Surgery for midgut carcinoid

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Abstract

Many clinicians prefer to avoid surgery in patients with carcinoid neoplasia, because of its slow growth and relatively favourable prognosis. Nevertheless, the commonest cause of death in patients with carcinoid is advanced metastatic disease, and both clinical and epidemiological data indicate that the more effectively the disease is ablated, the more long-lasting the benefit. Multidisciplinary management of patients with carcinoid must consider inherited risk, possible multiple carcinoids and/ or synchronous non-carcinoid cancer, and the use of a range of investigations that also evaluate the 10% of patients with carcinoid syndrome with or without valvular heart disease. Although primary size is correlated with the presence of nodal with or without liver metastases, carcinoid tumours < 1 cm in diameter may be metastatic at presentation, particularly those arising within the small intestine. In the jejunum and ileum, resection of all sizes of carcinoid with local and regional nodes is preferred, to prevent nodal dissemination causing mesenteric ischaemia with or without infarction. Resection of nodal metastases should be undertaken in those with persistent or recurrent nodal disease if possible. Appendiceal and right colonic carcinoids are most effectively treated by right hemicolectomy with local and regional nodal clearance, as for adenocarcinoma. However, for most appendiceal carcinoids which are < 1 cm in diameter and non-invasive, appendicectomy alone is sufficient. For appendiceal carcinoids 1–2 cm in diameter, histopathological assessment helps to determine the need for hemicolectomy. Liver resection has been followed by prolonged 5 year survival in several series and is recommended in appropriate patients to attempt cure or to debulk metastatic disease. Liver transplantation has had only qualified success in highly selected patients without extra-hepatic disease in whom other therapies have failed.

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Historical introduction

The term carcinoid was first applied a century ago to a distinct gastrointestinal neoplasm that appeared less aggressive than adenocarcinomas (Oberndorfer 1907). Over the next 50 years further endocrine tumours of the gastrointestinal tract were identified, and their excessive production and release of peptides recognised, including insulinoma (Wilder *et al.* 1927) and gastrinoma (Zollinger & Ellison 1955). By then the malignant potential of carcinoid tumours had been recognised, as well as their excessive production and release of serotonin (5-hydroxytryptamine) (Lembeck 1953) as in carcinoid syndrome (Pernow & Waldenström 1954, Thorson *et al.* 1954). Since then, further such neoplasms have been described, including tumours currently classified as 'nonfunctioning' (Kent *et al.* 1981). Familial patterns of inheritance were observed in some affected individuals, and following advances in pathology, tumour classification underwent repeated revision (Williams & Sobin 1963, World Health Organisation 1990, Solcia *et al.* 2000). Carcinoid tumours remain broadly separated into foregut, midgut and hindgut types (Williams & Sobin 1963; see Table 1). A presumed neuroectodermal origin led to the use of the term neuroendocrine, also applied to the diffuse neuroendocrine system. Carcinoid came to be defined as those tumours arising from enterochromaffin, enterochromaffin-like and other endocrine

Table 1 Characteristics of foregut, midgut and hindgut carcinoids

	Foregut*	**Midgut**	**Hindgut**
Site of primary	Oesophagus Stomach Duodenum Liver Gallbladder Bile ducts Pancreas	Jejunum Ileum Appendix Right colon Transverse colon	Descending colon Sigmoid colon Rectum
Cell of origin	Epithelial endocrine cell Enterochromaffin-like cell in stomach	Epithelial endocrine cell Subepithelial endocrine cell in appendix	Epithelial endocrine cell
Typical histology	Well differentiated, often multiple, occurs in MEN-1 Often invasive in sporadic carcinoid	Well differentiated, often multiple Nodal metastases very common except from appendix	Well differentiated Nodal metastases common
Usual syndrome	Atypical with prolonged purple flush, headache, lacrimation, bronchoconstriction	Typical short pink/red flushes with diarrhoea, cardiac fibrosis, wheezing, dyspnoea, pellagra	Syndrome very rare
Possible mediators	5-Hydroxytryptophan, histamine, others	Serotonin, kinins, others	

*Not characterised are carcinoids arising in the trachea, bronchi, lungs or elsewhere.

cells (see Table 1); atypical varieties with higher mitotic indices, goblet cell and/or adenocarcinoid features were found to have a worse prognosis (Subbuswamy *et al.* 1974, Soga 1998*a*, McCusker *et al.* 2002, Van Eeden *et al.* 2002). Nevertheless the slow growth of many gastrointestinal neuroendocrine neoplasms and the lack of effective treatments for metastases led to a conservative approach to treatment, which cannot now be justified.

Clinical epidemiology

A population-based perspective of natural history and of the impact of treatment is essential to formulating an overall approach to tumour management. This is especially true for rarer and complex forms of neoplasia that have been subject to few randomised trials, to determine criteria for resection and strategies for residual or recurrent disease.

Post-mortem studies

Thorough necropsy studies of many individuals have demonstrated gastrointestinal neuroendocrine tumours to be far commoner than expected from the number of tumours identified in living patients (Berge & Linell 1976, Kimura *et al.* 1991). Carcinoid tumours were found in 199 out of a series of 16 294 necropsies (62.6% of all deaths) in Malmo, the majority in the digestive tract; 90% were identified incidentally post-mortem (Berge & Linell 1976). During the same period, 44 carcinoids were diagnosed in surgical specimens examined in Malmo. The average annual frequency of carcinoid in the entire series was 8.4 per 100 000, about seven times greater than that recorded by the Swedish Cancer Registry for the same period.

Gastrointestinal neuroendocrine neoplasms that present during life are likely to produce a defined syndrome from excessive peptide secretion, or may be more invasive, producing symptoms from mass effects. Thus the commonest cause of death in patients with carcinoid tumours diagnosed during life is metastatic carcinoid disease, through either tumour burden, or peptide effects, including valvular heart disease (Ross & Roberts 1985, Norheim *et al.* 1987, Wängberg *et al.* 1996, Makridis *et al.* 1997, Doherty *et al.* 1998, Westberg *et al.* 2001).

Epidemiological studies

A number of population-based studies of carcinoid have examined patterns of incidence and survival, from which several conclusions can be drawn. First, the incidence of carcinoid tumours diagnosed during life is rising with gastrointestinal carcinoids making up the majority; earlier estimates were of fewer than 2 per 100 000 per year (Godwin 1975, Watson *et al.* 1989, Newton *et al.* 1994) but more recent studies have found rates approaching 3 per 100 000 (Levi *et al.* 1993, 2000, Hemminki & Li 2001*a,b*, Modlin *et al.* 2003). The changes in incidence may result more from changes in detection than in the underlying burden of disease.

Secondly, an inherited predisposition to carcinoid that has been recognised for several decades (Moertel & Dockerty 1973, Yeatman *et al.* 1989) has been better defined. The risk

of carcinoid in an individual with one affected first-degree relative has been estimated to be approximately four times that in the general population; with two affected first-degree relatives, this risk has been estimated at over 12 times that in the general population (Hemminki & Li 2001*a*). No single gene disorder causing familial carcinoid has yet been identified (Oliveira *et al.* 2001), although foregut and occasionally midgut carcinoids develop in individuals with multiple endocrine neoplasia type 1 (MEN-1) (Thakker 2001). This is in addition to the pituitary, parathyroid and pancreatic endocrine tumours occurring in this disease, caused by germline mutations of the menin tumour suppressor gene (Chandrasekharappa *et al.* 1997). Sporadic midgut carcinoids are usually characterised by deletions of chromosome 18 (Lollgen *et al.* 2001), and may also feature somatic mutations of the menin gene (Gortz *et al.* 1999).

Thirdly, there is a wide range of cell types and peptide products that characterise carcinoid neoplasia, but patterns depend on the site of origin. Also, whilst many carcinoids grow so slowly that they remain localised, symptomless and undetected (Berge & Linell 1976, Kimura *et al.* 1991), some carcinoids of < 1 cm in diameter arising from the small intestine may present with multiple liver metastases (Makridis *et al.* 1990, Burke *et al.* 1997, Shebani *et al.* 1999). Nevertheless the size of a primary carcinoid does bear upon the likelihood of metastasis (Moertel *et al.* 1968, MacGillivray *et al.* 1991, McDermott *et al.* 1994, Soga 1997, 1998, Onaitis *et al.* 2000), which affects treatment policy as discussed below.

Fourthly, carcinoid neoplasia has been demonstrated to be associated with other carcinomas (Shebani *et al.* 1999, Hemminki & Li 2001*b*, Modlin *et al.* 2003). Although not all studies have shown this association to be strong (Westergaard *et al.* 1995), recent data from over 13 000 carcinoid cases in the USA have shown that ~20% of patients with carcinoid tumours develop other cancers (Modlin *et al.* 2003). At least one-third of these second cancers have been found in the gastrointestinal tract (also in the lung, cervix and ovaries (Saha *et al.* 1989, Modlin *et al.* 2003)), indicating the need for appropriate surveillance either at the time of carcinoid diagnosis, or during follow-up.

Fifthly, and encouragingly, recent increases in the survival of individuals with carcinoid have been documented (Quaedvlieg *et al.* 2001, Modlin *et al.* 2003). Thus in the Netherlands, 58 patients diagnosed between 1992 and 1997 with distant carcinoid metastases had a median survival of 43 months compared with 24 months in 49 patients diagnosed between 1980 and 1991 (Quaedvlieg *et al.* 2001). These improvements may be partially due to improvements in technology, leading to increased identification of less malignant cases, and greater willingness to treat carcinoid. Nevertheless overall 5 year survival of all carcinoid cases in the largest series to date was 67.2% (Modlin *et al.* 2003), not indicative of a benign disease.

Diagnosis

Clinical presentation

A critical component in the diagnosis of carcinoid is suspicion of its presence, otherwise the diagnosis may be made very late in the course of the disease, perhaps by histopathology, or possibly not at all. Suspicion is all the more important because symptoms are often non-specific (see Table 2). Midgut carcinoids can present with abdominal pain (up to 60%), nausea and/or vomiting (up to 40%), weight loss (up to 30%), intermittent or continuous diarrhoea (up to 20%), blood loss (up to 20%) and carcinoid syndrome (up to 20%); also, a significant number are discovered incidentally (Shebani *et al.* 1999). Midgut carcinoid may present with an acute abdomen in a minority of patients, with clinical features consistent with appendicitis, intestinal obstruction, intestinal perforation or gastrointestinal haemorrhage. Alternatively, carcinoid may remain unconsidered until histopathology is obtained following surgery for presumed jejunal, ileal or colonic inflammatory or neoplastic disorders, including Crohn's disease, lymphoma or adenocarcinoma. Also,

Table 2 Differential diagnoses for midgut carcinoid: representative list of more likely alternative diagnoses

Requiring emergency management
  Infective
    Appendicitis
    Yersinia enterocolitis
    Diverticulitis
    Typhoid
    Ileocaecal tuberculosis
  Vascular
    Mesenteric ischaemia
    Mesenteric infarction
    Mesenteric vasculitis
  Mechanical
    Adhesions
    Internal hernia
    Volvulus
    Foreign body perforation
Requiring emergency or elective management
  Neoplastic
    Adenocarcinoma
    Lymphoma
    Sarcoma
    Extra-adrenal phaeochromocytoma
    Gastrinoma
    Islet cell carcinoma
  Inflammatory
    Crohn's disease
    Coeliac disease
    Chronic pancreatitis
    Retroperitoneal fibrosis
  Cardiac
    Ischaemic heart disease
    Rheumatic heart disease

Table 3 Frequency of nodal and liver metastases at presentation of midgut carcinoid*

	Nodal metastases	Liver metastases
Jejunum and ileum		
< 1 cm	40%	10%
1–2 cm	60%	25%
> 2 cm	85%	60%
Appendix		
< 1 cm	< 0.1%	< 0.1%
1–2 cm	< 5%	< 5%
> 2 cm	30%	20%
Right and transverse colon		
< 1 cm	10%	5%
1–2 cm	20%	15%
> 2 cm	80%	40%

*Approximate percentages from collected publications (Anderson & Wilson 1985, Thompson *et al.* 1985, Moertel *et al.* 1987, Norheim *et al.* 1987, Saha *et al.* 1989, MacGillivray *et al.* 1991, Ballantyne *et al.* 1992, McDermott *et al.* 1994, Öberg 1994, Burke *et al.* 1997, Cunningham *et al.* 1997, Modlin & Sandor 1997, Soga 1997, 1998*a,b*, Sandor & Modlin, 1998, Shebani *et al.* 1999, Onaitis *et al.* 2000, Talamonti *et al.* 2002, Modlin *et al.* 2003).

carcinoid tumours may be found in the midgut or in resected specimens when surgery has been undertaken for other intra-abdominal disease, notably carcinoma, borne out by the association of carcinoid with other tumours evident in population-based studies (Hemminki & Li 2001*b*). More than half of midgut carcinoids (except appendix, see Table 3) present with nodal metastases (up to 80% of small bowel cases), whilst a smaller proportion present with liver metastases (up to 40% of small bowel cases), features that do not necessarily help the unsuspecting surgeon to identify the primary. Carcinoids may also be multiple, notably in the small bowel, and < 1 cm in diameter despite nodal and liver metastases, so a careful search is mandatory.

Diagnostic tests

Routine haematological, biochemical, radiological and other tests should be undertaken as required, for general medical assessment and to determine whether the patient is fit enough for surgery, should there be a choice. Investigations that may help include plasma chromogranin A (Stridsberg *et al.* 1993), platelet serotonin (Meijer *et al.* 2000) and/or plasma substance P levels, 24 h urinary 5-hydroxyindoleacetic acid, serotonin and catecholamine (to exclude phaeochromocytoma) excretion, computed tomography (CT) or magnetic resonance imaging (MRI), endoscopy and biopsy, small bowel radiology, somatostatin receptor and ^{131}I-metaiodobenzylguanidine scintigraphy (Krenning *et al.* 1989, 1999, Kaltsas *et al.* 2001), and single-positron emission computed tomography (Orlefors *et al.* 1998). Elevated plasma

chromogranins, notably chromogranin A, have become increasingly recognised as sensitive and specific markers of gastrointestinal neuroendocrine tumours, including carcinoid (Stridsberg *et al.* 1993, Eriksson *et al.* 2000); pancreatic polypeptide may also be useful (Eriksson *et al.* 2000). Tests for MEN (prolactin, growth hormone, parathyroid hormone, islet hormones) should also be considered. Plasma chromogranin A and somatostatin receptor scintigraphy are also of use during follow-up to detect the presence or progression of recurrence. In the UK, chromogranin A assay is currently available at two major endocrine laboratories, at the Hammersmith Hospital in London and at the Royal Victoria Hospital in Belfast. If midgut carcinoid has been diagnosed and/or ischaemia is suspected, and surgery for nodal disease and/or vascular reconstruction is planned, angiography is helpful, since carcinoid tumours can be highly vascular or can compromise larger branches of the superior mesenteric artery through nodal compression (Warner *et al.* 1979, Eckhauser *et al.* 1981). Multi-slice spiral CT angiography is an alternative, since information can also be obtained on the resectability of carcinoid nodal metastases (see below). Further information may be obtained on the possible presence of other associated non-carcinoid tumours (Hemminki & Li 2001*b*), and a general search considered.

Carcinoid syndrome

Carcinoid syndrome most commonly develops in patients with midgut carcinoid that has metastasised to the liver, the symptoms of which result from a variety of peptides produced by tumour tissue, including serotonin, kallikrein, tachykinins and prostaglandins. Short-lived flushes, diarrhoea, wheezing, dyspnoea, valvular heart disease and pellagra are typical. Pellagra with dermatitis and hyperpigmentation occurs because of the conversion of tryptophan into 5-hydroxytryptamine and thus 5-hydroxyindoleacetic acid rather than into nicotinic acid; the skin disorders may require dermatological attention. A small number of patients with carcinoid syndrome from foregut carcinoids develop an atypical picture from 5-hydroxytryptophan, histamine and other peptides, which result in a prolonged, violaceous flush, headache, lacrimation and bronchoconstriction; this atypical picture must be differentiated from the typical syndrome caused by midgut carcinoids. As with all gastrointestinal neuroendocrine tumours, carcinoids vary in the extent to which they cause clinically evident symptoms from excessive peptide production. Thus carcinoid syndrome may result from a large primary and/or nodal mass of midgut carcinoid that has not spread to the liver, whereas carcinoid syndrome may be absent in some patients who have a midgut carcinoid with extensive liver metastases. In any event, if there is clinical suspicion that a patient has the carcinoid syndrome, a full peptide profile should be obtained, as outlined above.

Valvular heart disease

Approaching 50% of patients with carcinoid syndrome have valvular heart disease, usually right-sided (Moyssakis *et al.* 1997). This complication develops after some time, from fibrosis with shrinkage and thickening of the tricuspid and pulmonary valve cusps that has been attributed to long-standing serotonin over-production. The lungs can usually metabolise serotonin but are occasionally overwhelmed, or harbour an extensive carcinoid primary, when left-sided valvular heart disease may occur. Any patient with carcinoid syndrome should undergo electrocardiography, echocardiography and chest X-ray, and if symptomatic with breathlessness and chest pain from valvular heart disease, will require medication to improve cardiac function. Cardiac catheterisation should be considered with a view to valve replacement surgery, although patient selection and management to ensure optimal cardiac function is mandatory to reduce mortality in this high-risk group (Robiolio *et al.* 1995, Di Luzio & Rigolin 2000, Connolly *et al.* 2002). Such cardiac surgery is better undertaken prior to elective abdominal surgery for carcinoid.

Perioperative management

General approach

Apart from general considerations that apply to the evaluation of any patient undergoing surgery, there are specific issues in carcinoid patients. These include careful staging of the tumour, identification of synchronous non-carcinoid tumours, recognition of fluid and electrolyte depletion from diarrhoea, detection of less obvious cases of carcinoid syndrome as well as detection of cardiac abnormalities. The treatment plan should be modified accordingly, whether to meet immediate or long-term objectives.

Carcinoid crisis

Of particular concern is carcinoid crisis, when a massive outpouring of various peptides may induce cardiorespiratory collapse. There is a risk of this complication occurring in any individual with carcinoid syndrome who undergoes any procedure that might trigger the release of vasoactive mediators. Thus regional or general anaesthesia, invasive radiological procedures including embolisation or radiofrequency ablation, and all forms of surgery can precipitate such a crisis. Although it is by no means clear what the mechanisms are which prompt the release of peptide mediators from tumour tissue, catecholamines are considered contributory (Nilsson *et al.* 1985), usually elevated following sympathetic nervous system responses to hypotension. Midgut carcinoid tumour cells possess β-receptors, stimulation of which by circulating catecholamines may initiate release of serotonin and other vasoactive amines (Nilsson *et al.* 1985).

In the same way that carcinoid tumours vary widely in the type of mediators released, there is a range of potential changes in carcinoid crises. Thus bradykinin may induce profound vasodilatation and hypotension, and in the presence of cardiac disease, bronchospasm; histamine may induce profound bronchospasm.

Somatostatin was first reported to control hypotension from manipulation of a carcinoid tumour over two decades ago (Thulin *et al.* 1978). Rapid resolution of severe hypotension from a carcinoid crisis developing during surgery followed the administration of octreotide (Kvols *et al.* 1985). An i.v. infusion of 50 µg/h octreotide, started prior to and continued for at least 48 h after any major intervention, is now standard prophylaxis (Kinney *et al.* 2001); it is also important to avoid drugs that release histamine or activate the sympathetic nervous system (Dougherty & Cronau 1998); adrenoreceptor blockade may also be helpful (Holdcroft 2000). Despite these measures patients may still develop life-threatening cardiorespiratory complications that can tax even the most experienced anaesthetist, who may have to use α- and β-blocking drugs to avoid severe complications (Holdcroft 2000).

Small intestinal carcinoid

Emergency surgery

Emergency surgery is likely to be indicated in the presence of an acute abdomen, whether carcinoid has previously been identified or not, or is suspected or not – more commonly not (see Table 2). Such surgery should be directed to remove the immediate threat to life, its extent being limited by the condition of the patient. With incipient or established multi-organ failure such circumstances are best managed with limited corrective surgery, reserving until recovery further surgery for tumour clearance or debulking if appropriate. Thus a limited emergency small bowel resection for an obstructing carcinoid tumour might be followed at a later date by elective surgery to remove further small bowel, particularly if by then a second tumour has been identified, and to undertake mesenteric lymphadenectomy. A substantial minority of patients with midgut carcinoid have multiple tumours (Makridis *et al.* 1990, Soreide *et al.* 1992), so a search should be made following removal of an obstructing lesion prior to any further surgery.

Elective surgery

Patients who are symptomatic but do not require emergency surgery can be more accurately staged pre-operatively, which assists in planning definitive treatment, whether for a single or multiple primary carcinoid, associated non-carcinoid tumour, nodal and/or liver metastases. Of all gastrointestinal

sites, the correlation between the size of the primary and spread of metastases is weakest for small intestinal carcinoid. Tumours < 1 cm in diameter are frequently (over 40% of cases) associated with nodal and/or liver metastases, which may result in presentation because of symptoms from metastases rather than from the primary tumour (see Table 3). Tumours 1–2 cm in diameter are associated with nodal and/or liver metastases in over 60% of cases, whereas tumours > 2 cm in diameter are usually associated with nodal and/or liver metastases (Kulke & Mayer 1999, Shebani *et al*. 1999, Falconi *et al*. 2001). Therefore by far the great majority of small intestinal carcinoids are malignant in nature. Whether liver metastases are present or not, resection of the primary and extensive resection of associated mesenteric lymph nodes are appropriate, to remove tumour for cure or to delay progression that would otherwise endanger the small bowel (see later section on mesenteric metastases). Patients who are only after surgery discovered to have small intestinal carcinoid may be candidates for further surgery, notably for extensive mesenteric lymphadenectomy. It is important to note that although the prognosis of small intestinal carcinoid exceeds that of all the other principal forms of small intestinal cancer (adenocarcinoma, lymphoma, sarcoma (Cunningham *et al*. 1997, Talamonti *et al*. 2002, see Table 4), this is not by a huge margin, and clearly indicates a malignant disease process. Approaches to liver metastases are discussed below (later section on hepatic metastases).

Mesenteric metastases

Natural history

Intermittent intestinal obstruction may be caused by fibrosis and shrinkage of the mesentery, with kinking of the small intestine. Debilitating abdominal pain, disabling diarrhoea, weight loss and malnutrition may lead to death if uncorrected (Kowlessar *et al*. 1959). Furthermore, intestinal ischaemia may result from compression of the main mesenteric vessels by nodal metastases, fibrosis or elastic vascular sclerosis (Warner *et al*. 1979, Eckhauser *et al*. 1981). This last phenomenon only occurs in association with midgut carcinoid and may result from the paracrine actions of serotonin or other factors (including acidic fibroblast growth factor and transforming growth factor-α) on smooth muscle cells and/or fibroblasts, producing elastic vascular sclerosis (Anthony & Drury 1970, Facco *et al*. 1998). Intestinal angina can occur from vascular compromise, which can be distinguished from intermittent intestinal obstruction by administration of sublingual glyceryl trinitrate. Whilst relief from intestinal angina may be immediate, little response would be expected from the pain of intestinal obstruction. At an advanced stage, intestinal ischaemia may cause necrosis and perforation of the intestinal wall, also a recognised cause of death in patients with midgut carcinoid (Eckhauser *et al*. 1981).

Table 4 Five year survival of midgut carcinoid by stage of presentation[1]

Jejunum and ileum	
Localised disease	70–80%
Nodal metastases	60–75%
Liver metastases	30–50%
Appendix	
Localised disease	> 95%
Nodal metastases	80–90%
Liver metastases	30–40%
Right and transverse colon	
Localised disease	55–80%
Nodal metastases	40–70%
Liver metastases	20–40%
All patients with liver metastases	
Hepatectomy[2]	70–80%
Transplantation[2]	60–70%
All cases	20–50%

[1]Approximate percentage survivals from collected publications that are higher for patients undergoing complete surgical resection (Anderson & Wilson 1985, Thompson *et al*. 1985, Moertel *et al*. 1987, Norheim *et al*. 1987, Saha *et al*. 1989, Makridis *et al*. 1990, Ballantyne *et al*. 1992, Soreide *et al*. 1992, Levi *et al*. 1993, 2000, DiSario *et al*. 1994, McDermott *et al*. 1994, Norton 1994, Ahlman 1996, Stinner *et al*. 1996, Wängberg *et al*. 1996, Burke *et al*. 1997, Cunningham *et al*. 1997, Modlin & Sandor, 1997, Soga 1997, 1998*a,b*, Sandor & Modlin 1998, Shebani *et al*. 1999, Onaitis *et al*. 2000, Quaedvlieg *et al*. 2001, McCusker *et al*. 2002, Talamonti *et al*. 2002, Modlin *et al*. 2003).

[2]Approximate percentage survivals in selected patients from collected publications (Bechstein & Neuhaus 1994, Lang *et al*. 1997, Le Treut *et al*. 1997, Chen *et al*. 1998, Lehnert, 1998, Chamberlain *et al*. 2000, Yao *et al*. 2001).

Resection of mesenteric metastases

A surgical approach to mesenteric metastases that can achieve clearance in the majority of cases has been described by workers in Uppsala (Ohrvall *et al*. 2000). This approach is suitable for all but those patients with what they classified as stage IV disease, where the superior mesenteric vessels have become completely surrounded by tumour, or when tumour has extended into the retroperitoneum. This has been determined in some patients by CT imaging, but in others can only be determined by surgical exploration (Ohrvall *et al*. 2000). The right colon and mesenteric root is mobilised from posterior adhesions, to permit identification of the mesenteric root below the pancreas. Sharp dissection is used to separate adhesions between the mesenteric root and serosa of the horizontal duodenum. By means of longitudinal incisions along the line of the major mesenteric vessels, the tumour capsule and nodal masses are then dissected off these vessels. Branches may require division, so particular emphasis is placed on preserving the distal arterial arcades, with intestinal resection left until mesenteric clearance has been

completed; occasionally, vascular reconstruction may be required (Ohrvall *et al.* 2000).

Resection of mesenteric metastases may alleviate symptoms dramatically, and importantly, prolong survival. Median survival of one series of patients who underwent resection of midgut primary carcinoids and mesenteric metastases was 139 months vs 69 months when no debulking was performed (Soreide *et al.* 1992). Similar results have been obtained by debulking of hepatic metastases (see later section on hepatic metastases). Thus the indications for surgery are many, not only to control symptoms, but also to prolong life (Makridis *et al.* 1990, Soreide *et al.* 1992, Ahlman 1996, Stinner *et al.* 1996, Wängberg *et al.* 1996, Ohrvall *et al.* 2000, see Table 5).

Appendiceal carcinoid

Natural history

The appendix is the commonest location for a carcinoid tumour, and is the location where benign behaviour is observed most frequently. Since population-based series focus on malignant cases, some may have underestimated the number of appendiceal carcinoids. Nevertheless incidence rates appear to have fallen in recent years (Hemminki & Li 2001*a*, Modlin *et al.* 2003), probably because incidental appendicectomy has been undertaken less frequently (Primatesta & Goldacre 1994), since incidental procedures are now rarely justified. Thus the majority are identified following appendicectomy for suspected appendicitis; up to 2

per 100 appendicectomy specimens may contain a carcinoid tumour (Primatesta & Goldacre 1994). The possibility of a carcinoid makes review of appendiceal histology mandatory, to inform the patient and to determine whether further management is required. Such tumours are most often identified at or near the tip of the appendix, arising from subepithelial endocrine cells, unlike the mucosal enterochromaffin cells from which most carcinoids arise (Lundqvist & Wilander 1987).

Recommendations derived from a study of 108 patients conducted in the 1960s (Moertel *et al.* 1968) came to define the conventional surgical approach to appendiceal carcinoid. These patients were treated by routine appendicectomy and all followed for at least 5 years (83 were followed for at least 10 years). It was concluded that appendicectomy was sufficient treatment for all patients found to have carcinoid tumours < 2 cm in maximum diameter, whereas right hemicolectomy should be considered selectively in favourable surgical candidates with carcinoid tumours > 2 cm in diameter, usually as a second operation. These authors re-evaluated the issues by study of an expanded series of 150 patients whose appendiceal carcinoid treatment spanned 50 years with follow-up of at least 20 years in the majority (Moertel *et al.* 1987). The findings of this second study were taken to support their previous recommendations. There were, however, several significant limitations to both studies.

Follow-up data on adenocarcinoid tumours were excluded. Five patients had multicentric carcinoids, four of whom had small intestinal carcinoids which were considered

Table 5 Summary of surgical recommendations for treatment of midgut carcinoid

Size	Nodes	Treatment
Jejunum and ileum		
< 1 cm	40%	Segmental resection with nodal clearance
1–2 cm	60%	Segmental resection with nodal clearance
> 2 cm	85%	Segmental resection with nodal clearance
Appendix		
< 1 cm	< 0.1%	Appendicectomy
1–2 cm	< 2%	Appendicectomy or right hemicolectomy[1]
> 2 cm	50%	Right hemicolectomy with nodal clearance
Right and transverse colon		
< 1 cm	40%	Hemicolectomy[2] with nodal clearance
1–2 cm	60%	Hemicolectomy with nodal clearance
> 2 cm	85%	Hemicolectomy with nodal clearance
Mesenteric metastases		
Up to SMA/SMV[3]		Resection of mesenteric nodal mass
Surrounding SMA/SMV		Nodal resection not possible
Hepatic metastases		
< 50% replacement		Liver resection if > 25% normal liver preserved
Unsuitable for resection		Consider transplantation[4]

[1]Depending on operative findings/histology; if hemicolectomy, wide nodal clearance.
[2]Right hemicolectomy or extended right hemicolectomy depending on site.
[3]Superior mesenteric artery/superior mesenteric vein.
[4]If no extra-hepatic disease and poor response to other treatments.

more important in their progress. Of the 122 patients with tumours < 2 cm in diameter, complete follow-up was possible in 105, so it is unknown whether late metastasis occurred in any of the 17 patients for whom follow-up was incomplete. There were 22 patients with tumours between 1 and 2 cm in diameter, but four were lost to follow-up after 7–14 years; a detailed breakdown of the follow-up periods completed in these 22 patients was not provided. No metastases were identified in any of the 122 patients with tumours < 2 cm in diameter, but the number of post-mortems was not reported. Nor was the study of sufficient size to determine any clear relationship between recurrence and invasion of the mesoappendix or vascular invasion. There are reports of lymphatic metastases from patients with appendiceal carcinoids < 2 cm in diameter (Anderson & Wilson 1985, Thompson *et al.* 1985), so caution must be advised in the assessment of patients with borderline lesions identified by histological analysis following appendicectomy. In a series of 147 carcinoid tumours of the appendix, two patients were identified with metastases at presentation associated with appendiceal tumours < 2 cm in diameter (Anderson & Wilson 1985). In a smaller series of 17 appendiceal carcinoids that were part of a larger institutional series of 154 patients with carcinoids of the gastrointestinal tract, two patients with appendiceal carcinoids < 2 cm in diameter presented with mesenteric nodes (Thompson *et al.* 1985). Nevertheless, the overall prognosis of appendiceal carcinoids is better than for carcinoid tumours at all other sites (Sandor & Modlin 1998, Modlin *et al.* 2003, see Table 4).

Surgical recommendations

Despite the limitations of the data on appendiceal carcinoids, several recommendations are appropriate. Any patient undergoing appendicectomy should have as full an examination of the small bowel as is possible at the time of surgery. Histopathological assessment of the resected appendix should include the location and size of any carcinoid, the detailed nature of the tumour, and the presence of mesoappendiceal or vascular invasion. If the lesion is > 2 cm in diameter, or is atypical with goblet cell or adenocarcinoid features (Soga 1998*a*), a right hemicolectomy with loco-regional lymphadenectomy should be considered. This decision is likely to be possible at the time of the primary procedure if the tumour is > 2 cm in diameter, even before histopathological analysis. If the lesion is 1–2 cm in diameter, and has any other unfavourable feature, such as location at the base of the appendix, mesoappendiceal and/or vascular invasion, a right hemicolectomy should be considered. Whether or not this is performed, the patient should be followed up for 5 years. If the lesion is < 1 cm in diameter, even if there is extension to the serosa, provided complete resection by appendicectomy has been undertaken, this procedure is so likely to be

curative that a further resection should not normally be considered, nor would extended follow-up appear necessary (see Table 5).

Colonic carcinoids

Most carcinoid tumours arising in the colon are right-sided, arising predominantly in the caecum (Modlin *et al.* 2003), and produce symptoms of abdominal pain and weight loss rather than alteration in bowel habit. There is a significant risk of multiple carcinoids in the region of the main tumour, and of associated non-carcinoid tumours in ~10% of cases (Modlin & Sandor 1997, Modlin *et al.* 2003). Although there is a relatively low rate of lymph node metastasis in association with tumours < 2 cm in diameter (~20% compared with ~80% for tumours > 2 cm in diameter (Morgan *et al.* 1974, Ballantyne *et al.* 1992)), standard resection with loco-regional lymphadenectomy is appropriate. Clearance of metastatic lymph nodes is a worthwhile objective that may contribute to long-term survival, and nodal clearance does not add significantly to the risk of surgery, which should in any case be < 2% when conducted by specialist colorectal teams (Khuri *et al.* 1997). Small lesions < 1 cm in diameter may be considered adequately treated by complete endoscopic removal, but the patient will require follow-up endoscopy to ensure this has been accomplished. Overall 5 year survival rates for colonic carcinoids are relatively low at ~40%, but remain significantly better than for colonic adenocarcinomas (Ballantyne *et al.* 1992, DiSario *et al.* 1994, see Table 4).

Hepatic metastases

Liver resection

A search for hepatic metastases should be made in every patient with suspected or proven intra-abdominal carcinoid, whether by percutaneous ultrasound, or during more complex work-up by CT or MRI, radionuclide imaging, laparoscopy or laparotomy, depending on the circumstances. Midgut carcinoids often metastasise to the liver, where multiple metastases may be present throughout both lobes, making curative resection impossible. When complete resection of primary and associated hepatic metastatic carcinoid or other neuroendocrine tumours can be achieved, extended survivals have been reported, with 5 year survival rates > 70% (Chen *et al.* 1998, Chamberlain *et al.* 2000, Yao *et al.* 2001). Chen and colleagues from Johns Hopkins University compared 15 patients who underwent potentially curative liver resections with 23 patients with comparable disease who did not undergo resection (Chen *et al.* 1998). Actuarial survival was 73% in the resected group, compared with 29% in the non-resected group. Chamberlain and colleagues at the Memorial Sloan-Kettering

Cancer Center studied 15 patients undergoing potentially curative liver resections and 19 undergoing palliative resection (Chamberlain *et al*. 2000). The estimated 5 year survival in patients having complete resections was 85%. Yao and colleagues at Northwestern University in Chicago demonstrated prolonged 5 year survival of 70% in patients undergoing potentially curative liver resection for metastatic carcinoid (Yao *et al*. 2001). Similarly excellent data have been reported in large series from the Sloan-Kettering and Mayo Clinic (Chamberlain *et al*. 2000, Sarmiento *et al*. 2003). Also, selective partial portal vein embolisation can be undertaken before a first or second hepatic resection, extending the applications of this surgical approach (Hemming *et al*. 2003). These data, although selective, demonstrate the potential of resecting all, or most, of a metastatic carcinoid tumour (see Table 4).

The indications for potentially curative liver resection are similar to those applicable to metastatic colorectal cancer, including an adequately fit patient, no unresectable extrahepatic disease, and sufficient residual liver for adequate liver function prior to full recovery. Bilobar disease is not a contraindication to surgery, although if > 50% of the volume of the liver is replaced by tumour, resectability is likely to be affected.

Palliative resection, where 90% or more of the volume of intrahepatic disease is removed by formal liver resection and/or enucleation, has also been used to control carcinoid symptoms and prolong survival (Norton 1994, Wängberg *et al*. 1996, Chen *et al*. 1998, Chamberlain *et al*. 2000, Yao *et al*. 2001, Sarmiento *et al*. 2003). Two reasons distinguish this approach from that to metastatic colorectal adenocarcinoma: symptoms from carcinoid syndrome, which does not occur with colorectal adenocarcinoma, are dependent on the total mass of tumour tissue producing active peptides; also, carcinoid is usually slow growing, and prolonged survival may result from significant debulking of the carcinoid tumour mass. A similar strategy is adopted in the use of radiofrequency ablation (Hellman *et al*. 2002), hepatic arterial embolisation and chemoembolisation (Venook 1999), radionuclide therapy with ^{131}I-metaiodobenzylguanidine or radiolabelled somatostatin analogues (Krenning *et al*. 1999, Kaltsas *et al*. 2001), and/or chemotherapy (Caplin *et al*. 1998, Kulke & Mayer 1999), with the objective of destroying as much tumour tissue as possible. These alternative approaches are more suitable for patients who cannot undergo surgery, or who have widely disseminated carcinoid metastases, which are common. Also, these approaches can be combined with cytoreductive surgery (Chung *et al*. 2001, Hellman *et al*. 2002). The relative efficacies of these alternatives are largely unknown, but optimum therapy will destroy as much carcinoid as possible with minimal complications. By extrapolation from the treatment of other malignancies, combination treatment using a physical intervention coupled with chemotherapy may be the most effective approach.

Liver transplantation

The long-term difficulties of managing carcinoid syndrome, the relatively long survival associated with carcinoid liver metastases and their frequent unsuitability for liver resection has prompted consideration of liver transplantation. Although the total number of patients worldwide who have undergone this therapy is small and earlier results were unpromising (Bechstein & Neuhaus 1994), some qualified success has since been reported (Lang *et al*. 1997, Le Treut *et al*. 1997, Lehnert 1998). For patients in whom other therapies have been of limited value, when metastatic disease is entirely located to the liver and is unsuitable for resection, liver transplantation can be curative; 5 year survivals of 70% have been obtained in highly selected patients (Le Treut *et al*. 1997, see Table 4). Recently further attempts have been made to define criteria including (i) disease unsuitable for partial hepatectomy which is (ii) unresponsive to alternative therapies and (iii) producing life-threatening complications and has (iv) a low proliferation index (Olausson *et al*. 2002, Rosenau *et al*. 2002, Pope & Poston 2003). The risk of extensive surgery and long-term immunosuppression must be balanced against the quality of life of the patient and the likelihood of achieving a cure. Occasionally it could be appropriate for palliation, but in the context of the shortage of donor organs for more established indications for liver transplantation, such treatment will only rarely be offered (Lehnert 1998).

Conclusions

Midgut carcinoid tumours are the commonest carcinoids, and have an increasing incidence largely because of increased detection, currently over 2 per 100 000 per year for all carcinoids. Prompt diagnosis and proper evaluation depend on a high index of suspicion, specific biochemical, imaging and histopathological tests, and the search for synchronous cancers. Surgery must be integrated into a multi-disciplinary team approach (see Table 5) that may also use medical, radionuclide, chemotherapeutic and/or radiological therapy (Caplin *et al*. 1998, Kulke & Mayer 1999), particularly in patients who have carcinoid syndrome with or without valvular heart disease. Despite the frequently indolent course of carcinoid, surgical resection remains the optimal treatment, since this is the only treatment that can achieve cure. Resection is also important in debulking mesenteric and/or liver metastases, controlling symptoms, preventing life-threatening complications and prolonging survival.

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