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Outcome of Cardiac Surgery for Carcinoid Heart Disease

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Objectives. **The hypothesis was that cardiac surgery for symptomatic carcinoid heart disease in conjunction with adjunctive therapy could improve the long-term outlook of patients with carcinoid heart disease.**

Background. **Patients with carcinoid heart disease have a dismal prognosis; most die of progressive right heart failure within 1 year after onset of symptoms. Improved therapies for the systemic manifestations of the carcinoid syndrome have resulted in symptomatic improvement and prolonged survival in patients without heart disease.**

Methods. **Twenty-six patients with symptomatic carcinoid heart disease underwent valvular surgery. Preoperative clinical, laboratory, Doppler echocardiographic and hemodynamic factors were evaluated. The survival of the surgical group was compared with that of a control group of 40 medically treated patients.**

Results. **There were nine perioperative deaths (35%), primarily from postoperative bleeding and right ventricular failure. Of the 17 surgical survivors, 8 were alive at a mean of 28 months of follow-up. The postoperative functional class of the eight surviving patients was substantially improved. Late deaths were primarily due to hepatic dysfunction caused by metastatic disease. The only predictor of operative mortality ($p = 0.03$) was low voltage on preoperative electrocardiography (limb lead voltage ≤5 mm). Predictors of late survival included a lower preoperative somatostatin requirement and a lower preoperative urinary 5-hydroxyindoleacetic acid level. There was a trend toward increased survival for the surgical group compared with the control group.**

Conclusions. **Because new therapies have improved survival in patients with the malignant carcinoid syndrome, cardiac involvement has become a major cause of morbidity and mortality. Valve surgery is the only definitive treatment. Although cardiac surgery carries a high perioperative mortality, marked symptomatic improvement occurs in survivors. Surgical intervention should therefore be considered when cardiac symptoms become severe.**

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The malignant carcinoid syndrome consists of vasomotor changes, gastrointestinal hypermotility, bronchospasm and right sided valvular heart disease. It portends a poor prognosis, particularly in patients with progressive cardiac involvement. Without treatment, the median duration of survival with the malignant carcinoid syndrome is 38 months from the onset of systemic symptoms. With clinical evidence of carcinoid heart disease, the median duration of survival is only 11 months (1). Because of this poor prognosis, patients with carcinoid heart disease had previously been treated only with medications for relief of symptoms of heart failure and experienced a continued high mortality rate from progressive right heart failure.

During the past decade, several new treatments have emerged for patients with the malignant carcinoid syndrome. Somatostatin is a ubiquitous hormone that inhibits the release of numerous peptides, such as growth hormone, insulin, glucagon and gut peptides (2). It was initially reported to be effective in blocking the carcinoid flush induced by pentagastrin as well as in controlling other symptoms associated with the carcinoid syndrome (3,4). However, the early use of somatostatin had limited therapeutic application because of the short half-life of the native somatostatin compound. The somatostatin analog sandostatin (SMS 201-995) was developed and has subsequently proved to be more potent and longer acting in its inhibitory effects than naturally occurring somatostatin (5). This therapeutic agent has resulted in marked symptomatic improvement and improved survival of patients with the malignant carcinoid syndrome (6–8). Hepatic dearterialization by ligation or occlusion has also been extremely effective in relieving the symptoms of the malignant carcinoid syndrome by inducing rapid tumor shrinkage in patients who have carcinoid tumors with hepatic metastases (9–12).

Despite the alleviation of systemic symptoms by these measures, patients in whom carcinoid cardiac involvement had already developed continued to experience progressive symptoms of right-sided heart failure and mortality from cardiac causes. It was our hypothesis that if the severe hemodynamic consequences of the valvular abnormalities of carcinoid heart disease could be corrected surgically, in conjunction with control of the systemic manifestations of the malignant carcinoid syndrome by the newer therapeutic methods, the long-term outlook for these patients could be substantially improved. Between 1985 and 1992, 26 patients with advanced carcinoid heart disease underwent valvular surgery in an

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Table 1. Hemodynamic Data in 26 Patients With Carcinoid Heart Disease

	Mean Value	Range	No. of Patients
Echocardiography			
TR velocity (mm Hg)	2.4 ± 0.6	1.25–3.6	25
Peak pulmonary velocity (m/s)	2.0 ± 0.9	1.6–3.5	21
TV mean gradient (mm Hg)	4.5 ± 1.7	2.0–8.0	23
LVEF (%)	60 ± 9	42–75	25
LVEF <55%	3/26 (11%)		
Reduced RV systolic function	12/26 (46%)		
Pericardial effusion	13/26 (50%)		
Catheterization			
PAP (mm Hg)	27 ± 6	14–36	17
RVEDP (mm Hg)	18 ± 4	14–29	14
RAP (mm Hg)	29 ± 9	13–40	16
CO (L/min)			
Dye method	3.9 ± 1.2	2.1–6.5	13
Fick method	4.0 ± 1.1	2.9–6.2	6

Data presented are mean value ± SD or number (%) of patients. CO = cardiac output; LVEF = left ventricular ejection fraction; PAP = mean pulmonary artery pressure; RAP = right atrial pressure; RV = right ventricle; RVEDP = right ventricular end-diastolic pressure; TR = tricuspid regurgitation; TV = tricuspid valve.

attempt to improve symptoms and longevity. We report the surgical outcome and postoperative survival of these patients.

Methods

Selection of patients. Fifty-eight percent of patients with the malignant carcinoid syndrome who are referred to our echocardiographic laboratory have evidence of carcinoid heart disease by echocardiography (13). Because of the known poor prognosis of patients with symptomatic carcinoid heart disease, a decision strategy was made to offer valve surgery to patients who met the following three criteria: 1) systemic carcinoid symptoms well controlled by somatostatin or hepatic dearterialization, 2) severe symptoms of right heart failure caused by carcinoid valvular involvement, and 3) no other concurrent major medical illnesses. Twenty-six patients met these criteria and were referred for valvular surgery (16 men, 10 women; mean age 54 years, range 25 to 72). Twenty-five patients had primary disease in the intestine with hepatic metastases. The remaining patient had primary ovarian carcinoid tumor without hepatic metastases (because of the systemic venous drainage of the ovary) (14). The mean interval from the diagnosis of carcinoid syndrome to operation was 42 months. As a means to assess the association between surgical treatment and survival outcome, the 26 patients who underwent operation were studied in the context of 66 total patients at the Mayo Clinic who had carcinoid heart disease and New York Heart Association class III or IV symptoms of heart failure. Thus, 40 patients who did not undergo operation served as a historical control group.

Clinical and laboratory findings. The preoperative evaluation included a complete history and physical examination, electrocardiography, chest radiography and determination of urinary 5-hydroxyindoleacetic acid levels in all patients. The urinary 5-hydroxyindoleacetic acid test is remarkably specific and reproducible and provides a reliable biologic marker for the assessment of tumor activity and treatment intervention (15). The mean preoperative 5-hydroxyindoleacetic acid value for the 26 patients was 197 mg/24 h (median 172, range 2.1 to 416, normal 0 to 6.0). The patient with primary ovarian carcinoid tumor without metastatic hepatic disease had the normal 5-hydroxyindoleacetic acid level (2.1 mg/24 h).

The preoperative somatostatin dose and duration of therapy were determined. The usual initial dosage is 150 μg administered subcutaneously three times daily. Increased dosages were administered for breakthrough symptoms or for the development of tachyphylaxis. The mean somatostatin dose at the time of cardiac operation was 952 μg/day (range 450 to 3,000). Three patients were not receiving somatostatin at the time of operation.

Physical examination demonstrated jugular venous distention, prominent *v* waves (caused by tricuspid regurgitation), variable *a* waves (caused by tricuspid stenosis), a right precordial lift (caused by right ventricular enlargement) and murmurs of tricuspid and pulmonary involvement in all patients.

The electrocardiogram (ECG) in patients with carcinoid heart disease demonstrated one or more of the following: low voltage in 22 (85%), right atrial enlargement in 9 (35%), right ventricular enlargement in 4 (15%) and right bundle-branch block in 11 (42%). The chest radiographic findings included cardiomegaly in 18 (69%), primarily from right-sided cardiac chamber and pulmonary artery enlargement; additional findings included pleural effusions in 15 (58%) and pleural thickening in 9 (35%).

Comprehensive preoperative echocardiographic-Doppler examination and cardiac catheterization were performed in 25 and 17 patients, respectively (Table 1). Of the nine patients who did not have preoperative cardiac catheterization, four had hemodynamic pressure assessment at the time of operation. All patients referred for cardiac operation had severe

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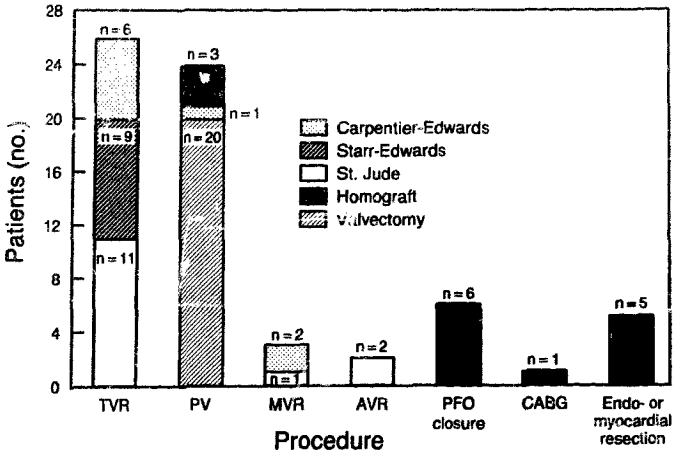


Figure 1. Number and type of cardiac procedures in 26 patients with carcinoid heart disease. AVR = aortic valve replacement; CABG = coronary artery bypass graft surgery; MVR = mitral valve replacement; PFO = patent foramen ovale; PV = pulmonary valve procedure; TVR = tricuspid valve replacement.

tricuspid regurgitation determined by echocardiography or catheterization or both. Severe elevation of right atrial pressure with a predominant large CV wave was present in all patients undergoing catheterization. The mean anterograde diastolic tricuspid gradient ranged from 2.0 to 8.0 mm Hg (mean 4.5 ± 1.7, n = 23). Pulmonary regurgitation was considered moderate or greater in 18 (72%) of the 25 patients who had preoperative echocardiography. Of 21 patients who had a pulmonary valve gradient measured, all had a systolic gradient ≥10 mm Hg, indicating intrinsic pulmonic stenosis. In addition to right-sided valvular heart disease, three patients had significant left-sided valvular disease that required surgical intervention (only one of these patients had a patent foramen ovale, and none had primary endobronchial carcinoid). Five patients were identified as having a patent foramen ovale by echocardiography or at operation. Coronary angiography was performed in 17 (65%) of 26 patients, and 2 patients had coronary artery stenoses ≥50% diameter narrowing.

Surgical management. The surgical procedures performed are shown in Figure 1. All patients had tricuspid valve replacement for the severe tricuspid regurgitation (20 mechanical and 6 bioprosthetic). A pulmonary valve procedure was performed in 24 of the 26 patients for relief of the right ventricular outflow obstruction: valvectomy in 20 and a pulmonary valve replacement in 4 (3 homograft, 1 bioprosthetic). The pulmonary annulus was enlarged with a pericardial patch in 13 patients. One patient underwent mitral and aortic valve replacement and closure of a patent foramen ovale in conjunction with pulmonary and tricuspid valve procedures. Two patients had mitral valve replacement, and four underwent closure of a patent foramen ovale. One patient had coronary artery bypass graft surgery performed at the time of the valvular procedure. Carcinoid endocardial plaques or intramyocardial carcinoid metastases were removed at the time of valvular surgery in five patients. One patient required a late pericardiectomy for recurrent pericardial effusions caused by carcinoid pericardial involvement.

Meticulous anesthetic care was instituted during the operative management of patients with carcinoid heart disease to prevent a life-threatening carcinoid crisis (16) or to institute early therapy should a crisis occur intraoperatively.

Statistical analysis. Clinical, echocardiographic and cardiac catheterization variables were compared between the patients who died and those who survived. Mean values ± SD were calculated for continuous variables and evaluated for statistical significance by a two-sample t test. Absolute and relative frequencies were measured for discrete variables and evaluated with the Fisher exact test. A p value ≤0.05 was considered to indicate statistical significance.

Survival curves were estimated with the Kaplan-Meier approach. Survival postoperatively was estimated in the surgical group. Survival in the entire group of 66 patients with functional class III or worse symptoms during medical therapy was estimated from the onset of functional class III symptoms, with the surgical patients censored at the time of operation. These two survival curves may not be directly comparable because the starting time is operation in one case and the onset of severe symptoms in the other. As a means to account for this, a time-dependent Cox proportional hazards model was fit on the entire group, with surgical treatment as a time-dependent covariant and onset of functional class III symptoms as the starting time. This analysis was further adjusted for age and gender.

Results

Surgical outcome. The outcome of valvular surgery for the 26 patients with carcinoid heart disease is demonstrated in Figure 2. There were nine (35%) perioperative deaths (death within 30 days of operation or during the same hospital stay). Four of these deaths were attributed to cardiovascular causes, including postoperative arrhythmic death in one patient, acute right ventricular failure in a patient whose stenotic pulmonary valve was not removed and progressive hemodynamic deterioration from right ventricular failure in two patients. Of the four perioperative cardiovascular deaths, one patient was in functional class IV, two were in functional class III, and one was in functional class II preoperatively. The preoperative

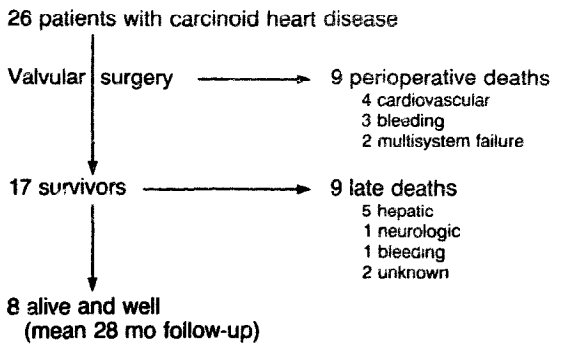


Figure 2. Outcome of valve surgery for 26 patients with carcinoid heart disease.

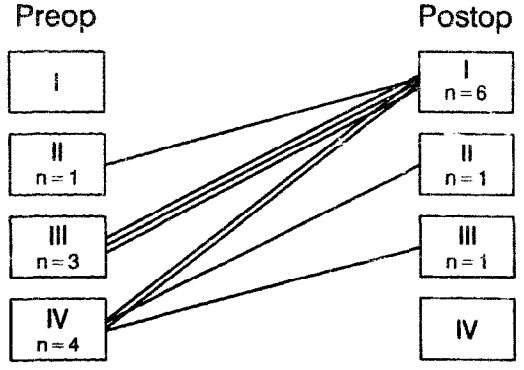


Figure 3. Preoperative and postoperative New York Heart Association functional class of eight patients with carcinoid heart disease.

functional class of patients who died perioperatively of cardiovascular causes was not substantially different from the functional class in the rest of the patients. In addition, the perioperative deaths were equally distributed over the 8-year period examined.

Three perioperative deaths were due to uncontrollable bleeding. These patients were 64, 67 and 70 years old; mean age of all other patients was 54 years. Significant perioperative hemorrhage requiring blood transfusion of ≥10 U occurred in six patients, the majority of whom had pleural and pericardial plaques (deposits of fibrotic material) present at operation. The number of units of blood transfused during operation ranged from 2 to 36 U (mean 9.4 ± 8). The remaining two late deaths that occurred in the hospital were due to multisystem failure. One of these deaths occurred in the youngest patient (age 25 years), who had extensive pleural fibrosis and died of respiratory failure following lung entrapment. This death reemphasizes that patients with extensive pleural or pericardial plaque at operation have an increased incidence of perioperative death (primarily from bleeding) and late death (from lung entrapment or restrictive cardiac hemodynamic variables).

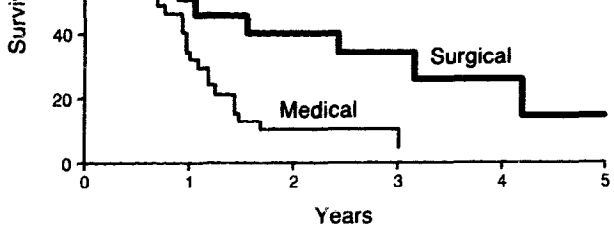
Of the 17 surgical survivors, 8 were alive at a mean of 28 months of follow-up (range 4 months to 5.2 years), with follow-up complete through April 1993. There were nine late deaths at a mean of 19 months postoperatively (Fig. 2). The majority (five) were due to hepatic dysfunction from metastatic disease. There was one late death from bleeding, which occurred after decortication for lung entrapment caused by proliferative pleural thickening. There was one neurologic death, and two deaths were of unknown causes. The mean time to late death was 19 months postoperatively (range 1 month to 4.3 years).

The preoperative and postoperative functional classes of the eight patients who were alive at follow-up are shown in Figure 3. The findings show significant symptomatic improvement in most patients who survive valvular surgery for symptomatic carcinoid heart disease.

Predictors of survival. The single statistical predictor of operative mortality (n = 9 patients) was low voltage (limb lead voltage ≤5 mm) on the preoperative ECG (5.8 ± 1.9 mm [n = 9] and 7.6 ± 1.9 mm [n = 17], p = 0.03). Predictors of late survival (n = 8) included a lower preoperative somatostatin requirement (525 ± 444 μg [n = 6] and 1,142 ± 648 μg [n = 17], p = 0.04) and a lower preoperative 5-hydroxyindoleacetic acid level (133 ± 97 mg/24 h [n = 8] and 210 ± 79 mg/24 h [n = 18], p = 0.04). There were no other clinical, echocardiographic or catheter-based hemodynamic variables associated with a higher operative or late mortality rate. The size and function of either the left or the right ventricle as assessed by two-dimensional echocardiography did not predict survival.

Postoperative survival. Survival after operation is shown in Figure 4. Survival at 2 years was estimated to be 40% (95% confidence interval [CI] 0.25 to 0.65). In the entire group, survival with medical therapy after onset of functional class III symptoms is shown in Figure 4. Survival at 2 years was 8% (95% CI interval 0.02 to 0.28). When a time-dependent model was fit with operation as the time-dependent covariant, operation was associated (p = 0.20 [NS]) with a reduced hazard of mortality. The hazard ratio was estimated at 0.64 (95% CI 0.32 to 1.29). There was evidence that the hazard ratio was not constant over time, namely, that operation was associated with a higher risk early (from perioperative mortality) but that the

Figure 4. Actuarial survival curves of medically **(narrow line)** and surgically **(bold line)** managed patients with carcinoid heart disease (p = 0.20).



relative hazard "flipped" at ~6 months, after which operation was associated with a lower hazard. When this analysis was adjusted for age and gender, the estimated relative hazard for operation was 0.71 (95% CI 0.35 . . 3).

Discussion

This study documents the results of the strategy to perform a cardiac operation for correction of the severe hemodynamic consequences of carcinoid heart disease. Even when the procedure is done by experienced surgeons, the perioperative mortality rate is high. In addition, the short-term postoperative mortality continues to be high, primarily because of metastatic hepatic disease. Nonetheless, our operative survivors uniformly experienced marked symptomatic improvement at a mean follow-up of >2 years. In comparison, the patients with severely symptomatic carcinoid heart disease managed without surgery underwent progressive hemodynamic deterioration and demonstrated a tendency toward reduced survival (Fig. 4).

Patients with carcinoid heart disease most commonly present with features of the malignant carcinoid syndrome (flushing, diarrhea and breathlessness) in addition to the symptoms of right-sided heart failure (hepatomegaly, edema, ascites, fatigue and low cardiac output). Rarely, patients present with symptomatic left-sided valvular lesions, restrictive cardiomyopathy (17), pericardial effusion (18), or cyanosis (19). The pathologic characteristics of carcinoid heart disease include diffuse collections of thick, pearly-white plaque, which are composed of smooth muscle cells called "myofibroblasts" (20). These plaques are deposited on the endocardial surface of the valve cusps on the right side of the heart, resulting in the characteristic pathologic and echocardiographic features, which include thickening and immobility of the tricuspid and pulmonary valve leaflets (13,21). Left-sided valvular involvement is rare and results from an intracardiac right-to-left shunt or a carcinoid endobronchial tumor (13,21).

Because of the previously described dismal outlook for this patient population (1), cardiac surgical intervention until recently was not considered an option. The advent of newer therapeutic methods (somatostatin, hepatic dearterialization) for the malignant carcinoid syndrome has resulted in improvement of the systemic carcinoid symptoms and in survival (6). However, despite somatostatin therapy patients with valvular involvement continued to experience symptoms of right heart failure and substantial cardiac mortality. The improvement in noncardiac symptoms and survival with somatostatin therapy as well as reported benefit from isolated case reports or series of valvular surgery (22–28) led us to pursue a more aggressive management of carcinoid heart disease with surgical intervention.

Present study. The current series demonstrated several important points. First, the need for relief of pulmonary valve obstruction was reemphasized by the patient who died of acute right ventricular failure when the stenotic pulmonary valve was not removed at the time of tricuspid valve replacement. Significant obstruction to right ventricular outflow may be underestimated because of low pulmonic transvalvular gradients as a result of the coexistent severe tricuspid regurgitation and low cardiac output. We now recommend pulmonary valvectomy or pulmonary valve replacement for patients with a transpulmonic gradient of >10 mm Hg. Pulmonary valve replacement increases the complexity of the operation but prevents the late complication of right ventricular failure from chronic pulmonary regurgitation after valvectomy. The best surgical approach to the pulmonary valve—valvectomy and outflow tract enlargement versus valve replacement—remains uncertain, although we would suggest pulmonary valve replacement in patients with elevated left-sided pressures.

Second, a significant proportion of patients in this series died of perioperative and postoperative bleeding. This was particularly evident in the older patient population and in patients with extensive pleural or pericardial carcinoid plaques. The high incidence of perioperative and postoperative bleeding is thought to be multifactorial, including abnormal hepatic synthetic function with prolonged prothrombin time, a reduced preoperative platelet count and a prolonged bleeding time. There appears to be no relation between hemorrhagic problems and therapy with the somatostatin analog (29). Finally, advanced malignant carcinoid syndrome with carcinoid heart disease manifests with progressive pericardial and pleural carcinoid plaques. The patients in this series with extensive pericardial and pleural fibrosis were at increased risk of death at the time of operation and had a poorer symptomatic outcome if they survived operation.

Surgical reports have largely recommended tricuspid valve replacement and pulmonary valvectomy for the management of carcinoid heart disease (23). The initial recommendation for a mechanical tricuspid prosthesis was based on the assumed damage to the bioprosthetic valve from the vasoactive carcinoid tumor substances, but this has not been well established (25,27) and was postulated before the introduction of synthetic somatostatin, which may potentially protect prosthetic valve tissue from the adverse effects of serotonin and other vasoactive peptides.

Bioprosthetic valves are now favored over mechanical prostheses for the tricuspid position at our institution because of a reduced risk of thrombosis and lack of need for systemic anticoagulation because patients with carcinoid syndrome are at higher risk of bleeding as a result of liver dysfunction. Hepatic dearterialization may be required for treatment of systemic carcinoid syndrome and further increases the risk of bleeding in patients receiving anticoagulation. Bioprosthetic tricuspid prostheses were placed in six patients, four of whom are still alive. No case of prosthetic valve failure caused by carcinoid involvement has been documented in the literature or from our series (mean follow-up, 28 months). A standard regimen for anticoagulation in our patients with carcinoid heart disease and mechanical tricuspid prostheses was instituted, and the target international normalized ratio was 3.0 to 4.5. Follow-up information regarding the number of bleeding episodes in patients receiving warfarin was not avail-

Patients with bioprosthetic valves were not treated with anticoagulants.

Operative survival was associated with higher voltage on the preoperative electrocardiogram (Fig. 3). Low voltage in carcinoid heart disease has been previously described (30) and may be related to more extensive endocardial and subendocardial involvement with carcinoid plaques, suggesting more advanced disease. Late survival was significantly associated with a lower preoperative somatostatin requirement and a lower preoperative 5-hydroxyindoleacetic acid level; these findings suggest that patients with less active or extensive metastatic carcinoid disease have improved longevity postoperatively.

The timing of cardiac operation for carcinoid heart disease remains difficult. No definitive guidelines could be established from this review. It must be reemphasized that right ventricular size and function, right atrial size and left ventricular function did not correlate with operative or late mortality. Our current practice includes functional evaluation by exercise testing to provide an objective assessment of the functional status and a guideline to the timing of cardiac surgery. Because of the very high perioperative mortality rate, patients with carcinoid heart disease currently are referred for cardiac operation only when they become markedly symptomatic.

Limitations of the study. This is the largest cardiac surgical series of patients with carcinoid heart disease studied to date. However, significant limitations exist in extrapolating these results to all patients with carcinoid heart disease. The heterogeneity of systemic and cardiac abnormalities and the small patient numbers reduce the significance of the data, with a resultant reduction in statistical power. The retrospective analysis, the use of a historical control group and incomplete preoperative data on all patients are also limitations.

Conclusions. Because new therapies have improved survival in patients with the malignant carcinoid syndrome, cardiac involvement has now become the major cause of morbidity and mortality. Cardiac operation is the only definitive treatment for patients with severe valvular involvement caused by carcinoid heart disease. Although cardiac operation for carcinoid heart disease is associated with a high perioperative mortality rate, and there is a significant late postoperative mortality rate in these patients, primarily from progression of the malignancy, marked symptomatic improvement occurs in most survivors after surgical intervention for carcinoid heart disease. It is therefore important to follow up the patients regularly and consider surgical intervention when cardiac symptoms become severe, albeit with a significant risk of perioperative mortality.

On the basis of this early experience there is clearly a subset of patients with carcinoid heart disease who benefit significantly from valvular surgery. Continued refinement of surgical technique and identification of preoperative determinants of outcome in addition to longer follow-up of bioprosthetic durability in the "carcinoid environment" are required to make specific treatment recommendations.

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