Carcinoid heart failure in a duodenal neuroendocrine tumor: role of cardiac surgery in a challenging patient and brief review of the literature

Carcinoid heart failure in a duodenal neuroendocrine tumour: role of cardiac surgery in a challenging patient and brief review of the literature.

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Disclosure summary

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Introduction

Carcinoid heart disease (CHD) is a potentially severe cardiac manifestation, generally involving the right-sided heart valves (1). In about 70% of patients, CHD occurs in patients with metastatic small bowel neuroendocrine tumours (NETs) and with carcinoid syndrome (CS). The precise pathophysiologic mechanism of CHD remains uncertain. It has been attributed to chronic exposure to excessive circulating levels of hormonal products, mainly serotonin, leading to the development of plaque-like, fibrous thickening involving the endocardial surfaces of heart valves (2). The management of patients with CHD is complex (1). Therapeutic options include pharmacotherapy, control of the systemic carcinoid disease and - in selected patients - cardiac valve replacement surgery, that have been associated with an improvement in clinical outcomes (3). Here we present a patient affected by well differentiated, G1, metastatic NET of duodenal origin, associated with CS and CHD, which progressed in a short time to cardiac failure and caused patient's death.

Case presentation

A Caucasian 63-year-old woman came to our attention in June 2015, due to persistent diarrhoea, haematochezia and abdominal pain which lasted for a year. Endoscopic colonoscopy with retrograde ileoscopy and gastroscopy resulted normal. A total body computed tomography (CT) scan showed bilateral pleural effusion, pathological mediastinal lymph nodes, ascites, a bone lumbar vertebra lytic lesion, multiple liver metastases and a lesion of the duodenum/pancreas uncinate process. Subsequently, a percutaneous liver biopsy revealed pathological features of hepatic localization of well differentiated NET, G1, with 2% proliferation index (Ki67) and 2 mitoses/10 HPF. The immunohistochemical profile oriented towards gastrointestinal origin, with CDX2 (caudal type homeobox transcription factor 2) and Chromogranin A positivity, while PAX-8 (paired box gene 8) turned out negative. The 111In-octreotide scintigraphy showed diffuse focal tracer uptake corresponding to abnormalities found on CT. Serum Chromogranin A and urinary 5-hydroxyindoleacetic acid (5-HIAA) were elevated (1039 ng/mL, upper normal limit 100; 270 mg/day, upper normal limit 10, respectively). The patient showed diarrhoea (10 intestinal movements per day) and flushing (2-3 episodes per day). Both long acting release (LAR) and short acting octreotide started. Intramuscolar octreotide LAR was administered at the dose of 30 mg every 28 days, while subcutaneous octreotide was administered at the dose of 500 micrograms twice daily.

After only two months of biological treatment, the patient developed acute dyspnea and a chest-CT scan depicted abundant bilateral pleural /pericardial effusion with minimally enlarged heart. N-terminal pro-brain natriuretic peptide

(NTpro-BNP) was elevated (2469 ng/L, upper normal limit 900). An echocardiography evidenced the presence of hypertrophic hypokinetic left ventricle with low ejection fraction (40%), mild mitral and pulmonary valve insufficiency, moderate aortic valve and severe tricuspid valve insufficiency. An angiotensin-converting enzyme inhibitor (perindopril) and ivabradine therapy was started. The patient was scheduled for the valvular surgical replacement, after the echocardiographic evidence of severe aortic and tricuspid regurgitation by a septal leaflet shortening, with a dilated right ventricle determining a massive cardiac failure (carcinoid heart failure, CHF). During the surgery both aortic and tricuspid valves were replaced with mechanical Carbomedics Sorin prostheses ® (21 mm for the aortic position and 31 mm for the tricuspid), avoiding the atrioventricular (AV) node and His bundle. A hypothermic (30°C) cardiopulmonary bypass (CPB) was established, the aorta was cross-clamped, opened with standard transverse incision. Cristalloid cardioplegia was infused directly in the coronary ostia. The aortic and tricuspid leaflets showed a compact fibrous tissue on both surfaces. The tricuspid commissures were fused, the septal leaflet was thickened and shortened. Given the risk of the onset of atrioventricular block, a wire (Myodexa®) was placed into the right ventricular wall for a prophylactic purpose. The bilateral pleural effusion was drained before opening the pleura and at the end of the operation chest tubes were placed. The pathological report showed large nodular areas of acellular fibrous thickening on aortic and tricuspid flaps valves. The day before the surgery the patient received intravenous continuous infusion of octreotide of 500 separated doses. Intraoperatively, an infusion at 50 μg h^{-1} was administered. The postoperative course was characterized by hypotension requiring octreotide administration as intermittently bolus injections of 20–100 μg. The patient was dialyzed, due to an acute renal failure. Fifteen days after surgery, a Klebsiella Pneumoniae septic syndrome occurred. The patient died in the intensive care unit 40 days after surgery from multiorgan failure.

Discussion

NETs are rare malignancies, heterogeneous in terms of origin, clinical presentation and behavior. Their incidence has markedly increased over the last years to 6.98 per 100 000 persons by 2012 (4). Approximately 60% of well and moderately differentiated tumours (classified as G1 and G2, respectively) originate in the digestive system, followed by the bronchopulmonary system (27%). According to the most recent SEER data, the most common primary site is the terminal ileum, while less common sites include the stomach, the duodenum and the distal colorectal tract. Regarding survival, metastatic small intestine NETs present the highest median overall survival (OS), amounting to 5.8 years, *and patients with G1 small intestine NETs have the longest median OS than G2??* (4). NETs can be classified as functioning (20-30%) or nonfunctioning on the basis of their capacity to produce hormones (i.e. insulin, glucagon, gastrin, vasoactive intestinal peptide (VIP) or somatostatin), peptides and neurotransmitters. Excessive production of these

hormones or peptides is a distinctive feature of neuroendocrine tumors. Patients with locally advanced/inoperable or metastatic NETs may develop the most common of these hormonal syndromes, represented by carcinoid syndrome (CS), a condition associated with tumoral secretion of serotonin and characterized by diarrhea, flushing, and bronchial constriction. As previously reported, the exact pathology of CHD remains obscure. However, there is a strong body of evidence implying that serotonin plays a major role in stimulating fibroblast growth and fibrogenesis (5). Although the onset of CHD in NET patients with CS has traditionally been reported in approximately 50% of patients, recent studies suggest the prevalence has fallen to approximately 20% (6). CHD is characterized by cardiac endocardial fibrosis, abnormalities of the right side of the heart, which could eventually lead to a serious heart failure (5). In some patients (up to 15%) CHD may affect left-sided valves. Considering that humoral products are inactivated by the lung parenchyma, the presence of left side disease could only be explained by a production of these substances in a concentration exceeding the capacity of pulmonary metabolism, or by the presence of any intracardiac communication (shunts) between left and right heart.

The primary site of our patient's tumour was duodenum, that should be considered a potential positive prognostic factor for survival (4). However, in these patients, the development of cardiac pathological involvement heralds a decline in clinical outcome regardless of the primary site (7). Without treatment, NET patients with CHD have generally a poor prognosis, severely reduced if compared to patients without CHD with 3-year survival rate of about 30% (compared to 68% in patients without CHD) (8).

However, it can remain undiagnosed as shown in a recent study of 150 patients with carcinoid syndrome, of whom 37% with CHD exhibited no physical signs (9). As a result, a challenge in daily clinical practice should be the early diagnosis of CHD, which requires 2-dimensional echocardiography and Doppler examination to assess the severity of valvular stenosis and regurgitation detailing the severity of cardiac involvement (2,6,10). Unfortunately, to date validated biomarkers of CHD are lacking. NT-pro BNP has been shown to exert a high sensitivity and specificity (87 and 80%, respectively) in predicting CHD and it has also been shown to correlate with patient survival (11). In this study, patients with elevated NT-pro BNP in addition to elevated Chromogranin A (CgA) levels showed worse overall survival than patients with elevated CgA alone. Telotristat ethyl, a novel, oral, inhibitor of tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin synthesis, has demonstrated in phase 3 study to reduce bowel movement frequency, with response rates of 40–44% (12). These encouraging data suggest a future role of this drug in the therapeutic armamentarium of CHD.

Recently, an algorithm for the management of CHD patients has been proposed (13). This expert statement suggested the importance of an early multidisciplinary discussion in order to determine the optimal treatment, potentially comprehending medical therapies such as somatostatin analogues, interferon, inotrope positive agents aimed to control

carcinoid syndrome, and in selected individuals, cardiac valve replacement. In our patient, a diagnostic delay of only two months could have determined a late surgical approach.

However, many relevant issues regarding the surgical replacement in CHD remain unaddressed. The choice of the type of valve prosthesis (biological vs. mechanical) is still controversial as the literature is limited to small, retrospective series or case report (14). The different type of prothesis are associated to different disadvantages, being allograft failure the most severe side effects reported with biological prothesis, and the oblige to anticoagulated patients with mechanical prothesis. Furthermore, the optimal timing of valve replacement surgery has not already been established. As a result the decision on the type of prosthesis and on time of valve replacement should be individually tailored on the individual patient risks and life expectancy.

A search of the literature, using PUBMED platforms, was performed to identify all studies evaluating the role of "cardiac surgery in CHD". The relevant studies were selected according to the following criteria: studies including patients with neuroendocrine tumours with a confirmed histopathological or cytological diagnosis; studies reporting case reports of G1 or G2 NET and CHD/CHF treated with cardiac surgery. Overall, 34 studies, with a total of 80 patients, met the identified criteria. The distribution of demographic, clinical and surgical treatment data are summarized in Table 1. The most frequent primary tumour site was: small bowel in 50 patients (62.5%), unknown origin in 9 patients (11.2%), pancreas in 3 patients, not reported in 14 patients. The time from the diagnosis of NET to cardiac surgery was 2-4 years in 48 patients (60%), longer than 5 years in 6 patients (7.5%), between 1 month and 1 year in 4 patients (5%); this date was not available in 13.7% of patients. Notably in 11 patients (13.7%) the time of diagnosis was coincident with the time of cardiac surgery. In the great majority of patients (96.2%) the surgery consisted in a valve replacement. Regarding the number of treated valves, in 47.5% and 46.2% of patients were replaced 2 and 1 valves, respectively. In 3 patients, 3 valves were treated and only in 2 patients the all 4 valves were replaced surgically. Almost all patients (92.5%) underwent a tricuspid valve replacement, 58.7% were subjected to a pulmonary valve replacement and only 5% and 3.7% underwent an aortic or mitralic replacement, respectively.

In conclusion CHD is a rare and severe complication of metastatic NETs and is associated with increased morbidity and mortality. On the basis of the experiences reported in our analysis including one patient treated at our Institution, we suggest to perform a surgical evaluation for asymptomatic CHD patients, maybe with an earlier and not severe cardiac damage. In fact, literature data evidenced a higher postoperative mortality for valvular surgical replacement in patients with advanced cardiac disease (15). Whereas, a prompt adequate management of CHD could ensure the patient to continue in the active treatments, allowing them to maintain a good hemodynamic function and has demonstrated to improve patients outcomes.

References

1 Hayes AR, Davar J, Caplin ME. Carcinoid Heart Disease: A Review. Endocrinol Metab Clin North Am. 2018 Sep;47(3):671-682.

2 Grozinsky-Glasberg S, Grossman AB, Gross DJ. Carcinoid Heart Disease: From Pathophysiology to Treatment 'Something in the Way It Moves'. Neuroendocrinology. 2015;101(4):263-73.

3 Raja SG, Bhattacharyya S, Davar J, et al. Surgery for carcinoid heart disease: current outcomes, concerns and controversies. Future Cardiol. 2010*;* 6:647-55.

4 Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3(10):1335-1342.

5 Gustafsson BI, Hauso O, Drozdov I, et al. Carcinoid heart disease. Int J Cardiol 2008;129:318-324.

6 Bhattacharyya S, Toumpanakis C, Burke M, et al. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging 2010; 3:103–11.

7 Kulke MH, Benson AB, Bergsland E, et al: National Comprehensive Cancer Network: Neuroendocrine Tumors, Clinical Practice Guidelines in Oncology. J Natl Compr Care Netw 10:724-764, 2012

8 Karimi A, Pourafshar N, Fudge JC. Pulmonary and Tricuspid Valvuloplasty in Carcinoid Heart Disease. Catheterization and Cardiovascular Interventions. 2016.

9 Bhattacharyya S, Toumpanakis C, Caplin ME, et al. Analysis of 150 patients with carcinoid syndrome seen in a single year at one institution in the first decade of the twenty-first century. Am J Cardiol 2008;101(3):378–81.

10 Castillo JG, Naib T, Zacks JS, Adams DH. Echocardiography in functional midgut neuroendocrine tumors: When and how often. Rev Endocr Metab Disord. 2017;18(4):411-421.

11 Korse CM, Taal BG, de Groot CA, et al. Chromogranin-A and N-terminal pro-brain natriuretic peptide: an excellent pair of biomarkers for diagnostics in patients with neuroendocrine tumor. J Clin Oncol. 2009 Sep 10;27(26):4293-9.

12 Kulke MH, Hörsch D, Caplin ME, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol. 2017;35(1):14-23.

13 Davar J, Connolly HM, Caplin ME et al. Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumours. An Expert Statement. JACC 2017; 69 (10): 1288-304.

14 Bhattacharyya S, Davar J, Dreyfus G, Caplin ME: Carcinoid heart disease. Circulation 2007;116:2860-2865.

15 Connolly HM, Schaff HV, Mullany CJ, et al. Surgical management of right sided heart disease. Circulation. 2001 Sep 18; 104(12 Suppl 1): I 36-40.

References of Table 1.

References

(1) De Rosa R, Schranz D, Zeiher AM, et al. Again, Two Melodies in Concert: Transcatheter Double Valve Replacement in Hedinger Syndrome. Ann Thorac Surg. 2017 Jul; 104(1):e61-e63.

(2) Florczak E, Pęczkowska M, Konka M, Różański J, Kolasińska-Ćwikła A. A 51-year-old patient with carcinoid heart disease and severe tricuspid regurgitation. Kardiol Pol. 2017;75(2):183.

(3) Bulur S, Hsiung MC, Nanda NC, Hardas S, Mohamed A, ElKaryoni A, Srialluri S, Barssoum K, Elsayed M, Wei J, Yin WH. Incremental value of live/real time three-dimensional transthoracic echocardiography over the two-dimensional technique in assessing carcinoid heart disease involving the aortic valve. Echocardiography. 2016 Nov;33(11):1741-1744.

(4) Loyalka P, Schechter M, Nascimbene A, Raman AS, Ilieascu CA, Gregoric ID, Kar B. Transcatheter Pulmonary Valve Replacement in a Carcinoid Heart. Tex Heart Inst J. 2016 Aug 1;43(4):341-4.

(5) Jahagirdar V, Kamal A, Steeds R, Ayuk J. Metastatic small bowel neuroendocrine tumour with bilateral carcinoid heart disease. BMJ Case Rep. 2016 Feb 3;2016. pii: bcr2015213693.

(6) Tsugu T, Iwanaga S, Murata M, Fukuda K. Bioprosthetic tricuspid valve replacement in carcinoid heart disease from primary ovarian carcinoid tumour. J Med Ultrason. 2015 Jul;42(3):401-3.

(7) Khan JN, Doshi SN, Rooney SJ, Bhabra MS, Steeds RP. Transcatheter pulmonary and tricuspid valve-in-valve replacement for bioprosthesis degeneration in carcinoid heart disease. Eur Heart J Cardiovasc Imaging. 2016 Jan;17(1):114.

(8) Proesmans S, Van Fraeyenhove F, Dossche K, Mattelaer C, Scott B Carcinoid heart disease: a remarkable recovery. Acta Clin Belg. 2015 Dec;70(6):453-6.

(9) Conradi L, Schaefer A, Mueller GC, Seiffert M, Gulbins H, Blankenberg S, Reichenspurner H, Treede H, Diemert P. Carcinoid Heart Valve Disease: Transcatheter Pulmonary Valve-In-Valve Implantation in Failing Biological Xenografts. J Heart Valve Dis. 2015 Jan;24(1):110-4.

(10) Laule M, Pschowski R, Pape UF, Pavel M, Stangl V, Baumann G, Wiedenmann B, Stangl K. Staged Catheter-Based Valve Treatment of Severe Carcinoid Heart Disease. Neuroendocrinology. 2016;103(3-4):259-62.

(11) Heidecker B, Moore P, Bergsland EK, Merrick SH, Rao RK. Transcatheter pulmonic valve replacement in carcinoid heart disease. Eur Heart J Cardiovasc Imaging. 2015 Sep;16(9):1046.

(12) Schaefer A, Sill B, Schoenebeck J, Schneeberger Y, Reichenspurner H, Gulbins H Failing stentless Bioprostheses in patients with carcinoid heart valve disease.. J Cardiothorac Surg. 2015 Mar 27;10:41.

(13) Paredes A, Valdebenito M, Gabrielli L, Castro P, Zalaquett R. Tricuspid and pulmonary valve involvement in carcinoid syndrome. Report of two cases. Rev Med Chil. 2014 May;142(5):662-6.

(14) Anselmi A, Corbineau H, Boulmier D, Ruggieri VG. Early diffuse coronary artery spasm after heart valve surgery in the carcinoid syndrome.. J Card Surg. 2013 Jul;28(4):402-3.

(15) Pêgo-Fernandes PM, Laurino AM, Ferronato Dde S, Costa FP, Anbar R, Jatene FB. Double valve replacement due to dysfunction secondary to carcinoid tumour.Arq Bras Cardiol. Arq Bras Cardiol. 2013 Mar;100(3):e32-4.

(16) Hastie MJ, Souh J, Ju A, Shanewise JS. Echo rounds: Undiagnosed severe pulmonic regurgitation in a carcinoid patient for tricuspid valve replacement and patent foramen ovale closure. Anesth Analg. 2013 Feb;116(2):300-2.

(17) Carrilho-Ferreira P, Silva D, Almeida AG, Infante de Oliveira E, Ferreira C, Miranda L, Rosa R, Canas da Silva P, Bicha Castelo H, Nunes Diogo A. Carcinoid heart disease: outcome after balloon pulmonary valvuloplasty. Can J Cardiol. 2013 Jun;29(6):751.

(18) Bhattacharyya S, Raja SG, Toumpanakis C, Caplin ME, Dreyfus GD, Davar J. Outcomes, risks and complications of cardiac surgery for carcinoid heart disease. Eur J Cardiothorac Surg. 2011 Jul; 40(1):168-72.

(19) Komoda S, Komoda T, Pavel ME, Morawietz L, Wiedenmann B, Hetzer R, Lehmkuhl HB. Cardiac surgery for carcinoid heart disease in 12 cases. Gen Thorac Cardiovasc Surg. 2011 Dec; 59(12):780-5.

(20) Takahashi H, Okada K, Asano M, Matsumori M, Morimoto Y, Okita Y. Bioprosthetic pulmonary and tricuspid valve replacement in carcinoid heart disease from ovarian primary cancer. Circ J. 2009;73:1554–6.

(21) Dworakowska D, Gueorguiev M, Laji K, Grossman AB. Multimodality palliative treatment of (111)In-pentetreotide negative/(123)I-MIBG positive metastatic carcinoid – a case report. Endokrynol Pol. 2008;59:342–7.

(22) Voigt PG, Braun J, Teng OY, Koolbergen DR, Holman E, Bax JJ, et al. Double bioprosthetic valve replacement in right-sided carcinoid heart disease. Ann Thorac Surg. 2005;79:2147–9.

(23) Warner RR. Carcinoid case presentation and discussion: the American perspective. Endocr Relat Cancer. 2003;10:489–96.

(24) Brunaud L, Antunes L, Sebbag H, Bresler L, Villemot JP, Boissel P. Ovarian strumal carcinoid tumour responsible for carcinoid heart disease. Eur J Obstet Gynecol Reprod Biol. 2001;98:124–6.

(25) Robiolio PA, Rigolin VH, Harrison JK, Lowe JE, Moore JO, Bashore TM, Feldman JM. Predictors of outcome of tricuspid valve replacement in carcinoid heart disease. Am J Cardiol. 1995 Mar 1; 75(7):485-8.

(26) Ohri SK, Schofield JB, Hodgson H, Oakley CM, Keogh BE. Carcinoid heart disease: early failure of an allograft valve replacement. Ann Thorac Surg. 1994 Oct; 58(4):1161-3.

(27) Lundin L, Hansson HE, Landelius J, Oberg K. Surgical treatment of carcinoid heart disease. J Thorac Cardiovasc Surg. 1990; 100:552–61.

(28) DiSesa VJ, Mills RM, Jr, Collins JJ., Jr Surgical management of carcinoid heart disease. Chest. 1985;88:789–91

(29) Forman MB, Byrd BF, III, Oates JA, Robertson RM. Two-dimensional echocardiography in the diagnosis of carcinoid heart disease. Am Heart J. 1984; 107:492–6.

(30) Gutierrez FR, McKnight RC, Jaffe AS, Ludbrook PA, Biello D, Weldon CS. Double porcine valve replacement in carcinoid heart disease. Chest. 1982; 81:101–3.

(31) Schoen FJ, Hausner RJ, Howell JF, Beazley HL, Titus JL. Porcine heterograft valve replacement in carcinoid heart disease. J Thorac Cardiovasc Surg. 1981; 81:100–5.

(32) Sworn MJ, Edlin GP, McGill DA, Mousley JS, Monro JL. Tricuspid valve replacement in carcinoid syndrome due to ovarian primary. Br Med J. 1980; 280:85–6

(33) Okada RD, Ewy GA, Copeland JG. Echocardiography and surgery in tricuspid and pulmonary valve stenosis due to carcinoid-syndrome. Cardiovasc Med. 1979; 4:871–81.

(34) McGuire MR, Pugh DM, Dunn MI. Carcinoid heart disease. Restrictive cardiomyopathy as a late complication. J Kans Med Soc. 1978; 79:661–2. 665.

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Table 1. Studies on cardiac surgical approach in carcinoid heart disease patients

No PTS	AGE/SEX	PRIMARY	Ki67	SURGERY	TIME DIAGNOSIS-SURGERY	VALVES	OS AFTER SURGERY	REFERENCE/ YEAR
1	46/M	Small bowel	NA NET G1 or G2	Valve replacement	0 mo	Pulmonary tricuspid	NA	(1); 2017
1	51/F	Small bowel	NA NET G1 or G2	Biological valve replacement	5 mo	Tricuspid	NA	(2)**;** 2017
1	65/F	Small bowel	NA NET G1 or G2	Replacement of valves with metallic prostheses	NA	Aortic, tricuspid, and pulmonary	NA	(3); 2016
1	67/M	Small bowel	NA NET G1 or G2	Valve replacement	NA	Tricuspid	48 mo	(4); 2016
1	63/F	Small bowel	NA NET G1	Mechanical valve replacement	0 mo	Aortic and mitral	Nearly 14 mo	(5); 2016
1	53/F	Ovarian	NA NET G1 or G2	Bioprosthetic Valve replacement	0 mo	Tricuspid	36 mo	(6); 2015
1	65/F	NA	NA NET G1 or G2	Bioprosthetic valve replacement	NA	Pulmonary and tricuspid	NA	(7); 2016
1	65/F	Small intestine	NA NET G1 or G2	Valves replacement	48 mo	Tricuspid and pulmonary	12 mo	(8); 2015
2	NA	NA	NA	Valve	NA	Tricuspid valve and	NA	(9); 2015

				replacement using biological xenografts		pulmonary		
1	NA/F	Small bowel	Ki67: 5% NET G2	Percutaneous valve implantation	84 mo	Tricuspid valve and pulmonary	12 mo	(10); 2016
1	55/F	Unknown	NA NET G1 or G2	Transcatheter valve replacement	0 mo	Pulmonary	12 mo	(11); 2015
3	31/M 58/F 55/F	Small bowel	NA NA NA	Valve replacement with stentless bioprostheses	0 mo 9 mo 36 mo	Pulmonary	30 mo 25 mo 18 mo	(12); 2015
2	33/M 35/F	Pancreas NA	NA NET G1 or G2 NA NET G1 or G2	Valve replacement	0 mo 0 mo	Tricuspid and pulmonary	36 mo NA	(13); 2014
1	66/M	NA	NA NET G1 or G2	Valve replacement	0 mo	Tricuspid	10 days	(14); 2013
1	48/M	Small bowel	NA NET G1 or G2	Valve replacement	96 mo	Tricuspid and pulmonary	24 mo	(15); 2013
1	67/M	NA	NA NET G1 or G2	Valve replacement	NA	Tricuspid and pulmonary	NA	(16); 2013
1	58/F	Small bowel	NA NET G1 or G2	Balloon valvuloplasty	60 mo	Pulmonary	6 mo	(17); 2013
21	Median age 60/ 11 F 10 M	Small bowel	NA NET G1 or G2	Valve replacement	48 mo (median value)	3: tricuspid 15: tricuspid and pulmonary 2: tricuspid, pulmonary and mitral 2: quadruple valve replacement	4: <30 days 18: >30 days	(18); 2013
12	Median age 63/ 8 M	8 Small bowel 4 Unknown	NA NET G1 or G2	Valve replacement	20 mo	Tricuspid	2: <30 days 6: 24 mo	(19); 2011

	4 F							
1	NA/F	Ovarian	NA NET G1 or G2	Valve replacement	0 mo	Pulmonary and tricuspid	6 mo	(20); 2009
1	46/F	Small bowel	NA NET G1 or G2	Valve replacement	6 mo	Pulmonary and tricuspid	12 mo	(21); 2008
1	58/M	Small bowel	NA NET G1 or G2	Valve replacement	60 mo	Pulmonary and tricuspid	24 mo	(22); 2005
1	55/M	Small bowel	NET G1 Ki67<1%	Valve replacement	36 mo	Pulmonary and tricuspid	12 mo	(23); 2003
1	68/F	Ovarian	NA NET G1 or G2	Valve replacement	0 mo	Tricuspid	36 mo	(24); 2001
8	Median age 64/ 4 F 4 M	4 Small bowel 1 Pancreatic 3 Unknow	NA NET G1 or G2	Valve replacement with bioprostheses	24 mo	Tricuspid	5: <30 days 3: >30 days (146, 153 and 48 mo)	(25); 1995
1	64/F	NA	NA NET G1 or G2	Valve replacement	NA	Pulmonary and tricuspid	NA	(26); 1994
4	NA/F	NA	NA NET G1 or G2	Valve replacement	NA	Pulmonary and tricuspid	NA	(27); 1990
2	56/F 32/F	Small bowel Unknown	NA NET G1 or G2	Valve replacement	96 mo 0 mo	Pulmonary and tricuspid	49 mo 61 mo	(28); 1985
1	62/M	NA	NA NET G1 or G2	Valve replacement	NA	Tricuspid	NA	(29); 1984
1	62/M	Small bowel	NA NET G1 or G2	Valve replacement	300 mo	Tricuspid	12 mo	(30); 1982
1	53/M	Pancreatic	NA NET G1 or 2	Valve replacement	NA	Tricuspid	8 mo	(31); 1981
1	60/F	Ovarian	NA NET G1 or G2	Valve replacement	8 mo	Tricuspid	NA	(32); 1980

1	30/F	NA	NA NET G1 or G2	Valve replacement	NA	Pulmonary and tricuspid	NA	(33); 1979
1	24/F	NA	NA NET G1 or G2	Valve replacement	NA	Tricuspid	NA	(34); 1978

Legends of Table 1

Table 1. Studies on cardiac surgical approach in carcinoid heart disease patients

Legend: Surgical experiences conducted to date evaluating the role of surgical approach in patients with neuroendocrine tumours and CHD.

Abbreviations: G1 grade 1, G2 grade 2, NA not available, NET neuroendocrine tumour, OS overall survival, PTS patients.