

Carcinoid: the disease and its implications for anaesthesia



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Key points

Carcinoid surgery carries a significant morbidity/mortality.

Thorough pre-operative assessment may at times require cardiology input.

Physiological changes are unpredictable and hazardous.

Octreotide plays a vital role in tumour control and should commence before operation.

Post-operative care should be provided in a high-dependency area.

This article describes the features of carcinoid tumours and the challenges involved in the anaesthetic management and post-operative care of patients undergoing surgery for carcinoid.

Carcinoid tumours were first described in 1888 by Lubarsch who found multiple tumours in the distal ileum of two patients at autopsy. Ransom then published the first detailed description of the classic symptoms of carcinoid¹ and Oberndorfer introduced the name when he used the term 'karzinoide tumoren' in 1907 because of the tumour's similarity to carcinomas despite their apparently benign nature. Gosset and Masson realized in 1914 that carcinoid tumours were related to endocrine tissue.² It is the endocrine-like nature of these tumours that lead to their unusual effects, which can be a major challenge to anaesthetists.

Epidemiology and aetiology of carcinoid tumours

Carcinoid tumours are derived from enterochromaffin or Kulchitsky cells and arise from the different embryonic divisions of the gut. They depend for their frequency of occurrence on the site density of neuroendocrine cells. Hence, foregut tumours arise in the lungs, bronchi, or stomach; midgut carcinoid tumours occur in the small intestine, appendix, and proximal large bowel; hindgut carcinoid tumours arise in the distal colon or rectum. As a group, carcinoid tumours represent a wide spectrum of neuroendocrine cell types. Under electron microscopy, they typically contain numerous membrane-bound neurosecretory granules composed of hormones and biogenic amines. The most familiar of these is serotonin, which is metabolized from its precursor, 5-hydroxytryptophan by a decarboxylase enzyme, but they are also known to secrete corticotrophin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein. A broad description of drugs used traditionally to

inhibit synthesis, prevent release, and antagonize receptors has been given by Veall.³

The classification of carcinoid tumours is hence based on the site of origin and the histological characteristics, with tumours being broadly described as either well-differentiated or poorly differentiated neuroendocrine tumours.

Recent epidemiology⁴ suggests that carcinoid tumours may be increasing in frequency with the highest incidence in some racial groups (4.5 per 100 000 in African males), suggesting a genetic role associated with their development. The sites of highest incidence are the gastrointestinal tract (67.5%) and the broncho-pulmonary system (25.3%). Within the gastrointestinal tract, approximately 40% of tumours occur in the small intestine, with a further 27% in the rectum and 10% in the stomach. In nearly all carcinoid tumours, irrespective of site of origin, staging of the tumour correlates with survival. The presence of regional or distant metastases significantly reduces the 5-yr survival from 71% of patients who have no metastases to approximately 38% for patients with metastases.

The clinical features of carcinoid syndrome

Many carcinoid tumours are found coincidentally during surgery for other conditions. Patients may describe vague upper or lower GI symptoms, with the average time from symptom onset to diagnosis being 9 yr.⁵

Carcinoid syndrome is relatively uncommon, affecting approximately 10% of patients with carcinoid tumours. Vasoactive substances secreted by tumours arising in the gut must pass through the liver via the hepatic portal vein before circulating more extensively. Consequently, these vasoactive hormones are metabolized before they can exert widespread systemic effects. However, tumours either

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Fig 1 Carcinoid heart. The carcinoid syndrome has resulted in fibrosis of the right-sided valve cusps of both pulmonary and tricuspid valves. They show a white coating (arrowed), which represents carcinoid plaque on their ventricular surfaces. Picture kindly provided by Dr Tim Stephenson, Consultant Pathologist, Royal Hallamshire Hospital.

originating or more commonly metastasizing to the liver may bypass this metabolism and thereby exert more widespread systemic effects.

The release of serotonin and other vasoactive substances such as histamine is responsible for the unpredictable, but classically described, ‘carcinoid syndrome’. This is typically intermittent and is characterized by flushing, sometimes associated with exercise, or the ingestion of alcohol or high tyramine content foods such as blue cheeses and chocolate. Diarrhoea, lacrymation, rhinorrhoea and ultimately right-sided valvular heart disease may also occur. Carcinoid heart disease (Fig. 1) classically affects the right side of the heart with fibrous thickening of the endocardium causing retraction and fixation of the tricuspid valve leaflets and is related to the duration of exposure to high concentration of 5-hydroxytryptamine. Consequently, mixed tricuspid and pulmonary valvular disease are well recognized.⁶ Such heart disease occurs in two-thirds of those with carcinoid syndrome and is associated with a statistically significant increase in peri-operative complications.⁷ Left-sided heart disease is uncommon and generally associated with bronchial carcinoid or right to left intracardiac shunting.

‘Carcinoid crises’ are an exaggerated form of the syndrome characterized by profound flushing, bronchospasm, tachycardia, and widely fluctuating blood pressure, including hypo- and hypertension. The most common cause of such dramatic crises is anaesthetic, radiological, or surgical interventions and such crises are potentially fatal. Carcinoid tumours may also present with bleeding.

Tumour location and presentation

Pulmonary carcinoids (Fig. 2) account for only 2% of all primary lung tumours and often present in a similar way to other lung

tumours. They are usually perihilar and present with recurrent pneumonia, cough, haemoptysis and, very occasionally, chest pain. Rarely, cushingoid or acromegalic features may occur and metastases occur in 15–50% of tumours dependent on its differentiation. They may be treated with lung lobectomy or where this is not feasible (such as in cases of multiple intraluminal bronchial polypoid tumours), they have been treated with laser/argon plasma coagulation. Survival of 92% at 10 yr has been reported.

Gastric carcinoid tumours account for <1% of gastric neoplasms and they may be associated with the Zollinger–Ellison syndrome or chronic atrophic gastritis and can be invasive, multiple, or be associated with carcinoid syndrome. Patients with small-bowel carcinoids tend to present in the fifth and sixth decades, most often with mass effects from the tumour (e.g. abdominal pain or obstruction). The majority of small-bowel carcinoids have metastases at presentation and approximately 5% have the carcinoid syndrome.

Carcinoid tumours are the commonest tumour of the appendix, with peak incidence in the fourth or fifth decade, more commonly in women. Fewer than 10% produce obstructive symptoms because of the tumour’s predilection to affect the distal third of the appendix. Metastases at the time of presentation are unusual and the size of the tumour is a good predictor of survival. Carcinoid syndrome may occur in those with liver metastases and thereby reduce the 5-yr survival of appendicular carcinoid from >90 to <35%. Liver metastases can be removed at surgery. If total removal is not feasible (which is often the case), surgical debulking and radiofrequency ablation will reduce the systemic effects of carcinoid and may postpone end-stage hepatic disease. Large-bowel carcinoid generally presents later in life, and prognosis is associated with tumour size and the presence of metastases.

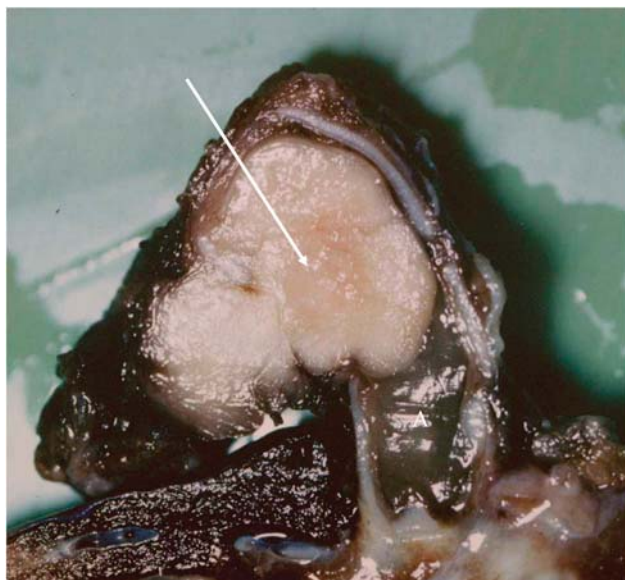


Fig 2 Intra-bronchial carcinoid tumour. Bronchial segment occluded by invasive carcinoid tumour (arrowed). Picture kindly provided by Dr Kim Suvarna, Consultant Pathologist, Northern General Hospital, Sheffield.

Diagnosis

Serology

The presence of carcinoid-like symptoms such as flushing and wheezing may indicate the need to measure urinary 5-HIAA and serum chromogranin A. The serotonin metabolite 5-HIAA, measured in a 24 h urine collection, may be used both diagnostically and as an aid to monitoring tumour activity. A positive result for 5-HIAA has a 73% sensitivity and a 100% specificity for carcinoid tumour.⁴ Serum chromogranin A is a glycoprotein secreted with other hormones by neuroendocrine tumours and is 95% specific and almost 80% sensitive for carcinoid tumours.⁸

Imaging

Metastatic disease is most commonly diagnosed using abdominal CT and contrast; deposits appearing as isodense, hypervascular lesions. Somatostatin receptor scintigraphy using indium-111-labelled octreotide is also useful.⁹

Principles of anaesthetic management for carcinoid

Patients may have limited disease, including the primary tumour, with or without affected lymph nodes (usually in the distal third of the appendix) or have liver metastases. The disease may be resectable or the patients may undergo surgery to decrease tumour load and symptoms. Primary tumour and hepatic resection for single lobe metastases is curative in approximately 10% of cases. The 5-yr survival for multi-lobe metastases after resection is up to 87% with

a peri-operative 30-day mortality of 6%.⁹ Patients may also present for surgery for removal of tumours from other sites or may present for correction of severe valvular dysfunction produced by carcinoid.

For anaesthetic purposes, patients with carcinoid tumours should be regarded as suffering from a multi-system disease and so require thorough pre-planning followed by post-operative management in a high dependency environment by clinicians who are well versed in the complications associated with carcinoid.

Pre-operative assessment

History and examination

Complications such as obstruction, malnutrition, dehydration, anaemia, and electrolyte imbalance will be as common as other obstructing or metastatic lesions. In addition, there may be symptoms or signs suggestive of ongoing uncontrolled excessive hormonal activity such as diarrhoea or less commonly the carcinoid syndrome.

There are two specific areas of concern for planning anaesthetic management. First, a cardiovascular history is essential as right or biventricular heart failure may complicate chronic, excessive hormone release, pulmonary stenosis, or all may also be present. Reduced exercise tolerance, orthopnoea, paroxysmal dyspnoea, and peripheral oedema may all be signs of carcinoid heart disease. Occasionally, coronary artery spasm may occur during flushing episodes associated with carcinoid.

Secondly, there is the potential for unpredictable, uncontrolled hormone release precipitated by haemodynamic variation, anaesthetic, or surgical stimulus. This may result in hypo- or hypertensive crises and haemodynamic collapse which is unresponsive to conventional inotrope and pressor therapy. Even if patients lack symptoms or have symptomatic control, peri-operative use of preventative drugs is essential, because the stimulus to release vasoactive hormones once anaesthesia and surgery commence will be much higher than in day-to-day life. Therefore, it is paramount that tumour activity is minimized before the day of surgery using octreotide. Octreotide acetate exerts pharmacological actions similar to the natural hormone, somatostatin, but it is an even more potent inhibitor of growth hormone, glucagon, and insulin. Similar to somatostatin, it also suppresses luteinising hormone (LH) response to gonadotrophin releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Octreotide has widespread effects, important among these are QT prolongation, bradycardia, conduction defects, abdominal cramps, nausea, and vomiting. Octreotide infusion $50 \mu\text{g h}^{-1}$ for at least 12 h immediately before surgery⁹ should reduce tumour hormonal activity, but ongoing symptoms or signs suggestive of excessive secretion should be treated aggressively with further octreotide before any anaesthetic or surgical intervention.

Investigations

Basic pre-operative investigations are as required for major surgical procedures. These normally include the following as a

minimum: a chest X-ray (which may show carcinoid lesions or rarely miliary shadowing of carcinoid lung), ECG (which may show right ventricular hypertrophy), electrolytes (which may show the effects of chronic diarrhoea), liver function tests (very rarely liver failure presents when the liver is completely infiltrated by carcinoid lesions), full blood count (may reveal signs of diffuse marrow spread), clotting studies and a cross match sample. A macrocytosis may suggest vitamin B12 and folate deficiency which may lead to anaemia. In carcinoid, high serotonin formation may lead to tryptophan depletion and niacin deficiency, which is associated with dermatitis, diarrhoea, and dementia and has rarely led to reversible encephalitis.

A thorough cardiovascular pre-operative work-up, including echocardiography to exclude right-sided carcinoid cardiac disease and possibly exercise testing for those with ischaemic heart disease, is appropriate, given the likely cardiovascular stress associated with surgery. High right-sided heart pressures in the face of pulmonary stenosis secondary to carcinoid may lead to tricuspid regurgitation, hepatomegaly, and a pulsatile liver. This may make hepatic resection impossible without excessive blood loss because of high central venous pressure and hence hepatic vein pressure. In these situations, serious consideration should be given to pulmonary valve surgery before hepatic resection.

Anaesthetic techniques

Regional anaesthesia

Thoracic epidural insertion before induction of general anaesthesia is a reasonable technique for any patient undergoing an elective laparotomy, especially involving the upper abdomen to help achieve good pain relief and reduce post-operative atelectasis. In the context of carcinoid surgery, epidurals have benefits, but, however, are associated with some drawbacks. Excellent analgesia and the avoidance of stressors such as pain will reduce the risk of a carcinoid crisis; however, the potential hypotension produced by an epidural may then require vasoconstrictors that may lead to an exaggerated response. The balance of risks would seem to favour the use of epidurals with drug volumes and concentrations cautiously titrated to blood pressure response.

General anaesthesia

The primary objective in anaesthesia for carcinoid surgery is to provide stable, controlled conditions, avoiding significant stimulatory factors such as blood pressure variation and inadequate analgesia. Reliable large bore access in case of rapid volume loss and the availability of fluid warmers and the use of a rapid infusion system are sensible standards.

Stable induction, adequate depth of anaesthesia before intubation and maintenance of anaesthesia and analgesia peri-operatively are key to preventing instability. The choice of technique and anaesthetic agents is probably most dependent on familiarity and

local preference, with both total intravenous anaesthesia (TIVA) and inhalation techniques being used successfully.

Morphine and atracurium have most potential for unwelcome histamine release and could feasibly be avoided even though the evidence for adverse effects is case based. Suxamethonium has been implicated in the release of peptides from the liver as a consequence of depolarization-induced fasciculations.³ Remifentanyl ($0.05\text{--}0.2\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$) may have a role in optimizing intubating conditions, provision of titratable analgesia and intra-operative blood pressure control.¹⁰ The benefits of its short context-sensitive half-life and titratability are attractive but must be balanced by the risk of hypotension and bradycardia.

Monitoring

Given the potential for haemodynamic instability because of vasoactive hormone release and the potential for large blood loss, invasive monitoring is vital. The exact nature of that monitoring will depend upon local resources and the nature of any cardiac involvement, but a system such as a pulmonary artery flotation catheter, LiDCO, or oesophageal Doppler in addition to arterial and central venous pressure monitoring will be useful to guide fluid therapy and aid in the management of hormone-induced pre- and afterload variations.

Vasoconstrictors

A significant proportion of the surgery related to carcinoid will be for the removal of metastases by hepatic resection. Here, the need to try to maintain a relatively low CVP, during clamping of the hepatic artery and portal vein to avoid backflow into the liver and venous bleeding, will further exacerbate the risk of hypotension. The response to inotropic and vasopressor agents is unpredictable and, in general, drugs such as norepinephrine and epinephrine can be hazardous in carcinoid patients. Norepinephrine has been shown to activate kallikrein in the tumour and can even lead to the synthesis and release of bradykinin resulting paradoxically in further vasodilatation and worsening hypotension, although exaggerated hypertensive responses may be seen. Indeed, any pharmacological stimulation of the autonomic nervous system has the potential to provoke further problems with vasoactive hormone release. In practice, cautious administration of small doses of phenylephrine has been found helpful in some patients.

Vasoactive hormone release intra-operatively is best treated with intravenous boluses of $20\text{--}50\ \mu\text{g}$ of octreotide, titrated to haemodynamic response. Vasopressin as an alternative vasoconstrictor that may be useful if prolonged vasoconstriction is required; however, the evidence base is small.

It must be borne in mind that concomitant fluid losses, especially bleeding, may be responsible for intra-operative instability rather than hormone excess and that fluid resuscitation may be the answer rather than further octreotide therapy. Monitoring of fluid losses, especially bleeding, is very important in these patients.

Portal hypertension and tumour involving the portal veins may contribute to rapid, large volume blood losses requiring rapid replacement, which may be exacerbated by clotting abnormalities. Hourly blood gas monitoring will track acid–base balance and glucose which may become problematical if surgery is prolonged, resection extensive, or bleeding excessive.

For prolonged hypertension, labetalol infusions have been used, as has alpha blockade. However, changes in blood pressure, although sometimes extreme, may be brief and it is possible for the effects of treatment and vasoactive substance release to become confused with one another.

Post-operative high-dependency care

As with the intra-operative management, post-operative care will focus on the provision of stable cardio-respiratory conditions and adequate analgesia. High-dependency care is recommended. Ongoing hormonal control of the tumour is important as post-operative crises are possible and surgery may have been aimed at reducing the bulk of carcinoid tumour present, rather than eliminating it. Intravenous and then subcutaneous octreotide follow-up will help control any further hormone release and there may well be residual, hormonally active tumour remaining. Forty-eight hours of invasive monitoring, analgesia and fluid management may be required to ensure safe recovery from the surgery.⁹

Conclusion

Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in better quality of life and longer survival times. Patients should be aware of the limitations of surgery, which will often debulk tumours, reducing the amount of vasoactive compound release to a point where medical management of symptoms is effective. Provision of anaesthesia for these patients, especially for the resection of hepatic metastases, carries significant risk and requires thorough pre-operative preparation and optimized medical control. Invasive monitoring will be required combined with the use of octreotide. Anaesthetists should preplan

responses to variations in blood pressure and be in a position to recognize the cause of any change. Most importantly, the potential for intra-operative release of vasoactive compounds must not be underestimated even in patients who are currently asymptomatic and peri-operative treatment with octreotide is vital.

Conflict of interest

None declared.

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Please see multiple choice questions 8–11.