GUIDELINES

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours

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1.0 SUMMARY OF RECOMMENDATIONS

1.1 Genetics

- Clinical examination to exclude complex cancer syndromes (for example, multiple endocrine neoplasia 1 (MEN1)) should be performed in all cases of neuroendocrine tumours (NETs), and a family history taken (grade C).
- In all cases where there is a family history of carcinoids or NET, or a second endocrine tumour, a familial syndrome should be suspected (grade C).
- Individuals with sporadic or familial bronchial or gastric carcinoid should have a family history evaluation and consideration of testing for germline MEN1 mutations. Management of MEN1 families includes screening for endocrine parathyroid and enteropancreatic tumours from late childhood, with predictive testing for first degree relatives of known mutation carriers (grade C).
- All patients should be evaluated for second endocrine tumours and possibly for other gut cancers (grade C)

1.2 Diagnosis

If a patient presents with symptoms suspicious of a gastroenteropancreatic NET:

- baseline tests should include chromogranin A (CgA) and 5-hydroxy indole acetic acid (5-HIAA) (grade C). Others that may be appropriate include thyroid function tests (TFTs), parathyroid hormone (PTH), calcium, calcitonin, prolactin, α-fetoprotein, carcinoembryonic antigen (CEA), and β-human chorionic gonadotrophin (β-HCG) (grade D);
- specific biochemical tests should be requested depending on which syndrome is suspected (see table 4).

1.3 Imaging

- For detecting the primary tumour, a multimodality approach is best and may include computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy (SSRS), endoscopic ultrasound (EUS), endoscopy, digital subtraction angiography (DSA), and venous sampling (grade B/C).
- For assessing secondaries, SSRS is the most sensitive modality (grade B).
- When a primary has been resected, SSRS may be indicated for follow up[1] (grade D).

1.4 Therapy

- The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment (grade C).
- Surgery should be offered to patients who are fit and have limited disease—that is, primary ± regional lymph nodes (grade C).
- Surgery should be considered in those with liver metastases and potentially resectable disease (grade D).
- Where abdominal surgery is undertaken and long term treatment with somatostatin (SMS) analogues is likely, cholecystectomy should be considered.
- For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life (grade D).
- The choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumour (grade C).
- Treatment choices for non-resectable disease include SMS analogues, biotherapy, radionuclides, ablation therapies, and chemotherapy (grade C).
- External beam radiotherapy may relieve bone pain from metastases (grade C).
- Chemotherapy may be used for inoperable or metastatic pancreatic and bronchial tumours, or poorly differentiated NETs (grade B).

2.0 ORIGIN AND PURPOSE OF THESE GUIDELINES

A multidisciplinary group compiled these guidelines for the clinical committees of the British

Abbreviations: NET, neuroendocrine tumour; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; CgA, chromogranin A; PTH, parathyroid hormone; CEA, carcinoembryonic antigen; β-HCG, β-human chorionic gonadotrophin; 5-HIAA, 5-hydroxy indole acetic acid; ACTH, adrenocorticotrophic hormone; CT, computed tomography; MRI, magnetic resonance imaging; SSRS, somatostatin receptor scintigraphy; SSTR, somatostatin receptors; EUS, endoscopic ultrasound; TFTs, thyroid function tests; DSA, digital subtraction angiography; SMS, somatostatin

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These guidelines are dedicated to the memory of Professor Keith Buchanan who devoted his life to the study of neuroendocrine tumours.

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Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland, as well as its Surgical Specialty Associations, and the United Kingdom Neuroendocrine Tumour Group (UKNET). Over the past few years there have been advances in the management of NETs, which have included clearer characterisation, more specific and therapeutically relevant diagnosis, and improved treatments. However, there are few randomised trials in the field and the disease is uncommon; hence all evidence must be considered weak in comparison with other commoner cancers. It is our unanimous view that multidisciplinary teams at referral centres should give guidance on the definitive management of patients with gastroenteric and pancreatic NETs with representation that should normally include gastroenterologists, surgeons, oncologists, endocrinologists, radiologists, nuclear medicine specialists, and histopathologists. The working party that produced these guidelines included specialists from these various disciplines contributing to the management of gastrointestinal NETs. The purpose of these guidelines is to identify and inform the key decisions to be made in the management of gastroenteropancreatic NETs, including carcinoid tumours. The guidelines are not intended to be a rigid protocol but to form a basis upon which to aim for improved standards in the quality of treatment given to affected patients.

3.0 FORMULATION OF GUIDELINES

3.1 Literature search

A search of Medline was made using the key words carcinoid tumour/malignant carcinoid syndrome/NETs/islet cell tumours, and a total of 41 553 citations were found. This search was updated every three months during the drafting of these guidelines, in the following categories: diagnosis, imaging, therapy, specific therapies, and prognosis.

3.2 Categories of evidence

The Oxford Centre for Evidence-based Medicine levels of evidence (May 2001) were used to evaluate the evidence cited in these guidelines.[2]

4.0 AETIOLOGY, EPIDEMIOLOGY, GENETICS, AND CLINICAL FEATURES

4.1 Aetiology

The aetiology of NETs is poorly understood. Most are sporadic but there is a small familial risk (see 4.4 Genetics). NETs constitute a heterogeneous group of neoplasms which share certain characteristic biological features, and therefore can be considered as a common entity. They originate from neuroendocrine cells, have secretory characteristics, and may frequently present with hypersecretory syndromes. Such tumours originate from pancreatic islet cells, gastroenteric tissue (from diffuse neuroendocrine cells distributed throughout the gut), neuroendocrine cells within the respiratory epithelium, and parafollicullar cells distributed within the thyroid (the tumours being referred to as medullary carcinomas of the thyroid). Pituitary, parathyroid, and adrenomedullary neoplasms have certain common characteristics with these tumours but are considered separately. Gut derived NETs have been classified according to their embryological origin into tumours of the foregut (bronchi, stomach, pancreas, gall bladder, duodenum,), midgut (jejunum, ileum, appendix, right colon), and hindgut (left colon, rectum).[3] These guidelines apply to carcinoid and NETs arising from the gut, including the pancreas and liver (gastroenteropancreatic), as well as those arising from the lung that have metastasised to the liver or abdominal lymph nodes. The term NET is to be encouraged as it is better defined than carcinoid, although the latter is still in common usage and usually denotes tumours secreting serotonin.

Table 1 Overall frequency of primary neuroendocrine tumours of the gut and its adnexa, with percentage at each site presenting with metastases at the time of diagnosis[11]

Location	% of total	Nodal mets*	Liver mets
Lung†	15	15	5
Stomach	3	35	15
Duodenum‡	3	60	30
Pancreas§	5	45	25
Jejunum	2	60	30
Ileum	15	60	30
Appendix¶	35	5	2
Right colon**	4	70	40
Left colon	3	40	20
Rectum	10	15	5
Other	5	50	30

*Includes those presenting with liver metastases.
†Trachea, bronchi, and lung.
‡Includes gastrinomas.
§Islet cell tumours.
¶Includes benign carcinoids.
**Includes transverse colon.

Apudoma as a term to describe these tumours has become obsolete as it is non-specific. It is recommended that it is no longer used in the management of this group of patients.

4.2 Epidemiology (tables 1, 2)

The incidence of NETs diagnosed during life is rising, with gastrointestinal carcinoids making up the majority; earlier estimates were of fewer than 2 per 100 000 per year[4] but more recent studies have found rates approaching 3 per 100 000, with a continuing slight predominance in women.[5–7] The changes in incidence may result more from changes in detection than in the underlying burden of disease as thorough necropsy studies have demonstrated gastrointestinal NETs to be far commoner than expected from the number of tumours identified in living patients.[8 9] The risk of NET 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[5] (see 4.4 Genetics). Recent data from over 13 000 NETs in the USA have shown that approximately 20% of patients with these tumours develop other cancers, one third of which arise in the gastrointestinal tract. Recent increases in the survival of individuals with NET have been documented[10] although overall five year survival of all NET cases in the largest series to date was 67.2%.[11]

Meticulous post mortem studies have identified pancreatic NETs in up to 10% of individuals[12] but the incidence of

Table 2 Location, association with multiple endocrine neoplasia (MEN1), and incidence of less rare types of pancreatic neuroendocrine tumours

	Metastases (%)	% MEN1	Incidence per year
Insulinoma	10	5	1–2/million
Gastrinoma*	60	25–40	1–2/million
Glucagonoma	50–80	10	0.1/million
VIPoma	40–70	5	0.1/million
Somatostatinoma*	70	45	<0.1/million
Ectopic GRFoma†	60–70	15	<0.1/million
Ectopic ACTHoma‡	90	<5	<0.1/million
Non-syndromic	60	20	1–2/million

*Approximately half of the cases arise in the duodenum.
†Also arise in the lungs and jejunum.
‡Occasionally arise elsewhere.

pancreatic NETs in life is far lower. This would predict an incidence far greater than that seen in life which has been assessed in population based studies as being 0.2–0.4 per 100 000 per year, with insulinoma and gastrinoma as the commonest among this rare group of tumours.

Because many NETs are slow growing or of uncertain malignant potential, and even malignant NETs are associated with prolonged survival, prevalence is relatively high.[13]

4.3 Clinical features

Primary gastroenteropancreatic tumours can be asymptomatic but may present with obstructive symptoms (pain, nausea, and vomiting) despite normal radiology. The syndromes described below are typically seen in patients with secretory tumours. The carcinoid syndrome is usually a result of metastases to the liver with the subsequent release of hormones (serotonin, tachykinins, and other vasoactive compounds) directly into the systemic circulation.[14] This syndrome is characterised by flushing and diarrhoea. Some patients have lacrymation, rhinorrhoea, and episodic palpitations when they flush. At the time of diagnosis in patients with the syndrome approximately 70% give a history of intermittent abdominal pain, 50% a history of diarrhoea, and about 30% a history of flushing. Less commonly wheezing and pellagra may occur as presenting features, with carcinoid heart disease typically not occurring unless the syndrome has been present for some years.[15 16] Occasionally, similar syndromes can occur when there are no measurable hormones detected in blood or urine.

Patients with bronchial carcinoid present with evidence of bronchial obstruction (41%)—obstructive pneumonitis, pleuritic pain, atelectasis, difficulty with breathing; cough (35%) and haemoptysis (23%)—while 15% present with a variety of other symptoms, including weakness, nausea, weight loss, night sweats, neuralgia, and Cushing's syndrome.[17] Up to 30% are asymptomatic.

The carcinoid crisis is characterised by profound flushing, bronchospasm, tachycardia, and widely and rapidly fluctuating blood pressure. It is thought to be due to the release of mediators which lead to the production of high levels of serotonin and other vasoactive peptides. It is usually precipitated by anaesthetic induction for any operation, intraoperative handling of the tumour, or other invasive therapeutic procedures such as embolisation and radiofrequency ablation.

Syndromes related to pancreatic NETs and their principal clinical features[18 19] are shown in table 3.

Recommendations (genetics)

- Clinical examination to exclude complex cancer syndromes (for example, MEN1) should be performed in all cases of NETs, and a family history taken (grade C).
- In all cases where there is a family history of carcinoids or NET, or a second endocrine tumour, a familial syndrome should be suspected (grade C).
- Individuals with sporadic or familial bronchial or gastric carcinoid should have family history evaluation and consideration of testing for germline MEN1 mutations. Management of MEN1 families includes screening for endocrine parathyroid and enteropancreatic tumours from late childhood, with predictive testing for first degree relatives of known mutation carriers (grade C).
- All patients should be evaluated for second endocrine tumours and possibly for other gut cancers (grade C).

4.4 Genetics

NETs may occur as part of complex familial endocrine cancer syndromes such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2),[20] neurofibromatosis type 1 (NF1),[21 22] Von Hippel Lindau, and Carney's complex although the majority occur as non-familial (that is, sporadic) isolated tumours. The incidence of MEN1 in gastroenteropancreatic NETs varies from virtually 0% in gut carcinoids to 5% in insulinomas to 25–30% in gastrinomas (see table 2).[18] However, it is important to search thoroughly for MEN1, MEN2, and NF1 in all patients with NETs by obtaining a detailed family history, clinical examination, and appropriate biochemical and radiological investigations. The diagnosis can also now be confirmed by genetic testing. A diagnosis of MEN1, MEN2,

Table 3 Clinical features of pancreatic neuroendocrine tumours

Tumour	Symptoms	Malignancy	Survival
Insulinoma	Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating	10% of patients develop metastases	Complete resection cures most patients
Gastrinoma	Zollinger-Ellison syndrome of severe peptic ulceration and diarrhoea	Metastases develop in 60% of patients; likelihood correlated with size of primary	Complete resection results in 10 year survival of 90%; less likely if large primary
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea	Metastases develop in 60% or more patients	More favourable with complete resection; prolonged even with liver metastases
VIPoma	Werner-Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia	Metastases develop in up to 70% of patients; majority found at presentation	Complete resection with five year survival of 95%; with metastases, 60%
Somatostatinoma	cholelithiasis; weight loss; diarrhoea and steatorrhoea. Diabetes mellitus	Metastases likely in about 50% of patients	Complete resection associated with five year survival of 95%; with metastases, 60%
Non-syndromic pancreatic neuroendocrine tumour	Symptoms from pancreatic mass and/or liver metastases	Metastases develop in up to 50% of patients	Complete resection associated with five year survival of at least 50%

and NF1 not only has important implications for the patient but also for the patient's relatives who should be considered for screening for the associated tumours and for genetic testing.

Most NETs are sporadic but epidemiological studies show a small increased familial risk, with standardised incidence ratios of 4.35 (n = 4, 95% confidence interval (CI) 1.86–7.89) for small intestinal and 4.65 (n = 4, 95% CI 1.21–10.32) for colon NETs in the offspring of parents affected with carcinoids. This familial clustering was seen to be more pronounced with midgut and hindgut tumours, and few patients had obvious MEN1, suggesting that much of this association is independent of MEN1.[6] Risks for second cancers, in males, were increased during the first year of follow up. Slightly lower risks were noted in females

5.0 DIAGNOSIS

Gastroenteropancreatic NETs may produce specific symptoms and hormones. The diagnosis is therefore based on clinical symptoms, hormone concentration, radiological and nuclear medicine imaging, and histological confirmation. The gold standard in diagnosis is detailed histology and this should be obtained whenever possible.

5.1 Blood and urine measurements

For symptomatic patients with hormone secreting tumours there are a variety of generalised and specific biochemical tests used in the investigation of these tumours such as calcium, TFTs, PTH (if low measure parathyroid hormone related protein), calcitonin, prolactin, α-fetoprotein, CEA, and β-HCG. Measurement of circulating peptides and amines in patients with NETs is helpful on three counts.

(1) It assists in making the initial diagnosis.
(2) It is helpful in the assessment of treatment.
(3) It may offer prognostic information.

Plasma chromogranin A (CgA)[23–24] may be useful in diagnosis, particularly in gastric carcinoids with metastases, but it is unclear how accurate this is in monitoring progression of disease. Other markers such as serum pancreatic polypeptide, serum calcitonin, and serum HCG (α and β) may indicate neuroendocrine disease. CgA is a large protein which is produced by all cells deriving from the neural crest.[26 27] The function of CgA is not known but it is produced in very significant quantities by NET cells regardless of their secretory status. Pancreatic polypeptide is produced by normal pancreas but is found in high concentrations in 80% of patients with pancreatic tumours and also in 50% of patients with carcinoid tumours.[16]

Recommendations (diagnosis)

If a patient presents with symptoms suspicious of a gastroenteropancreatic NET:

- Baseline tests should include CgA and 5-HIAA (grade C). Others that may be appropriate include TFTs, PTH, calcium, calcitonin, prolactin, α-fetoprotein, CEA, and β-HCG (grade D).
- Specific biochemical tests should be requested depending on which syndrome is suspected (table 4).

Certain foods and drugs will affect urinary excretion of 5-HIAA if they are taken just before collection of the urine sample. Banana, avocado, aubergine, pineapple, plums, walnut, paracetamol, fluorouracil, methysergide, naproxen, and caffeine may cause false positive results. Levodopa, aspirin, adrenocorticotrophic hormone (ACTH), methyldopa, and phenothiazines may give a false negative result. Serum 5-hydroxytryptamine concentrations vary with time of day and meals and are not currently used clinically.

Peptide markers for gastroenteropancreatic NETs are presently measured in two laboratories in the UK—The Regional Regulatory Peptide Laboratory, Royal Victoria Hospital, Belfast, and the Peptide Laboratory, Hammersmith Hospital, London. Blood samples can be sent through local laboratories.

The presence of symptoms, liver metastases, and a positive humoral test is highly suggestive of an NET but histology is usually necessary for confirmation and will allow proliferation indices to be assessed, which may influence management. If histology is available from a previous primary site, biopsy of the secondaries may not be necessary.

6.0 IMAGING

The optimum imaging modality depends on whether it is to be used in detecting disease in a patient suspected of an NET or for assessing the extent of disease in a known case.

Table 4 Additional specific biochemical tests used in the diagnosis of neuroendocrine tumours (NETs)[16 26–30]

Syndrome	Test	Result
Carcinoid		
Foregut	24 h urinary 5-HIAA	Sometimes raised[31]
Midgut	24 h urinary 5-HIAA	Usually raised (70% of patients)
	Tachykinins (neurokinin A and B)	Raised
Hindgut	24 h urinary 5-HIAA	Not raised (general markers used instead)
Other NETs		
Gastrinoma	Fasting gastrin, gastric secretion studies	Raised basal serum gastrin, high gastric acid secretion
Insulinoma	Fasting insulin, glucose, C peptide (sulphonylurea screen negative)	Raised fasting insulin/glucose ratio, proinsulin, or C peptide
Glucagonoma	Fasting gut hormones, skin biopsy	Raised serum pancreatic glucagons and enteroglucagon
VIPoma	Fasting gut hormones	Raised fasting vasointestinal peptide
Ppoma	Fasting gut hormones	Raised fasting pancreatic polypeptide
Somatostatinoma	Fasting gut hormones	Raised fasting somatostatin
All NETs	Serum chromogranin	Raised chromogranin A in most cases[23–25]
Ectopic hormones	GHRH, ACTH, HCG-α and -β	Raised but incidence very low

5-HIAA, 5-hydroxy indole acetic acid; GHRH, gonadotrophin releasing hormone; ACTH, adrenocorticotrophic hormone; β-HCG, β-human chorionic gonadotrophin.
Currently in the UK, the following are the hormones normally performed when gut hormones are requested: gastrin, glucagon, somatostatin, pancreatic polypeptide, vasointestinal peptide, and neurotensin. Chromogranin A will be performed on the same sample when requested. Blood is taken in a 10 ml standard heparin bottle with trasylol (aprotinin 0.2 ml, 2000 KIU) and spun immediately before being frozen and sent to one of the reference laboratories.

6.1. Imaging in suspected NET/carcinoids

Gastric, duodenal, chest, and colonic primary sites are easier to find as they are likely to be shown at endoscopy or CT scanning as appropriate. A primary midgut NET may not be seen on imaging and thus a patient with abdominal pain and change in bowel habit over many years is often labelled as having irritable bowel syndrome. Barium series and CT scans may be normal but will show larger lesions (fixation, separation, thickening, and angulation, and often calcification at the centre of a ''starburst'' appearance of the desmoplastic reaction). SSRS (octreoscan) and mesenteric angiography may be useful but are not practical in all cases with these symptoms.

Pancreatic NETs with no syndrome are usually detected late in the course of the disease and seen on CT, MRI, or SSRS. Functioning pancreatic NETs may be identified earlier and the potential for surgical cure necessitates accurate localisation which may be performed using CT, MRI, EUS, often together with SSRS, and in some centres DSA with intra-arterial calcium stimulation.

6.2 Imaging for detecting the primary tumour when the patient has already presented with metastases

Many patients present with metastatic disease with no known primary site. Investigations for localising the primary site may include (depending on the type of tumour and symptoms): ultrasound scans of the abdomen, testes, and ovaries; EUS; CT scan of the chest (bronchial carcinoid), abdomen, and pelvis; endoscopy-colonoscopy and gastroscopy; barium studies; and nuclear medicine functional imaging. In one series, primary tumours were localised in 81–96% of cases using radiological and/or nuclear medicine imaging.[32] Opinion is divided on whether locating the primary changes prognosis. EUS is a major diagnostic investigation in a patient with a suspected pancreatic NET. Its sensitivity may be less with extrapancreatic gastrinomas (80% of gastrinomas in MEN1 are found in the duodenum) for which an upper gastrointestinal endoscopy and CT or MRI should be performed first.[33 34]

Neuroendocrine tumours express somatostatin receptors (SSTR) and this has led to the development of radiolabelled somatostatin analogues for diagnostic imaging. There are five receptor subtypes, of which 2 and 5 are currently the only two SSTRs that can be readily detected. With the exception of insulinomas (50% of tumours express SSTR2), SSRS plays a central role in locating and assessing the primary in gastroenteropancreatic NETs.[35–37] For foregut, midgut, and hindgut tumours, a sensitivity of up to 90% has been noted with SSRS. The sensitivity could be further enhanced by the use of single positron emission computed tomography and fusion imaging with CT.[38–40] However, in patients whose octreoscan is negative and in whom no diagnosis is reached after upper and lower gastrointestinal endoscopy, a triple phase CT scan of the thorax and abdomen is regarded as the investigation of choice.

A CT scan is the best modality for localising lung lesions but this could be followed by SSRS to assess the full extent of the disease.

Intra-arterial calcium with digital subtraction angiography may be particularly important for localising gastrinomas.[41 42] Intra-arterial calcium stimulation combined with hepatic venous sampling for insulin gradients has been reported to achieve up to 90% success rate in localising insulinomas. The sensitivity is further increased by combining it with imaging modalities such as intraoperative ultrasonography (table 5).[43 44]

Recommendations (imaging)

- For detecting the primary tumour, a multimodality approach is best and may include CT, MRI, SSRS, EUS, endoscopy, DSA, and venous sampling (grade B/C).
- For assessing secondaries, SSRS is the most sensitive modality (grade B).
- When a primary has been resected, SSRS may be indicated for follow up (grade D).

6.3 Searching for secondaries

The diagnostic test of choice to locate secondaries is SSRS.[59] This applies also to insulinomas as it is believed that secondary insulinomas may show positive SSTR more often than the primary. The sensitivity of SSRS for detecting metastases is 61–96%.[1 47 49 50 60–63] Demonstration of SSTR status by ^{111}In octreotide imaging positively predicts response to somatostatin analogue therapy. The role of ^{123}I-MIBG is limited to identifying patients that will be suitable for MIBG therapy and the sensitivity of MIBG imaging for metastases is only up to 50%.[61 64] MIBG or SSRS will identify patients with inoperable or metastatic disease who might be candidates for high dose targeted radiotherapy. SSRS prior to surgery revised the staging and changed management in 33% in Krenning's series.[35]

6.4 Monitoring progression of disease

Spiral CT scanning, MRI, and ultrasound scans are useful for monitoring lesions.[65 66] Urinary 5-HIAA levels do not accurately correlate with disease progression and response to treatment. CgA has been reported to be a sensitive marker which may correlate with response and relapse,[26 27] with fast rising levels correlating with poor prognosis,[25] although further data are needed to confirm if it correlates with survival.

Table 5 Sensitivities (%) of the various imaging modalities for locating specific neuroendocrine tumours[35 45–58]

	Primary carcinoid tumour	Carcinoid liver metastases	Primary gastrinoma	Gastrinoma liver metastases	Primary insulinoma*
Ultrasound	46	83	23	50	27
CT	64	88	38–75	54–88	30
MRI	56	85	22–90	63–90	10
SSRS	80	90	72	97	25
EUS	80 gastric		90–100		88
Angio+Ca Stim			93		95

CT, computed tomography; MRI, magnetic resonance imaging; SSRS, somatostatin receptor scintigraphy; EUS, endoscopic ultrasound; Angio+Ca Stim, angiography with calcium stimulation.
*Metastatic insulinoma is rare; no data available.
All of the above sensitivities for detecting tumour are further enhanced by intraoperative ultrasound.

7.0 ASSESSMENT OF QUALITY OF LIFE

Metastatic disease is a common presentation in patients with NETs; therefore, the aim of treatment is frequently improvement of their quality of life rather than cure. A specific quality of life score is being developed. For now the best tool is the EORTC QLQ C-30,[67]and it is recommended that quality of life should be assessed regularly throughout treatment.

8.0 PATHOLOGY

8.1 Pathological reporting of enteropancreatic NETs

Pathologists dealing with these tumours should have a special interest in endocrine or gastrointestinal pathology or participate in a network with the opportunity of pathology review. Tumours should be classified according to the recent WHO classification.[68–70] This places all enteropancreatic NETs into one of four categories, based on a combination of gross and histological features (see table 6 in the appendix).

(1) Well differentiated endocrine tumour of probable benign behaviour.
(2) Well differentiated endocrine tumour of uncertain behaviour.
(3) Well differentiated endocrine carcinoma.
(4) Poorly differentiated endocrine carcinoma.

There is currently no TNM staging system for these tumours.

8.2 Specimen handling

Details of the protocols for specimen handling and histological analysis are given in the appendix. General points are outlined below.

When the diagnosis of NET has been made or is suspected preoperatively and specimens are to be used for research, informed consent should be sought from the patient. The resection specimen should, where possible, be placed on ice immediately after removal and brought fresh to the pathology laboratory.

A standard protocol should be followed for assessment of the specimen based, where appropriate, on those produced for the Royal College of Pathologists (RCPath) for cancers at the sites,[71–73] and those published by the Cancer Committee of the College of American Pathologists.[74]

Where possible, frozen tissue should be stored in addition to standard formalin fixed paraffin blocks. The endocrine nature of the tumour should be confirmed by immunohistochemistry, using a panel of antibodies to general neuroendocrine markers. Where a syndrome of hormone excess is present, the tumour can also be confirmed as the source using antibodies to the specific hormone(s). Details of these and prognostic features such as proliferation index are discussed in the appendix.

9.0 TREATMENT

9.1 Objectives

The aim of treatment should be curative where possible but is palliative in the majority of cases. These patients often maintain a good quality of life for a long period despite having metastases. Although the rate of growth and malignancy are variable, the aim should always be to maintain a good quality of life for as long as possible. For those patients who are diagnosed early with limited and operable disease, the aim is to keep the patient disease and symptom free for as long as possible.

9.2 Surgery

In this section, tumours of the luminal gastrointestinal tract will be referred to as carcinoids as this is in common usage, and references usually refer to this term in surgical journals to date.

9.2.1 General approach

This is the only curative treatment for NETs. As with all gastrointestinal tumours, conduct of surgery with intent to cure is dependent on the method of presentation and stage of disease. Specific issues in carcinoid patients include determining the extent of local and distant tumour, identification of synchronous non-carcinoid tumours, recognition of fluid and electrolyte depletion from diarrhoea, and in advanced cases, 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, within a multidisciplinary framework. With carcinoid, if the primary lesion is less than 2 cm in diameter, the incidence of metastasis is low.[78] However, nodal or liver metastases are present at the presentation of carcinoid tumours in 40–70% of patients[32 75–78] (see also table 1).

9.2.2 Prevention of carcinoid crises

When a functioning carcinoid tumour is found before surgery, a potential carcinoid crisis should be prevented by prophylactic administration of octreotide, given by constant intravenous infusion at a dose of 50 μg/h for 12 hours prior to and at least 48 hours after surgery.[79–81] It is also important to avoid drugs that release histamine or activate the sympathetic nervous system.[82] Despite octreotide therapy, patients may still develop life threatening cardiorespiratory complications that can tax even the most experienced anaesthetist, who may have to use alpha and beta blocking drugs to avoid severe complications.[83]

Similar prophylactic measures may be required for pancreatic and periampullary NETs (for example, glucose infusion for insulinoma, proton pump inhibitor (oral or infusion), and intravenous octreotide for gastrinoma).

9.2.3 Lung

The treatment of choice is a major lung resection or wedge resection plus node dissection; five year survival after such surgery is 67–96% depending on the histology of the tumour.[84–87]

9.2.4 Emergency abdominal presentations

Those patients presenting with suspected appendicitis, intestinal obstruction, or other gastrointestinal emergencies are likely to require resections sufficient to correct the immediate problem. Once definitive histopathology is obtained, a further more radical resection may have to be considered. The commonest circumstance is when a carcinoid of the appendix has been removed which is 2 cm or more in diameter. Under these circumstances a right hemicolectomy is usually indicated, despite the frequent absence of obvious malignant features characterising the carcinoid tumour.[88–90] Tumours 1–2 cm or invading the serosal surface may require further resection, particularly if atypical with goblet cell or adenocarcinoid features,[91] or if it is located at the base of the appendix, or if histology shows mesoappendiceal and/or vascular invasion, when a right hemicolectomy with locoregional lymphadenectomy should be considered. Whether or not this is performed, the patient should be followed up for five years. If the lesion is less than 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. In the case of small bowel tumours, a limited emergency small bowel resection for an obstructing carcinoid tumour can be followed at a later date by elective

surgery to remove further small bowel. This is particularly appropriate if by then a second tumour has been identified, or to undertake mesenteric lymphadenectomy. A substantial minority of patients with midgut carcinoid have multiple tumours,[92 93] so a search should be made following removal of an obstructing lesion prior to any further surgery.

9.2.5 Stomach

In patients with gastric carcinoid the approach depends on the type of tumour of which there are three types. Type 1 gastric carcinoids are associated with hypergastrinaemia and chronic atrophic gastritis, originate from enterochromaffin-like cells, and can synthesise and store histamine. The frequency of metastasis is low, and in many cases surveillance only is appropriate,[24 94] although limited surgery with endoscopic polypectomy and/or antrectomy may be preferable.[24 95–97] Type 2 gastric carcinoids occur in patients with hypergastrinaemia due to Zollinger-Ellison syndrome in combination with MEN type1.[98] Type 3 gastric carcinoids are sporadic and have a more malignant course.[94 99] They are not associated with hypergastrinaemia. These tumours have often metastasised by the time of diagnosis. Small tumours less than 1 cm with no extension into muscle on EUS or CT could be resected endoscopically but most lesions will need resection and clearance of regional lymph nodes.[24]

9.2.6 Small intestinal carcinoid

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 is appropriate, to remove tumour for cure or to delay progression that would otherwise endanger the small bowel. Nodal metastases cause sclerosis with vascular compromise of the associated small bowel, which can lead to pain, malabsorption, and even death. Patients, who only after laparotomy and histological examination are discovered to have small intestinal carcinoid, may be candidates for further surgery, notably for extensive mesenteric lymphadenectomy. Resection of mesenteric metastases may alleviate symptoms dramatically, and possibly prolong survival.

9.2.7 Colorectum

Standard resection with locoregional 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. Small lesions less than 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.

9.2.8 Pancreas

Pancreatic and periampullary NETs form a special group that requires particular consideration. As with all other neoplasms at these sites, surgery should only be undertaken in specialist hepatopancreatobiliary units. Often the diagnosis is established biochemically prior to surgery, and although preoperative localisation can be difficult, the biochemical diagnosis provides some indication of the site of the tumour (for example, the gastrinoma triangle) and the likelihood of malignancy (for example, low with insulinoma). Thus for insulinoma, if the lesion is clearly localised before surgery, and is near or at the surface of the pancreas and easily defined at surgery, enucleation may be sufficient, provided histopathology demonstrates complete excision and benign features. However, this may not be possible and Kausch-Whipple pancreatoduodenectomy, left pancreatectomy, or even total pancreatectomy may be justified in selected cases. These operations are also applied to selected cases with localised disease arising from other functioning, as well as non-functioning, NETs of the pancreas.[100] In patients with the Zollinger-Ellison syndrome that do not have MEN1, surgical exploration should be offered for a possible cure of the disease. There is controversy concerning those patients with this syndrome who have MEN1 however, as older data suggest poorer survival in patients treated surgically. Nevertheless, the majority of these patients die from malignant spread of their gastrinomas, suggesting that resection is preferable at a suitable stage to prevent metastatic spread.

9.2.9 Liver

In the presence of liver metastases, ''curative'' liver resection is possible in approximately 10% of cases if the lesion(s) is (are) confined to one lobe. With bilobar metastases and one very dominant lesion causing symptoms, a debulking operation may be carried out for palliation, particularly if there is resistance to medical therapy. The five year survival after resection of the primary and/or liver secondary is up to 87% and postoperative mortality is 6%.[101–105] Several series have shown low morbidity and excellent medium term survival after liver resection with worse outcomes in other patients not resected,[104 106 107] but this may partly reflect stage of disease. A minority of patients with no obvious primary may have primary hepatic neuroendocrine malignancy and surgery can be curative[108]; for such patients, surgery is the treatment of choice, with a recurrence rate of 18% and five year survival of 74% reported in one series.[109] Many patients will need somatostatin analogues which predispose patients to gall stones, hence the gall bladder is usually removed at the time of liver surgery.

9.3 Liver transplantation

Patients with end stage carcinoid disease and uncontrollable symptoms that are unresponsive to any other therapy have been considered for liver transplantation.[110–116]

All UK transplants for NET/carcinoid have recently been analysed[117] and actuarial disease free survival was 62% at one year and 23% at five years, with similar data in a series from France.[118] These series both include patients from many years ago where survival rates would be expected to be lower and many patients in these series predate modern imaging techniques. The data bring into question whether orthotopic liver transplantation should be considered at all for this disease. At present, the organ shortage combined with the low survival data suggest this should not be used in general but might be considered in exceptional circumstances. Further research is needed to try to assess pretransplant prognostic factors.

9.4 Symptomatic treatment

There are a number of treatment options available for patients displaying symptoms due to hormones/peptides secreted by a secretory tumour. These include somatostatin analogues, proton pump inhibitors for gastrinomas, and diazoxide for insulinomas, which are indicated in patients with secretory tumours and distressing symptoms from peptide production. They could be commenced immediately in patients with inoperable disease or preoperatively in patients who have operable disease (liver resection with or without resection of the primary).

The only proven hormonal management of NETs is administration of somastostatin analogues. Somatostatin is a brain-gut peptide that inhibits the release of many hormones and can impair some exocrine functions. Somatostatin receptors are present in the vast majority (70–95%) of NETs but only in about half of insulinomas, and less in poorly differentiated NETs and somatostatinoma.

Somatostatin analogues bind principally to receptor subtypes 2 and 5.[119]

Somatostatin analogues inhibit the release of various peptide hormones in the gut, pancreas, and pituitary, antagonise growth factor effects on tumour cells, and at very high dosage may induce apoptosis. The elimination half life of the natural hormone somatostatin is only a few minutes, making it of no value in routine therapy. Octreotide has a half life of several hours, making intermittent therapy possible. This drug is administered by subcutaneous injection starting at 50–100 μg twice or three times a day to a maximum daily dose of 1500 μg.[120] More recently, analogues with sustained release from depot injections have been synthesised and these are given every 2–4 weeks.[121] These drugs, lanreotide (fortnightly injection), Sandostatin LAR (monthly), and Lanreotide Autogel (also monthly), have shown significant improvement in the quality of life of patients and have as good or better efficacy compared with short acting octreotide.[121–123] Patients may be stabilised with octreotide (short acting) for 10–28 days before converting them to long acting somatostatin analogues. Escalation of dose is often needed over time. Biochemical response rates (inhibition of hormone production) are seen in 30–70% of patients with symptomatic control in the majority of patients; tumour growth may stabilise and rarely shrinkage of tumour may occur.[123–129] In instances of stress (for example, anaesthesia, surgical operations (see above), hepatic artery embolisation), patients with the carcinoid syndrome or even with the tumour but without syndrome should have increased coverage by somatostatin analogues, preferably short acting octreotide by intravenous administration (50 μg/h). This extra cover should be administered 12 hours before, during, and 48 hours after the procedure to prevent a cardiovascular carcinoid crises.[79]

Few side effects from somatostatin analogues have been reported[130–132] and they include fat malabsorption, gall stones and gall bladder dysfunction, vitamin A and D malabsorption, headaches, diarrhoea, dizziness, and hypo- and hyperglycaemia. Monitoring of circulating and, where relevant, urinary hormone levels should be undertaken during periods of treatment. Patients should also have the regular relevant imaging.

9.5 Efficacy of drugs in the various syndromes

In those with midgut and lung carcinoid syndromes, although hormone levels are not normalised during treatment there is substantial relief of the main symptoms of flushing and diarrhoea in the majority of patients.[121 133] There may an indication for a trial of these drugs in patients without a secretory syndrome. There may also be long term prevention of the advancement of carcinoid heart disease and intestinal fibrosis, although studies are conflicting.

9.5.1 VIPomas (*w*atery *d*iarrhoea *h*ypokalaemia *a*chlorhydria (*WDHA*) syndrome/Werner-Morrison syndrome)

Rehydration is always indicated and may improve the clinical condition considerably. Patients with this rare life threatening syndrome frequently respond dramatically to small doses of somatostatin analogues with cessation of diarrhoea.[134] The dose of the drug may be titrated against vasoactive intestinal peptide levels with normalisation of levels being the target.

9.5.2 Glucagonomas

Improvement by somatostatin analogues has been reported in patients with the syndrome although there is no indication for the drugs if the patient has no syndrome. It is unlikely that circulating glucagons levels can be normalised as these patients frequently have massive amounts of circulating glucagon. The characteristic rash of necrolytic migratory erythema can be life threatening.

9.5.3 Gastrinomas

The syndrome is adequately controlled with high dose proton pump inhibitor drugs and there is no definite added benefit in the control of symptoms by addition of somatostatin analogues. However, some groups advise the addition of somatostatin analogues.

9.5.4 Insulinomas

Only 50% of insulinomas have type II somatostatin receptors. Diazoxide has been shown to be effective in controlling hypoglycaemic symptoms in patients with insulinoma.[135] Side effects (fluid retention and hirsutism) are common but not troublesome. This treatment therefore should be considered in patients not cured by surgery or unsuitable for surgery. Administration of somatostatin analogues has variable effects on blood glucose levels, possibly also acting by suppression of counterregulatory hormones such as glucagon. Glucose infusion and glucagon intramuscularly can be added to achieve immediate effect.

9.6 Other drugs

Ondansetron has been used for general symptom control in the carcinoid syndrome and can be useful. Cyproheptadine is still occasionally used for carcinoid syndrome. Pancreatic enzyme supplements or cholestyramine are often used to control diarrhoea, which may be especially troublesome after intestinal resection. Pancreatic insufficiency can also occur with octreotide/lanreotide therapy.

In glucagonoma patients, zinc therapy can be used to prevent further skin lesions, and anticoagulation (for the high incidence of thrombosis) is used for patients with this tumour. Steroids can be used in urgent situations for insulinoma patients.

9.7 Interferon-alpha

This is used both in secreting carcinoid tumours and other NETs on its own or added to long acting somatostatin analogues if the patient is not responding to the maximum dosage of somatostatin analogues. Interferon-alpha 3–5 MU 3–5 times per week subcutaneously is the usual dose employed. However, there is conflicting evidence as to its efficacy, with only one major group supporting its widespread use and there is some evidence it may have greater effect in tumours with low mitotic rate. There has been biochemical response in 40–60% of patients, symptomatic improvement in 40–70% of patients, and significant tumour shrinkage in a median of 10–15% of patients.[136–138] In combination with somatostatin analogues, the effect may be enhanced.[139–141]

9.8 Chemotherapy

The role of chemotherapy for NETs is uncertain but is being actively researched. It is essential to consider the tumour types individually in view of their varying response to chemotherapy and the indications to use it. Certain prognostic factors may also help in determining the use of chemotherapy and one paper showed an inverse correlation between imaging with SSRS radioscintigraphy and response to treatment. Response to chemotherapy in patients with strongly positive carcinoid tumours was of the order of only 10% whereas patients with SSRS negative tumours had a response rate in excess of 70%.[142] The highest response rates with chemotherapy are seen in the poorly differentiated and anaplastic NETs: response rates of 70% or more have been seen with cisplatin and etoposide based combinations.[143 144] These responses may be relatively short lasting in the order of only 8–10 months.[142] Response rates for pancreatic islet cell

tumours vary between 40% and 70% and usually involve combinations of streptozotocin (or lomustine), dacarbazine, 5-fluorouracil, and adriamycin.[145 146] However, the best results have been seen from the Mayo clinic where up to 70% response rates with remissions lasting several years have been seen by combining chemoembolisation of the hepatic artery with chemotherapy.[147] The use of chemotherapy for midgut carcinoids has a much lower response rate, with 15–30% of patients deriving benefit, which may only last 6–8 months. Again, the most commonly used agents will be those listed above. The management of pulmonary carcinoids is more likely to involve a platinum and etoposide combination and may reflect the fact that a pulmonary oncologist will be involved and that bronchial carcinoids may represent one end of the spectrum, which includes small cell lung cancer, which is exquisitely chemosensitive. If possible, patients should be entered into formal trials of new agents (see 9.13 emerging therapies below).

9.9 Targeted radionuclide therapy

This is a useful palliative option for symptomatic patients with inoperable or metastatic tumour.

The principle of treatment is only to give radionuclide therapy when there is abnormally increased uptake of the corresponding imaging agent. No randomised controlled trials have been performed. The gamma emitting imaging radionuclide is replaced by a beta imaging therapy radionuclide: ^{131}I-MIBG for ^{123}I-MIBG, ^{90}Y-octreotide for ^{111}In-octreotate, and ^{90}Y-lanreotide for ^{111}In-lanreotide.[148] Treatment indications include evidence of avid uptake of ^{123}I-MIBG or ^{111}In octreotide at all known tumour sites on diagnostic imaging. Contraindications include pregnancy and breast feeding, myelosuppression, and renal failure (glomerular filtration rate <40 ml/min). Patients should be continent and self caring to minimise risk to nursing staff.[149]

9.9.1 ^{131}I-MIBG Therapy

Treatment protocols vary between different centres. For radiation protection reasons, ^{131}I-MIBG therapies necessitate admission to a dedicated isolation facility. Potassium iodide/iodate thyroid blockade is given pretreatment to prevent thyroidal uptake of free radioiodine. The usual prescribed activities in the UK range between 7.4 and 11.2 GBq administered at 3–6 month intervals. MIBG therapy is the only licensed radionuclide therapy for NETs. Symptom control is up to 80% and a five year survival rate of 60% has been recorded.[150 151] Treatment is well tolerated and toxicity limited to temporary myelosuppression 4–6 weeks post therapy.[152] This will be more severe in patients who have bone marrow infiltration by tumour at the time of treatment or who have undergone previous chemotherapy or targeted therapy. Myelosuppression is cumulative and may be dose limiting after repeated treatment cycles.

9.9.2 ^{90}Y-octreotide therapy

Experience using ^{90}Y-DOTATOC is growing although it is not widely available at present. Usual cumulative activities range from 12 to 18 GBq administered in 3–6 GBq fractions at 6–8 week intervals. Most patients report subjective benefit within two treatment cycles, often associated with reduction in biochemical tumour markers. The majority of patients achieve tumour stabilisation although significant tumour regression is unusual (approximately 20% of treated patients).[153–159] Toxicity includes myelosuppression, particularly lymphopenia, and nephrotoxicity.[160 161] Pretreatment with amino acids, particularly D-lysine, reduce tubular octreotide binding and is essential to minimise renal damage.[162] Clinical trials using ^{90}Y-DOTATOC are in progress.[163]

9.9.3 ^{90}Y-lanreotide therapy

Experience with ^{90}Y-lanreotide therapy is limited but it is clear that the range of tumours taking up ^{111}In-lanreotide differs from those taking up ^{111}In-octreotide, and therefore ^{111}In-lanreotide imaging is required to select patients for ^{90}Y-lanreotide therapy. The results of the trial in 154 patients showed stable disease in 41% and regression in 14%.[164]

9.10 Embolisation of hepatic artery

This procedure is indicated for patients with non-resectable multiple and hormone secreting tumours with the intention of reducing tumour size and hormone output. Arterial embolisation induces ischaemia of the tumour cells, thereby reducing their hormone output and causing liquefaction. Ischaemia of tumour cells also increases their sensitivity to chemotherapeutic substances and this underlies the principle of chemoembolisation. There are two types of embolisation: particle and chemoembolisation. Particles used include polyvinyl alcohol and gel foam powder. For chemoembolisation, agents such as doxorubicin and cisplatin are used primarily.[165] Contraindications for chemoembolisation include complete portal vein obstruction, liver insufficiency, and biliary reconstruction.

The overall five year survival post embolisation is 50–60%. Symptomatic response to this treatment is 40–80% and biochemical response is 50–60%. Mortality overall is 4–6% and adverse events have been reported in 10–17% of cases post embolisation.[165–170] Only one lobe should be embolised per session and the patency of the portal vein must be confirmed before the procedure is undertaken. Post embolisation syndrome (nausea, fever, and abdominal pain) is the commonest side effect. Hormone therapy should be used prior to all embolisations: 50–100 µg octreotide per hour intravenously for 12 hours prior (or bolus two hours before plus infusion) and 48 hours post procedure. Some units use hydrocortisone 100 mg intravenously and prophylactic antibiotics prior to the procedure, and pre-dosing with allopurinol to prevent a tumour lysis syndrome.

9.11 Ablation therapies

9.11.1 Radiofrequency ablation

This has been used with some effect in stabilising or reducing tumour size but randomised trials are lacking. It may be indicated in patients with inoperable bilobar metastases in whom hepatic artery embolisation has failed.[171] It is a relatively new modality which can be performed percutaneously or laparoscopically. The percutaneous approach is the most commonly used, as it is least invasive, cheapest, and has the additional benefit of CT or MRI guidance. The laparoscopic approach has the benefit of intraoperative ultrasound scanning, which is ideal for the detection of tiny tumours but does require considerable skill.[172] Ablation can be used to reduce hormone secretion and/or to reduce tumour burden. Most patients with neuroendocrine metastases have a large number of small metastases that are hormonally active.

The main limitation for radiofrequency ablation is the size and number of tumours. For colorectal cancer, most groups will treat up to five tumours up to 5 cm in size. Neuroendocrine metastases are small, numerous, and very slow growing. Therefore, it is possible to treat patients with indolent disease with as many as 20 small (<3 cm) tumours at multiple treatment sessions over a period of years. Destroying the largest lesion may not necessarily switch off hormone production. To achieve a reduction in hormone secretion it is necessary to ablate at least 90% of the visible tumour.[173–178] Tumour location is not as important as for liver resection. Patients who have biliary-enteric anastomoses following pancreatic surgery are at risk of infection in the

ablated area of the liver and require three months of rotating oral antibiotics after the procedure.

9.11.2 Miscellaneous

Alcohol injection, laser therapy, and cryotherapy have also been used anecdotally but with no large series and no controlled trials.

9.12 External beam radiotherapy

Carcinoid tumours have often been regarded as being radioresistant. However, external bean radiotherapy may provide excellent relief of the pain from bone secondaries and there has been a suggestion that some secondary deposits in the liver and elsewhere shrink in response to radiotherapy.[179]

9.13 Emerging therapies

^{188}Re-octreotide may be substituted for ^{99m}Tc-EDTA-HYNIC-octreotide.[148] ^{177}Lu-octreotate therapy has been recently introduced.[159 180–182] These are being studied at present and are not yet licensed for the treatment of NETs. Some very interesting new data are emerging about the potential role of the cell signalling transduction agents, which affect tyrosine kinase and other molecular markers, and important clinical trials are about to start using these new agents. Imatinib has been used for carcinoid tumours but no adequate data are available. Trials using vaccines against various peptides are planned.

10.0 ALGORITHM OF OVERALL CARE

An algorithm for the investigation and treatment of gut NETs is given in fig 1.

11.0 PROGNOSIS

See also section 4.2 and table 3.

These are slow growing tumours but survival depends on the histological type, degree of differentiation, mitotic rate, Ki67 or MIB-1 index, tumour size (>3 cm), depth, location, presence of liver or lymph node metastases, and age over 50 years.[183–189] Following complete resection of the primary tumour and liver metastases if present, the overall five year

Recommendations (therapy)

- The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment (grade C).
- Surgery should be offered to patients who are fit and have limited disease—primary with or without regional lymph nodes (grade C).
- Surgery should be considered in those with liver metastases and potentially resectable disease (grade D).
- Where abdominal surgery is undertaken and long term treatment with SMS analogues is likely, cholecystectomy should be considered.
- For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life (grade D).
- The choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumour (grade C).
- Treatment choices for non-resectable disease include SMS analogues, biotherapy, radionuclides, ablation therapies, and chemotherapy (grade C).
- External beam radiotherapy may relieve bone pain from metastases (grade C).
- Chemotherapy may be used for inoperable or metastatic pancreatic and bronchial tumours, or poorly differentiated NETs (grade B).

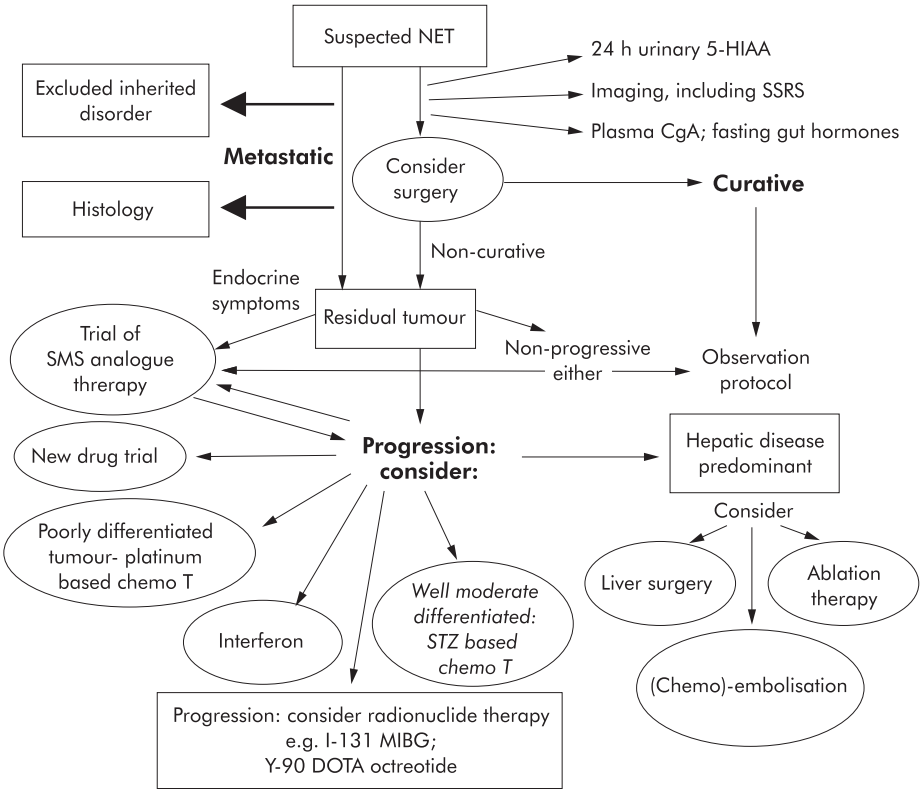

Figure 1 Algorithm for the investigation and treatment of gut neuroendocrine tumours.

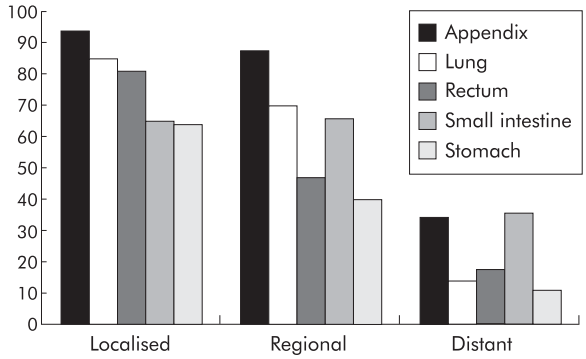

Figure 2 Five year survival of patients with carcinoid tumours related to the primary site and degree of spread.

survival is 83% but in cases where this is not possible survival ranges from 30% to 70% depending on the factors above and the treatment employed.[75 91 102 190–196] The best prognosis is in bronchial and appendicular carcinoids with a five year survival for typical lung carcinoids and carcinoid tumours of the appendix being 80–90% whereas that for atypical lung tumours is 40–70%.[193 197–199]

The overall five year survival for pancreatic NETs is 50–80%, with insulinoma and gastrinoma having up to 94% five year survival,[134 200–204] although clearly there is large variation depending on the stage at presentation and whether curative surgery is possible.

Figure 2 shows the five year survival of patients with carcinoid tumours related to the primary site and degree of spread.[195]

12.0 SUMMARY

There are many treatment modalities available and most are very expensive. With poor evidence base, it is important therefore for all cases to be discussed and managed within a multidisciplinary team. The patient should have information available with which to make rational choices about various treatments. This information can be obtained through centres who regularly treat these patients

UKNET is an organisation set up to discuss management of carcinoid and gastroenteropancreatic NETs. Contact is the UKNETWORK website: www.uk-network.org.uk

The patient support group can be contacted at livingwithcarcinoid.org.uk (website under construction).

Conflict of interest: None declared.

13.0 APPENDIX

PROTOCOL FOR HANDLING PANCREATIC TUMOURS

This is modified from the RCPath document on the minimum dataset for the reporting of pancreatic carcinoma[73] and the protocol for endocrine tumours of the pancreas of the Cancer Committee of the College of American Pathologists.[205] Unless otherwise referenced, the criteria for classification are those defined in the WHO classification (see table A1).[69]

The type of specimen should be recorded (for example, Whipple's pancreatoduodenectomy, left pancreatectomy). Where possible, the site of the tumour should be stated as in the head, body, or tail of the pancreas. The tumour should be measured in three dimensions. The maximum dimension is important in classification. Gross extension into surrounding tissues is noted as this is regarded as a criterion of malignancy. Completeness of excision should be assessed by gross examination and confirmed by histological examination.

Representative blocks should be taken of the tumour (at least one per cm diameter) and of encapsulated and infiltrative margins.[205] The closest margin should be sampled. Samples of other pancreatic lesions should be processed but not all nodules need be taken if they are multiple. Two or three random blocks of apparently normal tissue should be processed. Lymph nodes, in the specimen, or submitted separately, should be processed. Their location should be noted.

PROTOCOL FOR HANDLING GASTROINTESTINAL SPECIMENS

These are modified from documents from the RCPath[71 72] and the Cancer Committee of the College of American Pathologists.[206]

The nature of the specimen should be recorded (for example, endomucosal resection, ileal resection). The gross appearances should be described and the site of the tumour should be documented. A diagram may be helpful. The tumour should be measured in three dimensions. The maximum dimension is important in classification. The serosal surface should be carefully examined in the area of the tumour to assess penetration. Completeness of excision should be assessed by gross examination and confirmed by histological examination.

The number of blocks taken will depend on the size of the tumour. They should be taken to permit the deepest level of penetration through the bowel wall to be determined. Serial transverse sections through the tumour should identify the appropriate areas to sample. The mesoappendix should be sampled in appendicectomy specimens. Excision margins are usually sampled. A random block of normal tissue should also be taken. Lymph nodes should be processed.

TISSUE PROCESSING

In general, standard blocks should be fixed in formalin, and additional tumour and normal tissue should be snap frozen and stored at −70°C. The nature of the frozen tissue should be confirmed by frozen section. If there is consent, additional formalin fixed and frozen tissue should be processed for research. Routine diagnostic sections should be stained with haematoxylin and eosin. Histochemical stains, such as the Grimelius silver stain, are non-specific and not recommended.

IMMUNOHISTOCHEMISTRY

All tumours should be immunostained with a panel of antibodies to general neuroendocrine markers. These include PGP9.5, synaptophysin, and CgA. Neurone specific enolase is not recommended as it has poor specificity. Chromogranin staining may be sparse or negative in poorly granulated tumours.

The hormones produced will vary with the site, as shown below. Where there has been evidence of ectopic hormone secretion (for example, ectopic ACTH syndrome), immunostaining should be performed for the appropriate hormones. Where there is a clinical syndrome related to a particular hormone and immunohistochemistry is negative, in situ hybridisation may be useful in identifying the messenger RNA. The tumour should also be stained with an antibody to Ki-67 protein, preferably MIB-1,[207] to generate a Ki-67 index. This has been shown to have diagnostic and prognostic relevance in pancreatic tumours, although the cut off points vary.[208 209] Data are less well established for gastrointestinal tumours.[210 211]

Table A1 WHO classification of gastroenteropancreatic endocrine tumours[1 2]

Site	Well differentiated endocrine tumour (Benign behaviour)	Well differentiated endocrine tumour (Uncertain behaviour)	Well differentiated endocrine carcinoma (Low grade malignant)	Poorly differentiated endocrine carcinoma (High grade malignant)
Pancreas	Confined to pancreas <2 cm <2 mitoses per 10 HPF <2% Ki-67 positive cells No vascular invasion	Confined to pancreas ⩾2 cm >2 mitoses per 10 HPF >2% Ki-67positive cells or vascular invasion	Well to moderately differentiated Gross local invasion and/or metastases Mitotic rate often higher (2–10 per 10 HPF) Ki-67 index >5%	Small cell carcinoma Necrosis common >10 mitoses per 10 HPF >15% Ki-67 positive cells Prominent vascular and/or perineural invasion
Stomach	Confined to mucosa-submucosa, ⩽1 cm. No vascular invasion	Confined to mucosa-submucosa, >1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Duodenum, upper jejunum	Confined to mucosa-submucosa, ⩽1 cm. No vascular invasion	Confined to mucosa-submucosa, >1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Ileum, colon, rectum	Confined to mucosa-submucosa, ⩽1 cm (small intestine) ⩽2 cm (large intestine). No vascular invasion	Confined to mucosa-submucosa, >1 cm (small intestine) >2 cm (large intestine) or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Appendix	Non-functioning Confined to appendiceal wall ⩽2 cm. No vascular invasion	Enteroglucagon-producing Confined to subserosa >2 cm or vascular invasion	Well to moderately differentiated Invasion to mesoappendix or beyond or metastases	Small cell carcinoma

HPF, high power field.

HORMONES

- *Pancreas*: insulin, glucagon, pancreatic polypeptide, somatostatin, gastrin, vasoactive intestinal peptide, ACTH, prolactin.
- *Stomach and duodenum*: gastrin, serotonin, somatostatin, gastrin releasing peptide.
- *Ileum and caecum*: serotonin, tachykinins, substance P.
- *Colon and rectum*: serotonin, somatostatin, peptide YY.
- *Appendix*: serotonin, somatostatin, enteroglucagon.

PATHOLOGY REPORT

The report should contain the following data for all tumour locations to allow the tumour to be classified according to the WHO classification:

- Gross description
  - nature of the specimen
  - description and dimensions of the specimen
  - description of lesion(s)—single or multifocal; solid or cystic

  dimensions (of largest if multifocal)

  - extension into surrounding tissues
  - distant metastases
- Microscopic report
  - general morphological description
  - immunohistochemical profile, general neuroendocrine markers
  - immunohistochemical (and/or in situ hybridisation) profile, hormones
  - mitotic rate (per 10 high power fields (×40))
  - Ki-67 index (%) (at low levels of proliferation it is necessary to count a large number of cells to produce robust data for a Ki-67 index. To facilitate this, a grid might be used that allows the data to be calculated from counting only a subset of total cells[212]).
  - vascular, perineural, or lymphatic invasion
  - completely excised (with distance to margin) or present at excision margin
  - infiltration of surrounding tissues
  - lymph node status
  - distant metastases
- For gastrointestinal tumours
  - level of invasion
  - tumour on serosal surface or not
  - if not, level of invasion
  - depth of maximal wall invasion (mm)
  - distance to serosal surface (mm)

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