Carcinoid tumours

What are carcinoid tumours?

Carcinoid tumours are rare, slow-growing tumours that originate in cells of the diffuse neuroendocrine system. They occur most frequently in tissues derived from the embryonic gut. Foregut tumours account for up to 25% of cases and arise in the lung, thymus, stomach, or proximal duodenum. Midgut tumours account for up to 50% of cases and arise in the small intestine, appendix or proximal colon. Hindgut tumours account for approximately 15% of cases and arise in the distal colon or rectum. Other sites include the gallbladder, kidney, liver, pancreas, ovary and testis.[1]

Carcinoid tumours account for about two thirds of neuroendocrine gastroenteropancreatic tumours. 30% of intestinal neuroendocrine tumours (NETs) are associated with carcinoid syndrome.[2] See also the separate Pancreatic Endocrine Tumours article.

Carcinoid tumours are often indolent asymptomatic tumours. However, a small but significant proportion are malignant and difficult to manage. The liver is the most common site for metastases in patients with NETs, occurring in 45-95% of patients.[3] Metastases to the mesenteric lymph nodes, ovaries, peritoneum and spleen may occur.

Carcinoid tumours may secrete various bioactive compounds, including serotonin and bradykinin, which cause carcinoid syndrome, which includes bronchospasm, diarrhoea, skin flushing and right-sided valvular heart lesions.[4] Carcinoid tumours of the ileum and jejunum, especially those larger than 1 cm, are most likely to cause carcinoid syndrome.

NETs of the lung account for 1-2% of all lung cancer. About 70% of all carcinoids are located in the major bronchi and the remainder in the periphery of the lungs. They occur more frequently in the right than in the left lung, and especially in the middle lobe.[5]

How common are carcinoid tumours?[6] [7]

- Carcinoid tumours are the most common NETs.
- The incidence of NETs is 2.7 per 100,000 population, whereas the incidence of the carcinoid syndrome (see below) is 0.27 per 100,000 population in the USA.
- Gastroenteropancreatic neuroendocrine tumours represent the second most common digestive cancer in terms of prevalence. The reported annual age-adjusted incidence rate grew from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012.
- The small intestine (30.8%), rectum (26.3%), colon (17.6%), pancreas (12.1%), and appendix (5.7%) are the most common primary NET sites in the digestive tract.
- Carcinoid tumours may be found as an incidental finding in up to 10% of post-mortem examinations.
- The risk is increased if there is a family history involving a first-degree relative.

Carcinoid tumour symptoms

- Most tumours are clinically silent but they may cause pain, weight loss or present as a palpable mass.
- Carcinoid tumours may produce vague right-sided abdominal discomfort but any symptoms are usually mild and have often been present for a number of years before a diagnosis is made.
- Diagnosis may be made after urgent surgery - eg, for gastrointestinal obstruction.

- Carcinoid heart disease:[4]
    - Endocardial fibrosis may occur, especially in patients with hepatic metastases.
    - The right side of the heart is most often affected, especially tricuspid valve regurgitation.[8] However, tricuspid stenosis, pulmonary regurgitation and pulmonary stenosis may occur.
    - Left heart lesions may occur in patients with pulmonary metastases.
- Carcinoid tumours may also cause fibrosis, including retroperitoneal fibrosis; therefore, presentation may include features such as hydronephrosis (obstruction of the ureter), mesenteric ischaemia or Peyronie's disease.
- In patients with widely metastatic carcinoid tumours, increased conversion of tryptophan to serotonin may lead to tryptophan and niacin deficiency, presenting as hypoalbuminaemia and pellagra.[4] [9]
- Examination is often normal but may reveal a right-sided abdominal mass, hepatomegaly, telangiectasia, pellagra, and tricuspid regurgitation.

Carcinoid syndrome

- Classic carcinoid syndrome occurs in fewer than 10% of patients with carcinoid tumours and occurs most often in patients with carcinoid tumours in the small intestine, appendix and proximal large bowel.[4]
- Features of carcinoid tumours are caused by the release of pharmacologically active mediators 5-hydroxytryptamine (5-HT), prostaglandins, kinins, substance P, gastrin, somatostatin, corticotropin and neuron-specific enolase into the peripheral circulation.
- Secretion of bioactive substances varies depending on the location of the tumour and the presence of metastases.[4]

- Presentation:
    - Flushing (especially after alcohol, coffee, various foods or drugs).
    - Other features include diarrhoea, abdominal pain, palpitations, hypotension and wheezing.
- Carcinoid syndrome variants may be seen in patients with bronchial and gastric carcinoid tumours - for example:[4]
    - Gastric carcinoid tumours may cause flushing which is pruritic and well demarcated, and an increased incidence of peptic ulcer.
    - Bronchial carcinoid tumours may cause flushing which lasts for days and is often associated with changes in mental state.

Differential diagnosis

- Other possible causes of site-related tumours.
- Other causes of flushing (carcinoid syndrome) - eg, alcohol, nitrates, spicy foods, systemic mastocytosis, medullary thyroid cancer, menopause, renal cancer, hyperthyroidism.
- Other causes of diarrhoea - eg, gastroenteritis, inflammatory bowel disease.
- Other causes of bronchospasm - eg, anaphylaxis, asthma, inhaled foreign body, chronic obstructive pulmonary disease.

Investigations[7]

The diagnosis of gastroenteropancreatic neuroendocrine tumours is based on clinical presentation, pathology, and conventional (CT/MRI) or functional imaging. Patients who present with symptoms of carcinoid syndrome should undergo measurement of 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), which is the breakdown product of serotonin. It has been reported that a plasma 5-HIAA assay is equivalent in accuracy to 24-hour urine 5-HIAA measurement.

- Plasma chromogranin A is an effective screening test because it is very sensitive but is not very specific.[4]
- 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA): 24-hour excretion greater than 25 mg provides strong evidence for the diagnosis of carcinoid syndrome:
    - False positive results may occur with certain foods (eg, bananas, kiwi fruit, pineapple, plums, tomato products) and some drugs (eg, paracetamol, antipsychotics, some cough remedies, caffeine, diazepam, nicotine, warfarin).
    - False negatives may occur with various drugs - eg, alcohol, aspirin, antidepressants, St. John's wort.
- Other baseline investigations, considering possible associated neuroendocrine neoplasia or bowel adenocarcinoma, include FBC, LFTs, TFTs, parathyroid hormone, calcium, calcitonin, prolactin. alpha-fetoprotein, carcinoembryonic antigen (CEA) and beta-hCG.
- Provocative tests (eg, pentagastrin test) may be considered if other screening test results are equivocal; however, close monitoring and ready access to intravenous somatostatin are essential in case of a carcinoid crisis (see below).[4]
- Gastric and intestinal tumours may be diagnosed by endoscopy or endoscopic ultrasound; barium studies may demonstrate polyps.
- CT or MRI scanning and laparotomy may be needed for localisation.
- Scintigraphic imaging with labelled somatostatin can provide accurate information on the site and dissemination of the tumour.[10]
- Somatostatin single-photon emission computerised tomography (SPECT) may also be used.
- In a young person whose pneumonia is slow to resolve, a bronchoscopy may reveal a carcinoid tumour.

Associated diseases

- Carcinoid tumours are associated with multiple endocrine neoplasia type 1 (MEN1) in about 10% of cases. Associated endocrine neoplasia should be sought in all patients presenting with carcinoid tumours.
- Adenocarcinoma in 10-20% (usually colorectal adenocarcinoma).

Treatment of carcinoid tumours[7] [11]

- If metastases are present, avoid precipitating factors - eg, alcohol, chocolate, spicy foods, strenuous exercise.
- Treatment is usually based on the size of the tumour. Surgical resection (local resection with node clearance) when possible is the treatment of choice. Surgery should be considered for patients with liver metastases and potentially resectable disease.[12]
- Options for nonresectable disease include somatostatin analogues - eg, octreotide (which blocks 5-HT release), biotherapy, targeted radionuclide therapy, radiofrequency ablation therapy and chemotherapy.
- For advanced metastatic disease, somatostatin analogue therapy and surgical debulking provide the best symptomatic relief and may improve survival.[13]
- Chemotherapy drugs currently being assessed in trials to palliate metastatic carcinoid disease include alkylating agents, doxorubicin and 5-fluorouracil.
- Interferon alfa is a useful additive therapy when symptoms of carcinoid syndrome do not resolve with a somatostatin analogue alone.[4]
- External beam radiotherapy may relieve bone pain from metastases.
- Chemoembolisation of the hepatic artery may provide effective, short-term relief of symptoms due to hepatic metastasis.
- Liver transplantation can be considered in selected cases - eg, young patients without documented spread outside the liver and resected primary tumour.[2]

- For patients with carcinoid valvular heart disease, surgical intervention can lead to improved prognosis and reduce the symptoms of heart failure.[8]

Complications

- Gastrointestinal carcinoid tumours may cause appendicitis, intussusception, bowel obstruction or bowel perforation (rare).
- The tendency for metastatic spread increases with tumour size and is substantially higher in lesions larger than 2.0 cm.[14]
- Carcinoid crisis:[4] [11]
    - Carcinoid crisis may dramatically worsen symptoms and be life-threatening.
    - The tumour may outgrow its blood supply and release large amounts of vasoactive mediators, causing cardiovascular collapse, tachycardia and altered mental state.
    - Carcinoid crisis may also occur during surgical removal but this can be prevented by octreotide infusion before surgical manipulation.
    - Management of carcinoid crisis includes infusion of octreotide and plasma.

Prognosis

- Advances in diagnostic methods and surgical techniques have allowed more active management and improved prognosis.[15]
- Surveys of national databases have shown a median survival of 170 months for patients with localised small bowel neuroendocrine tumours, 145 months for regional disease, and 70 months for those with metastatic disease. With aggressive hepatic cytoreduction of liver metastases, median survival may be improved to well over 100 months.[16]

- Five-year survival for carcinoid tumours of the lung has been reported as 96% in one study (14% had lymph node involvement and none had carcinoid syndrome).[17]

Further reading

- Gastrointestinal Carcinoid Tumor; National Cancer Institute

Authored by:	Peer Reviewed by: Dr Hayley Willacy, FRCGP	
Originally Published: 20/11/2023	Next review date: 14/12/2022	Document ID: doc_1905