Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours†

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Patients with metastatic carcinoid tumours often undergo surgical procedures to reduce the tumour burden and associated debilitating symptoms. These procedures and anaesthesia can precipitate a life-threatening carcinoid crisis. To assess perioperative outcomes, we studied retrospectively the medical records of adult patients from 1983 to 1996 who underwent abdominal surgery for metastatic carcinoid tumours. Preoperative risk factors, intraoperative complications and complications occurring in the 30 days after surgery were recorded. Perioperative complications or death occurred in 15 of 119 patients (12.6%, exact confidence interval 7.2–19.9). None of the 45 patients who received octreotide intraoperatively experienced intraoperative complications compared with eight of the 73 patients (11.0%) who did not receive octreotide (P=0.023). The presence of carcinoid heart disease and high urinary output of 5-hydroxyindoleacetic acid preoperatively were statistically significant risk factors for perioperative complications.

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The perioperative course and anaesthetic management of patients with carcinoid tumours have been described only anecdotally because of the low incidence of symptomatic tumours that require surgical intervention.[1–23] Given an annual incidence of 0.28 per 100 000 population, the average general surgeon in the USA will see approximately one case every 50 yr.[23] Most, but not all, carcinoid tumours that are surgically managed are metastatic from a gastrointestinal origin. Patients with these metastatic carcinoid tumours often undergo surgical procedures to reduce the tumour burden and associated debilitating symptoms despite the fact that these procedures and anaesthesia can precipitate a life-threatening carcinoid crisis.[1–3] Unfortunately, the frequencies, outcomes and factors predictive of complications in this population of surgical patients are unknown. To address this problem, we evaluated the perioperative courses and anaesthetic management of 119 adult patients who underwent elective surgery for symptomatic carcinoid tumours at a single institution and by one surgeon during a 14 yr period.

Methods

With approval of the Mayo Institutional Review Board, we identified consecutive adult (18 yr of age or older) patients from 1 January 1983 to 31 December 1996, who underwent abdominal surgery for metastatic carcinoid tumours by one surgeon at our institution. For patients who had multiple abdominal operations for symptomatic carcinoid, only the first operation was included. Abdominal procedures included hepatic arterial ligation, resection or biopsy of hepatic metastases, hepatic carcinoid cryotherapy, and small or large bowel resection or diversion. One or more of these procedures could have been performed during the first operation.

The perioperative medical, surgical, nursing and anaesthesia records of 119 patients were reviewed to identify preoperative risk factors, intraoperative complications and

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postoperative complications occurring up to 30 days after surgery according to well-established criteria.[24 25]

Preoperative information included age, sex, the presence of comorbid disease [cardiovascular, renal, biliary, central nervous system (CNS), respiratory], the presence of carcinoid heart disease as determined by a cardiologist and confirmed by a preoperative echocardiogram, American Society of Anesthesiology physical status, preoperative symptoms of flushing, diarrhoea and/or shortness of breath, preoperative use of bronchodilators, corticosteroids and histamine receptor type 2 antagonists, the preoperative daily dose of octreotide, the dose of octreotide administered in the 8 h preceding the start of anaesthesia, the site of the primary carcinoid tumour, if known, and the most recent preoperative urinary output of 5-hydroxyindoleacetic acid (5-HIAA).

Intraoperative information included the type and duration of anaesthesia, the principal maintenance anaesthetic agent, the use of invasive monitors, the volume and type of i.v. fluids and blood products administered, and the total amount of octreotide administered during anaesthesia. Intraoperative observations included the presence of flushing, urticaria, ventricular dysrhythmia, bronchospasm, acidosis (defined as arterial pH <7.2), lowest Pa_{O_2}, lowest Sp_{O_2}, lowest systolic blood pressure (SBP), highest SBP, death, total duration of SBP <80 mm Hg to the nearest 5 min, and treatment with vasopressor(s) (SBP <80 mm Hg for >10 min), and total duration of sustained tachycardia (defined as pulse >120 beats min^{-1}) to the nearest 5 min.

Postoperative morbidity occurring within 30 days of the index surgery was identified using criteria developed by Hosking *et al*.[25] and detailed elsewhere.[26] Adverse outcomes included myocardial infarction, pulmonary embolism, CNS changes, renal dysfunction, biliary dysfunction, prolonged endotracheal intubation, systemic sepsis and death.

Statistical analysis

Univariate analyses of potential risk factors were performed using the rank sum test for continuous variables and Fisher's exact test for categorical variables. Exact confidence intervals for complication frequencies were calculated. In all cases, two-sided tests were performed and $P \leqslant 0.05$ was used to denote statistical significance.

Results

One hundred and nineteen patients underwent abdominal surgery by one surgeon for metastatic carcinoid tumours during the study period. The median age at the time of surgery was 59 yr (range 30–78 yr). The percentages of male and female patients were similar (53.8 and 46.2% respectively). Before surgical intervention, 76 patients (64%) had experienced flushing, 83 patients (70%) had intermittent or sustained diarrhoea and 15 patients (12.6%) had episodes of shortness of breath. The median preoperative urinary 5-HIAA output was 96 mg/24 h (502.1 μmol day^{-1}) (range 3.9–837 mg/24 h) (20.4–4377.5 μmol day^{-1}). Twenty-four patients (20%) had carcinoid heart disease. Thirty-one patients (26%) received octreotide preoperatively, with a median dose of 300 μg intravenously or subcutaneously (range 50–1000 μg). Only six of these patients did not receive any additional octreotide intraoperatively. Forty-five patients (38%) received octreotide intraoperatively, with a median dose of 350 μg i.v. or s.c. (range 30–4000 μg) (Table 1). All patients received narcotics and volatile anaesthetics intraoperatively. Vasopressors were used in 43% of patients, phenylephrine was used in 31% and ephedrine in 16%.

Table 1 Procedural characteristics for 118 patients who underwent abdominal resection of carcinoid tumours during 1983–1996. All intraoperative data were missing from one patient's medical record

Characteristic	Value
Surgery type (%)	
Resection of carcinoid tumour	48.3
Arterial ligation	19.5
Other intra-abdominal procedure	32.2
Primary induction agent (%)	
Thiopental sodium	71.2
Etomidate	22.9
Propofol	4.2
Other	1.7
Volatile anaesthetic use (%)	100.0
Narcotic	100.0
Succinylcholine	63.6
Primary neuromuscular blocking agent (%)	
Vecuronium	78.0
Pancuronium	11.9
Atracurium	7.6
Other	1.7
Intraoperative vasopressor use (%)	42.9
Phenylephrine	31.4
Ephedrine	16.1
Dopamine	1.7
Epinephrine	0.8
Mephentermine	0.8
Artery catheter (%)	90.7
Central venous catheter (%)	61.0
Pulmonary arterial catheter (%)	3.4
Intraoperative octreotide (μg)	39.8
Mean (SD) (μg)	523.0 (624.8)
Median (μg)	350
Range (μg)	30–4000
Duration of anaesthesia (min)	
Mean (SD)	244.7 (76.9)
Median	240
Range	105–455

Perioperative complications or death occurred in 15 of 119 patients [12%, 95% confidence interval (CI) 7.2–19.9%]. Patients who experienced perioperative complications had a higher frequency of carcinoid heart disease than those who did not experience complications (53 *vs* 15%, P=0.002). Although most patients (94%) had a preoperative urinary 5-HIAA output that was above normal (>6.0 mg/24 h) (>31.4 μmol day^{-1}), the median urinary 5-HIAA output was significantly higher in patients who

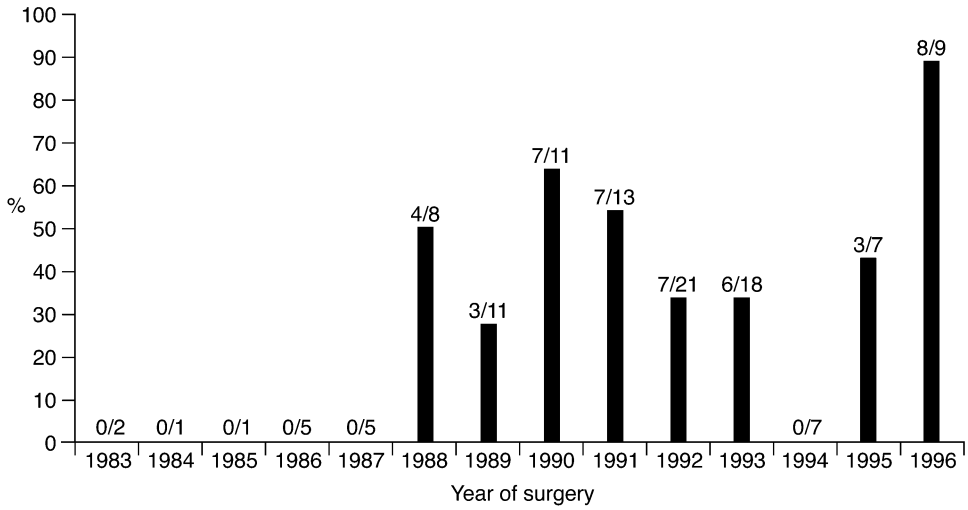

Fig 1 Percentage of patients receiving octreotide intraoperatively. Octreotide was available on a compassionate-use basis from 1984 to 1987 and received FDA approval in 1988. Its intraoperative use began in 1988 for the patients in our study.

experienced complications (200 *vs* 78 mg/24 h, $P<0.006$) (1046 *vs* 407.9 μmol day^{-1}).

Of the 15 patients who experienced perioperative complications or death, eight experienced one or more intraoperative complications. Intraoperative complications included flushing in four patients, sustained hypotension in two patients, and bronchospasm, acidosis and ventricular tachycardia in one patient each. There were no intraoperative deaths, episodes of urticaria or ventricular fibrillation.

None of the 45 patients who received octreotide intraoperatively experienced significant intraoperative complications compared with eight of the 73 patients (11%) who did not receive octreotide ($P=0.023$). Patients who received octreotide intraoperatively and those who did not had similar preoperative characteristics, similar comorbidities including carcinoid heart disease and similar preoperative urinary 5-HIAA output. Octreotide received approval by the Food and Drug Administration (FDA) in 1988, and intraoperative use in this study began in the same year (Fig. 1). We performed an additional analysis restricted to the period during which octreotide was approved for use by the FDA (1988–1996) to rule out any confounding variables created by possible changes in anaesthetic or surgical management after 1988. This analysis demonstrated that patients receiving octreotide intraoperatively experienced significantly fewer intraoperative complications than patients who did not receive octreotide (0/45 *vs* 8/60, $P=0.010$).

Of the six patients who received octreotide only preoperatively, one (17%) developed an intraoperative complication. Four of the 45 patients (9%) who received octreotide intraoperatively developed postoperative complications. We therefore have no evidence that preoperative administration of octreotide is associated with a reduced frequency of intraoperative complications or that intraoperative administration is associated with a reduced frequency of postoperative complications.

Nine patients experienced one or more postoperative complications. Four patients (3%) developed biliary dysfunction, two patients had renal dysfunction and one patient required prolonged endotracheal intubation. Three patients (2.5%) died postoperatively. Details of the events preceding the three deaths follow.

Death 1

A 67-yr-old woman with severe carcinoid heart disease and a preoperative 5-HIAA output of 218 mg/24 h (1140.1 μmol/24 h) underwent a right hemicolectomy, ileotransverse colostomy, wedge biopsy of the right lobe of the liver and cholecystectomy for carcinoid of the small bowel, hepatic metastasis and cholelithiasis. Surgery was uneventful, and she was haemodynamically stable throughout the procedure. Twelve days later, the ileotransverse colostomy partially dehisced and she underwent resection of a portion of the terminal ileum and proximal transverse colon and an end-to-end ileotransverse colostomy. Four days after surgery, she developed intra-abdominal sepsis. She died 2 days later.

Death 2

A 30-yr-old man with Wolff–Parkinson–White ventricular pre-excitation syndrome, severe carcinoid heart disease and a preoperative urinary 5-HIAA output of 495 mg/24 h (2588.9 μmol day^{-1}) underwent hepatic artery ligation, resection of a portion of the ileum, and an end-to-end ileo-ileostomy for metastatic carcinoid tumour of the ileum. He was haemodynamically stable throughout the procedure. Postoperatively, he experienced progressive fluid retention (7.5 kg in 9 days) that was refractory to diuresis, as well as

dyspnoea and bronchospasm, abdominal distension and lower extremity oedema. Ten days after surgery, he developed shortness of breath, sinus tachycardia and hypotension. These symptoms and signs deteriorated rapidly into electromechanical dissociation from which he could not be resuscitated.

Death 3

A 50-yr-old man was admitted to another hospital for nausea and vomiting, and was found to have abnormal liver function tests. He was transferred to our hospital 8 days later for further evaluation. Computed tomography of the abdomen revealed hepatic lesions consistent with metastases. Preoperative laboratory investigations included a preoperative urinary 5-HIAA output of 837 mg/24 h (4377.5 μmol day^{-1}), an aspartate aminotransferase concentration of 89 U $litre^{-1}$, alkaline phosphatase of 590 U $litre^{-1}$, total bilirubin of 5.0 mg dl^{-1} (85.5 μmol $litre^{-1}$) and direct bilirubin of 3.4 mg dl^{-1} (58.1 μmol $litre^{-1}$). A transthoracic echocardiogram demonstrated moderate tricuspid valve regurgitation, but the valves were insufficiently visualized to make a definitive diagnosis of carcinoid heart disease. Five days after admission the patient underwent a retrocolic, isoperistaltic gastrojejunostomy for gastric outlet obstruction secondary to metastatic carcinoid tumour. At surgery, his liver was noted to be 50–75% replaced by tumour. Surgery and anaesthesia were uneventful, and he was haemodynamically stable throughout the procedure. He was discharged 8 days after surgery and died 1 week later of unknown cause(s). No autopsy was performed.

Discussion

The major finding of this study is that the use of octreotide intraoperatively for patients with metastatic carcinoid tumours undergoing intra-abdominal surgery was associated with a decreased frequency of intraoperative complications. Also, the presence of carcinoid heart disease and high preoperative urinary 5-HIAA output were statistically significant risk factors for perioperative complications including death.

There are several case series of patients with metastatic carcinoid tumours. Two of these case series predate the availability of octreotide. Kleine *et al*.[20] described the anaesthetic management and intraoperative course of three surgical patients. All three of these patients experienced intraoperative hypertension, one patient also experienced an episode of hypotension and flushing and there were no intraoperative deaths. Miller *et al*.[19] reviewed the intraoperative management of nine patients. Again, no intraoperative deaths were noted. However, one patient had life-threatening haemodynamic instability, four other patients had hypertensive episodes and another developed bronchospasm.

Two more recent case series include reports of patients who received octreotide perioperatively. Ockert and White[4] reviewed the perioperative outcomes of six patients who underwent cardiac surgery for carcinoid heart disease. Four patients received octreotide perioperatively. One patient with widespread carcinoid metastases and carcinoid heart disease received octreotide pre- and intraoperatively but still experienced an intraoperative carcinoid crisis. This patient developed a severe coagulopathy after cardiopulmonary bypass and died within 12 h of surgery. The other three patients who received perioperative octreotide did not experience a carcinoid crisis intraoperatively, but one never recovered after the operation and died of respiratory failure and multiple metastases several months later. Veall *et al*.[22] reviewed 22 anaesthetic records of 21 patients with carcinoid syndrome who underwent laparotomy. Eight patients received octreotide preoperatively, and further boluses were administered intraoperatively to an unspecified number of patients. There were no intraoperative deaths, but two patients had sustained tachycardia and another two patients exhibited flushing intraoperatively. It is not stated whether these patients received octreotide intraoperatively. After the introduction of octreotide, intraoperative hypotension was generally reported to be less severe and was rapidly responsive to additional i.v. boluses of octreotide.

Urinary 5-HIAA appears to be a good biological marker for the assessment of carcinoid tumour activity[23] and its association with perioperative morbidity. We found that patients who had higher preoperative urinary 5-HIAA output were more likely to develop perioperative complications, including death. Similarly, Connolly *et al*.[27] reviewed the perioperative courses of 26 patients who underwent cardiac surgery for carcinoid heart disease and found that high preoperative urinary 5-HIAA output predicted decreased survival after operation. Their finding is not surprising because involvement of the heart disease is typically a late manifestation in the course of carcinoid disease. Pellika *et al*.[28] found that the mean output of urinary 5-HIAA among patients with carcinoid tumours was higher in 74 patients with carcinoid heart disease than in 51 patients without carcinoid heart disease (270 *vs* 131 mg/24 h, $P<0.001$) (1412.1 *vs* 685.1 μmol day^{-1}). However, an association between high preoperative urinary 5-HIAA output and perioperative morbidity was not detected in the series of 21 patients reviewed by Veall *et al*.[22] These authors noted that preoperative urinary 5-HIAA output was a poor predictor of perioperative cardiovascular stability in their patient population. In fact, severe hypotension occurred in one patient with a preoperative urinary 5-HIAA output of 11.8 mg/24 h (62 μmol day^{-1}).

Two of the three postoperative deaths in our study occurred in patients with severe carcinoid heart disease. The

other death occurred in a patient with tricuspid regurgitation, whose valves were poorly visualized on transthoracic echocardiogram and therefore a definitive diagnosis of carcinoid heart disease could not be made. Patients with carcinoid heart disease usually experience symptoms of carcinoid syndrome (i.e. flushing, diarrhoea and shortness of breath) along with the symptoms of right-sided heart failure because of carcinoid-induced tricuspid or pulmonary valve involvement. Carcinoid heart disease and the associated right heart failure are a major cause of morbidity and mortality in these patients.[27]

Limitations of our study include the reliability of data notation on the medical record. However, we used rigorous definitions and abstracted only major events to increase our chances of capturing information reliably. There is clearly a referral bias at this tertiary care centre in that the patients in this study are not representative of any general population. It is quite likely that referred patients have more severe carcinoid disease, more comorbidities, and require more extensive surgery than those from our local population. We did not assess geographical characteristics in this study. The retrospective nature of this study precludes discovery of the reasons for which octreotide was administered before or after operation. It also prevents us from evaluating any causal relationship between medications or risk factors and perioperative complications. Specifically, this study was not able to evaluate the efficacy of intraoperative octreotide therapy to prevent intraoperative carcinoid crises. Additionally, although this investigation identified some characteristics that were associated with perioperative complications, the interpretation of no association between other patient or procedural characteristics and perioperative complications should be made with caution. In general, with only 15 of 119 patients experiencing complications, an analysis of potential risk factors has statistical power of less than 55% to detect a risk factor with a corresponding odds ratio of 3.0.

Our findings suggest that most people with metastatic carcinoid tumours can undergo intra-abdominal surgery safely. In our patient population, no intraoperative complications occurred in those who received octreotide intraoperatively. Overall, perioperative complications and death were strongly associated with the preoperative presence of carcinoid heart disease and higher elevated urinary 5-HIAA output.

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