Gastric Neuroendocrine Tumours

David A. Crosby\textsuperscript{a} Claire L. Donohoe\textsuperscript{a} Louise Fitzgerald\textsuperscript{a} Cian Muldoon\textsuperscript{b} Brian Hayes\textsuperscript{b} Dermot O’Toole\textsuperscript{c} John V. Reynolds\textsuperscript{a}

\textsuperscript{a}Department of Surgery, Trinity Centre for Health Sciences, Trinity College Dublin/St James’s Hospital, and Departments of \textsuperscript{b}Histopathology and \textsuperscript{c}Gastroenterology, St. James’s Hospital, Dublin, Ireland

Key Words
Autoimmune atrophic gastritis · Chromogranin A · Clinical and pathological staging · Gastrin-independent lesions · Gastric neuroendocrine tumours · 5-Hydroxyindolacetic acid · Hypergastrinaemia · Neuroendocrine tumours · Type I–III gastric NETs · Zollinger-Ellison syndrome

Abstract

Background: Gastric neuroendocrine tumours (NETs) are increasingly recognised, and management decisions may be difficult due to an incomplete understanding of aetiology, natural history and optimum therapy. This article presents a current understanding based on recent advances in epidemiology, classification, molecular profiling, and treatment. Methods: Relevant medical literature was identified from searches of PubMed and references cited in appropriate articles identified. Selection of articles was based on peer review, journal and relevance. Results: Gastric NETs may be divided into three clinical prognostic groups: type I is associated with autoimmune atrophic gastritis and hypergastrinaemia, type II is associated with Zollinger-Ellison syndrome, and type III lesions are gastrin-independent, have the greatest metastatic potential and poorest prognosis. There has been an increased frequency of gastric NETs reported. Management approaches have evolved in parallel with advances in endoscopic staging and surgery, as well as improved understanding of the biology and natural history of NETs. Conclusions: Gastric NETs present a spectrum of activity from indolent tumours to metastatic malignancy. Treatment decisions for patients must be individualised and are best managed by a multidisciplinary team approach. The current evidence base is limited to small series and efforts to treat patients within clinical networks of expertise are warranted.

Introduction

Neuroendocrine-derived tumours, originally termed carcinoid tumours, are derived from enterochromaffin or Kulchitsky cells. The term carcinoid was first used by Oberdorfer in 1907 to describe a carcinoma-like tumour, which was considered to have less malignant potential than adenocarcinomas and which may have a broad spectrum of biological behaviours [1, 2]. The term neuroendocrine tumour (NET) has supplanted carcinoid in the current nomenclature, although carcinoid tumours may be considered a specific subtype of functioning NETs that produces serotonin [3].

D.A. Crosby, C.L. Donohoe, and L. Fitzgerald contributed equally to this paper and should be viewed as co-first authors.

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Prof. John V. Reynolds
Trinity Centre for Health Sciences
St. James’s Hospital
Dublin 8 (Ireland)
E-Mail reynoljv@tcd.ie
The literature on NETs overall and gastric NETs in particular until recently has been sparse and based on small series. Clinical trials are rare, as are clinical registries for these rare tumours [1]. Recent advances include consensus evidence-based guidelines produced by the European Neuroendocrine Tumour Society (ENETS) which enables clinical and scientific research and clinical trials [2, 3]. There has also been an alteration in the epidemiology of gastric NETs in recent years. A greater understanding of their clinical behaviour has led to changes in the management of gastric NETs. This review seeks to present an overview of recent developments in understanding of the biology of gastric NETs and the current approach to classification, staging and management.

Methods

Relevant medical literature was identified from searches of PubMed and references cited in appropriate articles identified. Search terms used included: carcinoid, neuroendocrine tumour, gastric. More detailed search terms were used following identification of relevant mechanisms and to identify epidemiological studies. Selection of other articles was based on peer review, journal and relevance. Where possible, review articles from high impact factor peer-reviewed journals were cited. Published literature until 01/03/2012 was considered for inclusion.

Classification and Epidemiology

Gastric NETs can be broadly categorised into well- and poorly-differentiated gastric NETs [4]. Well-differentiated gastric NETs arise from enterochromaffin-like (ECL) cells of the gastric corpus and fundus. ECL cells normally produce histamine to regulate gastric acid secretion. Gastric NETs can be further subdivided into three types (table 1).

<table>
<thead>
<tr>
<th>Type</th>
<th>Proportion of gastric NETs, %</th>
<th>Metastases, %</th>
<th>Pathology</th>
<th>Characteristics</th>
<th>Serum gastrin levels</th>
<th>Tumour-related death, %</th>
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<tbody>
<tr>
<td>Type I</td>
<td>70–80</td>
<td>2–5</td>
<td>Well differentiated</td>
<td>Multiple, usually small (&lt;1–2 cm), polypoid</td>
<td>Increased</td>
<td>0</td>
</tr>
<tr>
<td>Type II</td>
<td>5–6</td>
<td>10–30</td>
<td>Well differentiated</td>
<td>Multiple, usually small (&lt;1–2 cm), polypoid</td>
<td>Increased</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Type III</td>
<td>No association</td>
<td>14–25</td>
<td>Well or moderately differentiated</td>
<td>Single, usually large (&gt;2 cm)</td>
<td>Normal</td>
<td>25–30</td>
</tr>
</tbody>
</table>

The majority of type I NETs are non-malignant, often multiple and typically <2 cm. Their overall survival rates are no different from the age-matched general population. The presence of metastases was the only factor which influenced long-term prognosis in a series of 51
cases [7]. There is a greater metastatic potential in larger tumours and more deeply infiltrating tumours, but there is no correlation between the degree of multicentricity and metastases [7–9]. It must be noted that these statements reflect only the published experience in the literature which include data from 320 individual patients included in six series [4, 5, 7, 10–12], the largest of which had 152 patients. In most of these series the disease-specific survival was 100%. In one series, patients with metastases had a 75% 5-year survival and those without metastases had a 98% 5-year survival [7]. What is unclear is whether a completely conservative approach to localised disease has merit, since these tumours may have low biological metastatic potential and the risks of surgery are not insignificant.

Since the 1950s, there has been a marked increase in the reported incidence of gastric NETs, accounting currently for approximately 1.8% of gastric malignancies compared to 0.3% previously [13]. Age-adjusted incidence rates have shown an 800% increase in incidence in Caucasian females [13]. This may reflect the increased incidence of chronic atrophic gastritis amongst females, increased rates of PPI use or better detection and reporting. Recent data reveal that gastric NETs are associated with a 5-year survival of 63% compared with previous data which estimated 51% [13]. Subtypes I and II of gastric NETs are associated with an approximate 80% 5-year overall survival and type III is associated with an approximate 33% 5-year survival [14–16].

There has been an 8- to 9-fold increase in the incidence of gastric NETs reported to two large databases (Florida Cancer Data System and SEER registries) over 20 years (1981–2000) [17]. This represents an increase in the age-adjusted incidence from <0.03 per 100,000 population to 0.18. Of these tumours, the majority were localised (94.3%), with distant metastases in just 1%. The mean age of the patient population was 65 (21–96) years. The authors speculate that this increased incidence is due to the increasing prevalence of PPI use since their introduction in 1989.

Acid suppression with PPIs has been shown to increase gastric NET formation in rodents [18]. In humans it is plausible that compensatory hypergastrinaemia due to proton pump inhibition may enable gastric NET formation, but this is not supported by studies in humans to date. The rate of PPI use was not recorded in registry patients and there has been more prevalent use of endoscopy over the study period, so the thesis linking PPI use
to gastric NETs remains unsubstantiated. Whether the true incidence of gastric NETs is increasing, or merely the reporting rate, has not been clarified. The increase in reporting may reflect a greater use of endoscopy and standardisation of pathological reporting.

The relationship of *Helicobacter pylori* and gastric NETs is unclear. Using case series of patients with Zollinger-Ellison syndrome (ZES) as a natural example of patients with hypergastrinaemia, it appears that the superimposition of *H. pylori* treatment on hypergastrinaemia does not have an increased effect on ECL density, hyperplasia or dysplasia [19]. In the *Mastomys* murine model, rodents have a polymorphism in the CCK-2 receptor gene, leading to constitutive activation and are, therefore, predisposed to the development of gastric NETs [20], with 50–80% developing tumours within 2 years [21]. This process is accelerated in the presence of *H. pylori*-induced hypergastrinaemia [22].

**Type II Gastric NETs**

Type II tumours, accounting for 5–8% of gastric NETs, are associated with multiple endocrine neoplasia type 1 (MEN-1) and ZES, and have intermediate malignant potential. The synergy of the presence of the tumour-suppressor gene mutation on chromosome 11 and the hypergastrinaemia of ZES associated with MEN-1 promotes the development of gastric NETs in 13% of MEN-1 patients [23]. The MEN-1 tumour suppressor gene interacts with a member of the AP-1 pathway JunD which may be co-stimulated by gastrin [24]. In contrast, NETs develop in the stomach of fewer than 1% of patients with sporadic ZES. Loss of heterozygosity of MEN-1 has also been described in the other types of gastric NET – in 17–73% of type I tumours and 25–50% in type III tumours [25, 26]. Type II NETs display relatively indolent behaviour but do have a greater metastatic potential than type I tumours, with approximately 30% metastasising [27]. Where type I tumours are limited to the mucosa of the body and fundus, type II may also occur in the antrum. Similarly, the majority of duodenal NETs are gastrin-secreting and associated with the ZES in patients with MEN-1 [28] and the location of the primary tumour in the majority of MEN-1 patients with gastrinomas and ZES patients is the duodenum [29].

**Type III Gastric NETs**

Type III tumours represent approximately 15–20% of gastric NETs, they arise sporadically and are the most aggressive gastric NET subtype, and 50–100% metastasise. Their development and biology is unrelated to gastrin concentration. They typically produce 5-hydroxytryptophan (5-HT) rather than serotonin. Some advocate the subdivision of type III tumours into two groups (type III and IV), where type III tumours are sporadic non-functioning gastric NETs and type IV tumours are those that are poorly differentiated or arise from ACTH or serotonin cells or are of mixed endocrine-exocrine aetiology [7]. The clinical behaviour of all of these tumour types is similar and distinguishing them as separate types is of little clinical utility.

Microarray technology has been used to identify altered gene expression signatures in type III compared with type I and II gastric NETs [20]. Of 270 genes differentially altered, CgA [30], MAGE-D2 (adhesin), MTA1 (histone deacetylase regulator) [31] and CCN2 (growth factor) [20] can differentiate between type III and I tumours. Mutation of the tumour suppressor gene p53 has been reported to be strongly correlated with type III tumours and functionally may play a role in stimulating proliferation [32].

**Diagnosis**

Gastric NETs are typically found at endoscopy performed for anaemia (>70%) and dyspepsia (almost 70%). Type I and II tumours are generally asymptomatic and are usually located in the gastric fundus. Endoscopically, type I gastric NETs have the appearance of mucosal polyps and may be multiple. Type III gastric NETs, although they may be discovered incidentally, are more likely to present with anorexia, dyspepsia and pernicious or iron deficiency anaemia compared with type I or II [7, 11].

In a series of 205 gastric NETs, 191 of 193 well-differentiated tumours were mainly composed of ECL cells, with 2 tumours derived from G cells [11]. There have been case reports of enterochromaffin cell and ghrelin-producing NETs [33]. Type III gastric NETs are occasionally functional and can elaborate kinins, prostaglandins, substance P, somatostatin, insulin, corticotrophin and neuron-specific enolase. Carcinoid syndrome, due to the systemic release of peptides from metastatic NETs [34], is a rare presentation of gastric NETs (<1%) and almost exclusively associated with type III tumours with associated liver metastases [16, 30, 31, 35]. Classical carcinoid syndrome relates to small intestinal NETs in over 80% of cases. A crisis is characterised by hypotension, tachycardia, arrhythmias, bronchial wheezing, flushing and central nervous system symptoms. Metastatic foregut NETs are more likely to be associated with atypical crisis symptoms such as wheeze, lacrimation, swelling and flushing, due
to histamine release, than NETs of other locations [36]. High concentrations of systemic amines over long periods stimulate fibroblast activity and may result in carcinoid heart disease which results in plaque-like fibrous deposits in the endocardium and subendocardium of the right-sided valves [37, 38].

It is recommended that at diagnosis of NETs, 5-hydroxyindolacetic acid (5-HIAA) and chromogranin A (CgA) should be measured and these markers may be used in the assessment of disease recurrence and treatment responses. In asymptomatic patients who have undergone resection and show no signs of disease, CgA should be measured as part of an annual surveillance. In patients with active functional growth, it is recommended that 5-HIAA and CgA are used to monitor treatment [39]. Although CgA may be used to monitor treatment response in some patients with NETs, there is variability in the range of CgA in different patients with metastatic disease and treatment with somatostatin receptor inhibitors may reduce the level of CgA which reflects only reduced hormone production rather than decreased tumour burden. Given the potential for false negative results in gastric NETs explored previously, the role of these biomarkers during surveillance of gastric NETs is unclear.

5-Hydroxyindolacetic Acid

Carcinoid tumours, as a subtype of NETs, are defined by their ability to synthesise 5-hydroxytryptamine (5-HTP) from dietary tryptophan. Usually, 99% of tryptophan is converted to nicotinic acid with the remainder made into 5-HTP. In patients with carcinoid tumours, 5-HTP production is increased resulting in an increase in the end-product of 5-HIAA). The measurement of 24-hour urine concentration of 5-HIAA has a high specificity but low sensitivity for NETs. A 24-hour urinary 5-HIAA test is used as a standard investigation for serotonin-producing NETs and is highly sensitive in the diagnosis of gastrin-dependent (types I and II gastric NETs) from gastrin-sporadic (type III) gastric NETs. Patients with chronic atrophic gastritis at biopsy have endoscopic biopsy and snaring of large (>2 cm) tumours, as well as biopsy of other parts of the stomach for atrophic gastritis. Gastric juice aspirates may reveal a high pH (of approximately 7), in contrast to acidic pH associated with ZES. Measurement of plasma B12, anti-gastric parietal cells antibodies and fasting gastrin should also be performed. Measurement of plasma gastrin levels allows differentiation of gastrin-dependent (types I and II gastric NETs) from gastrin-sporadic (type III) gastric NETs. Patients with chronic atrophic gastritis at biopsy need investigations for pernicious anaemia and autoimmunity [52]. Furthermore, hypergastrinaemia in the absence of chronic atrophic gastritis requires further investigation with suspicion of MEN-1-associated ZES [29]. Patients with hypergastrinaemia (>1,000 pm) and a gastric pH <2 have ZES. Secretin provocation testing may help clarify whether a gastrinoma is present – secretin provokes gastrin release in patients with gastrinoma rather than the normal suppressive response [53]. Patients with flushing symptoms should have urinary histamine levels measured, although these levels are raised in 33% of type I and 80% of type III tumours.

Histopathology

NETs typically have a solid, yellow-tan or white gross morphology (fig. 2). Histologically, the tumour cells, with faint pink granular cytoplasm and round nuclei with few
mitoses, form trabecular, glandular or rosette-shaped patterns [54]. The typical features of well-differentiated NETs are observed on routine haematoxylin and eosin preparations (fig. 3). In poorly-differentiated tumours, neuroendocrine origin can be clarified by immunohistochemical staining using neuron-specific enolase, synaptophysin, CgA and CD56 markers [39]. Vesicular monoamine transporter-2 is an element of the secretory vesicles of histamine-secreting ECL cells and may be a marker with both good sensitivity and specificity for gastric NETs but remains to be validated beyond preliminary studies [55].

The metastatic potential of NETs correlates most closely with size and site of the primary tumour. Microscopically NETs may have a typical or atypical appearance (characterised by nuclear atypia, increased mitotic index (>10 mitoses per high-powered field) or necrosis) [56]. However, biological behaviour is not directly correlated with histologic appearance. Malignant NETs can only be defined by whether metastases are present.

There may be a degree of overlap in the clinical behaviour of the different subtypes of gastric NET. A multivariate analysis of a number of clinicopathological variables and tumour markers found that the best predictors of tumour behaviour included a combination of tumour size, clinicopathological subtype, mitotic index, angioinvasion and Ki-67 grade [57]. Solcia et al. [58] reported a further refinement of the histopathological classification system for gastric NETs which classifies hyperplastic and dysplastic features of the tumours. Diffusely hyperplastic lesions have at least a doubling of ECL cell numbers in a scattered distribution. This type is associated with G-cell hyperplasia and ZES. Both linear sequences of 5 or more ECL cells and micronodular clusters (<150 μm) of ECL cells are found in patients with hypergastrinaemia such as from ZES or atrophic body gastritis. With severe hypogastrinaemia, the cells form into adenomatoid hyperplasia with multiple membrane bound micronodules within strands of lamina propria. These forms of hyperplasia are benign. It is not known whether patients with more severe hyperplastic changes would benefit from antrectomy to remove the source of gastrin. Dysplastic lesions are 150–500 μm with enlarged nuclei and reduced immunoreactivity. Under this schema, lesions were then further classified into intramucosal carcinoid tumours and those infiltrating into the submucosa. However the true malignant potential of NETs may not be reflected by the depth of penetration and submucosal lesions may still

Fig. 2. Macroscopic appearance of a type III gastric NET found incidentally at upper gastrointestinal endoscopy. This tumour was well differentiated at histopathological examination (see fig. 3). a Endoscopy reveals a polypoid submucosal lesion with poor lifting following saline injection. b EUS demonstrates a hypoechoic submucosal lesion in the distal stomach 1.1 × 1.3 cm. The lesion is in close proximity to and seems to invade the muscularis propria. c Gross appearance following laparoscopic sleeve gastrectomy: 1.3 cm polypoid lesion. d Transverse section shows a firm, white tumour predominantly submucosal.
have a benign clinical course. The benefit of classifying gastric NETs according to Solcia et al. [58] is that the occurrence of pre-neoplastic lesions in patients without chronic atrophic gastritis at biopsy of normal adjacent gastric mucosa may have MEN-1.

**Clinical Staging**

The usual staging modalities are computerised tomography (CT) imaging, \(^{111}\)In-octreotide imaging, and endoscopic ultrasound (EUS). For lesions approaching or exceeding 1 cm [16], EUS may be used to assess the depth of tumour invasion [59] and EUS-guided fine-needle aspiration can be used accurately to obtain a tissue diagnosis for submucosal lesions [60, 61]. CT may detect polypoid lesions in the stomach but poorly visualises submucosal lesions. Angiography of the coeliac trunk and superior mesenteric artery has been used to show neovascularisation at tumour sites but is not used routinely due to its invasive nature. It may help to distinguish invasion versus displacement of adjacent large vessels or localisation of gastrinomas [62]. Assessment of hormonal gradients using angiographic techniques has a reported sensitivity of 80–100%, although, in this context, it is generally only required for gastrinomas where the location of the primary tumour (gastric, duodenal or pancreatic) is not defined using other imaging modalities. Positron emission tomography (PET) scanning is not used routinely as NETs usually have a low uptake of \(^{18}\)F-deoxyglucose [63]. Using \(^{11}\)C-hydroxytryptophan for PET imaging may be an alternative which has not yet been explored in detail for diagnosis of gastric NET metastasis [64].

The expression of somatostatin receptors in over 90% of NET cells has been exploited to show uptake of labelled octreotide (synthetic somatostatin) or labelled meta-iodobenzylguanidine (MIBG) [16]. Somatostatin receptor scintigraphy is more sensitive than MIBG uptake scanning for the detection of both primary and metastatic tumours [65]. An alternative strategy of image fusion of CT and dual isotope scintigraphy (with \(^{99}\)mTc-hydroxymethylene diphosphonate for bone and a somastatin analogue for tumour) is denoted single photon emission computed tomography (SPECT) [66]. It can be of benefit in diagnosis of liver metastases when used in conjunction with conventional imaging modalities. In a recent study, SPECT detected more than 92% of liver metastases in patients with NETs [67]. The radionuclide \(^{68}\)Ga-DOTATOC has a greater affinity for somatostatin receptors than other somatostatin analogues and appears to have better resolu-
tion for smaller NETs [68]. In one series, MRI had increased sensitivity for neuroendocrine liver metastases (95%) versus somatostatin receptor scintigraphy (79%) and CT (49%) [69]. Molecular MRI approaches with antibodies or gadolinium-labelled peptides may be a future imaging development allowing prediction of anti-tumour therapy responsiveness [70].

**Pathological Staging**

A variety of terms and classification systems arose in the attempt to classify NETs. The World Health Organisation (WHO) classification of NETs (2000) is based on prognosis and subdivides NETs into: (a) well-differentiated NETs (which may be benign or of uncertain malignant potential), (b) well-differentiated neuroendocrine carcinomas, and (c) poorly-differentiated neuroendocrine carcinomas.

This classification (table 2) recognises that NETs may have a wide spectrum of disease activity ranging from low risk, benign tumours to high-risk carcinomas which may be either well or poorly differentiated. Under this system, features of aggressive tumour behaviour pathologically can be envisaged as a continuum from benign to malignant based on pathological features of aggressive disease. The distinguishing characteristic between well-differentiated tumours and carcinomas is based on increased cellular pleomorphism and mitotic activity, necrosis and angioinvasion present in carcinomas. Poorly-differentiated carcinomas, in addition to the marked alterations in pleomorphism, mitotic activity and degree of necrosis, may resemble small cell lung cancer.

However, this classification system does not encompass variability of NET clinical behaviour according to anatomic location. The behaviour of NETs is also determined by their site of origin and hence the ENETS group proposed the first site-specific TNM staging system for NETs in 2006 [35]. In addition to the TNM staging (table 3), a grading system for NETs with malignant features was added to account for differences in prognosis within this group (table 4). It is intended that G1 and G2 refer to well-differentiated NETs. Punctate necrosis is a feature of G2 tumours, however grade should be confirmed by mitotic count. G3 tumours are poorly differentiated and often have extensive necrosis and reduced CgA expression with maintained synaptophysin. A cohort of 202 patients with gastric, duodenal and pancreatic NETs was used to

| Table 2. WHO classification of NETs [122, 123] |
| Well-differentiated endocrine tumour | Well-differentiated endocrine carcinoma | Poorly-differentiated endocrine carcinoma |
| benign behaviour | uncertain behaviour | |
| <2 cm | ≥2 cm | |
| <2 mitosis | ≥2 mitosis | |
| < 2% Ki-67 | > 2% Ki-67 | |
| No vascular invasion | Vascular invasion | |
| | | |
| Local invasion | 2–10 mitosis | >10 mitosis |
| 2–10 mitosis | >5% Ki-67 | >15% Ki-67 |
| Vascular invasion ± metastasis | | |
| Vascular or perineural invasion | | |

| Table 3. TNM staging for gastric NETs, proposed by ENETS [124] and AJCC Cancer Staging Manual, 7th edition [125] |
| T primary tumour |
| Tx | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma in situ/dysplasia (tumour size <0.5 mm) |
| T1 | Tumour invades muscularis propria or submucosa and ≤1 cm in size |
| T2 | Tumour invades the muscularis propria or >1 cm in size |
| T3 | Tumour penetrates subserosa |
| T4 | Tumour invades muscularis propria or >1 cm in size |
| | For any T add (m) for multiple tumours |
| N – regional lymph nodes |
| Nx | Cannot be assessed |
| N0 | None involved |
| N1 | Regional lymph node metastasis |
| M – distant metastasis |
| Mx | Cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Disease stage |
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| IIa | T2 | N0 | M0 |
| IIb | T3 | N0 | M0 |
| IIIa | T4 | N0 | M0 |
| IIIb | Any T | N1 | M0 |
| IV | Any T | Any N | M1 |
validate the ENETS TNM staging system. This classification system was able to differentiate between different tumour stages and Cox regression analysis confirmed an increased risk of reduced survival in patients with stage III or IV disease or grade 2 or 3 disease [71]. The AJCC Cancer Staging manual (7th edition) published a TNM staging system for NETs based on site for the first time in 2009. It replicates that proposed by ENETS for gastric tumours.

**Treatment**

**Treatment with Curative Intent**

Management of gastric NETs is determined by subtype, and whether the disease is localised or metastatic. Traditionally, open surgery was the only treatment utilised with potential for curative outcomes, but endoscopic therapy now plays an emerging role in the management of some subtypes of gastric NETs, as does laparoscopic surgery. Since the commonest subtype of gastric NET (type I) displays benign clinical behaviour, simple surveillance or localised endoscopic treatment modalities should be employed, with open or laparoscopic resection confined to tumours with criteria indicating a poor future prognosis. Concerning features in type I gastric NETs would be size >2 cm, extended multiplicity, and atypical pathology particularly with a Ki-67 more than 2%. In this scenario an antrectomy and Roux-en-Y reconstruction may be considered, increasingly performed laparoscopically. Radical surgery and lymph node resection is rarely performed, in particular for type I or II NETs, and is most usually reserved for type III tumours where the same surgical principles apply as for gastric adenocarcinoma. Small tumours, with growth within areas of chronic atrophic gastritis and benign pathological appearance, are usually treated by endoscopic ablation or local excision or simple surveillance [10]. This particularly applies to type I and II gastric NETs, which typically pursue an indolent course. Lesions <1 cm should be resected endoscopically, with interval follow-up [72]. Lesions greater than 1 cm may be resected using endoscopic resection, and repeated resections may be required as long as long as there is no evidence of invasion [73]. The recurrence rates in one series of patients treated endoscopically was 63.6% (21/33) at a median of 8 months and of these, 66.6% (14/21) had a second recurrence [74]. The TNM staging system uses 1 cm in size as a cut off to define T1/2 tumours, although there is inconsistency in guidelines as to whether tumours between 1 and 2 cm should be treated with local resection.

Recurrence after endoscopic resection of type I gastric NETs in the setting of chronic atrophic gastritis is anticipated, as antral G-cell hyperplasia and hypergastrinaemia persists, but the low-risk natural history of this approach in combination with surveillance is the most common treatment approach. In cases where more than five tumours exist, or any tumour is >2 cm in diameter, particularly with an increased proliferation index, or recurrence is early, antrectomy can be considered with the goal of eliminating the source of gastrin production [7]. This procedure has been shown to induce regression of residual tumour after resection and of multiple tumours in small series of such cases [7, 75]. Regular surveillance is required to ensure that tumours regress and any tumours which progress such be treated with radical excision. A recent retrospective review illustrated the surgical, clinical and histological outcomes of laparoscopic antrectomy in type I gastric NETs. All patients were found to be disease-free at follow-up (n = 8) [76]. A case of gastric neuroendocrine hyperplasia where antrectomy, and thus elimination of the source of hypergastrinaemia, did not prevent gastric NET development has been recorded [77]. This implies that there are other factors which predispose to tumour formation. Since the risk of malignancy is extremely low in type I disease, a strong case exists for a conservative approach where there are no concerning endoscopic or pathological features. It has been suggested that an octreotide suppression test to investigate whether tumours are sensitive to gastrin secretion would be useful but this remains to be tested. A single case reported a decrease in the secretory components of ECL cells after an octreotide infusion [78].

The algorithm for management of well-differentiated gastric NETs is depicted in figure 4. This algorithm is de-
derived from consensus recommendations, based on biological outcomes derived from large epidemiological reports. No large series of prospectively treated gastric NETs nor randomised controlled trials have been reported in the literature to date. Reports of surgical approaches to treatment of gastric NETs are summarised in Table 5. Enrolment of patients in multicentre clinical registries with consideration for trial recruitment for type III patients should further improve the evidence base for treatment decisions in the future. Designation of 10 large centres in Europe (4 of which are in the UK) by ENETS as centres of excellence should facilitate future in-depth research. Although there are no clear data implicating an association between lymph node metastases and prognosis in type III lesions, the most recent UK and Ireland Neuroendocrine Tumour Society guidelines (endorsed by the British Society for Gastroenterology) advise routine lymph node clearance as for gastric adenocarcinomas in surgery for type III NETs [79]. Similarly, a surgical rather than endoscopic approach is recommended for lesions which penetrate into the submucosa [79]. More detailed studies on the biological behaviour of type III and large or invasive type I and II tumours are indicated in order to inform optimal surgical practice. The guidelines also support biopsy of all gastric polypoid lesions, in particular to identify gastric NETs.

Surgery for gastrinomas (which may be localised to the stomach (type II gastric NETs)) should include routine duodenotomy and intraoperative transillumination as these tumours may often be <1 cm in diameter [80]. Tumours <1 cm are generally treated with enucleation (if amenable) or local resection. Concerns have been raised about the suitability of duodenal gastrinomas for endoscopic removal as they are associated with nodal metastases in more than 50% of cases and are often multifocal and associated with pancreatic macroadenomas in MEN-1 cases [29] and thus may be best treated by pancreaticoduodenectomy.

Prophylactic cholecystectomy has been recommended at the time of surgery to prevent toxicity resulting from somatostatin analogue therapy or chemoembolisation in the future [39]. All functioning tumours require preop-
operative somatostatin analogue therapy to prevent carcinoid crisis.

Somatostatin receptors are located on the surface of NET cells, and when bound by somatostatin, secretion of hormone is inhibited. Non-metastatic type I gastric NETs can be treated with somatostatin analogues, such as octreotide and its long-acting analogue lanreotide (octreotide LAR) (they are equally effective). This has shown to cause regression of type I and II gastric NETs when more than five lesions localized in the body and the fundus having a diameter <1 cm with pathological confirmation of well-differentiated endocrine tumour [81–85]. However, gastrin secretion may not be reduced and endoscopic surveillance is required. The evidence favouring the efficacy of medical therapy in treatment of gastric NETs does not extend beyond small series (<10 patients) [82, 84, 86] and this therapy is usually reserved for patients not fit for surgery. A recent series of 5 patients treated with 1 year of LAR octreotide reported disease progression in all patients at 5 years, indicating limitations associated with medical therapy and that ongoing maintenance treatment may be required [85]. Somatostatin analogues are not recommended for type III or poorly-differentiated gastric NETs [87] where surgical therapy is the treatment of first choice.

**Treatment of Metastatic Gastric NETs**

Synthetic somatostatin analogues are the most successful medical therapy at the present time for managing symptomatic metastatic disease [2]. It reduces flushing in more than 70% and diarrhoea in more than 60% of patients with carcinoid syndrome. In some patients in prospective trials, it inhibits tumour growth. For example, the PROMID study of metastatic midgut NETs (interim analysis) showed octreotide LAR therapy increased median time to tumour progression versus placebo [88]. Interpretation of trials in the metastatic disease setting and the applicability of these results to adjuvant settings is hampered by use of disease activity as the primary outcome – tumours with less aggressive tumour biology can appear to stabilise with treatment when in fact they were unlikely to progress rapidly.

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<th>Series</th>
<th>n</th>
<th>Treatment modality</th>
<th>Results</th>
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<tr>
<td>Schindl et al. 2001 [10]</td>
<td>16</td>
<td>Local excision (9/16)</td>
<td>8 (89%) had persistent atrophic gastropathy during follow-up. 5-Year cumulative survival was 100%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Radical extended resection (4/9 locally advanced)</td>
<td>5-Year cumulative survival was 75%</td>
</tr>
<tr>
<td>Ichikawa et al. 2003 [73]</td>
<td>5</td>
<td>Endoscopic mucosal resection (5/5)</td>
<td>No evidence of recurrence at follow-up. Range 6–66 months, mean 32.6</td>
</tr>
<tr>
<td>Guillem 2005 [75]</td>
<td>38</td>
<td>Antrectomy</td>
<td>Preoperative gastrin was elevated in the 32 patients Postoperative 19/32 gastrin in normal range Mean follow-up 34 months (1–120), disappearance of carcinoid tumours observed in 27/38 patients (71%) The 11 others had tumour recurrence or persistence No antrectomy-related complication reported</td>
</tr>
<tr>
<td>Ozao-Choy et al. 2010 [76]</td>
<td>8</td>
<td>Laparoscopic antrectomy</td>
<td>6/8 mild reflux (medically treated) 1/8 wound infection, resolved with cephalixin Gastrin levels significantly decreased (98.9%) in all patients (p = 0.001) Chromogranin A levels significantly decreased (81.4%) At mean of 17 months’ follow-up (range 2–35), 8/8 no recurrence ECL hyperplasia after resection in 8/8 4/8 (50%) showed regression of ECL hyperplasia on postoperative biopsy 4/8 (50%) showed no evidence of regression No antrectomy-related complications</td>
</tr>
</tbody>
</table>
Surgery is an important aspect of the management of neuroendocrine liver metastasis, both for survival and symptom control [89, 90], particularly for patients where curative resection is not possible. A 5-year survival of 76–81% [91] has been reported with aggressive surgical resection of liver metastasis compared to 20–30% where left untreated [92]. Survival is limited with more extensive hepatic involvement. Contraindications include diffuse bilobar involvement, compromised liver function or extensive extrahepatic metastases. In a small number of patients, resection of both the primary tumour and hepatic metastases can be performed. In a large multicentre report of patients with liver metastases from intestinal NETs (n = 360), multivariate analysis indicated that age at diagnosis (p = 0.014), Ki-67 level (p = 0.039) and resection of primary (p = 0.015) were independent predictors of survival.

Surgery with palliative intent may prevent mechanical obstruction and debulking the tumour has been shown to improve survival in some studies. For example, in a large series (n = 314) of patients with intestinal NETs with lymph node and liver metastases, patients who underwent resection of the primary tumour had a longer survival than those with no resection (median survival 7.4 vs. 4.0 years; p < 0.01). Patients who underwent successful excision of mesenteric metastases had a significantly longer survival than those with remaining lymph node metastases [93]. It is not known whether the biology of gastric tumours is similar.

Hepatic artery embolisation may be used for symptomatic control and also for control of metastatic disease, usually in patients not suitable for surgical resection [94, 95]. Biochemical response is observed in 80% of patients and median survival increases, however the duration of response only ranges from 4 to 24 months [96]. The addition of chemotherapeutic agents may further improve results [96]. Small hepatic metastases may be treated with RFA or cryoablation using a percutaneous or laparoscopic approach and in conjunction with surgical debulking [97]. The long-term outcome is uncertain.

For the small group of patients who develop type III gastric NETs, chemotherapy may be indicated as adjuvant treatment or for control of metastatic disease. Unfortunately, NETs are only modestly chemosensitive [98]. Most trials of chemotherapeutic agents in the setting of NETs include patients with tumours from a variety of locations, which makes analysis of the response rate at each site difficult (summarised in table 6). Chemotherapy is often reserved from patients with symptomatic or progressing metastases on somatostatin analogues therapy.

The exact role of adjuvant chemotherapy for type III or poorly-differentiated NETs is not clear and there is no standardised regimen. Patients with hepatic metastases amenable to resection should undergo liver resection. The most frequent combination is streptozotocin, 5-fluorouracil, doxorubicin or cyclophosphamide [99, 100]. Only one-third of patients show any tumour regression and the effect is not prolonged (median survival 11 months). Pancreatic NETs appear to have slightly increased response rates than other NETs (approx. 45%) [101]. Etoposide and cisplatin are often used in poorly-differentiated tumours [102]. Temozolamide, an oral alternative to dacarbazine, has shown similar response rates when used in combination with other chemotherapies such as capcitabine [103] or thalidomide [104]. The addition of interferon-α to octreotide or fluorouracil treatment may increase the biochemical response rate to 50% but only 10–20% have observable tumour regression [94, 105].

Novel approaches to treatment of metastatic disease include the addition of growth factor receptor targeted therapies [100] such as bevacizumab [106] and tyrosine kinase inhibitors (e.g. imatinib [107]) or targeted radiotherapy. A recent RCT of everolimus versus placebo in patients with metastatic pancreatic NETs (n = 410) reported a median progression-free survival of 11.0 months with everolimus compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus 0.35; 95% confidence interval (CI) 0.27–0.45; p < 0.001), representing a 65% reduction in the estimated risk of progression or death [108]. A similar sized treatment effect was noted in a trial of sunitinib versus placebo of patients with metastatic NETs (n = 171) with median progression-free survival of 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death 0.42; 95% CI 0.26–0.66; p < 0.001) [109]. Treatment response rates of the tyrosine kinase inhibitors at early phase trials have been disappointing (with response rates of less than 20% and in many cases nearer to 10%) [70, 100] but angiogenic inhibitors appear more promising [110]. Although these trials demonstrate that NETs (at least of pancreatic) origin are responsive to targeted therapies, it is unclear whether these agents are suitable in the neoadjuvant or adjuvant treatment setting or whether they should be combined with standard chemotherapeutic agents or in combination.

Patients who display avid uptake of 313In-labelled octreotide and 123I-MIBG in diagnostic scintigraphy may respond to treatment with a radioactively labelled soma-
Somatostatin peptides with high receptor affinity conjugated to the DOTA chelator have been labelled with β-emitters $^{90}$Y or $^{177}$Lu. Initial findings showed a 25% response rate of greater than 50% tumour shrinkage [111] but they remain to be tested in a randomised setting and the heterogeneous tumour types included in the studies make interpretation of response rates and comparison to other therapies difficult. Radio-

Table 6. Phase II/III trials of chemotherapeutic regimes in neuroendocrine tumours

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Agent</th>
<th>n</th>
<th>Number of gastric NETs</th>
<th>Results</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinke et al. 2009</td>
<td>III (RCT)</td>
<td>Octreotide LAR</td>
<td>85</td>
<td>21 unknown site, all others were midgut</td>
<td>Stable disease 66.7 vs. 37.2% with placebo</td>
<td></td>
</tr>
<tr>
<td>Yao et al. 2008</td>
<td>II</td>
<td>Bevacizumab, PEG interferon-α2b (monotherapy)</td>
<td>44</td>
<td>6 foregut, 1 gastric (2.3%)</td>
<td>Bevacizumab: 18% partial response 77% stable disease 5% disease progression PEG intron: 68% stable disease 27% disease progression</td>
<td>Progression-free survival at the end of 18 weeks of monotherapy: 95% bevacizumab 68% PEG interferon</td>
</tr>
<tr>
<td>Kulke et al. 2008</td>
<td>II</td>
<td>Sunitinib</td>
<td>107</td>
<td>14 foregut (lung and stomach), 1 unknown</td>
<td>Excluding pancreatic NETs: 2.4% partial response 83% stable disease</td>
<td></td>
</tr>
<tr>
<td>Yao et al. 2007</td>
<td>II</td>
<td>Imatinib</td>
<td>27</td>
<td>2 gastric, 7 site unknown</td>
<td>1 partial response 17 stable disease</td>
<td></td>
</tr>
<tr>
<td>Bajetta et al. 2007</td>
<td>II</td>
<td>Capecitabine and oxaliplatin (XELOX)</td>
<td>40</td>
<td>7, site not specified</td>
<td>11 partial response 14 stable disease</td>
<td></td>
</tr>
<tr>
<td>Duran et al. 2006</td>
<td>II</td>
<td>Temsirolimus</td>
<td>36</td>
<td>21 'carcinoids', site not specified</td>
<td>1 partial response 12 stable disease</td>
<td>mTOR pathway downregulated; activity does not warrant further single-agent evaluation</td>
</tr>
<tr>
<td>Kulke et al. 2004</td>
<td>II</td>
<td>Gemcitabine (monotherapy)</td>
<td>18</td>
<td>3 NETs, site not specified</td>
<td>No partial responses 11 stable disease</td>
<td></td>
</tr>
<tr>
<td>Kulke et al. 2006</td>
<td>II</td>
<td>Irinotecan Citiplatin (combination therapy)</td>
<td>18</td>
<td>2, site unknown</td>
<td>1 partial response 11 stable disease</td>
<td>Regimen effective in poorly-differentiated NETs rather than well-differentiated NETs</td>
</tr>
<tr>
<td>Sun et al. 2005</td>
<td>II/III</td>
<td>Doxorubicin with fluorouracil (FU/DOX) or streptozocin with fluorouracil (FU/STZ) [crossover to dacarbazine (DTIC) after disease progression following first-line treatment]</td>
<td>249</td>
<td>30, site not specified</td>
<td>Objective response rate: FU/DOX 15.9% FU/STZ 16% (not statistically significant p = 0.82) Crossover to DTIC 8.2%</td>
<td>Progression-free survival statistically significant difference between FU/DOX and FU/STZ on stratified analysis based on performance status. p = 0.013</td>
</tr>
<tr>
<td>Kulke et al. 2006</td>
<td>II/III</td>
<td>Temozolomide Thalidomide (combination therapy)</td>
<td>29</td>
<td>15 NETs, site not specified</td>
<td>40% B&lt;IOCHEMICAL response (CgA) 25% overall radiological response</td>
<td>Regimen more active in pancreatic endocrine tumours (45% radiological response rate) than other NETs (7% radiological response rate)</td>
</tr>
<tr>
<td>Ekeblad et al. 2007</td>
<td>Retrospective</td>
<td>Temozolomide</td>
<td>36</td>
<td>1 gastric, 1 foregut</td>
<td>53% stable disease</td>
<td></td>
</tr>
<tr>
<td>Ansell et al. 2001</td>
<td>II</td>
<td>Paclitaxel</td>
<td>24</td>
<td>14 NETs, site not specified</td>
<td>2 partial response Disease progressed in remainder</td>
<td>Activity does not warrant further single-agent evaluation</td>
</tr>
<tr>
<td>Fjallstog et al. 2001</td>
<td>II</td>
<td>Cisplatin and etoposide</td>
<td>36</td>
<td>18 foregut</td>
<td>Of foregut: 10 partial response 6 stable disease</td>
<td></td>
</tr>
</tbody>
</table>

Phase II/III trials from year 2000. The number of gastric NETs or tumours of unknown site was recorded where specified.
labelled somatostatin analogues can be utilised for targeted radiotherapy [112]. Radiologic response rates have varied from 7–9% in some series [113] to 16–30% in others [114–116]. The largest series of 310 patients, utilising a low-energy β-particle emitter, 177Lu, demonstrated a complete response rate of 2% and partial response rate of 28% and median progression-free survival of 40 months [117]. The best response rates are in functioning pancreatic NETs.

**Prognosis**

Prognosis of patients with NETs depends on site, histological appearance, presence of metastatic disease and carcinoid syndrome. In general, patients are at higher risk of disease recurrence if the primary tumour is >2 cm, there is nodal involvement or the Ki-67 proliferation index is greater than 5%, and should undergo more intensive follow-up including 5-HIAA and CgA levels every 3–6 months, CT scanning annually and further imaging (e.g. with MIBG scintigraphy) if there are any abnormalities detected [39]. The current consensus is that surveillance should be performed every 2 years for type I tumours and every year for type II lesions [16]. Areas of chronic atrophic gastritis should also be biopsied due to the risk of development of adenocarcinoma. Serum gastrin levels should be monitored in type I and II patients [118]. In patients with type III well-differentiated gastric NETs treated by curative resection, it is recommended that imaging and CgA are performed at 6-month intervals for 2 years and then yearly for a further 3 years. In well-differentiated metastatic tumours, imaging should be performed every 3 months [16].

Prognosis is varied with gastric NETs depending on subtype. Overall, 5-year survival has increased over the past number of decades from 51 to 63% [14]. The 5-year survival of patients with type I gastric NETs has been shown to be 100% in several studies, with no progression into malignant phenotype, with a very rare case with a lethal outcome [77]. The 5-year prognosis of type II disease is 60–75%, reflecting the morbidity of MEN-1 and the increased metastatic potential of type II tumours [119]. Type III gastric NETs treated with a radical extended resection has been shown to have a 5-year survival of 75%. Among patients with metastatic gastrinomas, 5-year survival rates are only 20–38% [120].

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**References**


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