valve motion. Furthermore, exposure to radiation potentially restricts the use of cardiac CT, particularly for serial scans.

Cardiac Magnetic Resonance Imaging

CMR uses high intensity magnetic fields to generate 3D images of the heart. This technique is often thought of as the gold standard modality for in-depth imaging of the heart. CMR imaging has an important role in the assessment of carcinoid heart disease. Its main advantage is the accurate and reproducible assessment of the right heart, which can be difficult using echocardiography alone (93). The problem of sub-optimal visualisation of the right-sided heart valves, particularly the pulmonary valve, can be overcome with MR imaging which provides precise functional and anatomical information, allowing accurate quantification of regurgitant volumes (94,95) (figure 1.4).



A) Dilated right atrium and ventricle in four chamber view (systole). Thickened, fixed and retracted tricuspid valve (arrows).

B) Thickened, retracted pulmonary valve leaflets (arrow).

C) Phase contrast flow map demonstrating severe tricuspid regurgitation (arrow).

Figure 1.4 Cine CMR (83)

In addition, CMR enables identification of extension into extra-cardiac structures, an aspect less well appreciated by echocardiography (83). The administration of a Gadolinium-based contrast agent can identify both myocardial metastases (59) and endocardial plaque deposition (96). CMR imaging is recommended in ENETS guidelines for evaluation of the pulmonary valve, for identification of cardiac metastases and for assessment of RV function (13).

Nuclear Medical Imaging

Single photon emission computed tomography (SPECT) uses a gamma-emitting radioisotope to assess myocardial blood flow at rest and during stress (diseased myocardium has reduced blood flow compared to normal myocardium). Positron emission tomography (PET) using a radionuclide tracer can be used to identify metastatic spread of carcinoid tumours (figure 1.5) and has a role in the identification of cardiac metastases, which occur in approximately four percent of patients with carcinoid syndrome (83). A variety of tracers have been utilised including ^{18}F-dihydroxy-phenyl-alanine (97) and octreotide labelled with Gallium^{68} and Indium^{111} (45,83).

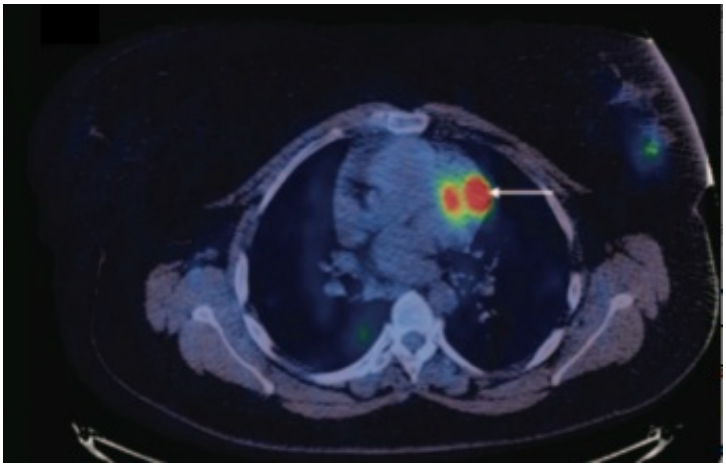


Figure 1.5 Gallium^{68} octreotide PET demonstrating avid focal uptake of tracer in the region of the metastatic carcinoid tumour within the heart (83).

Variable	2D Transthoracic Echo	3D Transthoracic Echo	Trans-oesophageal Echo	Dual source multi-slice CT	Cardiac MRI
Spatial resolution	++ (79)	+ (98)	+++	++++ (99)	+++ (100)
Temporal resolution	++++	+	+++	++	+++ (101)
Approximate scan time (minutes)	40 – 45 (102)	45-60; Full 2D exam + focused 3D (103)	45 - 60 (104)	15 (105)	15 (106)
Average cost per study (£)	142(107)	292 (107)	292 (107)	320 (contrast) (108)	673 (109)
Availability	12,000 scans per million population in 2006 (110)	Now widely available	3500 scans per million population in 2006 (110)	45 centres in the UK in 2011 (111)	60 centres in the UK in 2011(112)
Radiation	None	None	None	1.5 – 5 mSv (113)	None
Limitations	None known	Time required for reconstruction of images	Oro-pharangeal injury, oesophageal laceration/perforation, gastric perforation, airway compromise. Contraindicated in oesophageal pathology, recent GI bleed, severe cervical arthritis (114)	Anaphylactoid reaction, urticaria, contrast medium extravasation, contrast nephropathy, skin reaction (115) Relatively contraindicated in CKD and pregnancy	As for CT plus: Nephrogenic systemic fibrosis (115) Contraindicated in patients with intracranial or intraocular metal work
Clinical validation in assessment of the right heart	Least accurate technique (116)	Well-validated (82)	In small studies (80,117)	Mainly validated for assessment of pulmonary hypertension (118)	Gold standard, most accurate technique (119)
Value in serial studies	Well established (4,49,52,56,120)	Not validated	Limited due to invasive nature	Not validated	Limited due to cost
Evidence of correlation with other markers of carcinoid heart disease	NTproBNP(53), Urinary 5HIAA (49), Chromogranin A (55), Histopathological examination of excised valves (83)	Histopathological examination of excised valves (83,121)	Histopathological examination of excised valves (83,121)	No data identified	No data identified

BSE – British Society of Echocardiography, GI – Gastrointestinal, CKD – Chronic kidney disease

Table 1.2 Comparison of imaging modalities for the assessment of carcinoid heart disease

1.36 Echocardiographic Scoring Systems for Carcinoid Heart Disease

Objective, repeated assessment of patients with carcinoid heart disease is imperative to ensure that progression of disease is identified and acted upon at an early stage. Several scoring systems for the echocardiographic assessment of carcinoid heart disease have been developed (table 1.3), but used with limited evaluation of their validity and utility. Consequently there is uncertainty surrounding the clinical relevance of these scoring systems.

Moller *et al.* performed a retrospective review of 103 patients with carcinoid heart disease and semi-quantitatively assessed their echocardiographic findings (122). A score was calculated for each patient, with a potential maximum of 20 points. Tricuspid and pulmonary anatomy and regurgitation were graded on a four-point scale, based on leaflet motion, thickening and retraction (with 0 denoting normal, 1 thickened with reduced mobility, 2 thickened with severe immobility, and 3 thickened and fixed). Valvular regurgitation was assessed semi-quantitatively on a scale of 0 (trivial or no regurgitation) to 3 (severe regurgitation). This was based on visual interpretation, and the width, size and/or ratio of the maximal regurgitant jet. A score of 0 to 3 was also used to assess RV size and function, with 0 representing normality and 3 representing severely enlarged or impaired. Scores were assigned for the presence (1) or absence (0) of diastolic forward flow in the pulmonary artery and systolic flow reversal in hepatic veins.

Bhattacharyya *et al.* (53) developed a scoring system, with a potential 15 points attributed to each valve, in addition to assessment of RV size and function, leading to a maximum of 66 points. Each valve was graded 0-3 for leaflet thickness, mobility and morphology, and valvular stenosis and regurgitation (see chapter two, table 2.2 for more details). RV function and size were also graded 0-3. There was no agreed threshold as to what

defined carcinoid heart disease. Two hundred patients were recruited to this observational cohort study, with 39 patients having evidence of carcinoid heart disease. The carcinoid heart disease scores obtained from this scoring system correlated highly with NTproBNP (r=0.81, 95% CI 0.67-0.89, P< 0.0001).

A third system was devised by Denney *et al.* for use in their prospective study of 23 patients with carcinoid syndrome, culminating in 126 echocardiographic studies (49). The score combined 2D and Doppler criteria to assess tricuspid valve anatomy (leaflet thickness and mobility) and tricuspid regurgitation (TR) (TR area/right atrial area), along with pulmonary regurgitation (PR) (PR neck width/pulmonary valve (PV) annular diameter) and stenosis (peak PV systolic velocity), producing a maximum score of 14.

An alternative scoring system was created by Mansencal *et al.* (123), used initially for their prospective study of 41 patients with carcinoid syndrome and then adapted in 2010 (56) to incorporate left heart assessment. A maximum score of 20 was achievable for right-sided disease, based upon RV size, tricuspid and pulmonary valvular anatomy, regurgitation and stenosis. Right-sided carcinoid heart disease was defined as valvular injury concomitant with regurgitation or stenosis, or RV enlargement with endocardial thickening or evidence of a metastatic carcinoid tumour to the heart. Patients without evidence of valvular immobility were not considered to have carcinoid heart disease. The adapted score awarded a further 10 points for left sided disease, based upon mitral and aortic valve anatomy and regurgitation.

Westberg *et al.* devised a score for use in their study of 52 patients with carcinoid syndrome who all underwent echocardiography (50). The tricuspid and pulmonary valves were scored for anatomy and regurgitation, but only the tricuspid valve was included in the overall score. A score of one or more was regarded as pathological. This score had a significant effect on survival (30% 5-year survival rate for those with a

score > 4 v 75% in patients with a normal score). This scoring system was adapted and used by Zuetenhorst *et al.* in 2003.

	Bhattacharyya (53)	**Denney** (49)	**Mansencal** (123)	**Moller** (122)	**Westberg** (50)
Year	2008	1998	2010	2003	2001
No. of patients	200	23	80	71	52
No. of echo studies	200	126	≥ 160	174	52
Population characteristics	Midgut carcinoid with syndrome	Carcinoid tumour with syndrome	Midgut carcinoid with syndrome	Carcinoid tumour with syndrome	Midgut carcinoid with syndrome
Age	64 +/- 13 †	59 +/- 12 †	62 +/- 12 †	56 (45 – 67) ◊	61 +/- 4 †
% of patients with CHD	19.5%	35%	33% (right) 8% (left)	50%	65%
No. of valves assessed	4	2	4	2	1
Maximum score	66	14	30	20	8
Right heart assessment	Yes	No	Yes	Yes	No
Weighting for right heart pathology	No	No	Yes	No	No
Left heart assessment	Yes	No	Yes	No	No
Clinical correlates	NTproBNP	Urinary 5HIAA	Chromogranin A Urinary 5HIAA	Urinary 5HIAA	Urinary 5HIAA, 5-year survival
Assessment of CHD progression (serial echo)	No	Yes	Yes	Yes	No
Other studies using same score	Bhattacharyya *et al.* (4, 54)	None identified	Mansencal *et al.* (56,92)	Bernheim *et al.* (128)	Zuetenhorst *et al.* (52)

CHD carcinoid heart disease, † Mean and standard deviation, ◊ Median and interquartile range from time of diagnosis of carcinoid syndrome in those with CHD at baseline

Table 1.3 Echocardiographic scoring systems for carcinoid heart disease

1.37 Management of Carcinoid Heart Disease

Carcinoid heart disease is a rare, complex disease, and should be managed in a specialist centre, with multi-disciplinary team (MDT) input from oncologists, cardiologists, endocrinologists, gastroenterologists, palliative care physicians, radiologists, nuclear medicine physicians, pathologists and surgeons (colorectal, hepatobiliary and cardiothoracic) (47,125). The management of NETs is discussed earlier in this chapter, section 1.21 and 1.22.

Screening for Carcinoid Heart Disease

Screening for carcinoid heart disease is a vital aspect of the multi-disciplinary management of patients with NETs. As for all conditions, management should be evidence-based and in line with current best accepted practice. However, there is considerable discordance in the recommendations for screening among international guidelines (table 1.4). There is a lack of clarity regarding who to screen, how frequently to screen and how best to utilise echocardiography.

The United Kingdom and Ireland Neuroendocrine Tumour Society (UKI NETs) guideline recommends a large cohort of patients to be screened, with NTproBNP used as a “gatekeeper” for echocardiography. In contrast, the European Neuroendocrine Tumor Society (ENETS) guideline advocates biochemical criteria rather than clinical or radiological criteria as the trigger to initiate cardiac screening. The North America Neuroendocrine Tumor Society (NANETS) guideline lacks detail on who or how frequently patients should be screened, but does concur with the UK guideline with regard to the use of NTproBNP.

Guideline	Cohort to be screened	Screening frequency/interval	Suggested biomarkers	Use of echocardiography
UKI NETS: Guideline for the management of gastroenteropancreatic (including carcinoid) tumours (NETs); 2011 (13)	Midgut NETS (with & without hepatic metastases) and all with carcinoid syndrome	Not stated	NTproBNP	Patients with NTproBNP >260pg/ml
ENETS: Consensus Guidelines for the Management of Patients with Neuroendocrine Neoplasms from the Jejuno-Ileum and the Appendix Including Goblet Cell Carcinomas; 2012 (126)	Functioning NET (elevated CgA/5HIAA) with carcinoid syndrome	"Regular basis" – suggested interval not stated	CgA 5HIAA NTproBNP	Symptomatic patients with elevated CgA & 5HIAA
NANETS: Consensus Guidelines for the Diagnosis of Neuroendocrine Tumor; 2010 (127)	Not stated	Not stated	NTproBNP	Patients with raised NTproBNP (no cut-off suggested)

UKI NETS - United Kingdom and Ireland Neuroendocrine Tumour Society, ENETS - European Neuroendocrine Tumor Society, NANETS - North America Neuroendocrine Tumor Society

Table 1.4 International guidelines for screening for carcinoid heart disease

Medical Management of Carcinoid Heart Disease

Although there is no current evidence that SSAs reduce the risk of developing carcinoid heart disease, or delay progression of established cardiac involvement, there is a belief that these drugs may be beneficial. Serotonin plays a pivotal role in the pathogenesis of carcinoid heart disease and therefore it is plausible that SSAs, through their reduction of serotonin levels, may be advantageous. However it is unlikely there will ever be a randomised controlled trial investigating the progression of carcinoid heart disease with SSAs as they are so well-established in the treatment of NETs, it would be unethical to withhold them.

At present, there is no evidence to suggest that interventions such as hepatic de-arterialisation or systemic chemotherapy have a beneficial effect on the progression of valvular disease (122). Bacterial endocarditis prophylaxis is not indicated in patients with carcinoid heart disease (128). General measures to treat right heart failure, such as the use of diuretics and fluid and salt restriction may improve symptoms of oedema. However these measures can be deleterious in advanced RV failure due to depletion of intravascular volume further reducing cardiac output, leading to fatigue and breathlessness (124). Digoxin is believed to improve RV contractility but there are limited data on its use in patients with pure right heart failure (129).

Surgical Management of Carcinoid Heart Disease

The first heart valve surgery for carcinoid heart disease was conducted in 1963 (130). Valve surgery is the only definitive treatment option for those with severe carcinoid heart disease; improving both quality of life and overall survival (120,131). Indications for valve surgery include progressive RV failure or dilatation, heart failure symptoms not responding to medical therapy or the need for hepatic resection (132,133). It is generally accepted that patients with significant carcinoid heart disease are precluded from hepatic resection due to the risk of problematic haemorrhage secondary to raised right atrial pressure and a pulsatile liver.

However a recent case report described a successful hepatectomy using venovenous bypass in a patient with severe carcinoid heart disease who then went on to have successful cardiac surgery (134).

Valve repair, although preferable, is not usually possible due to the degree of leaflet restriction causing post-repair stenosis (57). The decision regarding which valve prosthesis to implant is complex and has to be made on an individual case-by-case basis. Mechanical prostheses were previously recommended because of fear of premature degeneration of the bioprosthesis due to active carcinoid disease (25). However bioprosthesis implantation, without valve degeneration or dysfunction, has been described in a patient who was followed up for over three years (135). A recent small case series described premature re-stenosis of a stentless bioprosthesis in the pulmonary position, necessitating trans-catheter valve replacement (136). However bioprosthetic valves have the advantage of not requiring long-term anticoagulation, making subsequent surgical procedures (e.g. hepatic artery embolisation or cytoreductive surgery) less complicated (137).

The first cardiac valve surgery for carcinoid heart disease had an unacceptably high peri-operative mortality rate of 20-50% (43). Peri-operative mortality rates following valve replacement range widely in the literature but have improved in recent years (table 1.5). A review of ten papers on the prognosis of patients with carcinoid heart disease after valvular surgery demonstrated an average 30-day mortality of 17% (range 1-63%) (138). This included a total of 285 patients undergoing valve surgery with data collected between 1985 and 2012. Nine papers were retrospective studies and one was a case series, with varying periods of follow-up. Survival data varied between the studies with only a minority of studies reporting one and two year survival. Most of the deaths were due to right heart failure, with carcinoid crisis, infection, valve thrombosis and advancing metastases accounting for the remainder. The improved survival of patients with carcinoid heart disease in recent years may reflect the increasing surgical experience in this field, and better peri-operative

management of the patient with octreotide.

More recently, a retrospective analysis of short and long term outcomes in 195 patients with carcinoid heart disease undergoing valvular surgery between 1985 and 2012 demonstrated a decrease in operative mortality from more than 20% to less than five percent (125). The authors attributed this improvement to a combination of factors; improved patient selection, involvement of a MDT, advances in the management of the underlying malignancy and also improvements in surgical technique.

Author; year, type of study	Number of patients	30 day peri-operative mortality	Long term survival
Connolly; 1995 Observational cohort study (139)	26	35%	40% 2 year survival
Robiolio; 1995 Retrospective study (140)	8	63%	38% 2 year survival
Castillo; 2008 Retrospective study (141)	11	18%	100% at median 21 months (4-75)
Bhattacharyya; 2011 Observational cohort study (137)	22	18%	56% 1 year survival 44% 2 year survival
Mokhles; 2012 Retrospective study (131)	19	5%	71% 1 year survival 43% 5 year survival
Connolly; 2015 Retrospective study (125)	195	10% overall 6% after 2000	69% 1 year survival 35% 5 year survival 24% 10 year survival
Edwards; 2016 Retrospective study (142)	32	13%	75% 1 year survival 69% 2 year survival

Table 1.5 Surgical outcomes for valve replacement in carcinoid heart disease

Carcinoid crisis is characterised by a potentially life-threatening combination of flushing, hypotension and bronchospasm (143) which can be precipitated by surgery (particularly direct manipulation of the tumour) and the administration of catecholamines and histamine-releasing drugs (57). Due to the risk of this and low output cardiac syndrome secondary to RV failure, all patients undergoing valve surgery require peri-operative

infusion of octreotide (141). Octreotide inhibits the secretion of vasoactive peptides such as bradykinin and serotonin, thereby controlling carcinoid symptoms (144,145).

Balloon valvuloplasty for pulmonary stenosis is an option for patients with a high operative risk, or in those considered unsuitable for valve surgery (146,147). This technique has also been described in patients presenting with failure of a pulmonary biological xenograft, with successful implantation of a balloon-expandable transcatheter heart valve (148). However there is limited evidence for this technique (149) and recurrence of obstruction has been reported (150). Transcatheter caval valve implantation is an alternative option for patients who are considered to be inoperable. This technique has been described in patients with severe valvular disease, with substantial symptomatic improvement obtained from the intervention (151,152). However, there are no long term data on the use of caval valve implantation.

1.38 Progression of Carcinoid Heart Disease

The progression of carcinoid heart disease is not wholly understood, with multiple factors likely to be implicated in its aetiology. Serotonin levels are higher in those with cardiac involvement, but reduction in these levels is not associated with regression of carcinoid heart disease (49,50). Furthermore, more than 50% of patients with increased serotonin do not develop carcinoid heart disease, suggesting that there are other unknown factors involved in the pathogenesis of the disease (153).

To date few authors have reported factors associated with the progression of carcinoid heart disease or defined which measure of progression is most useful. In a study of 71 patients with carcinoid syndrome and 32 patients referred directly for valve replacement, Moller *et al.* demonstrated that progression of cardiac involvement, in 35% of patients, was

associated with higher urinary 5HIAA levels and was more likely in patients who had received chemotherapy (122). The authors noted that the relationship between chemotherapy and progression of carcinoid heart disease may be explained by the fact that those receiving chemotherapy were more likely to have more aggressive underlying disease.

More recently, Bhattacharyya *et al.* demonstrated a 17.5% progression rate in patients with carcinoid syndrome over a median follow-up duration of 29 months (4). Independent predictors of the development or progression of carcinoid heart disease were urinary 5HIAA levels > 300 umol/24 hours and three or more daily episodes of facial flushing. In both of these studies, carcinoid heart disease progression was defined as a 25% or more deterioration in the echocardiographic score of the patient.

A third study, which defined progression of carcinoid heart disease as a score increase of greater than twice the standard deviation of the mean intra-observer variability also demonstrated an association between post-therapy 5HIAA levels and the progression of carcinoid heart disease although the study only included 23 patients (49).

An additional study investigated the rate of progression of carcinoid heart disease but did not investigate potential factors associated with this (56). The prospective study of 80 patients with carcinoid syndrome, followed up for 26 months, demonstrated a progression rate of 20% with a further 20% of patients developing carcinoid heart disease during the study period but the authors did not clearly define what was meant by “progression” of carcinoid heart disease.

1.39 Prognosis of Carcinoid Heart Disease

Carcinoid heart disease has a significant impact on patient morbidity and mortality. It is associated with a relatively poor clinical outcome, and whilst prognosis has improved in recent decades, average survival is still only around four years (120). Carcinoid heart disease with NYHA functional class III or IV symptoms has a particularly bleak prognosis with a median survival of 11 months (139). In a cohort of patients with carcinoid syndrome, Pellikka *et al.* demonstrated a mean survival of 1.6 years in those with cardiac involvement, compared to 4.6 years in those without (42). Westberg *et al.* found that carcinoid heart disease was the main predictor of prognosis in patients with midgut neuroendocrine disease (50). Westberg *et al.* demonstrated a risk ratio of 2.55 for each increasing grade of tricuspid regurgitation (0-4, none, mild, moderate, severe), which translates to a more than tenfold increased risk of death for patients with severe tricuspid regurgitation compared to those with no tricuspid regurgitation. The commonest cause of death in patients with carcinoid heart disease is right-sided heart failure (around 50%) (154) with tumour progression responsible for around 45% of deaths.

Moller *et al.* postulated that the recent improvement in survival from carcinoid heart disease may be related to increasing valve surgery interventions for patients with the disease (120). Furthermore, the increasing use of SSAs to lower plasma serotonin concentrations may also have contributed to the improved survival from the disease however there is a lack of contemporary survival data from patients diagnosed within the last decade to confirm this assumption.

1.40 Future Perspectives

There are still many uncertainties surrounding the pathophysiology and management of carcinoid heart disease. Although high circulating levels of serotonin are necessary for the development of carcinoid heart disease, not all patients with raised serotonin develop the disease and therefore it is probable that there are other contributory factors, including environmental, genetic and inflammatory factors that are yet unknown. It is not known why approximately 20% of patients with carcinoid syndrome develop valvular pathology, or what protects the other 80% of patients.

With regard to the management of carcinoid heart disease, further investigation into the progression of carcinoid heart disease is required, with particular emphasis on the role of SSAs.

The need for cohesive, evidence-based guidelines for carcinoid heart disease has been recognised by a panel of experts in the UK, and a consensus guideline for the management of the condition is in the process of being written. This will enable health care professionals managing patients with NETs to provide the best possible standard of care.

Chapter 2: Methods

2.1 Patient Recruitment

2.11 Patient source

2.12 Inclusion and exclusion criteria

2.13 NET diagnosis

2.14 Clinical history and measurements

2.2 Biochemistry

2.3 Transthoracic Echocardiography

2.31 Data acquisition

2.32 Data analysis

2.4 Statistical Methods

2.41 Basic principles

2.42 ROC analysis

2.43 Likelihood ratios

2.44 Logistic regression

2.45 Intra-observer variability

2.46 Inter-observer variability

2.1 Patient Recruitment

2.11 Patient Source

Patients with non-pancreatic NETs were recruited from hospitals within the catchment area of four tertiary referral NET centres of excellence. The four centres were University Hospital Aintree National Health Service (NHS) Trust, Liverpool; Royal Liverpool & Broadgreen University Hospitals NHS Trust, Liverpool; The Christie Hospital NHS Trust, Manchester; and St James's University Hospital, Leeds. These hospitals have a collective catchment area of over 9 million patients (155-158).

The research contained within this thesis is part of an ongoing clinical research programme, supported by the Liverpool Neuroendocrine Tumour Group. Prior to the author's involvement in the programme, 89 patients were already recruited. Subsequently the author recruited a further 179 patients during the period December 2011 - September 2013.

The author personally attended the tertiary centres, and their feeder hospitals, to prospectively recruit, interview, examine, perform echocardiography, and obtain blood from patients. Patients were either recruited at the time of their appointment in the NET outpatient clinic, or for those patients without an outpatient appointment, were identified by their NET consultant and then invited via letter to participate in the study.

The studies conformed to the *Declaration of Helsinki* and ethical approval was obtained from Liverpool Research Ethics Committee (reference 09/H1005/40). All patients gave written informed consent.

2.12 Inclusion & Exclusion Criteria

The inclusion criteria were diagnosis of a non-pancreatic NET, with liver metastases and/or carcinoid syndrome (episodes of cutaneous flushing,

diarrhoea or wheezing) by a specialist neuroendocrine team and clear visualisation of all four valves at echocardiography to enable comprehensive echocardiographic assessment.

The exclusion criteria were presence of a prosthetic heart valve or inadequate visualisation of valves such that an echocardiographic score could not be determined.

2.13 NET Diagnosis

Diagnosis of a NET was based on histological evidence where available, with characteristic immunostaining for Chromogranin A (CgA) and synaptophysin. In patients with unknown primary tumour sites, metastatic tissue was immunostained for CDX2, cytokeratin 20, thyroid transcription factor-1 and/or cytokeratin 7 to enable differentiation between gastrointestinal or bronchial primary sites. Histological grading was based on the Ki67 proliferative index (antigen Ki-67 is a nuclear protein that is a marker of cellular proliferation). Where histological evidence was not available, the diagnosis was made on the basis of characteristic appearances on cross-sectional (CT and/or MR) and functional (^{111}In-Octreotide scan) imaging. No patients with inherited cancer syndromes were included in the study.

2.14 Clinical History and Measurements

All patient records were reviewed and the following information obtained: histological diagnosis, tumour proliferative index, duration of disease, primary tumour site, presence or absence and size of hepatic metastases, presence of carcinoid syndrome, use of proton pump inhibitor therapy and therapeutic interventions. In addition, NYHA category was ascertained by verbally asking the patient the following questions:

1. Are you able to walk up hills without restriction?

2. *Are you more short of breath than expected walking up hills or stairs?*
3. *Are you short of breath performing basic tasks, for example, getting washed or dressed?*
4. *Are you short of breath watching television or sitting still?*

At the time of echocardiography and blood sampling, the patient's height and weight were ascertained. Body mass was measured, without shoes, to the nearest 0.5kg, using calibrated electrical digital scales (Seca, Germany). Height was measured with a stadiometer to the nearest 0.5 cm (Seca, Birmingham, UK). Body mass index (BMI) was calculated as weight in kilograms divided by height in metres, squared.

2.2 Biochemistry

Venous (non-fasting) blood samples were taken on the day of baseline echocardiography and at the time of subsequent echocardiograms. Plasma and serum were separated by centrifugation (3,500 rpm) and stored at -80^{o}C until further analysis. All biochemical measurements were made without knowledge of the clinical status of the patient. The concentration of the following biomarkers was determined:

Serum Chromogranin A (CgA):
A synthetic porcine pancreastatin, Peninsula, CA, USA, comparable to the Cisbio and Dako assays (159), measured at Hammersmith Hospital, Imperial College, London. The upper limit of normal is 3 ng/ml with an inter-assay variation of 22%. The intra-assay variation is 12.3% at 12.4 pmol/l (160).

Serum Chromogranin B (CgB):
A Gawk immunoassay, Cambridge Research Biochemical, Cambridge, UK, measured at Hammersmith Hospital, Imperial College, London. The upper limit of normal is 12 ng/ml with an inter-assay variation of 11%. The intra-assay variation is 6.8% at 134 pmol/l (160).

Serum N-terminal Pro-Brain Natriuretic Peptide (NTproBNP):
Electrochemiluminescence technology on the fully automatic Elecsys® analyser, Roche Diagnostics, measured at University Hospital Aintree NHS Trust. The upper limit of normal is 146 ng/L with an intra-assay variation below 4% and inter-assay variation below 5% at concentrations above 70 pg/ml (161).

Plasma 5-Hydroxyindoleacetic Acid (5HIAA):
Liquid Chromotography–Mass Spectrometry/Mass Spectrometry (LCMS/MS) method comparable to that used by Tellez (67) with QuanLynx^{TM} software (Waters, Watford, UK), measured at University Hospital of South Manchester NHS Trust. The upper limit of normal is 118

nmol/L with an inter-assay coefficient of variation of 2.6 – 9.8% and an intra-assay variation of 2-4.7%) (162).

Plasma Neurokinin A (NkA):

An in-house radioimmunoassay developed and measured by the Regional Regulatory Peptide Laboratory, Royal Victoria Hospital, Belfast. The upper limit of normal is 20 ng/L with an inter-assay co-efficient of variation of 6.4-8.4% and an intra-assay variation of 1.6-4.6% (71).

2.3 Transthoracic Echocardiography

2.31 Data Acquisition

Transthoracic echocardiography was performed using a General Electric (GE) Vivid 7 or Vivid Q machine (2.5 MHz phased array transducer, Horten, Norway) by one of two experienced operators (CW 89 echocardiographic studies, RD 179 echocardiographic studies). Patients were positioned semi-supine, in the left lateral position. Video loops were acquired triggered to the ECG (3 cardiac cycles) in end-expiration.

The tricuspid valve was visualised from the parasternal long axis, (with a downward tilt for the RV inflow view), the parasternal short axis, the apical four chamber and the subcostal view. The pulmonary valve was visualised from the parasternal long axis, (with an upward tilt for the RV outflow view) and the parasternal short axis. The mitral valve was visualised from the parasternal long and short axes, the apical four chamber, apical two chamber and apical long axis views. The aortic valve was visualised from the parasternal long and short axes, the apical five chamber and apical long axis views.

M-mode, with the cursor aligned with the leaflet tips, was used to assess aortic and mitral valve leaflet motion in the parasternal long axis view. Colour flow mapping Doppler was utilised with the sector positioned over each valve to assess turbulent blood flow and regurgitant jets. PW Doppler was used to assess trans-mitral and left ventricular outflow tract (LVOT) flow. CW Doppler was used to assess blood flow across all four valves. Care was taken to optimise all images in terms of time-gain compensation, depth, focus and sector width, thereby improving frame rate.

2.32 Data Analysis

All echocardiographic studies, (regardless of who obtained the images) were analysed off line using Echopac (V9.01, GE, Horten, Norway) by the author. A diagnosis of carcinoid heart disease was decided by the operator based on consensus guidelines (81). Carcinoid heart disease was defined as thickening and reduced excursion of valvular leaflets, cusps or chordae, with subsequent valvular regurgitation and/or stenosis (53).

In all chapters, other than chapter five, the Bhattacharyya score (table 2.1) (53) was used to quantify carcinoid heart disease and therefore valvular disease was quantified using the same methods that were used in their original paper.

Characteristic	**Degree of severity and score assigned**			
Leaflet thickening	< 3mm 0	≥ 3 - < 4mm 1	≥ 4 - < 5mm 2	≥ 5 mm 3
Leaflet mobility	Normal 0	Mildly reduced excursion 1	Moderately reduced excursion 2	Severely reduced excursion/fixed leaflets 3
Leaflet morphology	Normal 0	Straightened & stiffened valve leaflets 1	Mild leaflet retraction 2	Moderate/severe retraction 3
Valvular stenosis	Normal 0	Mild 1	Moderate 2	Severe 3
Valvular regurgitation	Normal 0	Mild 1	Moderate 2	Severe 3
Right ventricular diameter	Normal 0	Mildly enlarged 1	Moderately enlarged 2	Severely enlarged 3
Right ventricular function	Normal 0	Mildly impaired 1	Moderately impaired 2	Severely impaired 3

Table 2.1 Carcinoid heart disease scoring system (53)

Valve stenosis was quantified according to European and American Society of Cardiology Recommendations (163) and using the same quantification used in Bhattacharyya's original paper (53). Tricuspid stenosis was quantified according to the mean gradient across the valve (mild 1-5mmHg, moderate 6-8mmHg, severe >8mmHg). The mean gradient was calculated by tracing the forward flow Doppler spectrum in either the parasternal long axis RV inflow view, or in the apical four chamber view.

Pulmonary stenosis was quantified according to the peak gradient across the valve (mild <25mmHg, moderate 25-50mmHg and severe >50mmHg). The peak gradient was calculated using CW Doppler, lined up parallel to the flow across the valve using colour flow mapping in the parasternal short axis view or parasternal long axis RV outflow view.

Mitral stenosis was quantified according to the mean gradient across the valve (mild <5mmHg and severe >10mmHg). Valve area was calculated with an area >1.5cm^2 consistent with mild stenosis and <1cm^2 consistent with severe stenosis. Pulmonary artery systolic pressure was calculated, but used only as a supportive sign rather than a surrogate marker.

Aortic stenosis was quantified using CW Doppler according to the mean gradient across the valve (<25mmHg mild, >40mmHg severe), the peak jet velocity across the valve (<3m/sec mild, >4 m/sec severe) and the valve area as assessed by the continuity equation (164) (>1.5cm^2 mild, <1cm^2 severe).

Valve regurgitation was quantified according to the American Society of Echocardiography Guidelines (165). Tricuspid regurgitation was assessed using a composite of Doppler and 2D imaging in the parasternal long axis RV inflow view, the parasternal short axis view and the apical four chamber view. Vena contracta width was measured using colour flow Doppler, with a width >0.7cm considered indicative of severe tricuspid

regurgitation. CW Doppler was used to record the jet velocity across the tricuspid valve. The contour and density of the jet was assessed to aid in the distinction between mild, moderate and severe regurgitation (mild: soft, parabolic shape, moderate: dense jet with variable contour and severe: dense spectral recording, with a triangular, early peaking of the velocity). The regurgitant jet area was assessed using colour flow Doppler. An area $<5cm^2$ was considered mild, moderate 5-$10cm^2$ and severe $>10cm^2$. Where possible, pulsed wave Doppler interrogation of the hepatic veins was used to detect the presence or absence of systolic flow reversal, its presence indicating severe tricuspid regurgitation. The size of the right atrium, RV and inferior vena cava was also taken into account when making the distinction between mild, moderate and severe regurgitation (usually normal in mild regurgitation and usually dilated in severe regurgitation).

Pulmonary regurgitation was assessed in the parasternal RV outflow view and the parasternal short axis view using a combination of Doppler and 2D imaging. Colour flow Doppler was used to identify pulmonary regurgitant jets. The length and area of the jet was determined (whilst accepting that both of these measurements are affected to some extent by the pressure difference between the pulmonary artery and the RV). The vena contracta was determined where possible. CW Doppler through the pulmonary valve was used to assess the density of the pulmonary regurgitant signal. A rapid deceleration rate was considered consistent with severe regurgitation, however this is influenced by several other factors such as RV diastolic properties and filling pressures. The size of the RV was also taken into consideration when grading the severity of the pulmonary regurgitation (normal size virtually excludes significant regurgitation).

Mitral regurgitation was assessed using 2D imaging, and Doppler in the parasternal long axis view and the apical views. The size of the regurgitant jet was estimated using colour flow Doppler with mild classed as $<4cm^2$ or <20% of left atrial area and severe classed as $>10cm^2$ or >40% of left atrial area or any wall-hugging jet which swirls into the left atrium. Colour

flow Doppler was also used to identify the vena contracta, with a width <0.3cm classed as mild and a width >0.7cm classed as severe. Where possible, the effective regurgitant orifice area (EROA) was measured in the apical four chamber view. An EROA <0.2cm^2 was classed as mild and >0.4cm^2 was classed as severe. CW Doppler through the mitral valve was used in order to assess the shape and density of the signal. An early peaking, triangular contour with a dense signal was considered suggestive of severe regurgitation. PW Doppler at the mitral leaflet tips, was used to assess trans-mitral flow. An E velocity higher than during atrial contraction and >1.2m/sec was considered suggestive of severe regurgitation. Pulmonary venous flow was assessed where possible to aid identification of severe mitral regurgitation (systolic flow reversal).

Aortic regurgitation was assessed in the parasternal long axis, apical five chamber and apical long axis view. Using colour flow Doppler the three components of regurgitant flow were all assessed where possible. The regurgitant jet size was assessed via measurement of the jet width in proportion to the LVOT width in the parasternal long axis view (<25% mild, >65% severe). Vena contracta was measured in the parasternal long axis view with a width of <0.3cm classed as mild and a width of >0.6cm classed as severe. In the apical five chamber view the EROA was calculated where possible (mild <0.1cm^2 and severe >0.3cm^2). CW Doppler through the aortic valve enabled EROA calculation, assessment of the shape and density of the Doppler signal and deceleration rate (pressure half time). A pressure half time <200msec was considered severe with >500msec considered mild.

RV size and function were assessed according to the American Society of Echocardiography guidelines (166). RV dimensions were measured at end-diastole from a RV-focused apical four chamber view. Basal and mid-ventricle dimensions were recorded, along with a longitudinal measurement. The RVOT was measured in the parasternal short axis view, above the aortic valve (RVOT1) and just proximal to the pulmonary

valve (RVOT2). Quantification into mild, moderate and severe dilatation of the RV and RVOT is shown in table 2.2.

Measurement	Reference range	Mildly dilated	Moderately dilated	Severely dilated
Basal RV diameter (cm)	2.0-2.8	2.9-3.3	3.4-3.8	>3.8
Mid-RV diameter (cm)	2.7-3.3	3.4-3.7	3.8-4.1	>4.1
Base-apex length (cm)	7.1-7.9	8.0-8.5	8.6-9.1	>9.1
RVOT 1 (cm)	2.5-2.9	3.0-3.2	3.3-3.5	>3.5
RVOT2 (cm)	1.7-2.3	2.4-2.7	2.8-3.1	>3.1

Table 2.2 Reference limits for RV and RVOT dimensions

RV systolic function was assessed using a combination of 2D fractional area change, TAPSE and RV S'. RV fractional area change was calculated in the apical four chamber view (percentage change in RV area between diastole and systole). Normal was considered to be 32-60% with mildly abnormal classed as 25-31%, moderately abnormal 18-24% and severely abnormal <18%. TAPSE was measured by passing the M-mode cursor through the lateral annulus of the tricuspid valve in the apical four chamber view and recording the maximal longitudinal displacement of the annulus. In a normal RV, the tricuspid annulus will descend 1.5-2.0 cm. Measurements <1.5 cm were considered abnormal. Pulsed tissue Doppler was used to measure the longitudinal velocity of excursion in the apical four chamber view. Ensuring optimum image orientation, the pulsed Doppler sample volume was placed in the middle of the basal segment of the RV free wall. RV S' was measured as the highest systolic velocity. S' <10cm/s was considered abnormal. If all three of fractional area change, TAPSE and RV S' were within normal limits, RV systolic function was considered normal. Degrees of abnormality were based on the fractional area change.

2.4 Statistical Methods

2.41 Basic Principles

Statistical analyses were performed using SPSS Version 20, statistical software (SPSS, Chicago, USA) and Stata/IC 12.0 software (StataCorp LP, College Station, TX, USA). A *P*-value<0.05 was considered statistically significant.

Comparisons between continuous variables were made using the Mann-Whitney U test, as the data did not satisfy the assumption of equal variances for the two-sample *t*-test. Categorical variables were compared using the Chi-square test, or Fisher's exact test where cell counts were insufficient.

Since relationships between the concentration of each biomarker and echocardiographic score were clearly non-linear, Spearman's rank correlation coefficient (r) was used to measure statistical dependence between the two variables.

2.42 ROC Analysis

In order to assess the value of each biomarker as a diagnostic test for carcinoid heart disease, non-parametric ROC curves were constructed. The sensitivity (true-positive rate) of each biomarker was plotted against 1-the specificity (false positive rate) so as to determine the performance of the biomarker as its discrimination threshold was varied.

2.43 Likelihood Ratios

In addition to sensitivity and specificity, likelihood ratios (LR) were used to assess the diagnostic accuracy of different scores. These ratios use the sensitivity and specificity of the test to determine whether the test result usefully changes the probability that the disease is present. They provide an indication of how more (LR+) or less (LR-) likely a patient with a given score is to have carcinoid heart disease, and can be used to calculate the 'post-test' probability of having the disease (167).

2.44 Logistic Regression

Multivariable logistic regression was used to assess whether any combination of biomarker assays was able to better discriminate between patients with and without carcinoid heart disease compared with any single assay.

Multinomial logistic regression was used to assess the univariate association between a number of variables and (simultaneously) disease progression and death.

2.45 Intra-observer Variability

To assess intra-observer variability in the calculation of the carcinoid heart disease score, the author re-analysed ten percent of the echocardiograms performed as baseline scans, blinded to the initial score and diagnoses. The echocardiograms that were re-analysed were chosen at random. All re-analyses were performed at least 12 months after the echocardiograms had initially been performed. The intra-observer correlation coefficient for the carcinoid heart disease score was 0.99, indicating very good repeatability between measurements. Figure 2.1 illustrates the agreement between the original score and the recalculated score, with just 1 measurement lying outside the 95% confidence interval.

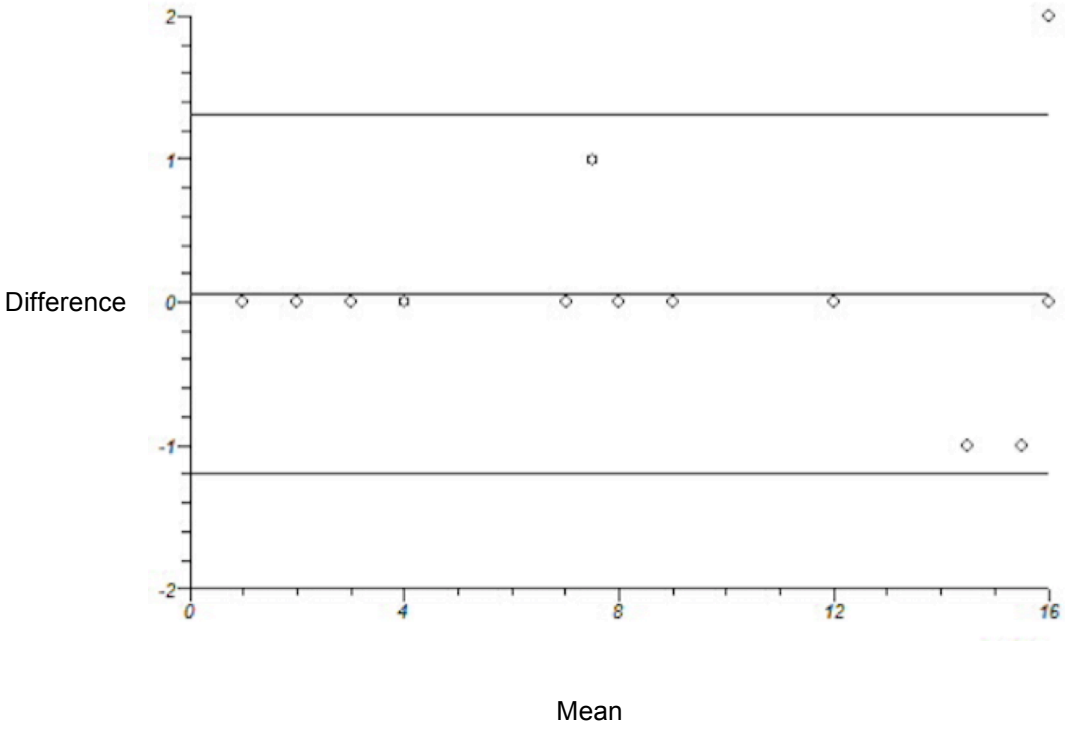


Figure 2.1 Agreement plot (with 95% limits of agreement -1.19 to 1.30)

2.46 Inter-observer Variability

To ensure accurate reporting of the carcinoid heart disease score, and to validate echocardiographic data analysis, a randomly selected sub-group of echocardiographic studies were cross-checked by a different observer (JJ) for each chapter of the thesis. The independent observer was blinded to the author's echocardiographic score. For the most complex scoring system, with a maximum score of 66, scores within two points were considered to be concordant. Where there was score discordance, a third independent observer (MB) analysed the echocardiographic study, blinded to the other scores. An average of the two most concordant scores was then used for these echocardiographic studies.

Chapter 3: Variation in Cardiac Screening And Management Of Carcinoid Heart Disease In The United Kingdom and Republic of Ireland

Abstract

3.1 Introduction

3.2 Methods

3.3 Results

3.31 Centre demographics

3.32 Carcinoid heart disease screening

3.33 Cardiology input and referral

Discussion

Conclusion

Abstract

Introduction Screening for carcinoid heart disease is an important, yet frequently neglected aspect of the management of patients with NETs. The aim of this study was to map current practice for the screening and management of carcinoid heart disease in specialist NET centres throughout the UK and Republic of Ireland.

Methods Thirty-five NET centres were invited to complete an on-line questionnaire outlining the size of NET service, patient selection criteria for carcinoid heart disease screening, and the modality and frequency of screening.

Results Twenty-eight centres responded (80%), representing over 5500 patients. Eleven percent of centres screened all patients with any NET, 14% screened only patients with midgut NETs, 32% screened all patients with liver metastases and/or carcinoid syndrome and 43% screened all patients with evidence of syndrome or raised urinary/serum/plasma 5-hydroxyindoleacetic acid (5HIAA). Mode of screening included clinical examination, echocardiography and biomarker measurement: 89% of centres performed echocardiography, ranging from at initial presentation only (24%), periodically without clearly defined intervals (28%), annually (36%) or less than annually (12%); three centres used a scoring system to report their echocardiograms. 50% of centres utilised biomarkers for screening (chromogranins, plasma/urinary 5HIAA or most commonly NTproBNP) at varying time intervals.

Conclusion There is considerable heterogeneity across the UK and Ireland in multiple aspects of screening and management of carcinoid heart disease.

3.1 Introduction

Disparity in clinical interventions is well described in common diseases, such as atrial fibrillation (168) and deep vein thrombosis (168,169), and also in rare conditions such as Duchenne Muscular Dystrophy (170) and paediatric nephrotic syndrome (171). This variation in clinical practice can impact significantly on patient outcomes and the cost of health care (172). However, cohesive evidence based guidelines can reduce this disparity (173).

Carcinoid heart disease occurs in 20-50% of patients with the carcinoid syndrome (25,153). The condition can be clinically silent, with no symptoms or signs of disease, even in patients with advanced pathology (50,54). There is considerable variation between international guidelines for the screening and management of carcinoid heart disease. Considering the heterogeneity in the literature, the aim of this study was to explore this further by mapping current UK and Republic of Ireland practice for carcinoid heart disease screening and management in specialist NET centres.

3.2 Methods

Thirty-five specialist NET centres in the UK and Republic of Ireland were invited by email to complete an on-line questionnaire (www.surveymonkey.com) between August and September 2013. Centres were identified from the UKI NETs committee members and the NET Patient Foundation Website (http://www.netpatientfoundation.org/net-expertise/net-centers/).

The questionnaire consisted of ten questions relating to respondent demographics, population screened for carcinoid heart disease, mode and frequency of screening, access to cardiology expertise and criteria for consideration of valve surgery. The questions required a mixture of multiple choice and short answer responses (box 1). Questionnaires were completed by consultants working within the NET specialist service. All responses were kept confidential.

1. Please state your name and institution

2. How many years has your NET service been running?

□0-5 □6-10 □11-15 □16-20 □>20

3. Approximately how many NET patients do you manage at your institution?

□<50 □50-100 □101-150 □151-200 □201-300 □>300

4. Who do you screen routinely for carcinoid heart disease?

□All NET patients □Patients with syndrome

□Patients with liver metastases □Do not screen routinely

□Other

5. How do you screen for carcinoid heart disease?

□Clinical examination (if yes, how frequently?)

□Regular echocardiography (if yes, how frequently?)

□Biochemically (which biomarkers and how frequently?)

□Patients are not screened routinely

6. What information do you receive about the echocardiogram?

□Standard echo report □Quantitative assessment using score

7. Do you have a cardiologist on your MDT or a cardiologist with an interest in carcinoid heart disease to refer patients to?

□Cardiologist on MDT □No cardiologist on MDT

□Refer to cardiologist with interest in carcinoid heart disease

□Refer to local general cardiology service

8. Which patients do you refer to a cardiologist?

□All patients with carcinoid heart disease □Other

9. How frequently do your patients with carcinoid heart disease have an echocardiogram?

□< Annually □Annually □Every 6 months □>Every 6 months

10. What are your criteria for consideration of valve surgery?

Box 1 – Questionnaire sent to all NET specialist centres

3.3 Results

3.31 Centre Demographics

Twenty-eight centres (80%) completed the survey, representing a total caseload of over 5500 patients. The experience of each centre varied from less than five years to more than 20 years, reflecting more than 300 centre years of clinical experience with NETs. The NET patient caseload of each centre ranged from less than 50 patients to greater than 300, with 50% of centres managing in excess of 200 patients (figure 3.1).

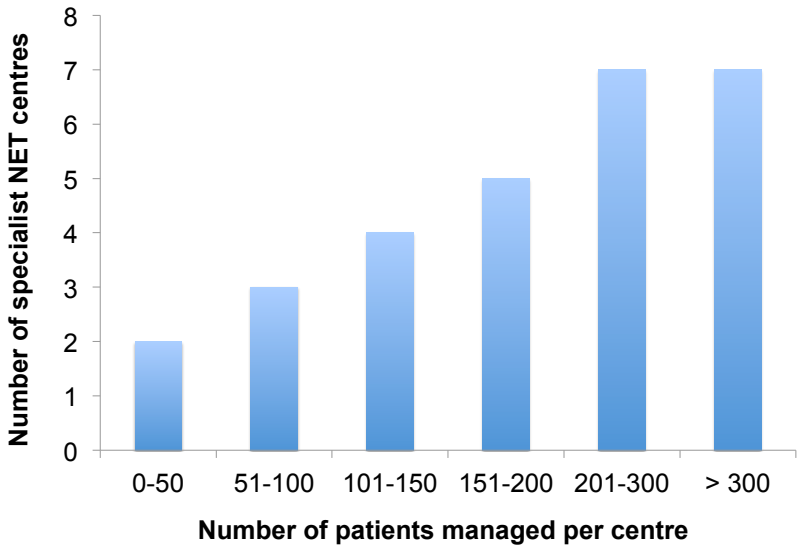


Figure 3.1 Relative size of each centre according to the total number of NET patients managed per centre

3.32 Carcinoid Heart Disease Screening

Screening for carcinoid heart disease occurred in all responding centres although the clinical characteristics of the population screened differed significantly between centres. Twelve centres screened only NET patients with carcinoid syndrome, nine centres screened patients with radiological

evidence of liver metastases or symptoms of carcinoid syndrome, four centres screened all patients with midgut NETs irrespective of the presence/absence of carcinoid syndrome/liver metastases and three centres screened all NET patients (figure 3.2).

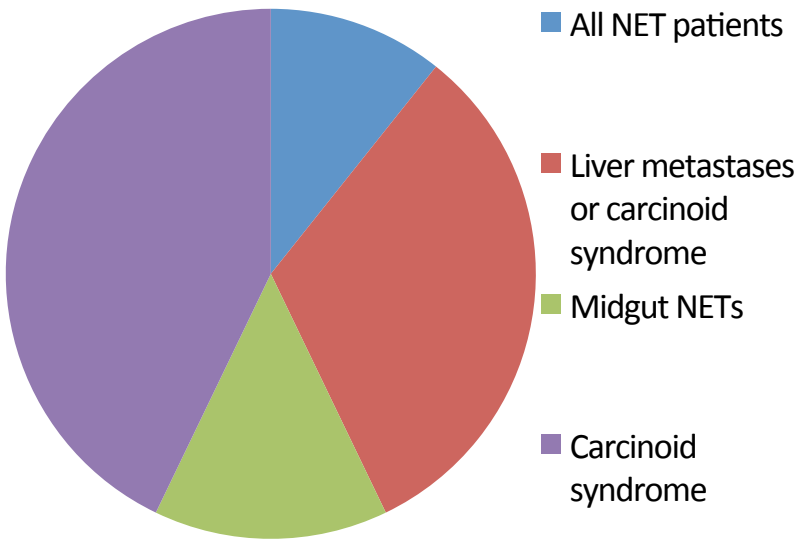


Figure 3.2 Clinical criteria for carcinoid heart disease screening

The method employed to screen for carcinoid heart disease also varied enormously between centres. Sixty-eight percent (n=19) of centres used clinical examination as part of their screening process for carcinoid heart disease. Eighty-nine percent (n=25) of centres performed transthoracic echocardiography to screen patients for carcinoid heart disease with wide variation in the frequency of scans; 21% at baseline only, 32% annually, 25% on an *ad hoc* basis and 11% less than annually. All centres received a standard clinical echocardiogram report with the exception of three centres which used an echocardiographic scoring system to quantify carcinoid heart disease.

The use of biomarkers for the screening of carcinoid heart disease varied between centres, with one centre using it as the sole method of screening,

and others using it as an adjunct to clinical examination and/or echocardiography. In the 50% (n=14) of centres that routinely measured biomarkers, 50% (n=7) measured NTproBNP, 14% (n=2) measured 5HIAA, 7% (n=1) measured chromogranins and 21% (n=3) measured a combination of the above. The frequency of biomarker measurement varied from bi-annually to once every two years. See table 3.1 for more details.

Centre	Clinical examination	Echocardiography	Biomarkers	Cardiologist on MDT
1	*Ad hoc*	Annually	NTproBNP annually	✗
2	6 monthly	Annually		✗
3	Annually	Baseline then depending on symptoms		✓
4	6 monthly	Baseline then depending on symptoms	Chromogranin	✗
5	3 monthly	Dependent on clinical signs		✗
6	3 monthly	As indicated by clinical findings	5HIAA, chromogranins	✗
7	At each visit	Less than annually	5HIAA	✓
8			NTproBNP every 2 years	✗
9		Annually	NTproBNP 6 monthly	✓
10		Every 2-3 years		✓
11		Annually		✗
12	Annually	Annually	Biomarker not stated but measured annually	✓
13	3 monthly	If clinical suspicion		✗
14	6 monthly			✓
15	6 monthly		NTproBNP 6 monthly	✓
16		Every 2-3 years		✗
17	At each visit	Baseline then if deterioration in carcinoid syndrome		✓
18		Baseline		✗
19	Annually	Baseline	NTproBNP at baseline	✗
20	Baseline	Those with elevated markers or symptoms	5HIAA & NTproBNP (no frequency stated)	✓
21	6 monthly	Annually		✓
22	3-12 monthly	Practice and intervals vary		✓
23	6 monthly	Dependent on 5HIAA & clinical findings	5HIAA 6-12 monthly	✓
24	6 monthly	Every 2 years	Chromogranin & NTproBNP (no frequency stated)	✓
25	Annually	Annually	NTproBNP 6 monthly	✓
26	6 monthly	Annually	NTproBNP 6 monthly	✗
27	6 monthly	Annually		✗
28		Baseline then depending on symptoms		✗

Table 3.1 Method of cardiac screening and cardiology involvement across each NET centre

3.33 Cardiology Input and Referral

A cardiology service with expertise in carcinoid heart disease was not available at all centres, with 50% (n=14) of centres lacking cardiology input to their MDT and 32% (n=9) of centres referring patients to their local general cardiology service. Eighty-six percent (n=24) of centres referred all patients with evidence of carcinoid heart disease to a cardiologist, with the remainder referring only those who were symptomatic, had moderate to severe valvular dysfunction, RV failure or cardiac metastases. Patients with established carcinoid heart disease were scanned at varying frequencies ranging from less than annually (35%), annually (48%), every 6 months (13%) and more frequently than every 6 months (4%).

Criteria for referral for valve surgery varied widely with some centres never referring patients (expressing the view that “surgery is not helpful in these patients”) and others referring all patients with carcinoid heart disease with a prognosis of greater than one year. There was a general feeling amongst respondents that decisions regarding valve surgery are difficult, and must be made in a multi-disciplinary setting.

3.4 Discussion

This study demonstrates that there is wide variation in clinical practice with respect to screening methods for carcinoid heart disease across the UK and Republic of Ireland. There are variations in the population screened, in the frequency and mode of screening and in access to local cardiology expertise.

Despite the uncertainty regarding the optimum management and timing of valvular surgery for patients with carcinoid heart disease, screening for cardiac involvement is imperative in order to identify patients who may be asymptomatic before they develop irreversible RV dysfunction. The clinical presentation of carcinoid heart disease is variable, with some patients presenting with fulminant heart failure, whilst others will be virtually asymptomatic. Early identification of patients enables monitoring for symptoms of right-sided heart failure or for echocardiographic evidence of RV dysfunction, and potentially an opportunity to slow the progression of carcinoid heart disease through the proactive reduction of serotonin levels by SSA therapy (54).

Which clinical group to screen for carcinoid heart disease remains a contentious issue, with inconsistencies between the various guidelines adding to the confusion (13,126). This is reflected in the variation of the populations screened in this study. As elevated concentrations of serotonin play a key role in the pathogenesis of carcinoid heart disease, the author advocates that all patients with raised plasma/serum/urine 5HIAA concentrations are at risk of cardiac involvement and warrant inclusion in a carcinoid cardiac surveillance programme. The risk of developing carcinoid heart disease is difficult to quantify as it varies in the literature, but a recent prospective study estimated the risk to be around 20% in patients with carcinoid syndrome (54).

Clinical examination is an unreliable method of identifying patients with carcinoid heart disease (54) and those centres that rely on this method for

screening are potentially missing patients with cardiac involvement. Echocardiography is the gold standard for detection of carcinoid heart disease (81) but is more expensive than biomarker measurement. Consensus guidelines recommend the use of serum NTproBNP measurement for carcinoid heart disease screening (13) but only 32% of centres measure this routinely.

The rate at which patients with carcinoid syndrome develop carcinoid heart disease is thought to be between 17 and 35% over two to three years (4,56,122). Carcinoid heart disease development is more common in patients with frequent daily episodes of flushing (4). Despite international agreement that screening for carcinoid heart disease is an important aspect of NET patient care, the optimum frequency of screening remains uncertain. The screening frequency in this study varied widely from a one-off event at presentation, to regular screening every three months.

Due to the relatively rare nature of carcinoid heart disease, it is recommended that all patients with evidence of carcinoid heart disease are considered for referral to a cardiologist with appropriate expertise or experience in this field (13). Only half of the centres surveyed had a cardiologist on their MDT and a third referred patients to the general cardiology service, who may have little or no experience in the management of carcinoid heart disease. Greater collaboration between specialist regional centres and centralisation of expertise would enable all NET services to access experienced specialist cardiology services. This study demonstrated that there is wide variation in the frequency of echocardiography in patients with documented carcinoid heart disease. As the presence of moderate to severe RV dilatation increases perioperative mortality (120), it has been suggested that early surgical intervention in patients with mildly symptomatic carcinoid heart disease is preferable (141). Therefore in order to identify patients before RV dilatation and failure ensues, annual echocardiography for patients with cardiac involvement is recommended (126).

Indications for valve surgery varied between centres with some referring all patients with carcinoid heart disease, and others referring none. ENETS guidelines recommend consideration of bioprosthetic valve replacement for patients in whom control of tumour growth and hormonal symptoms has been achieved. Valvular surgery prior to major liver surgery or liver embolisation is also recommended (126).

A limitation of this study is that only 80% of centres responded to the survey, and not all patients with NETs are managed in specialist centres. Therefore, it is not a reflection of 100% of practice in the UK and Ireland. It is possible that there is a selection bias in the method by which centres were identified. Use of the National Cancer Registry may have allowed a more comprehensive assessment of the treatment of NET patients within the UK and Republic of Ireland. One further limitation is that it is possible that different clinicians in the same hospital might follow different protocols, or even the same clinician may use different criteria from one patient to the next. This was not reflected in the information obtained from the centres but cannot be completely ruled out. Finally, these data are not validated, we have only the information given to us by each centre but as a review of the case notes of every individual with a NET was not possible, this was the best way of discerning clinical practice.

3.5 Conclusion

This study has demonstrated that compliance with current guidelines for carcinoid heart disease is relatively poor. There are several possible reasons for this, including lack of clinician awareness, lack of clinical resources and conflicting guidelines. Standardisation of nationwide practice in the management of carcinoid heart disease in accordance with a consensus guideline would facilitate a UK registry of patients with carcinoid heart disease to better understand the natural history and prognosis of this condition and potentially improve patient outcomes for the disease across the UK and Ireland.

Chapter 4: Validation of Biochemical Markers of Presence and Severity of Carcinoid Heart Disease Using Echocardiography

Abstract

4.1 Introduction

4.2 Methods

4.21 Interobserver variability

4.3 Results

4.31 Patient demographics

4.32 Echocardiography results

4.33 Predictive value of biomarkers for the diagnosis of carcinoid heart disease

4.34 Correlation between biomarkers and echocardiographic severity score

4.4 Discussion

4.5 Conclusion

Abstract

Introduction

Metastatic NETS secrete serotonin and other vasoactive substances that are responsible for carcinoid syndrome and carcinoid heart disease. The aim of this study was to evaluate the discriminatory utility of diagnostic biomarkers in determining the presence and severity of carcinoid heart disease in patients with metastatic NETs.

Methods

A cross-sectional study of patients with NETs with documented liver metastases and/or carcinoid syndrome between April 2009-October 2012 in four tertiary referral centres was undertaken. Serum was analysed for CgA, Cg B and NTproBNP. Plasma was analysed for Nk A and 5HIAA. Echocardiography was used to determine the presence and severity of carcinoid heart disease. Non-parametric ROC were constructed for each biomarker, and the area under the curve (AUC) determined. The severity of cardiac involvement was correlated with the concentration of each biomarker.

Results

A total of 187 patients were identified of whom 37 (20%) had carcinoid heart disease. Significantly higher median values of all biomarkers were found in the patients with cardiac involvement. NTproBNP and plasma 5HIAA had the highest AUCs for the prediction of carcinoid heart disease: NTproBNP 0.82 (95% confidence interval 0.74-0.90, $p<0.0001$) and 5HIAA 0.85 (95% confidence interval 0.78-0.92, $p<0.0001$). NTproBNP was moderately correlated ($r=0.48$, $p<0.001$) whereas plasma 5HIAA was only weakly correlated ($r=0.34$, $p<0.001$) with the echocardiographic severity score.

Conclusion

NTproBNP and plasma 5HIAA are both sensitive and specific biomarkers for the presence of carcinoid heart disease whereas only NTproBNP moderately correlates with disease severity.

4.1 Introduction

Metastatic mid-gut NETs secrete serotonin and a variety of other vasoactive substances that are responsible not only for the characteristic carcinoid syndrome, but also for the significant long-term complication of carcinoid heart disease.

Echocardiography is a pivotal tool for the assessment of carcinoid heart disease. Whilst echocardiography is the gold-standard investigation, the use of biomarkers to identify those patients most at risk is cheaper, less time-consuming and a more practical option. The identification of a sensitive and specific biochemical marker that can predict the presence and severity of carcinoid heart disease may direct more rational use of echocardiographic screening.

A variety of biomarkers for carcinoid heart disease have been identified in previous studies (see chapter one, section 1.34). The most useful to date has been NTproBNP, which has both diagnostic and prognostic significance for cardiac involvement (52,55). No studies of patients with metastatic NETS that compare the discriminatory ability of a panel of biomarkers in the assessment of the presence and severity of carcinoid heart disease have been identified in the literature.

The aim of this study was to determine which biomarker was best associated with the presence and severity of carcinoid heart disease in patients with metastatic NETs.

4.2 Methods

For an in-depth explanation of recruitment, echocardiographic, biochemical and statistical methods, please refer to chapter two.

Inter-observer Variability

Inter-observer agreement was ascertained as per the methods in chapter 2. One hundred and eight echocardiographic studies (57%) were validated. In 98 studies the assigned scores were concordant, in ten there was a discrepancy of >2 points, (mean difference 0.269).

4.3 Results

4.31 Patient Demographics

Two hundred and eighteen patients were invited to participate. Figure 4.1 details the reasons for exclusion of 31 patients. A total of 187 patients were included. The baseline characteristics of the patients are shown in Table 4.1.

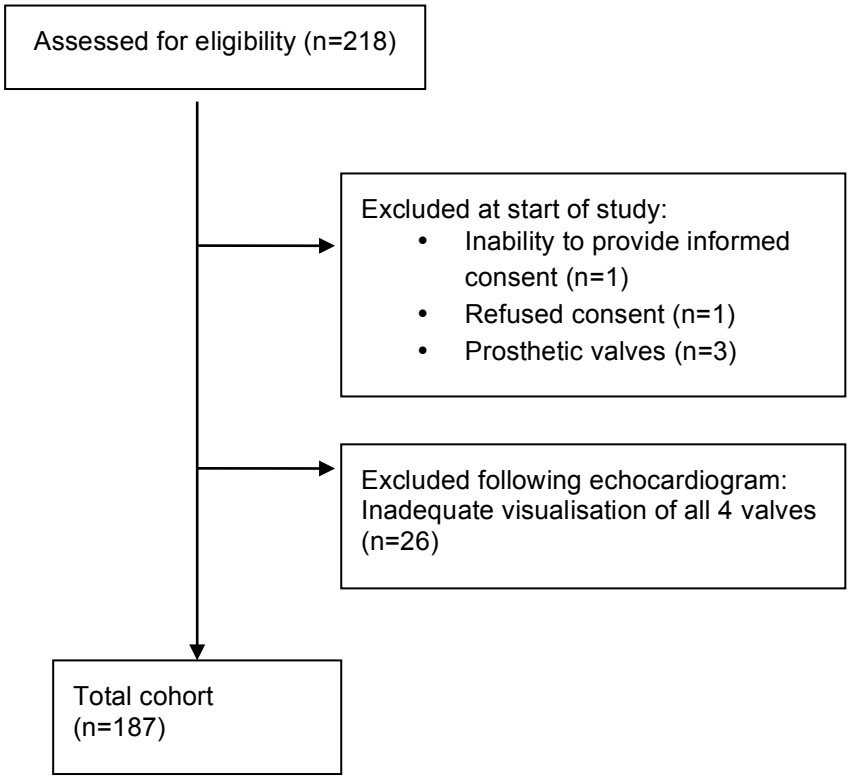


Figure 4.1 Consort flow diagram

One hundred and sixty-six patients had a histologically confirmed NET. Of the 121 patients with a Ki67 proliferative index reported: 69 patients had a grade one tumour (Ki67 <2%), 50 patients had grade two tumours (Ki67 2-20%) and two patients' tumours were grade three (Ki67 >20%). Thirty-one patients were newly diagnosed (<three months since presentation) while 156 had an established diagnosis with a median duration of 56 months

(interquartile range 35-93 months).

There were no significant differences with respect to age, gender, or primary tumour site between the groups with and without carcinoid heart disease. Furthermore there was no difference in duration of disease between the two groups (median duration 47 v 29 months, *P*=0.102). There were no significant differences in the proportions of patients with a history of chronic obstructive pulmonary disease or ischaemic heart disease between the groups.

The proportions of patients with liver metastases and symptoms of heart failure were higher in those with carcinoid heart disease than in those without. Those patients who had undergone primary tumour resection had a significantly lower prevalence of carcinoid heart disease than those without primary tumour resection, although this was not the case for patients who had or had not undergone hepatic resection.

Variable	All patients (*n*=187)	No carcinoid heart disease (*n*=150)	Carcinoid heart disease (*n*=37)
Demographics			
Age (years) †	67 ± 10	66 ± 10	68 ± 12
Male sex	101 (54%)	84 (56%)	17 (44%)
Body mass index (kg/m^2) †	25.9 ± 5.0	26.6 ± 4.5 *	22.1 ± 6.0 *
Clinical Characteristics			
Histologically confirmed diagnosis	166 (89%)	136 (90%)	30 (83%)
Duration of disease (months) ◊	42 (26-74)	47 (28-79)	29 (9-63)
New NET diagnosis at time of echocardiogram	32 (17%)	23 (15%)	9 (24%)
Proton pump inhibitor therapy	54 (29%)	46 (30%)	8 (22%)
Liver metastases	156 (83%)	119 (79%) *	37 (97%) *
Carcinoid syndrome	120 (64%)	95 (63%)	25 (68%)
Site of Primary Tumour			
Small bowel	132 (71%)	108 (72%)	24 (67%)
Large bowel	12 (6%)	11 (7%)	1 (3%)
Lung	5 (3%)	5 (3%)	0
Other	7 (4%)	4 (3%)	3 (8%)
Unknown	31 (16%)	23 (15%)	8 (22%)
NYHA Class/Medical History			
I	133 (71%)	117 (78%) *	16 (44%) *
II	49 (26%)	33 (22%)	16 (44%)
III	4 (2%)	1 (0.5%)	3 (8%)
IV	1 (1%)	0	1 (3%)
History of COPD	9 (5%)	7 (5%)	2 (5%)
History of IHD	13 (7%)	11 (7%)	2 (5%)
Therapeutic Intervention			
SSA therapy	89 (48%)	68 (45%)	21 (58%)
Primary tumour resection	118 (63%)	101 (67%) *	17 (47%) *
Hepatic resection	19 (10%)	18 (12%)	1 (3%)

† Mean ± standard deviation, ◊ Median and interquartile range, * $P<0.05$, COPD Chronic obstructive pulmonary disease, IHD Ischaemic heart disease

Table 4.1 Baseline characteristics of patients

4.32 Echocardiography Results

Thirty-seven patients (20%) had echocardiographic evidence of carcinoid heart disease. The median echocardiographic score in those with cardiac involvement was 12 (interquartile range (IR) 8-21), compared to a median of two (IR 1-3) in those without cardiac involvement. There were 24 cases of single valve involvement (tricuspid in 23 cases, pulmonary in one), 12 cases of dual valve pathology, and one patient with three valves involved. The right heart was dilated in 34 cases and RV function was affected in ten cases. Eight patients (4%) had evidence of left sided carcinoid heart disease. The echocardiographic score was weakly correlated with NYHA class, i.e. patient symptoms (Spearman r=0.22; *P*=0.002).

4.33 Predictive Value of Biomarkers for The Diagnosis of Carcinoid Heart Disease

Significantly higher median values of all biomarkers were found in the patients with carcinoid heart disease compared to those without (figure 4.2). NTproBNP 474 vs. 79 ng/L, 5HIAA 353 vs. 57 ng/ml, CgA 16 vs. 7 ng/ml, CgB 13 vs. 8 ng/ml and NkA 27 vs. 16 ng/L. Plasma 5HIAA and NTproBNP had the greatest AUCs (0.85 plasma 5HIAA and 0.82 NT-proBNP, figure 4.3). The AUCs for CgA, CgB and NkA were 0.69 (0.57-0.80), 0.77 (0.67-0.88) and 0.72 (0.62-0.82) respectively.

The effect of age, sex and creatinine on NTproBNP was investigated using a multivariable prediction model. NTproBNP remained statistically significant whereas age, gender and creatinine did not (*P*=0.599, 0.521 and 0.749 respectively). A stepwise model selection method (minimising Akaike's Information Criterion (AIC)) demonstrated that age, gender and creatinine do not offer any additional information to discriminate between patients with and without carcinoid heart disease (univariate *P*-values of 0.277, 0.300 and 0.822 respectively).

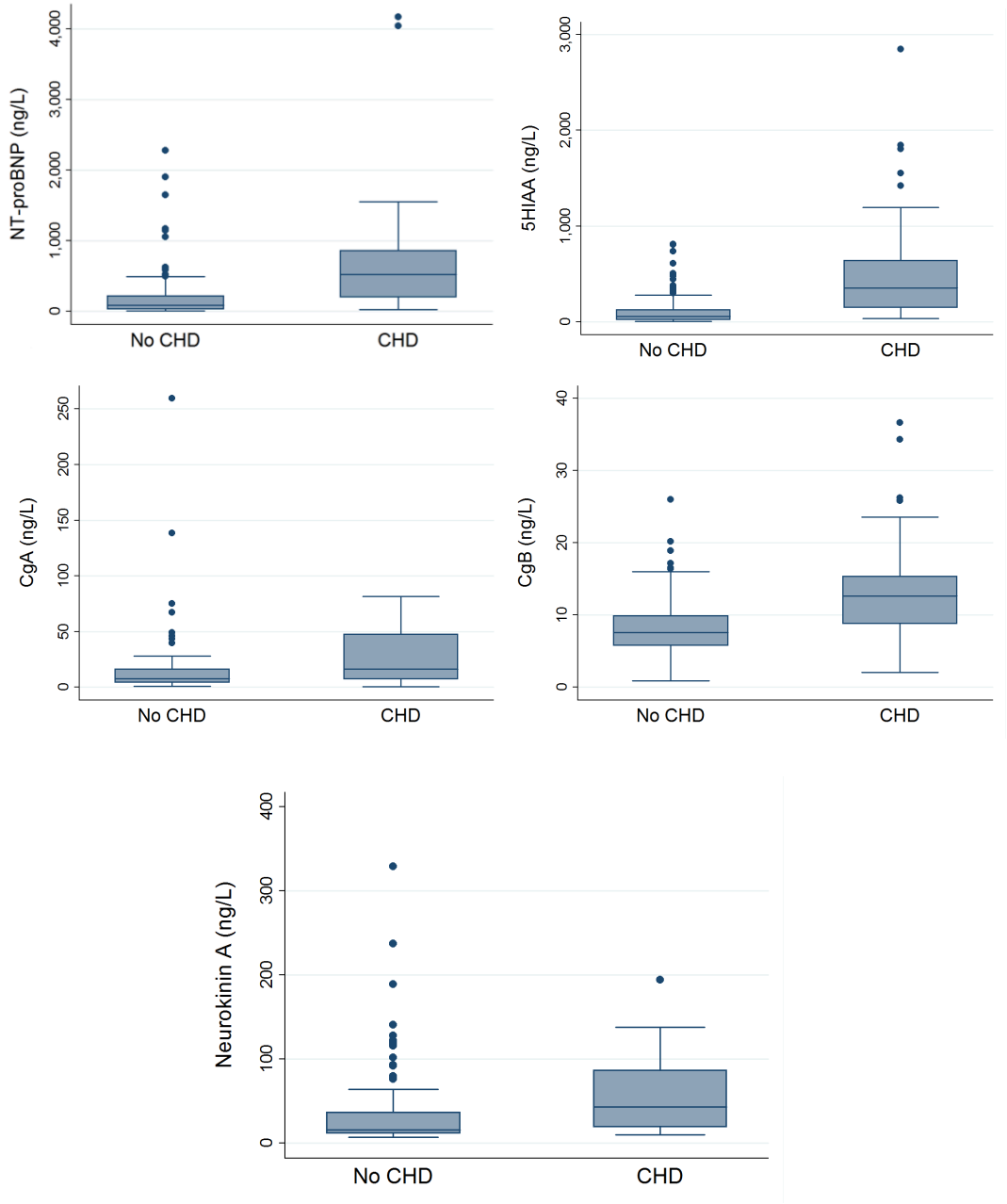
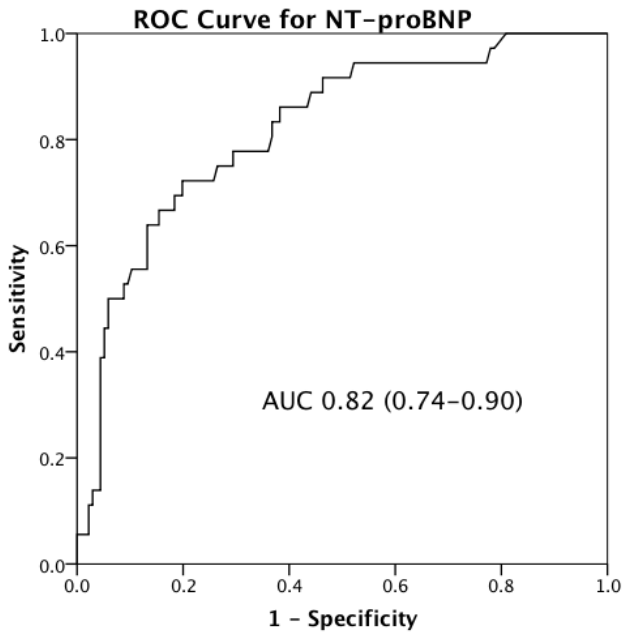


Figure 4.2 Box plots demonstrating spread of results for all five biomarkers



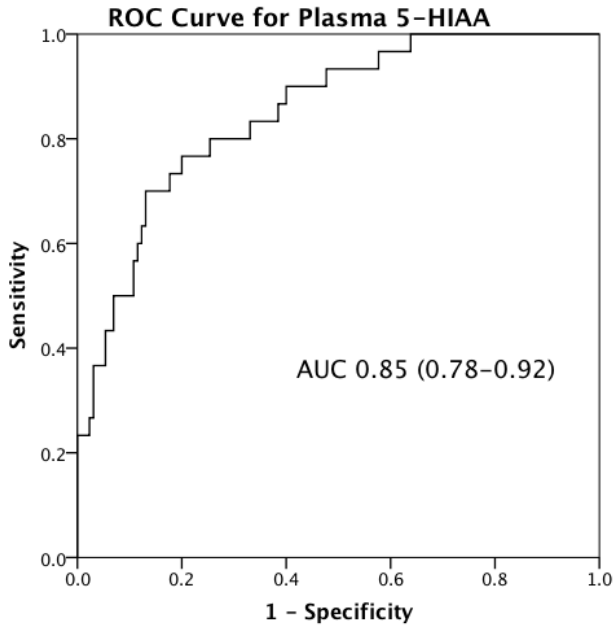


Figure 4.3 Receiver operator characteristic curves for NTproBNP and plasma 5HIAA

The cut-off points for NTproBNP and plasma 5HIAA with their respective sensitivities and specificities in this patient cohort are illustrated in table 4.2. The improvement in discriminatory power by inclusion of additional assays into a final logistic regression model was negligible (less than 5-point change in AIC; direct comparison of full model with plasma 5HIAA yielded *P*=0.682). For every 50 ng/l increase in NTproBNP concentration,

the odds of carcinoid heart disease increased by 11% (95% confidence interval 5-17%, *P*<0.0005) and for every 50 ng/ml increase in plasma 5HIAA the odds of carcinoid heart disease increased by 26% (95 confidence interval 14-39%, *P*<0.0005).

NTproBNP cut point (ng/L)	**Sens.**	**Spec.**	**Correctly classified**	**Proportion above cut-point**	**LR +**	**LR -**
100	88	54	55%	55%	1.9	0.2
200	74	73	73%	37%	2.8	0.3
300	67	82	79%	28%	3.6	0.4
400	61	87	81%	23%	4.6	0.4
500	50	93	84%	16%	6.8	0.5
600	42	95	84%	13%	8.1	0.6
5HIAA cut point (ng/ml)						
50	93	45	54%	96%	1.7	0.1
100	80	68	71%	82%	2.5	0.3
150	73	80	79%	74%	3.7	0.3
200	70	85	83%	68%	4.8	0.4
250	67	87	83%	63%	5.1	0.4
300	57	88	83%	58%	4.9	0.5
350	50	92	84%	54%	5.9	0.5

Sens Sensitivity, Spec Specificity, LR + Positive likelihood ratio, LR - Negative likelihood ratio

Table 4.2 Diagnostic accuracy of NTproBNP & plasma 5HIAA

4.34 Correlation Between Biomarkers and Echocardiographic Severity Score

There were significant correlations between the echocardiographic score and concentrations of all biomarkers except CgA. The score correlated most significantly with NTproBNP (Spearman r=0.48; *P*<0.0001) while for the other biomarkers the correlation coefficients were low: plasma 5HIAA (Spearman r=0.34; *P*<0.0001), CgA 0.09 (*P*=0.25), CgB 0.29 (*P*<0.0001) and NkA 0.19 (*P*=0.03), figure 4.4.

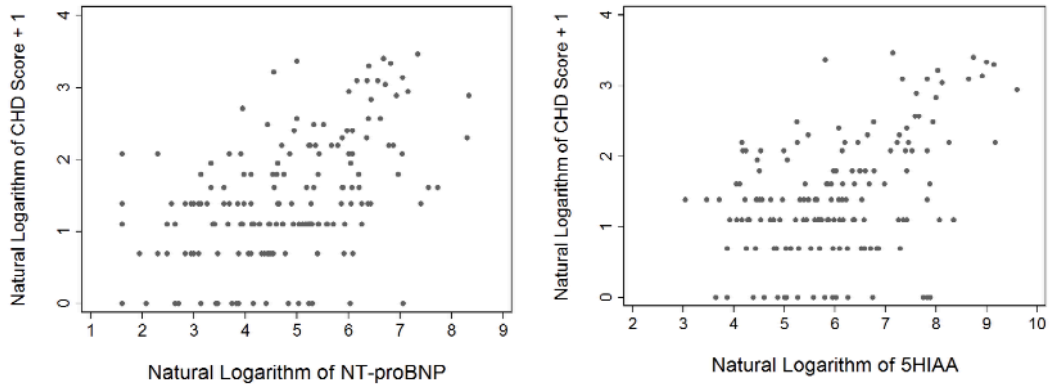


Figure 4.4 Scatter diagram demonstrating correlations of NTproBNP and plasma 5HIAA with the echocardiographic score

4.4 Discussion

This is the first large prospective clinical study of patients with metastatic NETs to compare the discriminatory ability of a panel of biomarkers in the assessment of the presence and severity of carcinoid heart disease. The data demonstrate that the median concentrations of all five biomarkers are significantly higher in patients with carcinoid heart disease, however NTproBNP and plasma 5HIAA have the greatest discriminatory value in the diagnosis of carcinoid heart disease, with NTproBNP most closely correlating with its severity. Thus in this panel of biomarkers for use in patients with metastatic NETs, NTproBNP concentration is the most useful biochemical assay for clinicians regarding the presence and severity of cardiac involvement. This finding is consistent with the most recent ENETS and NANETs consensus guidelines advocating the use of natriuretic peptides where available (126,127).

The optimum cut-off point for NTproBNP is determined by the relative importance of the sensitivity and specificity of the test. In this circumstance, sensitivity assumes greater importance than specificity, as it is preferable to perform echocardiography on too many patients, rather than miss a diagnosis of carcinoid heart disease. Unlike the results of Korse *et al.* (55), no incremental benefit in combining NTproBNP with CgA was found, although there was minor incremental benefit in combining NTproBNP and plasma 5HIAA in terms of increasing the diagnostic accuracy of the test. A single variable model was considered to be favourable due to its enhanced ease of use in clinical practice. In this series, the cut-off point for NTproBNP of 260 pg/ml suggested by Bhattacharya (53), would have a sensitivity of 69% and a specificity of 80%, meaning that 11 patients with carcinoid heart disease would not have been detected.

NTproBNP is released from cardiac myocytes with myocyte stretch being the main stimulus for its synthesis and secretion (161). Elevated levels reflect increased wall tension and pressure making its measurement of

value in carcinoid heart disease. The finding of the correlation between the degree of elevation of plasma 5HIAA and the development of carcinoid heart disease gives mechanistic insight into the likely contribution of serotonin to the pathogenesis of cardiac involvement. The use of SSAs that are known to reduce circulating levels of serotonin may be expected to be protective against the development of carcinoid heart disease but we were unable to confirm this hypothesis. This negative association likely reflects a treatment bias, in that patients with a greater tumour burden are more likely to require treatment with SSAs. Furthermore 83% of this cohort had liver metastases and 64% had carcinoid syndrome but only 48% received SSAs, which may have influenced the findings. Ideally, prospective human studies are needed to determine whether SSAs can prevent or decrease the severity of carcinoid heart disease, although the anti-proliferative effect of SSAs may result in an increasingly higher proportion of patients with metastatic NETs receiving them.

In this study there was a poor correlation between CgA and the severity of carcinoid heart disease which may be because CgA is falsely elevated by proton pump inhibitor (PPI) therapy in healthy individuals (174), and those with NETs (175). Thirty percent of patients who did not have carcinoid heart disease were taking PPI therapy, which undoubtedly will have influenced the CgA results. CgB, however, is not affected by renal function or PPI therapy (72). This may explain why our data demonstrate that CgB is more sensitive and specific than CgA for carcinoid heart disease. NkA is a specific marker for tumours of the mid-gut (73) and the inclusion of a minority of patients with NETs not of mid-gut origin may have affected the NkA results for this patient cohort.

The distribution of NYHA categories in patients with carcinoid heart disease (88% of patients in categories one and two) demonstrates that the disease is often clinically silent, with no discernable attributable symptoms. This is reflected in the weak correlation of the echocardiographic score with NYHA class.

While the strength of this study is the large population of NET patients, carefully characterised prospectively from a multi-modality perspective with a comparison of multiple biomarkers, there are some limitations. Most significantly, the exclusion of patients in whom it was not possible to visualise all four cardiac valves may have led to an underestimate in the prevalence of carcinoid heart disease.

The findings suggest that NTproBNP or plasma 5HIAA could direct the use of transthoracic echocardiography in the assessment of patients with metastatic NETs. As a result, the author proposes that all such patients undergo a baseline echocardiogram at diagnosis or initial assessment, and if there is no evidence of cardiac involvement, echocardiography is only repeated in the event of an increase in NTproBNP. Such an approach would necessitate a proportion of patients without carcinoid heart disease being screened unnecessarily but would successfully identify the vast majority of patients with the disease. The author recognises that NTproBNP is not highly specific and therefore unsuitable for monitoring patients with an elevated NTproBNP attributable to a different pathology. In this scenario, it is necessary to resort to annual echocardiography.

4.5 Conclusion

In conclusion, this study demonstrates that NTproBNP and plasma 5HIAA are equally useful in determining the diagnosis of carcinoid heart disease. NTproBNP correlates better with severity of disease and may be superior to determine progression but both biomarkers could be used as part of the routine surveillance protocol in patients with metastatic NETs.

Chapter 5: Determination of the Optimal Echocardiographic Scoring System to Quantify Carcinoid Heart Disease

Abstract

5.1 Introduction

5.2 Methods

5.21 Literature review

5.22 Scoring systems

5.23 Inter-observer variability

5.3 Results

5.31 Patient demographics

5.32 Echocardiographic characteristics of the cohort

5.33 Biomarkers

5.34 Scoring systems

5.4 Discussion

5.5 Conclusion

Abstract

Introduction Carcinoid heart disease is an important complication of metastatic neuroendocrine disease, requiring regular monitoring to enable intervention prior to right heart failure. The aim of this study was to identify the most appropriate echocardiographic scoring system for the quantitative assessment of carcinoid heart disease.

Methods In this prospective study of patients with NETs with liver metastases and/or carcinoid syndrome, patients underwent transthoracic echocardiography and blood sampling for serum NTproBNP and plasma 5HIAA. Each patient was assessed according to six echocardiographic scoring systems. The individual scoring system's feasibility, observer variability, sensitivity, specificity and correlation with the concentration of biomarkers were determined.

Results One hundred patients were included, 21% had echocardiographic evidence of carcinoid heart disease. All scores discriminated highly between those with/without carcinoid heart disease, with no single score performing significantly better than another. Severity of disease, determined using all of the scoring systems, correlated with the concentration of both biomarkers. However the strongest correlations were seen between the Bhattacharyya score and serum NTproBNP.

Conclusion All scoring systems were comparable in terms of sensitivity and specificity for the detection of carcinoid heart disease. There was variation in the feasibility of the scoring systems due to the varying complexity of the score components. All scores correlated with NTproBNP and plasma 5HIAA. The Westberg score appeared to be the most optimal scoring system for use in the screening of carcinoid heart disease whereas the more complex scoring systems were more suited to the patient with established disease who may require surgical intervention.

5.1 Introduction

Carcinoid heart disease is associated with considerable morbidity and mortality and is characterised by thickening of the right-sided valves, reduced excursion of the valve leaflets and consequent regurgitation and/or stenosis which can lead to right heart failure (25,42).

Early diagnosis and regular monitoring for progression of carcinoid heart disease is important as it can impact drastically on long-term survival, and timely valve replacement is imperative for a successful outcome (57,120). Transthoracic echocardiography is the gold standard investigation for the diagnosis and surveillance of carcinoid heart disease (9,81) but there is no consensus over which screening method most accurately quantifies disease.

Several echocardiographic scoring systems have been developed for the assessment of carcinoid heart disease, but have been used with limited evaluation of their validity and utility. Consequently there is uncertainty surrounding the clinical relevance of these scoring systems.

A prospective study was conducted to apply and compare different echocardiographic scoring systems in a large population of patients with metastatic NETs attending specialist neuroendocrine clinics in ENETS Centres Of Excellence. The aims of the study were to identify the different uses of the scoring systems and to determine the most appropriate echocardiographic scoring system for the quantitative assessment of carcinoid heart disease.

5.2 Methods

For an in-depth explanation of recruitment, echocardiographic, biochemical and statistical methods, please refer to chapter two.

5.21 Literature Review

PubMed and Medline databases were searched with the terms *carcinoid heart disease, echocardiography, scoring system, score and grade*, with identification of 17 papers. Ten papers were excluded as they related to different cardiac imaging modalities or did not use an echocardiographic scoring system. Several papers utilised the same scoring systems; there was ultimate identification of five different scoring systems (49,50,53,120,123), see chapter one for more details.

5.22 Scoring Systems

The five scoring systems are described in detail in chapter one. Table 1.4 illustrates the different echocardiographic scoring systems for carcinoid heart disease, which range considerably in their complexity. A score for each scoring system was calculated, wherever possible, for each patient.

Valve regurgitation and stenosis were quantified according to the same standards or guidelines used in the original papers citing the scores. An additional score (Dobson), incorporating what the author considered to be the most clinically relevant aspects of the other scores, was also calculated. This comprised a 33-point score, with three points (0 points equating to normality and 3 points equalling severe abnormality) attributable to each of the following variables: tricuspid and pulmonary valve thickening, leaflet mobility, regurgitation, and stenosis (each valve scored separately) and right atrial size, RV size and RV function.

5.23 Inter-observer Variability

Inter-observer agreement was ascertained as per the methods in chapter two. To evaluate inter-observer agreement a randomly selected subsample of ten echocardiographic scans were crosschecked by a different observer blinded to the initial echocardiographic scores, who calculated all six scores for each scan. There was concordance between the two reviewers' interpretation of all of the different scoring systems for all of the scans: the mean difference between the different scoring systems was 1.1 (Bhattacharyya), 0.4 (Denney), 0.6 (Dobson), 0.8 (Mansencal), 0.9 (Moller) and 0.5 (Westberg).

5.3 Results

5.31 Patient Demographics

One hundred and three patients were assessed for their eligibility for the study with three patients meeting the criteria for exclusion (one patient had an aortic valve prosthesis and two patients had poor echocardiographic images precluding comprehensive assessment of all four cardiac valves). Of the 100 patients included, 21 had echocardiographic evidence of carcinoid heart disease.

There were no significant differences between those with and without carcinoid heart disease in terms of age, gender, disease duration, primary tumour site, presence of liver metastases or carcinoid syndrome or therapeutic intervention received. The demographics, clinical characteristics, biochemistry and therapeutic interventions for the cohort are shown in table 5.1.

Variable	All patients (n=100)	No carcinoid heart disease (n=79)	Carcinoid heart disease (n=21)	*P* value
Demographics				
Age (years) ◊	66.3 ± 10.6	65.6 ± 10.1	68.7 ± 12.2	0.24
Male sex	55 (55%)	46 (58%)	9 (43%)	0.21
Body mass index (kg/m^2) ◊	26.7 ± 4.9	27.5 ± 4.8	23.5 ± 4.0	**0.002** *
Clinical Characteristics				
Duration of disease (months) †	40 (15-74)	41 (18-74)	30 (9-71)	0.62
Time from NET diagnosis to echocardiogram (months) †	34 (9-69)	36 (11-69)	22 (6-66)	0.33
Site of primary tumour				
Small bowel	73	57 (72%)	16 (76%)	0.78
Large bowel	6	5 (6%)	1 (5%)	
Lung	2	2 (3%)	0	
Ovarian	1	0	1 (5%)	
Gastric	1	1 (1%)	0	
Unknown	17	14 (18%)	3 (14%)	
NYHA Class				
I	63	51 (65%)	12 (57%)	0.68
II	36	27 (34%)	9 (43%)	
III	1	1 (1%)	0	
IV	0	0	0	
Liver metastases	90	70 (89%)	20 (95%)	0.37
Carcinoid syndrome	71	56 (71%)	15 (71%)	0.96
Biochemistry				
NTproBNP ng/L †	109 (46-307)	79 (27-185)	290 (110-611)	**0.013** *
5HIAA nmol/L †	415 (140-1474)	285 (103-854)	2288 (999-3294)	**0.004** *
Management				
Somatostatin Analogue	51	41 (52%)	10 (48%)	0.95
Primary tumour resection	52	43 (54%)	9 (43%)	0.35
Hepatic resection	10	9 (11%)	1 (5%)	0.37

NYHA New York Heart Association, ◊ Mean ± standard deviation, † Median (interquartile range), * *P*< 0.05

Table 5.1 Characteristics of the patient population

5.32 Echocardiographic Characteristics of the Cohort

All patients with carcinoid heart disease had moderate or severe tricuspid regurgitation, making it the most common valvular pathology observed. Two thirds of patients with carcinoid heart disease had pulmonary regurgitation. Tricuspid stenosis occurred in 43% of patients, and pulmonary stenosis was the least prevalent right-sided valvular lesion, occurring in 24% of cases. Forty-three percent of patients with carcinoid heart disease had a degree of RV dilatation. Fourteen patients had single valve pathology and seven had two or more valves involved. Determining the presence of left-sided valve disease is challenging, as it possible to have right-sided carcinoid heart disease, concomitant with degenerative left-sided valvular disease. Two patients had clear echocardiographic evidence of right and left-sided carcinoid heart disease, both of which had patent foramen ovale. The specific features of cardiac involvement in this cohort are illustrated in tables 5.2a, 5.2b and 5.3.

Morphology			
Variable – no (%)	**All (n=100)**	**No CHD (n=79)**	**CHD (n=21)**
Tricuspid leaflet thickening			
None	60	60 (76%)	0
Mildly thickened	26	19 (24%)	7 (33%)
Moderately thickened	8	0	8 (38%)
Severely thickened	6	0	6 (29%)
Tricuspid leaflet mobility			
Normal	78	78 (99%)	0
Mildly reduced	12	0	12 (57%)
Moderately reduced	5	0	5 (24%)
Severely reduced	4	0	4 (19%)
Pulmonary leaflet thickening			
Unable to visualise	3	2	1
None	73	67 (87%)	6 (30%)
Mildly thickened	22	10 (13%)	12 (60%)
Moderately thickened	1	0	1 (5%)
Severely thickened	1	0	1 (5%)
Pulmonary leaflet mobility			
Unable to visualise	3	2	1
Normal	92	77 (97%)	15 (71%)
Mildly reduced	3	0	3 (14%)
Moderately reduced	2	0	2 (10%)
Severely reduced	1	0	1 (5%)
RV dilatation			
None	83	71 (90%)	12 (57%)
Mild	10	7 (9%)	3 (14%)
Moderate	2	1 (1%)	1 (5%)
Severe	5	0	5 (24%)

Table 5.2a Echocardiographic characteristics of the right heart (morphology)

Function			
Variable – no (%)	**All (n=100)**	**No CHD (n=79)**	**CHD (n=21)**
Tricuspid stenosis			
None	93	79 (100%)	12 (57%)
Mild	5	0	7 (33%)
Moderate	2	0	2 (10%)
Severe	0	0	0
Tricuspid regurgitation			
None	26	26 (33%)	0
Mild	49	49 (62%)	0
Moderate	15	4 (5%)	11 (52%)
Severe	10	0	10 (48%)
Pulmonary stenosis			
None	95	79 (100%)	16 (76%)
Mild	4	0	4 (19%)
Moderate	1	0	1 (5%)
Severe	0	0	0
Pulmonary regurgitation			
None	59	52 (66%)	7 (34%)
Mild	37	27 (34%)	10 (48%)
Moderate	2	0	2 (9%)
Severe	2	0	2 (9%)

Table 5.2b Echocardiographic characteristics of the right heart (function)

Morphology				Function			
Variable – no (%)	**All (n=100)**	**No carcinoid heart disease (n=79)**	**Carcinoid heart disease (n=21)**	**Variable – no (%)**	**All (n=100)**	**No carcinoid heart disease (n=79)**	**Carcinoid heart disease (n=21)**
Mitral leaflet thickening				**Mitral stenosis**			
None	50	44 (56%)	6 (29%)	None	100	79 (100%)	21 (100%)
Mildly thickened	44	31 (39%)	13 (62%)	Mild	0	0	0
Moderately thickened	6	4 (5%)	2 (9%)	Moderate	0	0	0
Severely thickened	0	0	0	Severe	0	0	0
Mitral leaflet mobility				**Mitral regurgitation**			
Normal	91	75 (95%)	16 (76%)	None	55	45 (57%)	10 (48%)
Mildly reduced	8	4 (5%)	4 (19%)	Mild	42	31 (39%)	11 (52%)
Moderately reduced	1	0	1 (5%)	Moderate	3	3 (4%)	0
Severely reduced	0	0	0	Severe	0	0	0
Aortic leaflet thickening				**Aortic stenosis**			
None	63	55 (70%)	8 (38%)	None	100	79 (100%)	21 (100%)
Mildly thickened	27	19 (24%)	8 (38%)	Mild	0	0	0
Moderately thickened	10	5 (6%)	5 (24%)	Moderate	0	0	0
Severely thickened	0	0	0	Severe	0	0	0
Aortic leaflet mobility				**Aortic regurgitation**			
Normal	95	76 (96%)	15 (71%)	None	71	61 (77%)	10 (48%)
Mildly reduced	5	3 (4%)	2 (10%)	Mild	22	15 (19%)	7 (33%)
Moderately reduced	0	0	4 (19%)	Moderate	7	3 (4%)	4 (19%)
Severely reduced	0	0	0	Severe	0	0	0

Table 5.3 Echocardiographic characteristics of the left heart

5.33 Biomarkers

The patients with carcinoid heart disease had significantly higher median values of both NTproBNP (290 v 79 ng/L, *P*=0.013) and plasma 5HIAA (2288 v 285 nmol/L, *P*=0.004) compared to patients without cardiac involvement. All of the scoring systems correlated weakly or moderately with both biomarkers (table 5.4). The Bhattacharyya score was the most closely correlated with a single biomarker (NTproBNP; r=0.43, *P*<0.0001).

5.34 Scoring systems

A comparison of the scoring systems in our patient population is shown in table 5.4. The Westberg and Denney scores were the simplest to calculate and had the highest feasibilities (ability to calculate the score for a given patient). All scoring systems were comparable in terms of their ability to discriminate between those with and without carcinoid heart disease. The new scoring system did not have a significantly higher discriminatory ability for the detection of carcinoid heart disease. Figure 5.1 illustrates the distribution of scores for each scoring system for those with and without carcinoid heart disease. Table 5.5 illustrates the diagnostic accuracy of the six scoring systems with the sensitivity and specificity for the diagnosis of carcinoid heart disease at different scores presented.

	Bhattacharyya	Denney	Dobson	Mansencal	Moller	Westberg
Feasibility	97%	100%	94%	96%	86%	100%
Score in carcinoid heart disease v no carcinoid heart disease ◊	12 (10-21) v 3 (2-5)	8 (8-10) v 4 (4-5)	8.5 (7-18) v 2 (1-2)	8 (6-14) v 2 (1-3)	7 (5-12) v 1 (1-2)	4 (4-6) v 0.5 (0-1)
Area under the ROC curve for diagnosis of carcinoid heart disease (95% CI)	0.988 (0.97-1)	0.984 (0.96-1)	0.995 (0.99-1)	0.989 (0.97-1)	0.964 (0.92-1)	0.994 (0.99-1)
Correlation with NTproBNP (*P* value)	0.43 (<0.0001)	0.39 (<0.0001)	0.39 (<0.0001)	0.39 (<0.0001)	0.36 (0.002)	0.37 (<0.0001)
Correlation with plasma 5HIAA (*P* value)	0.35 (0.001)	0.26 (0.014)	0.28 (0.011)	0.31 (0.004)	0.27 (0.017)	0.35 (0.001)

◊ Median (interquartile range), ROC – Receiver operating characteristic

Table 5.4 Comparison of the echocardiographic scores in the patient population

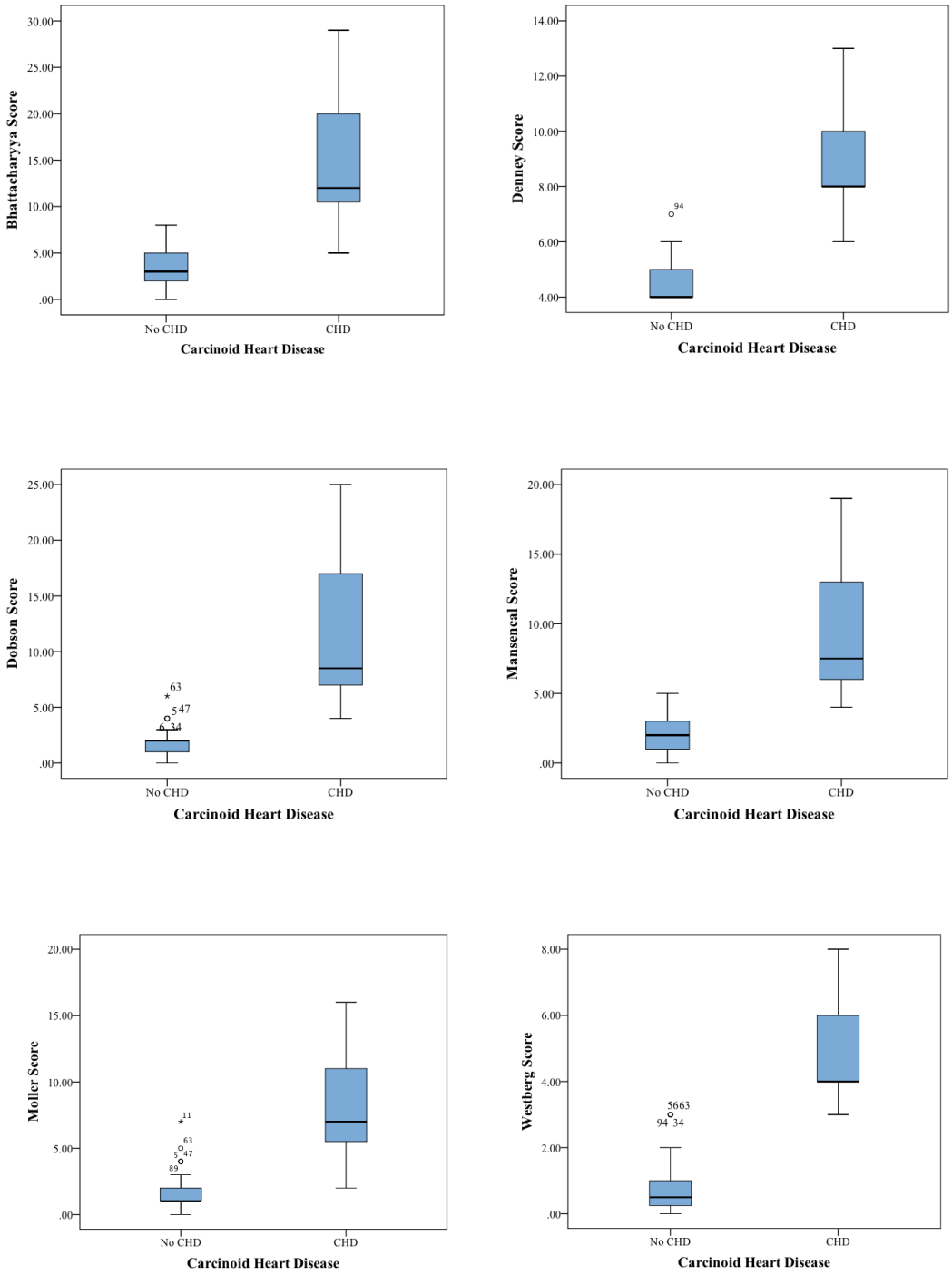


Figure 5.1 Distribution of scores for each scoring system for patients with and without carcinoid heart disease

Scoring system	Score	Proportion at/above cut-point	Sensitivity	Specificity	Correctly classified	LR +	LR -
Bhattachary -ya	10	16%	80	100	96%	-	0.20
	8	21%	90	97	96%	34.7	0.10
	7	27%	95	91	92%	10.5	0.06
	6	30%	95	86	92%	6.7	0.06
Denney	10	8%	38	100	87%	-	0.62
	8	16%	76	100	95%	-	0.24
	7	19%	86	99	96%	67.7	0.14
	6	36%	100	81	85%	5.27	0
Dobson	8	15%	70	100	94%	-	0.3
	7	17%	80	100	96%	-	0.2
	6	20%	90	99	97%	66.6	0.1
	4	27%	100	93	95%	14.8	0
Mansencal	7	14%	65	100	93%	-	0.35
	6	18%	85	100	97%	-	0.15
	5	23%	90	95	94%	17.1	0.11
	4	30%	100	88	90%	8.4	0
Moller	6	17%	74	99	93%	49.4	0.27
	5	20%	79	97	93%	26.5	0.22
	4	27%	89	91	91%	10.3	0.12
	3	38%	95	78	81%	4.4	0.07
Westberg	5	8%	38	100	87%	-	0.62
	4	16%	76	100	95%	-	0.24
	3	25%	100	95	96%	19.8	0
	2	34%	100	89	87%	9.3	0

LR + Likelihood ratio positive, LR – Likelihood ratio negative

Table 5.5 Diagnostic accuracy of the scoring systems

5.4 Discussion

This is the first study comparing a range of echocardiographic scoring systems for the quantitative assessment of carcinoid heart disease. There is variation in the feasibility of each of the scoring systems due to the varying complexity of the score components. The data demonstrate that all five of the established scoring systems are comparable in terms of their discriminatory ability for the detection of cardiac involvement. All of the scores correlate weakly, to a similar degree, with NTproBNP and plasma 5HIAA. The simplest score appears to be the most optimal scoring system for use in screening for carcinoid heart disease whereas the more complex scoring systems are more suited to the patient with established disease who may require surgical intervention.

The feasibility of the scoring systems varied according to the complexity of the system. Moller's score had the lowest feasibility, due to the inclusion of systolic flow reversal in the hepatic veins as not all patients had adequate sub-costal echocardiographic images for assessment of this variable. Similarly those systems that included assessment of the pulmonary leaflets had a lower feasibility as it was not possible to adequately visualise the pulmonary valve in all patients. Predictably, the simplest scoring systems had the highest feasibility.

The five established scoring systems and the new system were all able to accurately identify carcinoid heart disease in this cohort of patients. It should be noted however, that for all of the scores, it is not possible to create a cut-off point that is synonymous with a diagnosis of carcinoid heart disease. This is because patients with completely different valvular pathology and aetiology may have the same scores (see below).

The purpose of an echocardiographic scoring system for carcinoid heart disease differs depending on which scoring system is used. The more complex scoring systems, such as the Bhattacharyya score, offer a lot more information than the simpler scoring systems and are therefore

advantageous in patients who are known to have carcinoid heart disease and are under consideration for valvular surgery as the surgeon would require as much information as possible about the valvular pathology. The simpler scoring systems, such as the Westberg score, are of more use in the screening of carcinoid heart disease, as a complex description of each valve is not required in these patients but discrimination between the presence or absence of carcinoid heart disease is paramount.

Assessment of progression of carcinoid heart disease is an important aspect of echocardiographic screening and it is in this area that the scoring systems are most useful. By quantitatively assessing cardiac involvement using the same scoring system on an annual basis, it is possible to identify subtle changes in disease, and minimise error due to observer variation. The ideal scoring system is able to discriminate between those with and without carcinoid heart disease, is an accurate descriptor of the severity of disease and is also clinically simple to calculate. Ideally, it identifies those patients at highest risk of deterioration/progression hence requiring intervention and also reflects the burden of disease through its correlation with other disease markers.

The morphological and functional consequences of carcinoid heart disease are both important aspects to include in a scoring system. The tricuspid valve is most frequently affected (176) therefore assessment of its leaflets, and the degree of tricuspid regurgitation must be included in any scoring system of carcinoid heart disease. The pulmonary valve is commonly affected (although isolated pulmonary valve carcinoid heart disease is rare) (54) and incorporation of this valve into a scoring system enhances the assessment of the burden of cardiac involvement. RV dilatation and dysfunction are the consequence of chronic volume overload and/or valvular stenosis. Inclusion of these factors in a scoring system provides data on the functional significance of right-sided involvement.

Involvement of left-sided cardiac structures occurs in less than ten percent of cases (42). There is a single case report of left sided carcinoid heart disease prior to right-sided disease (39). Conversely degenerative disease of the aortic and/or mitral valves occurs in approximately two to seven percent of the population aged over 65 years (177). Carcinoid heart disease scoring systems that include the left heart can potentially produce a falsely high score in a patient without carcinoid heart disease who has degenerative left-sided valvular disease. For example a patient with a calcified mitral valve and severe mitral regurgitation may score the same as a patient with a thickened tricuspid valve and severe tricuspid regurgitation, however the aetiology of the valvular diseases is likely to be very different.

This study was a relatively small study, with only 100 patients. A large, prospective study is needed to assess whether the more complex echocardiographic scoring systems can identify minor valvular pathology that may have prognostic importance, and therefore enable identification of patients who require early surgical intervention. Furthermore, correlation of all the echocardiographic scoring systems with a patient symptom score would determine if the more complex scoring systems are able to predict a decline in symptoms or survival.

The prevalence of carcinoid heart disease in this patient population is 21%. This is comparable to other studies in the literature (52,54,55). The prevalence of significant tricuspid valve involvement in this cohort is similar to that described by Pellikka who reported that 90% of patients with carcinoid heart disease had moderate or severe tricuspid regurgitation (42).

Screening for carcinoid heart disease using echocardiography fulfills many of the criteria for an effective screening programme. The disease has an early latent phase, echocardiography is relatively easy to perform, widely available, relatively cheap, and has a high sensitivity and specificity for the detection of the disease. The majority of patients in this study with

carcinoid heart disease were asymptomatic, or had exertional symptoms only. Regular screening of patients with metastatic NETs is clearly justifiable in order to facilitate early diagnosis before the development of RV decompensation.

5.5 Conclusion

In conclusion, there is variation in the feasibility of the echocardiographic scoring systems for carcinoid heart disease, with the simplest systems having the highest feasibility. All of the scoring systems are comparable in terms of their discriminatory ability and correlation with biomarkers of carcinoid heart disease. However, the more complex scoring systems offer certain advantages over the simpler systems, as they provide a lot more information about both the structural and functional consequences of carcinoid heart disease, which is useful, particularly in the surgical setting. Universal standardisation of the approach to the assessment of carcinoid heart disease would have advantages in terms of future research studies.

The simplest scoring system, devised by Westberg *et al.*, based on tricuspid valve anatomy and regurgitation only, had the highest feasibility and was not inferior to the other scores in terms of prediction of diagnosis of carcinoid heart disease or correlation with NT-proBNP and plasma 5HIAA. This simple, eight point scoring system may be the most optimal for use in screening of carcinoid heart disease whereas the more complex scoring systems are more suited to the patient with established disease who may require surgical intervention.

Chapter 6: Serial Surveillance of Carcinoid Heart Disease: Factors Associated with Echocardiographic Progression and Mortality

Abstract

6.1 Introduction

6.2 Methods

6.21 Assessment of disease severity

6.22 Definitions of progression

6.23 Categorisation of progression vs. non-progression vs. death

6.24 Inter-observer variability

6.3 Results

6.31 Patient demographics

6.32 Clinical variables

6.33 Biochemical variables

6.34 Radiological variables

6.35 Carcinoid heart disease score

6.36 Death

6.4 Discussion

6.5 Conclusion

Abstract

Introduction Carcinoid heart disease is a complication of metastatic NETs. The aim of this study was to identify factors associated with echocardiographic progression of carcinoid heart disease and death in patients with metastatic NETs.

Methods Patients with advanced non-pancreatic NETs and documented liver metastases and/or carcinoid syndrome underwent prospective serial clinical, biochemical, echocardiographic and radiological assessment. Patients were categorised as carcinoid heart disease progressors, non-progressors or deceased. Multinomial regression was used to assess the univariate association between variables and carcinoid heart disease progression.

Results One hundred and thirty-seven patients were included. Thirteen patients (nine percent) were progressors, 95 (69%) non-progressors and 29 (22%) patients deceased. Baseline median levels of serum NTproBNP and plasma 5HIAA were significantly higher in the progressors. Every 100 nmol/L increase in 5HIAA yielded a five percent greater odds of disease progression (OR 1.05, 95% CI: 1.01, 1.09; *P*=0.012) and a seven percent greater odds of death (OR 1.07, 95% CI: 1.03, 1.10; *P*=0.001). A 100ng/L increase in NTproBNP did not increase the risk of progression, but did increase the risk of death by 11%.

Conclusion The biochemical burden of disease, in particular baseline plasma 5HIAA concentration, is independently associated with carcinoid heart disease progression and death. Clinical and radiological factors are less useful prognostic indicators of carcinoid heart disease progression and/or death.

6.1 Introduction

NETs have a heterogeneous natural history. They may follow an indolent course, progressing slowly over many years (9). However the development of carcinoid heart disease is associated with adverse clinical outcomes (129). Serotonin is implicated in the development of carcinoid heart disease (43,153), however high circulating levels of serotonin have a limited specificity for cardiac involvement and it is likely that there are other contributing factors to the pathogenesis and progression of carcinoid heart disease. There are limited data on factors associated with the progression of carcinoid heart disease in the literature. Several papers have identified high urinary 5HIAA levels to be independent predictors of progression (4,49,122).

It is not known how frequently NET patients should be screened for carcinoid heart disease, with consensus guidelines recommending 'regular' echocardiography (126). Furthermore, there is uncertainty surrounding how frequently to scan those with established carcinoid heart disease to monitor for disease progression. Identification of factors associated with the development and progression of carcinoid heart disease may aid development of more specific, evidence-based guidelines both for screening, monitoring and management of the disease.

No previous studies that have assessed the progression of carcinoid heart disease in a population of patients with liver metastases, with or without the carcinoid syndrome have been identified. The purpose of this observational cohort study was therefore to prospectively identify the clinical, biochemical and radiological characteristics that are associated with the development and progression of carcinoid heart disease and overall survival, in a population of patients with metastatic NETs and/or carcinoid syndrome.

6.2 Methods

For an in-depth explanation of recruitment, echocardiographic, biochemical and statistical methods, please refer to chapter two.

6.21 Assessment of Disease Severity

Clinical: Patients' symptoms were assessed at the time of echocardiography, with specific questions regarding frequency of flushing, diarrhoea, wheezing, breathlessness and/or ankle swelling. Carcinoid syndrome was defined as episodes of cutaneous flushing, diarrhoea or wheezing.

Radiological: Baseline contrast enhanced CT imaging of the chest, abdomen and pelvis was performed in all patients and repeated at 12 monthly intervals. All CT scans were reviewed by radiologists with expertise in the assessment of NETs and radiological progression was defined in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (178).

Echocardiographic: Echocardiograms were performed as per the methods delineated in chapter two. Echocardiograms were performed at 12 monthly intervals, or sooner if clinically indicated.

6.22 Definitions of Progression

Symptomatic progression was defined as >50% increase in the number of daily flushing episodes or bowel movements compared to the previous visit, as used in a similar previous study (4).

Biochemical progression was defined as > 50% increase in NTproBNP or plasma 5HIAA from the baseline value.

Echocardiographic progression of carcinoid heart disease was defined as an increase in the degree of tricuspid regurgitation, and/or an increase in the degree of tricuspid leaflet thickening or immobility.

6.23 Categorisation of Progression vs. Non-progression vs. Death.

Patients were classified as carcinoid heart disease progressors or non-progressors. Patients who died prior to a second echocardiogram, in whom assessment of progression was not possible were categorised as deceased. Those who died after their second scan were classified as either progressors or non-progressors. Where a subject died prior to the second echocardiographic assessment the interval between first assessment and date of death was recorded. The presence or absence of carcinoid heart disease at baseline was also noted.

6.24 Inter-observer Variability

Inter-observer agreement was ascertained as per the methods in chapter two. A randomly selected sub-group of 80 echocardiographic studies (58%) was cross-checked by a different observer blinded to the initial echocardiographic score. In 70 studies (88%) the assigned scores were concordant, whilst in the remaining ten studies there was discordance, (mean difference 0.234).

6.3 Results

6.31 Patient Demographics

One hundred and forty-eight patients were prospectively assessed for their eligibility to participate in the study. Four patients were lost to follow up and seven patients were excluded due to inadequate echocardiographic windows precluding clear visualisation of all valves, resulting in a total of 137 patients studied (figure 6.1).

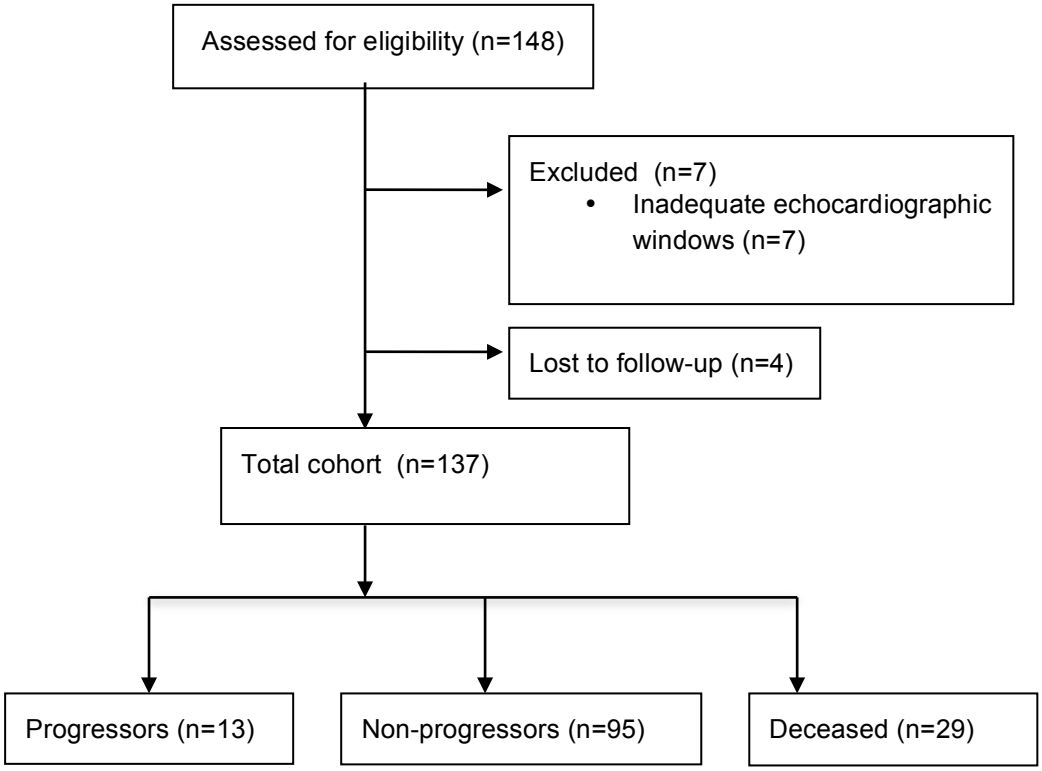


Figure 6.1 Consort flow diagram

The median duration of follow up from first scan to last scan or death was 27 months (interquartile range 12-37), with a total of 2862 patient years. Twenty-six patients (19%) had carcinoid heart disease at the beginning of the study.

6.32 Clinical Variables

During the follow-up period, nine patients had echocardiographic evidence of progression of carcinoid heart disease and four patients developed *de novo* cardiac involvement. Twenty-nine patients died in the first year of follow-up, without undergoing a second echocardiogram. The baseline characteristics of the patient population are illustrated in table 6.1.

There were no significant differences in age, gender or primary tumour site between the three groups. Disease duration was significantly shorter in the deceased group (15 months, P=0.005) but there was no difference in duration of disease between progressors and non-progressors (52 v 64 months, P=0.554). Tumour grade differed significantly between the groups (P<0.0001) with a higher proportion of grade two (intermediate) tumours in the progressor group, and a higher proportion of grade three (high grade) tumours in the deceased group. The origin of the primary tumour in those with grade three disease was small bowel (one patient), stomach (one patient) and recto-sigmoid (two patients). All of these patients had hepatic metastases.

Variable	Progression of CHD (n=13)	No progression of CHD (n=95)	Died prior to 2nd echo (n=29)	P value
Demographics				
Age (years) †	68 ± 13	67 ± 10	70 ± 11	0.112
Male sex (no %)	5 (39%)	55 (58%)	16 (55%)	0.417
Follow up (months) ◊	29 (13-41)	27 (12-37)	-	0.887
Clinical Characteristics				
Tumour grade (no %)				
Grade 1	1 (8%)	55 (58%)	9 (31%)	**0.007**
Grade 2	3 (23%)	7 (7%)	2 (7%)	
Grade 3	0	0	4 (14%)	
Unknown	9 (69%)	33 (35%)	14 (48%)	
Duration of disease (months) ◊	52 (27-138)	64 (40-88)	15 (9-59)	**0.005**
Site of primary tumour:				
Small bowel	8 (62%)	71 (75%)	19 (66%)	0.126
Large bowel	1 (8%)	7 (7%)	1 (3%)	
Lung	0	1 (1%)	2 (7%)	
Other	1 (8%)	1 (1%)	3 (10%)	
Unknown	3 (24%)	15 (16%)	4 (14%)	
Liver metastases	11 (85%)	80 (84%)	27 (93%)	0.473
Carcinoid syndrome	12 (92%)	63 (66%)	21 (72%)	0.151
Baseline carcinoid heart disease	9 (70%)	5 (5%)	12 (41%)	**<0.001**
Baseline echocardiographic score	9 (7.5-14)	3 (1-5)	5 (2.5-14.5)	**<0.001**
Baseline NTproBNP (ng/L)	267 (108-578)	84 (29-224)	401 (116-978)	**0.001**
Baseline 5HIAA (nmol/L)	2247 (807-2939)	316 (138-661)	1221 (167-4370)	**0.009**
Therapeutic Intervention				
SSA therapy	12 (92%)	78 (82%)	17 (59%)	**0.012**
Primary tumour resection	6 (46%)	63 (66%)	7 (24%)	**<0.001**
Resection of hepatic metastases	1 (8%)	9 (10%)	2 (7%)	0.903
Interferon	0	8 (8%)	2 (7%)	0.547
Chemotherapy	0	10 (10%)	6 (21%)	0.111
Targeted radio-nuclide therapy	4 (31%)	27 (28%)	4 (14%)	0.259
Chemo-embolisation	1 (8%)	11 (12%)	0	0.154
Radio-frequency ablation	0	6 (6%)	0	0.25

† Mean ± standard deviation, ◊ Median and interquartile range

Table 6.1 Baseline characteristics of patients

Worsening of carcinoid syndrome symptoms was associated with progression of carcinoid heart disease. Eighty-five percent of those with symptom deterioration demonstrated progression of carcinoid heart disease compared with five percent of those with no symptom deterioration (*P*<0.001, table 6.3). Although worsening of symptoms was independently associated with progression of carcinoid heart disease; OR 99 (95% CI 17-573, *P*<0.001, table 6.2) the wide confidence interval implies some uncertainty in this estimate.

The numbers of patients that underwent primary tumour resection or received SSAs were significantly different between the groups (table 6.1). There was however, no difference in the proportions of patients undergoing hepatic resection, trans-arterial chemo-embolisation, targeted radionuclide therapy, radiofrequency ablation or chemotherapy between the groups. The risk of death in those who had not had a primary tumour resection was approximately 3.7 times greater than in those who had undergone a primary resection (OR 3.72, 95% CI: 1.60-8.69; *P*<0.002) but primary resection did not increase the odds of carcinoid heart disease progression (OR 2.30, 95% CI: 0.71-7.40; *P*=0.164).

6.33 Biochemical Variables

Baseline plasma 5HIAA and NTproBNP concentrations were significantly different between the groups (table 6.1 & figure 6.2) with the highest NTproBNP levels seen in the deceased group and the highest 5HIAA concentrations in the progressors. Baseline 5HIAA concentration was significantly associated with disease progression: every 100 nmol/L increase in 5HIAA yielded a five percent greater odds of disease progression (OR 1.05, 95% CI: 1.01, 1.09; *P*=0.012) and a seven percent higher odds of death before second follow-up (OR 1.07, 95% CI: 1.03, 1.10; *P*=0.001, see table 6.2). The proportion of patients with NTproBNP or 5HIAA progression was significantly higher in the progressors

compared to the non-progressors (62% v 31%, *P*=0.04 and 46% v 18%, *P*=0.035 respectively, see table 6.3).

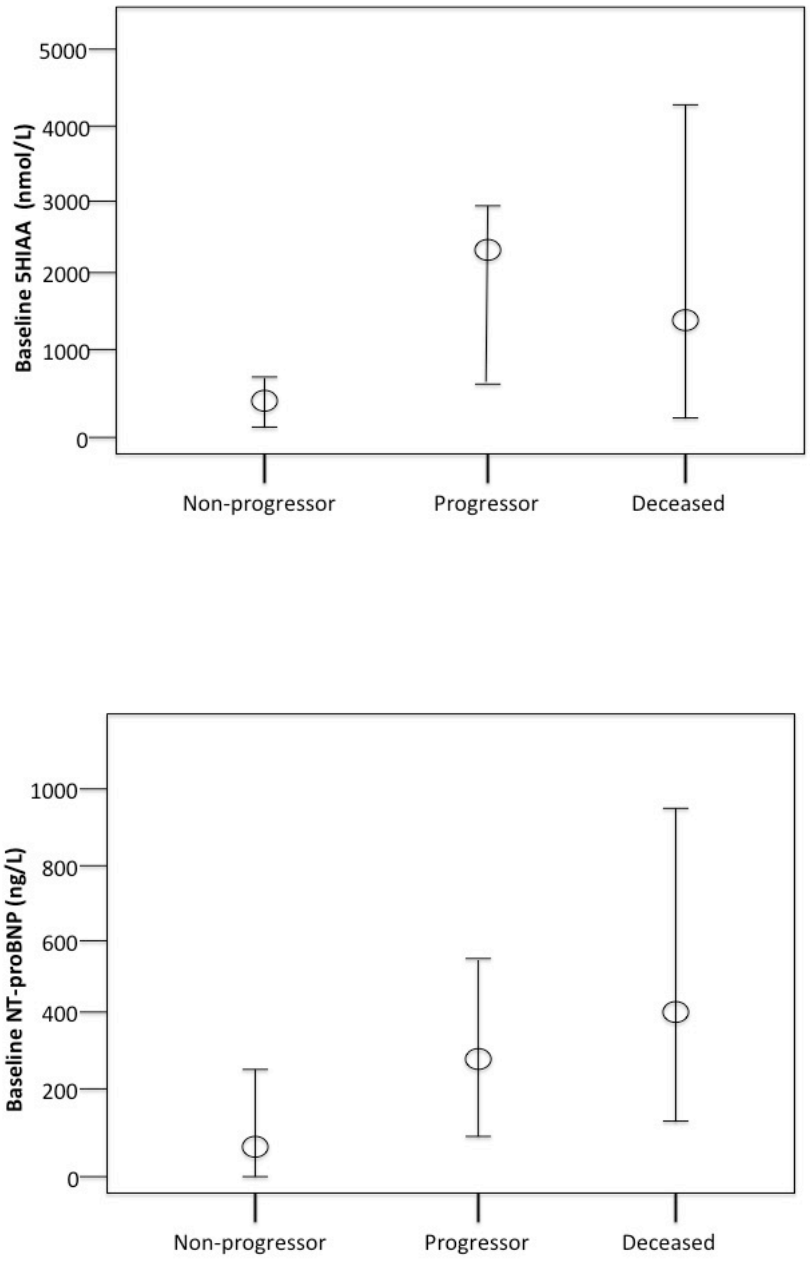


Figure 6.2 Baseline 5HIAA and NTproBNP according to patient group

6.34 Radiological Variables

Increase in tumour bulk was not associated with progression of carcinoid heart disease. Ten percent of those with stable disease demonstrated progression of carcinoid heart disease compared to 13% of those with an increase in tumour bulk (*P*=0.669), OR 0.76 (95% CI 0.22-2.66, *P*=0.670, table 6.2).

Variable	Unit change	Group	OR (95% CI)	P value
Age (years)	5 years	Progression	1.09 (0.82-1.45)	0.570
	5 years	Death	1.16 (0.94-1.43)	0.167
Disease duration (months)	100 months	Progression	0.99 (0.36-2.72)	0.986
	100 months	Death	0.22 (0.07-0.73)	**0.013**
Symptom deterioration	-	Progression	99 (17-573)	**<0.001**
Baseline NTproBNP (ng/L)	100 units	Progression	1.04 (0.92-1.18)	0.486
	100 units	Death	1.11 (1.02-1.21)	**0.014**
Baseline 5HIAA (nmol/L)	100 units	Progression	1.05 (1.01-1.09)	**0.012**
	100 units	Death	1.07 (1.03-1.10)	**0.001**
Radiological increase in tumour bulk	-	Progression	0.76 (0.22-2.66)	0.670

Table 6.2 Multinomial logistic regression analysis

Variable	Progression of carcinoid heart disease (n=13)	No progression of carcinoid heart disease (n=95)	*P* value
Symptomatic deterioration **Δ**	11 (85%)	5 (5%)	**<0.001**
NTproBNP progression **Ψ**	8 (62%)	24 (31%)	**0.04**
Plasma 5HIAA progression **Ψ**	6 (46%)	14 (18%)	**0.035**
Radiological progression ϒ	4 (31%)	35 (37%)	0.461

Δ > 50% increase in the number of daily flushing episodes or bowel movements compared to the previous visit
Ψ > 50% increase from the baseline value
ϒ in accordance with RECIST (Response Evaluation Criteria in Solid Tumors) guidelines

Table 6.3 Association of variables with progression of carcinoid heart disease

6.35 Carcinoid Heart Disease Score

Increasing echocardiographic score was an independent predictor of both carcinoid heart disease progression and death. A five-point increase in the score was associated with an OR of 2.95 (95% CI 1.71-5.09, *P*<0.005) for carcinoid heart disease progression and 2.66 (95%CI 1.63-4.35, *P*<0.005) for death.

6.36 Death

The deceased patients had significantly shorter durations of disease (15 months v 64 months in the non-progressors and 52 months in the progressors, *P*=0.005). They also had histologically more aggressive tumours (14% high grade v 0% in the other groups, *P*<0.001). Of the 29 deceased patients, 12 (41%) had carcinoid heart disease. In a univariate Cox proportional hazard model, the risk of death in those with carcinoid heart disease at baseline was significantly greater than in those without carcinoid heart disease (hazard ratio 3.61, 95% CI (1.69 - 7.69), *P*=0.001). Figure 6.3 shows Kaplan Meier survival estimates according to presence or absence of baseline carcinoid heart disease.

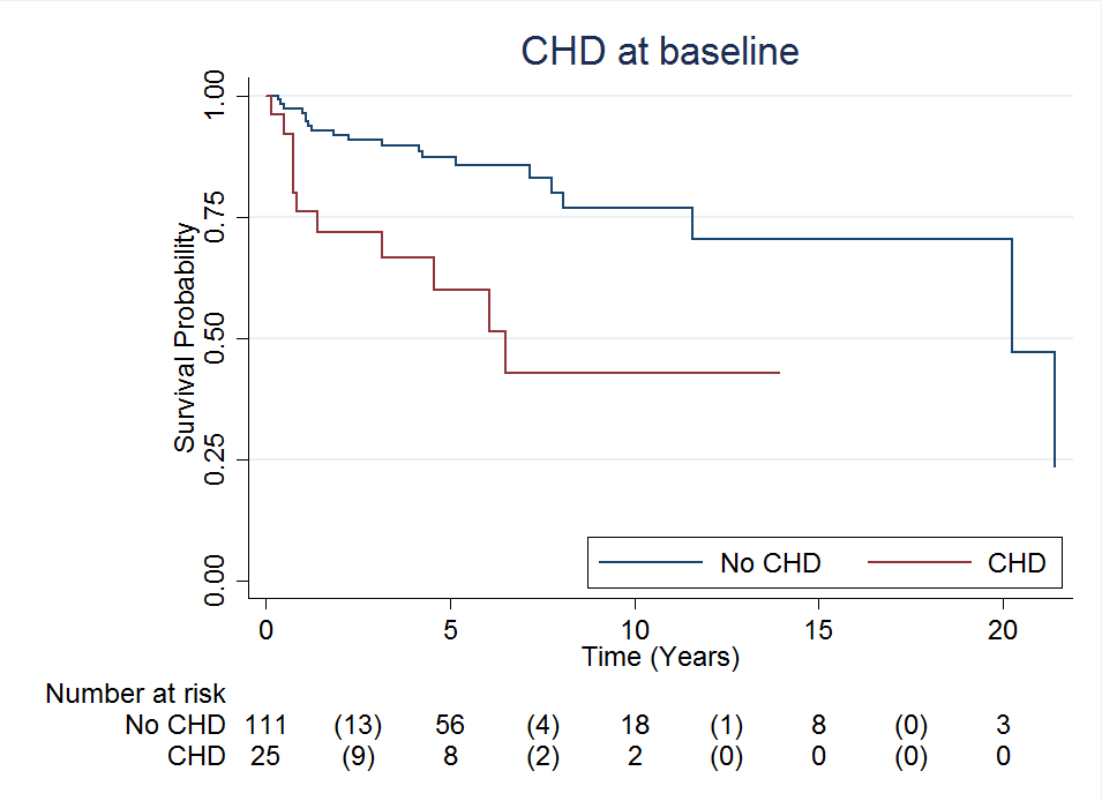


Figure 6.3 Effect of baseline carcinoid heart disease on survival

6.4 Discussion

This large, prospective, observational cohort study has demonstrated that biochemical variables, in particular baseline plasma 5HIAA concentration, are independently associated with carcinoid heart disease progression in patients with metastatic NETs and have greater prognostic value than clinical or radiological variables.

The finding of the value of plasma 5HIAA concentration in the prediction of carcinoid heart disease progression is consistent with results from Bhattacharyya *et al.* and Moller *et al.* who demonstrated similar associations between carcinoid heart disease progression and urinary 5HIAA concentrations (4,122). Serotonin is a major biochemical mediator of carcinoid heart disease (179,180) and therefore the measurement of its main metabolite, 5HIAA, is a logical biomarker to measure. Plasma measurement of 5HIAA is easier for the patient, and correlates well with the more traditional 24-hour urinary measurement (67). The data demonstrate that both NTproBNP and 5HIAA are independently associated with death in patients with metastatic NETS and/or carcinoid syndrome. An elevated NTproBNP concentration may reflect other factors known to increase risk of death such as NYHA class III-IV or RV dilatation. Biochemical measurement is, however, a more objective measurement than attempting to evaluate NYHA class which is notoriously difficult to estimate (181).

Patients with symptomatic deterioration were more likely to demonstrate carcinoid heart disease progression than those with stable symptoms. This finding is similar to that of Bhattacharyya *et al.* and is likely to be due to higher serotonin levels in the patients with worsening symptoms of the carcinoid syndrome. Use of SSA therapy was more common in the progressors, which may be a reflection of more advanced disease in this patient group.

This study found no relationship between radiological progression and progression of carcinoid heart disease. However, resection of the primary tumour was more common in the non-progressors than in the progressors or deceased groups. This may support previous findings suggesting that a reduction in tumour burden by hepatic resection may decrease the risk of progression of carcinoid heart disease through the reduction in circulating hormone levels (124).

The rate of progression of carcinoid heart disease is difficult to estimate due to the number of deaths in this study (no progression data available for these patients). The progression rate could be as low as ten percent (13/137) or as high as 31% (42/137), but is likely to fall somewhere within this range, in keeping with the progression rates of similar studies (4,122).

There are several limitations to this study. First is the lack of a standardised definition of carcinoid heart disease progression, although this limitation can be applied to all similar studies. As the echocardiographic score assesses both sides of the heart, an increase in the score could be due to co-existing pathology such as degenerative mitral valve disease, and therefore using an absolute increase in the echocardiographic score as the determinant of carcinoid heart disease progression would lead to an overestimate of the number of patients demonstrating progression. For this reason a clinical definition was used. The author also acknowledges the relatively short duration of follow up in the study and the heterogeneity of the study population with differences in tumour biology/grade, types and duration of treatment modalities and duration of diagnosis. This limitation may be overcome in larger, perhaps national studies, in which common therapeutic pathways and algorithms may be adopted and longer-term outcome available. Finally cause of death was unknown and it is uncertain in all individuals whether death was attributable to NET disease progression, to carcinoid heart disease progression or to an unrelated cause.

6.5 Conclusion

The findings of this study suggest that it is the biochemical or hormonal burden of disease, rather than radiological extent or duration of disease that dictates development and progression of carcinoid heart disease. This implies that any treatments, medical (e.g. SSAs) or surgical (resection of primary tumour) that reduce secretion of vasoactive substances may be protective against the development and progression of carcinoid heart disease.

Chapter 7: Discussion

7.1 Introduction

7.2 Variation in screening for and management of carcinoid heart disease

7.3 Biochemical markers of presence and severity of carcinoid heart disease

7.4 Echocardiographic assessment of carcinoid heart disease

7.5 Progression of and mortality from carcinoid heart disease

7.6 Conclusion and future directions

7.1 Introduction

Carcinoid heart disease, a rare form of valvular heart disease, is an important complication of neuroendocrine disease. Due to a lack of data within the literature, there is considerable heterogeneity within international consensus guidelines for this condition. This project was conducted to add to the evidence base for carcinoid heart disease so that some of the gaps in the literature could be addressed and clearer guidelines for the condition could be developed.

7.2 Variation in Screening for and Management of Carcinoid Heart Disease

Screening for carcinoid heart disease amongst patients with metastatic NETs is imperative in order to identify patients who may have asymptomatic cardiac involvement, before they develop irreversible RV dysfunction. Due to inconsistencies in international guidelines, it was suspected that clinical practice varied considerably with respect to carcinoid heart disease across the UK and Republic of Ireland.

In chapter three it was demonstrated that compliance with current UK guidelines for carcinoid heart disease is relatively poor. It was found that the management of carcinoid heart disease is often sub-standard, reflected by the wide variations in the population screened, in the frequency and mode of screening and in access to local cardiology expertise.

Standardisation of nationwide practice in the management of carcinoid heart disease in accordance with a consensus guideline would facilitate a UK registry of patients with carcinoid heart disease to better understand the natural history and prognosis of this condition and potentially improve patient outcomes for the disease across the UK and Ireland.

7.3 Biochemical Markers of Presence and Severity of Carcinoid Heart Disease

Biochemical markers are useful clinical aids in the assessment of carcinoid heart disease. A variety of biomarkers have been investigated for the diagnostic and prognostic assessment of carcinoid heart disease but many have limited clinical utility due to difficulties in their measurement, false-positive results or lack of data (29,55,68,71,175).

In chapter four a panel of biomarkers (NTproBNP, 5HIAA, CgA, CgB and NkA) was investigated and it was demonstrated that the median concentrations of all five biomarkers are significantly higher in patients with carcinoid heart disease compared to those with metastatic NETs and no evidence of carcinoid heart disease. However NTproBNP and plasma 5HIAA have the greatest discriminatory value in the diagnosis of carcinoid heart disease.

We advocate the use of NTproBNP in patients with metastatic NETs as a tool to assess the presence of cardiac involvement. We propose that all such patients undergo a baseline echocardiogram at diagnosis or initial assessment, and if there is no evidence of cardiac involvement, echocardiography is only repeated in the event of an increase in NTproBNP.

It is likely that, with continued research, new biomarkers with increased specificity and sensitivity for carcinoid heart disease will be identified and used in the future.

7.4 Echocardiographic Assessment of Carcinoid Heart Disease

Transthoracic echocardiography is the key imaging modality for the evaluation of carcinoid heart disease. The chronic and progressive nature of the disease mandates serial assessment in order to identify progression of cardiac involvement, an important aspect of managing patients with NETs.

A range of echocardiographic scoring systems have been described in the literature for the quantitative assessment of carcinoid heart disease (49,50,53,122,123). Chapter five compares these scoring systems and investigates their differing uses.

Variation in the feasibility of each of the scoring systems was identified, however all of the established echocardiographic scoring systems, and a newly devised scoring system, were able to accurately discriminate between NET patients with and without carcinoid heart disease.

The simplest scoring system, devised by Westberg *et al.*, (50) was the most optimal for use in the screening of carcinoid heart disease. The more complex and comprehensive scoring systems were more suited to the patient with established disease, who requires serial echocardiograms and who may require surgical intervention.

Universal standardisation of the echocardiographic approach to the assessment of carcinoid heart disease would have advantages in terms of future research studies and would enable a structured, cohesive approach to all patients with metastatic NETs.

7.5 Progression of and Mortality From Carcinoid Heart Disease

Progression of carcinoid heart disease is an adverse prognostic sign (50). There are limited data on factors associated with the progression of carcinoid heart disease in the literature, due, in part, to the lack of a standardised definition of progression of carcinoid heart disease. Several papers have identified a high urinary 5HIAA level to be independent predictor of progression (4,49,122).

In chapter six the effect of biochemical, radiological and clinical variables on the progression of carcinoid heart disease was investigated. The data demonstrate that biochemical variables, in particular baseline plasma 5HIAA concentration, are independently associated with carcinoid heart disease progression in patients with metastatic NETs and have greater prognostic value than clinical or radiological variables.

With regard to mortality, the data demonstrate that both NTproBNP and 5HIAA are independently associated with death in patients with metastatic NETS and/or carcinoid syndrome. This implies that any treatments, medical (e.g. SSAs) or surgical (resection of primary tumour) that reduce secretion of vasoactive substances may be protective against the development and progression of carcinoid heart disease.

7.5 Conclusion and Future Directions

This thesis has attempted to address the gaps in the literature with regard to the screening, diagnosis and progression of carcinoid heart disease.

- There is wide variation in clinical practice with respect to screening methods for carcinoid heart disease and there is a need for a comprehensive, consensus guideline on the screening and management of carcinoid heart disease in order to standardise the clinical approach and optimise patient care.
- NTproBNP and plasma 5HIAA have the greatest discriminatory value in the diagnosis of carcinoid heart disease and should be used in the screening and assessment of the disease.
- The Westberg scoring system is the most optimal for use in the screening of carcinoid heart disease whereas the more complex scoring systems are more suited to the patient with established disease who may require surgical intervention.
- Biochemical variables, in particular baseline plasma 5HIAA concentration, are independently associated with carcinoid heart disease progression in patients with metastatic NETs and have greater prognostic value than clinical or radiological variables.

There are still some questions left to be answered, which require further research. In particular, we have not yet ascertained why only 20% of patients with carcinoid syndrome develop carcinoid heart disease, or what protects the other 80% of patients. Despite a theoretical advantage of treating carcinoid heart disease with SSAs, we have been unable to demonstrate any clear benefit in terms of a lower incidence of the disease or delayed progression of the condition. This may be explained by a treatment bias (the most symptomatic patients are the most likely to have the highest 5HIAA levels and be using SSAs). Further research is required to address these issues and better integration between NET centres and

greater centralisation of care is also required to optimise management of this important condition.

At a local level, the author has produced a screening protocol for carcinoid heart disease for the NET centres involved in the project and has established a dedicated cardiologist on the NET multi-disciplinary team at the base site.

Since the completion of this project, the UK guidelines for the screening and management of carcinoid heart disease have been re-developed with a more up-to-date evidence base (in progress). The work contained within this thesis has contributed to the drafting of these guidelines and the author of this thesis is one of the guideline's 12 co-authors.

Appendix I Consent Form

Consent form (V 3, 2012)

Centre Number:
Patient Identification Number for this trial:

Title of Project: *Improving our understanding of carcinoid heart disease*

Name of Researcher: Dr. Rebecca Dobson

	Please initial boxes to confirm
I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study.	☐
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree to my GP being informed of my participation in the study.	☐
I agree to take part in the above research study.	☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

When complete, 1 copy for patient: 1 copy for researcher site file: 1 (original) to be kept in medical notes.

Appendix II Patient information Sheet

Improving our understanding of carcinoid heart disease

(Using novel biochemical and genetic markers to predict severity of carcinoid heart disease described using modern echocardiographic techniques.)

Participant Information Sheet

Invitation

We invite you to participate in a research project. Before you decide we need to ensure you understand why the project has been set up and what it involves.

Please read through this leaflet carefully. You may, if you wish, discuss this with family, friends or your GP. We will be available to explain and provide any further information you may require. You do not have to make an immediate decision.

As your GP is your primary care provider we will inform your GP of your participation in this study. Your GP will receive an information sheet similar to this.

Background

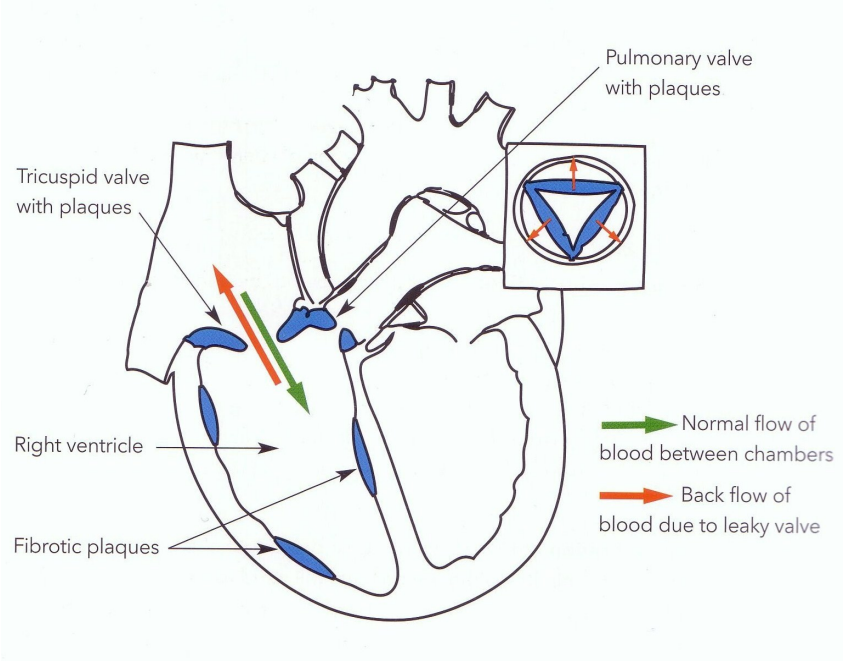
Carcinoid tumours are a form of slow growing cancer, which is often associated with a very good outlook. Carcinoid tumours may arise from anywhere but are predominantly found in the digestive tract (bowel). At diagnosis it is common to find the Carcinoid tumour has spread from the digestive tract to the peritoneum (the outer lining of the bowel) and/or the liver a process called metastasis. The outlook for patients with carcinoid tumours and metastases is good, unlike many other cancers.

Patients with carcinoid tumours may have no symptoms. Some patients (approximately 1 in 4) experience flushing (intense redness commonly of the face) and diarrhoea. This combination of symptoms is referred to as *Carcinoid syndrome*. Hormones produced by the tumour cause carcinoid syndrome. Not all Carcinoid tumours produce hormone and in many cases the hormone produced is removed in the liver before it can produce symptoms. Carcinoid syndrome is more common in patients who have liver metastasis.

The same hormones that produce the symptoms of the Carcinoid syndrome may also cause damage to the valves on the right side of the heart (tricuspid and pulmonary valves), called *Carcinoid Heart Disease (CHD)*. There is currently no evidence on who is most likely to develop CHD, when it develops, or how to screen for it. CHD does not usually require active management. However, rarely,

surgery is required to replace the damaged valve. In these situations valve surgery has been shown to improve outcome.

It is usual practice for patients with carcinoid tumours to have assessments every 6-12 months. These will include blood and urine tests and an echocardiogram (heart scan). As we are interested in carcinoid disease we would like to take some additional blood and urine tests and additional echocardiographic images.



Reproduced with permission NET patient foundation

What does the study involve?

You will be asked to see Dr. Rebecca Dobson (study investigator) in a private examination room. She will ask you to give written consent to take part in the study. With your permission the following tests will be performed:

Blood samples

A needle will be inserted into a vein in your arm. We will use this to take approximately 20mls (4 teaspoons full) of blood. The needle will then be removed.

Echocardiogram

An echocardiogram is an ultrasound scan of the heart. Ultrasound is a technology which uses high frequency sound waves (above the audible range) to form an image. This is the same technology that is used to look at unborn children and is completely safe. During the scan a probe is placed in particular regions on your chest the image being acquired through the probe. The image is improved with the use of a water-based gel (applied to the skin on the chest) which wipes off at the end of the procedure. This whole process will take between 30-45minutes.

Possible disadvantages and risks of taking part
The risks involved in blood sampling are very small. Occasionally there is mild bruising due to leakage from a blood vessel but this is rare with good practice.

There are no risks in collecting additional echocardiographic images.

Occasionally we may find an unexpected abnormality (unrelated to the study), which may require medical follow-up with either further investigation or (more rarely) treatment. If this is the case we will send a report to your GP and your consultant allowing prompt investigation and treatment.

The tests we will perform are an extension of normal clinical care so we will not be offering financial reimbursement.

What happens to the blood samples that have been taken?
The samples taken will be stored securely in University Hospital Aintree. They will then be analysed and the results anonymised (i.e. linked to a special code that is stored separately on a password protected computer file) and stored on a computer file. The computer file will be stored on a secure University computer in the Clinical Sciences Building University Hospital Aintree. Only members of the research team will have access to your details, samples and results. Samples will be sent for analysis to the Royal Victoria Hospital, Belfast, and to the University Hospital of South Manchester (Wythenshawe Hospital).

How long will it take?
The additional tests will take 60 minutes. You will be asked to return for a further similar assessment in 6-12 months.

Audit
In studies such as this it is a requirement for the data collected to be available for review by an external professional body for the purpose of audit (to check the data is collected in the proper manner). Should this be required the data will be made available.

Finally I would like to reassure you that if you do not participate your treatment will **not** be compromised. If you decide to participate you are free to withdraw at any time. If you desire any data collected, as part of the project, relating to you can be erased.

Contact numbers:
If there are any questions please contact:
Dr Rebecca Dobson
Specialist Registrar in Cardiology
Clinical Sciences Centre,
University Hospital Aintree,
University of Liverpool.
L9 7AL
Email: rebecca.dobson@liverpool.ac.uk
Tel: 0151 5295917

Appendix III– Title pages of publications pertaining to results chapters(182-185)

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Original Article

Variation in Cardiac Screening and Management of Carcinoid Heart Disease in the UK and Republic of Ireland

R. Dobson *†, J.W. Valle ‡, M.I. Burgess *, G.J. Poston *, D.J. Cuthbertson *†

* *Neuroendocrine Tumour Group, University Hospital Aintree, Liverpool, UK*
† *Department of Obesity and Endocrinology, University of Liverpool, Clinical Sciences Building, University Hospital Aintree, Liverpool, UK*
‡ *Manchester Academic Health Sciences Centre, Department of Medical Oncology, The Christie NHS Foundation Trust, Withington, Manchester, UK*

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Abstract

Aims: Screening for carcinoid heart disease is an important, yet frequently neglected aspect of the management of patients with neuroendocrine tumours (NETs). Screening is advocated in international guidelines, although recommendations on the modality and frequency are poorly defined. We mapped current practice for the screening and management of carcinoid heart disease in specialist NET centres throughout the UK and Republic of Ireland.
Materials and methods: Thirty-five NET centres were invited to complete an online questionnaire outlining the size of NET service, patient selection criteria for carcinoid heart disease screening and the modality and frequency of screening.
Results: Twenty-eight centres responded (80%), representing over 5500 patients. Eleven per cent of centres screen all patients with any NET, 14% screen only patients with midgut NETs, 32% screen all patients with liver metastases and/or carcinoid syndrome and 43% screen all patients with evidence of syndrome or raised urinary/serum/plasma 5-hydroxyindoleacetic acid (5HIAA). The mode of screening included clinical examination, echocardiography and biomarker measurement: 89% of centres carry out echocardiography, ranging from at initial presentation only (24%), periodically without clearly defined intervals (28%), annually (36%) or less than annually (12%); three centres use a scoring system to report their echocardiograms. Fifty per cent of centres utilise biomarkers for screening (chromogranins, plasma/urinary 5HIAA or most commonly N-terminal pro-brain natriuretic peptide) at varying time intervals.
Conclusion: There is considerable heterogeneity across the UK and Ireland in multiple aspects of screening and management of carcinoid heart disease.

Key words: Carcinoid heart disease; management; neuroendocrine; screening

Introduction

Carcinoid heart disease is a complication of metastatic neuroendocrine disease and occurs in 20–50% of patients with the carcinoid syndrome [1,2]. The cardiac manifestations of neuroendocrine tumours (NETs) are a consequence of tumour secretion of vasoactive substances such as serotonin, prostaglandins, tachykinins and histamine [3,4]. Hepatic metastases enable these substances to reach the right heart without being inactivated [5]. Rarely, carcinoid heart disease may occur in the absence of liver metastases, for example, in primary ovarian NETs, when the ovarian venous drainage bypasses the portal venous system [6,7].

Carcinoid heart disease can be clinically silent, with no symptoms or signs of disease, even in patients with advanced pathology [8,9]. However, cardiac involvement has significant prognostic implications; a 3 year survival for patients with carcinoid heart disease of 31% compared with 68% for those with no cardiac involvement [10]. The prognosis has improved in recent years, with the median survival about 4 years from diagnosis [11], but this is still significantly shorter than the median survival duration of 10 years of patients with grade 1 NETs [12]. As moderate to severe right ventricular dilatation and New York Heart Association Class III–IV symptoms are associated with

Author for correspondence: R. Dobson, Clinical Sciences Centre, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, UK. Tel: +44-151-529-5917; Fax: +44-151-529-5888.
E-mail address: rebecca.dobson@liverpool.ac.uk (R. Dobson).

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0936-6555/

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PLOS ONE

The Association of a Panel of Biomarkers with the Presence and Severity of Carcinoid Heart Disease: A Cross-Sectional Study

Rebecca Dobson[1,11]*, Malcolm I. Burgess[1,2], Melissa Banks[1], D. Mark Pritchard[3,4], Jiten Vora[4], Juan W. Valle[5], Christopher Wong[1,2], Carrie Chadwick[1], Keith George[6], Brian Keevil[7], Joanne Adaway[7], Joy E. S. Ardill[8], Alan Anthoney[9], Uschi Hofmann[10], Graeme J. Poston[1], Daniel J. Cuthbertson[1,11]

1 Neuroendocrine Tumour Group, University Hospital Aintree, Liverpool, Merseyside, United Kingdom, **2** Department of Cardiology, University Hospital Aintree, Liverpool, Merseyside, United Kingdom, **3** Department of Gastroenterology, Institute of Translational Medicine, University of Liverpool, Liverpool, Merseyside, United Kingdom, **4** Neuroendocrine Tumour Group, Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom, **5** Manchester Academic Health Sciences Centre, Department of Medical Oncology, The Christie NHS Foundation Trust, Withington, Manchester, United Kingdom, **6** Research Institute for Sport & Exercise Sciences, Liverpool John Moores University, Liverpool, Merseyside, United Kingdom, **7** Department of Clinical Chemistry, University Hospital of South Manchester, Wythenshawe, Manchester, United Kingdom, **8** Regional Peptide Laboratory, Kelvin Building, Royal Victoria Hospital, Belfast, United Kingdom, **9** Medical Oncology, CRUK Clinical Cancer Centre, St James University Hospital, Leeds, Yorkshire, United Kingdom, **10** Medical Oncology, Huddersfield Royal Infirmary, Lindley, Huddersfield, Yorkshire, United Kingdom, **11** Department of Obesity and Endocrinology, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool Merseyside, United Kingdom

Abstract

Purpose: Metastatic neuroendocrine tumors secrete serotonin and other vasoactive substances that are responsible for carcinoid syndrome and carcinoid heart disease. We sought to evaluate the discriminatory utility of diagnostic biomarkers in determining the presence and severity of carcinoid heart disease in patients with metastatic neuroendocrine tumors.

Patients and methods: A cross-sectional study of patients with neuroendocrine tumors with documented liver metastases and/or carcinoid syndrome between April 2009–October 2012 in 5 tertiary referral centers. Serum was analyzed for Chromogranin A, Chromogranin B and N-terminal pro Brain Natriuretic Peptide (NT-proBNP). Plasma was analyzed for Neurokinin A and 5-Hydroxyindoleacetic acid (5HIAA). Echocardiography was used to determine the presence and severity of carcinoid heart disease. Non-parametric receiver operating characteristic curves were constructed for biomarkers, and the area under the curve determined. The severity of cardiac involvement was correlated with the concentration of each biomarker.

Results: A total of 187 patients were identified of whom 37 (20%) had carcinoid heart disease. Significantly higher median values of all biomarkers were found in the patients with cardiac involvement. NT-proBNP and plasma 5HIAA had the highest areas under the curve for the prediction of carcinoid heart disease [NT-proBNP 0.82 (95% confidence interval 0.74–0.90, $p<0.0001$) and 5HIAA 0.85 (95% confidence interval 0.78–0.92, $p<0.0001$]. NT-proBNP was moderately correlated ($r=0.48$, $p<0.001$) whereas plasma 5HIAA was only weakly correlated ($r=0.34$, $p<0.001$) with the echocardiographic severity score.

Conclusion: NT-proBNP and plasma 5HIAA are both sensitive and specific biomarkers for the presence of carcinoid heart disease whereas only NT-proBNP is moderately correlated with disease severity.

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* E-mail: rebecca.dobson@liverpool.ac.uk

Introduction

Metastatic mid-gut neuroendocrine tumors (NETs) secrete serotonin and a variety of other vasoactive substances that are responsible not only for the characteristic carcinoid syndrome, but also for the significant long-term complication of carcinoid heart disease.

The pathophysiology of carcinoid heart disease has been elucidated from human and animal studies with increased plasma concentrations of serotonin strongly implicated from several lines of evidence. The specific serotonin re-uptake inhibitors fenfluramine and dexfenfluramine, used as appetite-suppressant drugs, and the ergot alkaloids, ergotamine and methysergide, used in the treatment of migraine, are known to cause valvular fibrosis [1,2]. Secondly, in an *in vivo* rodent model of carcinoid syndrome, in which there are significant increases in plasma serotonin, mice exhibited fibrotic cardiac valvular disease, which was abrogated by

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Neuro
endocrinology

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Determination of the Optimal Echocardiographic Scoring System to Quantify Carcinoid Heart Disease

Rebecca Dobson[a, b] Daniel J. Cuthbertson[a, b] Julia Jones[c] Juan W. Valle[d]
Brian Keevil[e] Carrie Chadwick[c] Graeme P. Poston[a] Malcolm I. Burgess[a]

[a]Neuroendocrine Tumour Group and [b]Department of Obesity and Endocrinology, University of Liverpool, at [c]Aintree University Hospital, Liverpool, [d]Department of Medical Oncology, Manchester Academic Health Sciences Centre, The Christie NHS Foundation Trust, and [e]Department of Clinical Chemistry, University Hospital of South Manchester, Manchester, UK

Key Words
Carcinoid heart disease · Echocardiography · Scoring system

Abstract
Background: Carcinoid heart disease (CHD) is an important complication of metastatic neuroendocrine disease, requiring regular monitoring to enable intervention prior to right heart failure. We aimed to identify the most appropriate echocardiographic scoring systems for the quantitative assessment of CHD. ***Methods:*** In this prospective study conducted between April and October 2012 in two European Neuroendocrine Tumor Society (ENETS) Centres of Excellence, patients with neuroendocrine tumours with liver metastases and/or carcinoid syndrome underwent transthoracic echocardiography and blood sampling for serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and plasma 5-hydroxyindoleacetic acid (5-HIAA). Each patient was assessed according to six echocardiographic scoring systems. The individual scoring systems' feasibility, observer variability, sensitivity, specificity and correlation with the concentration biomarkers were determined. ***Results:*** 100 patients were included; 21% had echocardiographic evidence of CHD. All scores discriminated highly between those with/without CHD, with no single score performing significantly better than another. The severity, determined using all of the scoring systems, correlated with the concentration of both biomarkers, but the strongest correlations were seen between the Bhattacharyya score and serum NT-proBNP. ***Conclusion:*** All scoring systems are comparable in terms of sensitivity and specificity for the detection of CHD. There is a variation in the feasibility of the scoring systems due to varying complexity of the score components. All scores correlate with NT-proBNP and plasma 5-HIAA. The Westberg score appears to be the most optimal scoring system for use in screening of CHD whereas the more complex scoring systems are more suited to the patient with established disease who may require surgical intervention.

Introduction

Carcinoid heart disease (CHD) occurs in up to 50% of patients with carcinoid syndrome [1]. It is mediated by serotonin released from neuroendocrine tumours (NETs), which is metabolised to 5-hydroxyindoleacetic

KARGER

E-Mail karger@karger.com
www.karger.com/nen

0028–3835/14/0992–0085$39.50/0

Rebecca Dobson
Clinical Sciences Centre
Aintree University Hospital
Longmoor Lane, Liverpool L9 7AL (UK)
E-Mail rebecca.dobson@liverpool.ac.uk

FULL PAPER

BJC

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Keywords: neuroendocrine tumours; carcinoid heart disease; progression

Serial surveillance of carcinoid heart disease: factors associated with echocardiographic progression and mortality

R Dobson*[,1,2], M I Burgess[1,3], J W Valle[4], D M Pritchard[5,6], J Vora[6], C Wong[1], C Chadwick[1], B Keevi[7], J Adaway[7], U Hofmann[8], G J Poston[1] and D J Cuthbertson[1,2]

[1]*Neuroendocrine Tumour Group, University Hospital Aintree, Lower Lane, Liverpool L9 7AL, UK;* [2]*Department of Obesity & Endocrinology, University of Liverpool, University Hospital Aintree, Lower Lane, Liverpool L9 7AL, UK;* [3]*Department of Cardiology, University Hospital Aintree, Lower Lane, Liverpool L9 7AL, UK;* [4]*Manchester Academic Health Sciences Centre, Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Withington, Manchester M20 4BX, UK;* [5]*Department of Gastroenterology, Institute of Translational Medicine, University of Liverpool, Liverpool L69 3GE, UK;* [6]*Neuroendocrine Tumour Group, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK;* [7]*Department of Clinical Chemistry, University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK and* [8]*Medical Oncology, Huddersfield Royal Infirmary, Lindley, Huddersfield, Yorkshire HD3 3EA, UK*

Background: Carcinoid heart disease is a complication of metastatic neuroendocrine tumours (NETs). We sought to identify factors associated with echocardiographic progression of carcinoid heart disease and death in patients with metastatic NETs.

Methods: Patients with advanced non-pancreatic NETs and documented liver metastases and/or carcinoid syndrome underwent prospective serial clinical, biochemical, echocardiographic and radiological assessment. Patients were categorised as carcinoid heart disease progressors, non-progressors or deceased. Multinomial regression was used to assess the univariate association between variables and carcinoid heart disease progression.

Results: One hundred and thirty-seven patients were included. Thirteen patients (9%) were progressors, 95 (69%) non-progressors and 29 (21%) patients deceased. Baseline median levels of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and plasma 5-hydroxyindoleacetic acid (5-HIAA) were significantly higher in the progressors. Every 100 nmol l^{-1} increase in 5-HIAA yielded a 5% greater odds of disease progression (OR 1.05, 95% CI: 1.01, 1.09; $P=0.012$) and a 7% greater odds of death (OR 1.07, 95% CI: 1.03, 1.10; $P=0.001$). A 100 ng l^{-1} increase in NT-proBNP did not increase the risk of progression, but did increase the risk of death by 11%.

Conclusions: The biochemical burden of disease, in particular baseline plasma 5-HIAA concentration, is independently associated with carcinoid heart disease progression and death. Clinical and radiological factors are less useful prognostic indicators of carcinoid heart disease progression and/or death.

Neuroendocrine tumours (NETs) have a heterogeneous natural history. They often follow an indolent course, progressing slowly over many years (Bhattacharyya *et al*, 2007). However, the development of carcinoid heart disease is associated with adverse clinical outcomes (Fox and Khattar, 2004). Cardiac involvement is characterised by right-sided valvular dysfunction, which can progress to right ventricular dilatation and failure. Serotonin is implicated in the development of carcinoid heart disease (Robiolio

*Correspondence: Dr R Dobson; E-mail: rebecca.dobson@liverpool.ac.uk

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