Systematic Review: Management of localised low grade upper gastrointestinal neuroendocrine tumours.

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SUMMARY

Background

Neuroendocrine tumours (NETs) of the stomach and duodenum are rare, but are increasing in incidence. Optimal management of localised, low grade gastric and duodenal NETs remains controversial.

Aims

To systematically review recent literature that has evaluated the management of localised low grade gastric and duodenal neuroendocrine tumours.

Methods

A systematic literature search was conducted. Articles were screened and eligible articles fully assessed. Additional articles were identified through the included articles' reference lists.

Results

Several relevant retrospective case series were identified, but there was considerable heterogeneity between studies and they reported a variety of parameters. Type I gastric NETs had an excellent prognosis and conservative management approaches such as endoscopic surveillance/resection were appropriate in most cases. Many type III gastric NETs were low grade and appeared to have a better prognosis than has previously been appreciated. Endoscopic rather than surgical resection was therefore effective in some patients who had small, low grade tumours. Duodenal NETs were more heterogenous. Endoscopic resection was generally safe and effective in patients who had small, low grade,

non-functional, non-ampullary tumours. However some patients, especially those with larger or ampullary duodenal NETs, required surgical resection.

Conclusions

Most type I gastric NETs behave indolently and surgical resection is only rarely indicated. Some type III gastric and duodenal NETs have a worse prognosis, but selected patients who have small, localised, non-functional, low grade tumours are adequately and safely treated by endoscopic resection. Due to the complexity of this area, a multidisciplinary approach to management is strongly recommended.

Keywords

Gastric, duodenal, neuroendocrine tumour, endoscopy, carcinoid

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs), previously known as carcinoid tumours, arise from the diffuse neuroendocrine system within the gastrointestinal tract and pancreas[1]. Foregut NETs include gastric and duodenal NETs and these tumours demonstrate a wide range of clinical behaviours from the commoner slow growing and indolent tumours to the rarer highly aggressive types which can have widespread metastases at the time of presentation.

GEP-NETs were previously thought to be rare, but recent evidence has suggested that they are increasing in both incidence and prevalence. A recent retrospective, population-based study using data from the US Surveillance, Epidemiology, and End Results (SEER) program demonstrated a 6.4 fold increase in age adjusted incidence rate between 1973 and 2012[2]. Across multiple observational studies gastric and duodenal NETs account for approximately 7% and 2% of all digestive neuroendocrine neoplasms (NENs), respectively[3,4]. All GEP-NENs have malignant potential. They are classified into NETs grade 1 (G1), grade 2 (G2) and grade 3 and neuroendocrine carcinoma (NEC), on the basis of mitotic count, Ki-67 index and differentiation status[5] (Table 1). Higher grade tumours are associated with an increased risk of angioinvasion and metastasis and often have a poorer prognosis.

GASTRIC NEUROENDOCRINE TUMOURS

Gastric neuroendocrine tumours (g-NETs) are subdivided into three main distinct types (Table 2)[6,7]. Type I g-NETs are associated with autoimmune atrophic gastritis and hypochlorhydria while Type II g-NETs develop in some patients who have gastrinomas, increased gastric acid secretion, Zollinger-Ellison syndrome (ZES) and multiple neuroendocrine neoplasia (MEN) type 1. Both type I and type II g-NETs are characterised by elevated fasting serum gastrin

concentrations. Hypergastrinaemia exerts a proliferative effect on enterochromaffin-like (ECL) cells in the stomach, leading to hyperplasia and subsequently dysplasia and neuroendocrine tumour development. In humans (unlike some rodent animal models) the current evidence in support of the hypothesis that the usually milder degree of hypergastrinaemia that is associated with chronic proton pump inhibitor use or with *Helicobacter pylori* induced chronic atrophic gastritis also induces type I g-NET development is relatively weak. However, there are some strong proponents of this view and more research in this area is certainly warranted[8]. Type III g-NETs are sporadic lesions and are not associated with hypergastrinaemia. They tend to behave more aggressively and sometimes have a poorer prognosis. Due to their rarity and the lack of published data on this topic, the assessment and management of patients who have type II g-NETs will not be discussed further in this article.

Patient assessment

It is imperative to identify the subtype of g-NET through biochemical, histological and endoscopic assessment in order to provide appropriate management for the tumour. The algorithm shown in Figure 1 can be used for diagnostic workup.

Clinically most g-NETs tend to be asymptomatic and many tumours are identified incidentally during endoscopy performed to investigate unrelated symptoms or anaemia. Most localised g-NETs do not secrete hormones or peptides into the circulation and are therefore not usually associated with functional syndromes; they are therefore referred to as non-functional or non-secretory tumours.

Biochemical investigations should include measurement of fasting serum gastrin concentrations[9]. Blood tests can also be helpful for the assessment of potential autoimmune

atrophic gastritis and pernicious anaemia and the presence of other associated autoimmune disorders such as hypothyroidism[10]. Serum chromogranin A concentrations correlate with the severity of ECL-cell hyperplasia, but may not be elevated above the upper limit of the normal range depending on the assay being employed.

Most type I g-NETs are multifocal (Figure 2A). Type III g-NETs are more likely to be single and larger (often >10mm in diameter) at the time of presentation (Figure 2B). Biopsies from suspected NETs as well as biopsies from the antrum and corpus of the stomach are needed to identify the type and grade of NET as well as the presence/absence of underlying pathology such as atrophic gastritis and intestinal metaplasia[11]. Immunohistochemical staining for markers of neuroendocrine differentiation such as CgA and synaptophysin are typical within the tumour and diffuse linear and/or micronodular ECL-cell hyperplasia may also be present in the unaffected background corpus mucosa (Figure 2 D,F)[12-15]. Determination of the Ki-67 proliferation index establishes the tumour grade (Figure 2E)[15,16].

Current treatment guidelines

The most recent treatment guidelines from the European Neuroendocrine Tumour Society (ENETS) were updated in 2016. For localised type I g-NETs, conservative management strategies are preferable to surgery depending tumour size. Annual or twice yearly endoscopic surveillance is advocated for type I g-NETs that measure <10mm in diameter. Endoscopic resection is suggested for lesions >10mm in diameter and surgery involving local excision or partial gastrectomy should be considered if the tumour invades the muscularis propria and/or there is suspicion of lymph node metastases. For type III g-NETs, surgical treatment involving partial or total gastrectomy and lymph node dissection remains the

recommended treatment option for localised tumours[6]. The management of patients who have metastatic g-NETs or functional syndromes is outside the remit of this article.

DUODENAL NEUROENDOCRINE TUMOURS

Duodenal neuroendocrine tumours (d-NETs) are heterogeneous. They can be classified into functional and non-functional tumours based on clinical presentation and hormone secretion and include duodenal gastrinomas; duodenal somatostatinomas; duodenal gangliocytic paragangliomas; poorly differentiated neuroendocrine carcinomas and non-functioning d-NETs (which do not give rise to a clinical hormonal syndrome)[17]. Non-functioning tumours represent up to 60-98% of all d-NETs and this subgroup tends to have a more favourable prognosis[18].

Another classification system distinguishes d-NETs based on their location into ampullary and non-ampullary. For reasons that are currently poorly understood, ampullary d-NETs exhibit more aggressive disease biology and have a different clinical, histological and immunohistochemical profile[19-21]. They tend to present at a more advanced stage with lymph node and/or liver metastases and are more likely to have a higher Ki-67 index and poorly differentiated histology.

Patient assessment

Similarly to g-NETs, d-NET characterisation greatly influences a patient's treatment plan. Biochemical assessment should include measurement of fasting gastrin and somatostatin concentrations[22]. The site, size and multiplicity of duodenal lesions and the relationship of tumours to the ampulla should be clearly noted[18]. The tumour should be biopsied to establish its grade, but biopsies of the normal stomach or duodenum are not usually helpful. Most d-NETs are solitary lesions measuring less than 10mm in diameter (Figure 2C).

Endoscopic ultrasound, CT scan and ^{68}Ga DOTA-peptide PET/CT scans are helpful to assess depth of d-NET invasion and the presence of local/distant metastases and should certainly be considered for tumours >10mm in diameter, high grade and ampullary lesions.

Current treatment guidelines

The current ENETS guidelines suggest surgical resection of all localised ampullary d-NETs; with endoscopic resection being recommended for smaller non-ampullary, non-functional lesions which have favourable staging[6]. The management of patients who have metastatic d-NETs or functional syndromes is again outwith the remit of this article.

AIM

As there is currently some controversy about the relative merits of endoscopic surveillance, endoscopic resection and surgical resection in patients who have localised, low grade, non-functional gastric and duodenal NETs, we aimed to conduct a systematic literature review of all recent studies that have included these treatment options for patients who have such neoplasms.

METHODS

A comprehensive literature search was performed through the Healthcare Databases for Advanced Research utilising PUBMED, MEDLINE and independently using SCOPUS. Additional articles were identified through the included articles' reference lists.

The methodology was developed from standard guidelines under the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' Statement[23] (see Figure 2 for PRISMA diagram and Supplementary Tables 1 and 2 for Pubmed MESH terms).

Inclusion and exclusion criteria

All relevant studies from 2000-2019 inclusive that were published in English were considered. Exclusion criteria were non-human studies, single case reports, small studies involving less than five participants and conference abstracts. We also excluded any articles which exclusively described the management of patients who had grade 3 NETs or NECs, functional or metastatic tumours. We also excluded articles which have primarily investigated the role of medical therapies such as CCK2 receptor antagonist drugs and somatostatin analogues in type I gastric NETs and refer readers to other articles on this topic[24,25]. Some identified articles included patients within their cohorts who had metastatic disease or who had received medical therapies such as somatostatin analogues; such studies were included but those aspects of the paper were not specifically considered.

Articles were screened by reading the abstract and eligible articles were then fully assessed. All data were extracted independently by two reviewers (KE and NH) using a data extraction form. The senior author (DMP) arbitrated if required. Extracted data included, where available, year of publication, study design, number of participants and data relevant to all outcomes. No formal statistical analysis was undertaken owing to the small number of eligible studies, the heterogeneity of the data presented and the fact that many studies did not describe important information such as tumour grade for all patients.

RESULTS

Type I gastric NETs

Twenty-three non-randomised retrospective studies involving 1094 participants with type I g-NETs were identified and included in this review. Patient demographics and tumour characteristics are summarised in Table 3. Most patients were diagnosed in the 5th or 6th decade of life and as expected a slight female predominance was noted at 58%. When

documented, tumours had a tendency to be multiple, located in the gastric body, small (maximum diameter <10mm) and low grade confirming the generally accepted type I g-NET characteristics. Only two cases of grade 3, type I g-NET were described, although not all studies included comprehensive descriptions of tumour grade. Overall, the studies demonstrated an indolent disease course with low disease specific mortality; specifically only five disease related deaths were reported across all the studies. Some studies however did not comment on mortality. The deaths that were described all occurred in patients who had unusual disease features such as a very large tumour (60mm)[26], metastatic disease at the time of diagnosis[27,28] or grade 3 histology[29]. Therefore, tumour related deaths seem to be very rare in this tumour type, and none were documented in patients who had a typical presentation with multifocal, small, localised, low grade neoplasms. Furthermore, the total local recurrence rate after resection was low but significant (74/544 patients (13.6%) in those studies that reported recurrence).

Role of active surveillance in type I g-NET

Only four studies included active surveillance as a potential management option for type I g-NET, with the outcomes of a total of only 57 patients being described. No disease related mortality over a follow up of at least three years was documented. Moreover, no patients demonstrated tumour progression or developed metastatic disease during follow up. In all four studies however, the tumours had very favourable characteristics, as most of the lesions measured <10mm in diameter and most had low Ki-67 indices (Table 4). In the largest patient cohort, described by Sato *et al.*, 25 individuals were followed up for up to 204 months with regular 6-12 monthly upper GI endoscopies. This study reported no disease progression or deaths related to disease.

Role of endoscopic management in type I g-NET

Fifteen studies involving 428 patients included endoscopic resection as a potential treatment modality for patients with type I g-NETs. Endoscopic techniques included polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) (Table 5). Most of the tumours were again small and low grade with only a few studies including any >10mm tumours. There is therefore considerable overlap in terms of tumour characteristics between these patients and those who underwent endoscopic surveillance alone (as discussed in the preceding section and detailed in table 4). Not all studies documented the presence/absence of lymphovascular invasion (LVI) or lymph node (LN)/distant metastases, however in total four patients were noted to have LVI, five LN metastases and one distant metastasis.

A range of endoscopic resection techniques were employed. Most cases appeared to involve polypectomy or endoscopic mucosal resection (EMR), but 76 patients underwent endoscopic submucosal dissections (ESDs) and in some studies the details of the resection technique were not provided. Some of the ESDs were however performed for very small polyps measuring <5mm in diameter and patients with similar polyps may simply have undergone endoscopic surveillance in other centres.

Fifteen patients developed a complication (15/181, 8% in the five studies which reported this parameter); these included 13 cases of bleeding which was either immediate or delayed, and two perforations (one of which was managed endoscopically and one surgically). However, unfortunately the majority of studies did not describe endoscopic complication rates. Local tumour recurrence rates ranged from 0-63.6% depending on which series was reviewed (median follow up varied from 24 to 84 months) and appeared to be higher when simple

polypectomy using biopsy forceps or endoscopic snare was performed[30]. No distant metastases were documented during follow up and there were no deaths related to disease.

Role of surgical management in type I g-NET

Seven studies described the details of some patients within their cohorts who had undergone surgical management of type I g-NETs (Table 6). A total of 81 such patients were described. In some cases the tumours were larger with a maximum diameter of 45mm being recorded in one patient. However, this series also included several patients who had type I g-NETs that measured <10mm in diameter (including a few patients who even had 1-2mm tumours), in whom surgical resection was probably not entirely justified. Only two patients had LN metastases and two had distant metastases at the time of presentation. The most common surgical procedures were subtotal or total gastrectomy and rather surprisingly only eight patients were reported to have had a gastric wedge excision. All studies documented tumour recurrence and patient mortality rates. Although there was heterogeneity between patients in terms of tumour characteristics, only one death related to disease was reported in the 81 patients (1.2%) and six local recurrences were documented during follow up periods that ranged from 48.5-138 months.

Type III gastric NETs

Ten non-randomised retrospective studies were identified that described the management of patients with type III g-NETs. Patient demographics, tumour characteristics and patient management are summarised in Table 7. 229 patients were included, of whom 63% were male. Most tumours were diagnosed in the 6th decade of life and the majority were solitary lesions. The most common tumour location in this series (when documented) was the body of the stomach. This cohort included 66 patients who had grade 1 and 52 who had grade 2

NETs, but also included 29 who had G3 NETs and 82 in whom no tumour grade was documented. These data suggest that in contrast to some historical cohorts, the majority of type III g-NETs being detected in the modern era have grade 1 or 2 histology. Nonetheless grade 3 tumours were still much more frequent in this tumour type than in type I g-NETs (Table 3).

The main treatment administered to these patients was tumour excision. Endoscopic surveillance and/or palliative surgery was only offered to a very small number of patients who were unfit for definitive management. Eight of the studies included 121 selected patients who underwent endoscopic resection (EMR or ESD) for small localised tumours. Complete resection rates varied between 72% and 80% in most of the series, but was 87% in the largest series[31-33]. There was insufficient information to determine whether complete resection was more likely following ESD than EMR and ESD was only reported in 44 patients. In the event of incomplete tumour resection margins being identified, patients were either followed-up endoscopically or underwent further endoscopic treatment. Only one patient presented with a LN recurrence during follow up at 68 months post resection of a 16mm G1 NET although some studies did not report tumour recurrence rates.

Surgical treatments were described in 75 patients and included wedge resection or subtotal/total gastrectomy with lymphadenectomy. 87% of patients underwent a major surgical resection (subtotal or total gastrectomy), with wedge excision only being described in 10 patients. Only one patient developed liver metastases during follow up (48 months after wedge resection for a G3 lesion, having previously declined a total gastrectomy).

Overall, 27 disease related deaths were documented. However nine of these patients were palliative at the time of presentation and did not undergo any treatment[28,34], one died of

surgical related complications[35], one from tumour bleeding[35] and three more died from distant metastatic disease[28,35]. The study by Vanoli *et al*. described a further 13 deaths, but the reasons are not documented in that manuscript[29]. The cohort described in this paper was somewhat atypical however, as 61% of the type III g-NET patients had metastatic (stage III/IV) disease at the time of presentation, 47% tumours were >2cm in diameter and 27% had grade 3 histology. Mortality was therefore more common in patients with type III g-NETs than type I g-NETs, but was only reported in approximately 12% of type-III g-NET patients in total. Unsurprisingly death appeared to occur more commonly in patients who had higher grade and more advanced stages of disease.

Complication rates were unfortunately not documented in most studies. However in those studies which solely employed endoscopic management, only two cases of delayed bleeding were noted and both of these occurred in the ESD group[32,36,37]

Duodenal NETs

Twenty-one non-randomised retrospective studies were identified that described the management of patients who had d-NETs, with a total of 721 participants. Patient demographics, tumour characteristics, treatment modalities and the limitations of the studies are summarised in Table 8. There was considerable heterogeneity between the studies and some papers also included patients who had functioning NETs (e.g. gastrinomas and somatostatinomas) which are beyond the scope of this article. These studies have however been included as it was not always possible to extract the data from these papers which specifically related to the patients who had non-functional d-NETs. The median age of patients included in the studies ranged from 55 to 74 years and males and females appeared to be approximately equally represented. Most tumours were solitary and most studies

documented a median tumour size of approximately 10mm, although a wide range of diameters from 1mm to 130mm were reported. The majority of tumours (when documented) had grade 1 or 2 histology, with only 18 grade 3 tumours being described in this series. The commonest tumour location was the first part of the duodenum, but the series also included some patients who had ampullary d-NETs and d-NETs that were located in the 3rd or 4th part of the duodenum.

Only two studies[38,39] evaluated the role of endoscopic surveillance in d-NETs and these studies involved only 14 patients. The lesions included in these studies were small (<10mm in diameter) and the patients had no evidence of LN metastases. None of these patients demonstrated any tumour progression during follow-up (which ranged from 12-102 months).

Thirteen papers reported surgical management of d-NETS in 320 patients. The commonest surgical procedure appeared to be a local excision (151/320 patients), but several patients also had some type of gastrectomy or pancreaticoduodenectomy (dependent on the site of the tumour). This cohort however included several patients who had ampullary and/or functional tumours. All deaths related to disease were in case series which included patients who had ampullary and/or functional tumours. These tumours were either metastatic at the time of presentation or they progressed during follow up reflecting the more aggressive nature of these tumours[40-42]. Surgical complications were documented in 66 patients, but most studies did not comment on this parameter. Sixty of these complications were noted in the paper by Margonis *et al*[43]. Unfortunately however this study did not document the exact complications, but recorded that 32 were minor and 28 were major according to the Clavien Dindo classification.

382 endoscopic resections were performed in total, including some that were conducted for multiple tumours in the same patient. A variety of techniques were employed, but the most common was EMR. The cohort included only six patients who underwent ESD. Endoscopic resection appeared to have a good safety profile and 24 complications were documented in the 279 procedures for which this parameter was recorded (mostly perforations or bleeding, with the details of all complications being shown in Table 9). Endoscopic resection techniques were however employed in some series only when tumours met certain criteria such as lesions being located in D1, of low grade and measuring <15mm in diameter. Local recurrence rates in these patients were also favourable, with some patients undergoing repeat endoscopic therapy if needed[44,45]. Length of follow up was comparable between endoscopically treated and surgical groups.

Twenty-nine disease related deaths were documented in the various studies that were evaluated. These occurred in both endoscopic and surgically managed groups, however detailed causes of death were not recorded in most studies and it was not always possible to determine the treatment group in which death occurred. Only one death as a result of a post-surgical complication was described[46].

DISCUSSION

Our review highlights a current lack of high-quality evidence to inform the optimal management of patients who have localised, low grade, non-functional gastric and duodenal NETs. All the studies that we identified during this systematic literature review were retrospective and non-randomised and did not include a standard form of reporting data about tumour type, size, grade, location or follow-up. No prospective clinical trials were identified in this field. The slow growing nature of many of these tumours means that trials

are difficult to perform and the optimal management strategy for individual patients can sometimes be difficult to establish.

Most practice that was described within the articles that we reviewed was in broad agreement with the management recommendations documented in the 2016 ENETS guidelines for gastroduodenal NETs; however we observed trends in the published data which suggest that a less aggressive management approach may be appropriate in certain cases.

Type I g-NETs

As previously documented for this tumour type, the type I g-NETs that were included in this systematic review tended to have a very favourable prognosis with low metastatic potential and very few disease related deaths. Moreover, the deaths that were documented seemed to occur in patients who had atypical tumours at the time of diagnosis.

Patients who had multiple lesions measuring <10mm in diameter and who had confirmed low grade (G1/2) histology appeared to suffer no harm as a result of receiving no specific treatment and simply being enrolled on an endoscopic surveillance programme. Patients who were managed in this way did not appear to progress after long periods of follow up and no disease related deaths were noted. One limitation to this conclusion however is that each of the published case series did not include many patients. Another possible advantage of an endoscopic surveillance strategy (but one which has not yet been fully explored) is that it may detect the gastric adenocarcinomas that are also more prevalent in this patient group at an earlier and potentially more treatable stage.

Endoscopic resection also appeared to be safe in this setting and resulted in very few life-threatening complications. In some cases however, endoscopic resection was performed for very small lesions and there was considerable overlap in tumour characteristics between the cohorts who underwent endoscopic resection and endoscopic surveillance. The local recurrence rate was significant in some studies and also depended on the endoscopic resection method used, as simple polypectomy using biopsy forceps or snare resulted in >50% recurrence rates, whereas EMR and ESD appeared to be more effective, with complete resection rates of ~95% being reported in some series involving ESD. However, ESD did not appear to confer any substantial benefit in this tumour type and in general this technique can result in higher complication rates. The relatively high tumour recurrence rate probably reflects the multifocal nature of these tumours in many patients. Endoscopists should be aware that not all lesions may be detected at the original endoscopy. It may be impossible to remove all tumours and therefore EMR/ESD should probably only be used when certain criteria are met; these could potentially include size >10mm or possibly grade 2 histology. In the event of tumour recurrence or missed lesions, the studies suggested that endoscopic treatments could usually be safely repeated without an apparent adverse effect upon patient outcomes.

In the papers included in this review, surgery was performed in some patients who had very small type I g-NETs. In such cases it may therefore have been unnecessary. However surgery did appear to be safe and effective in most of the patients in whom it was performed. In view of the general behaviour of type I g-NETs however, the data suggest that surgery should probably be reserved for larger type I g-NETs that are not suitable for endoscopic resection or those rare tumours which have a substantially higher grade. Even in these cases, a less aggressive surgical approach involving a wedge resection may be most appropriate. A

subtotal or total gastrectomy could however still be considered in the presence of LN metastases.

Type III g-NETs

Many of the type III NETs that were described in the papers included in this systematic review had low grade histology and were associated with a good prognosis, in contrast to some historical reports about this tumour type (see table 2 which has been adapted from the most recent ENETS guidelines). However, overall mortality was still substantially higher in these patients than in those who had type I g-NETs.

For type III g-NETs the traditional management approach has been radical surgical resection. Type III g-NET patients who were treated in this way had generally good outcomes, but in many cases major gastric resections were performed, which are likely to have resulted in some long-term morbidity. Gastric wedge resections also appeared to be effective in some patients, but were only rarely performed, so their utility has not yet been fully established.

Recent studies have expanded the role of endoscopic resection in a selected group of type III g-NET patients. The literature showed that EMR or ESD could be used with curative intent in small (<20mm), low grade (G1/G2) type III g-NETs where there is no evidence of LN or distant metastases. Although reported follow up was slightly shorter than in surgically treated patients, endoscopic treatment appeared to be suitable and safe in patients who had early lesions without compromising oncological outcomes. The data did not show any superiority of ESD over EMR, with the limitation that relatively few cases of ESD were performed. Furthermore, in the event of tumour recurrence or an increase in tumour grade, further endoscopic or surgical treatment appeared to be feasible without compromising oncological outcomes.

The presence of distant metastatic disease at the time of presentation was a marker of poor outcome and such patients should not be managed operatively.

d-NETs

The d-NETs identified in this systematic review were heterogeneous. For example, the largest series reported by Massironi[40] and Margonis[43] included functioning and ampullary tumours as well as non-functional d-NETs which made it difficult to draw conclusions. Overall, sporadic functional, ampullary and locally advanced d-NETs should be managed in a similar way to pancreatic adenocarcinoma with surgical resection being the mainstay of management. However, such tumours have not specifically been considered in this paper.

In the case of small non-ampullary, grade 1, non-functional d-NETs, which generally have a favourable prognosis, there may be a case for endoscopic surveillance in some patients, in particular those who are frail or have comorbidities. However there is currently very limited evidence to support this approach and further studies in this area are required.

Endoscopic resection also appears to be safe and suitable for small, low grade d-NETs with comparable resection rates and tumour recurrence rates to surgery. Current evidence is however currently insufficient to support the use of one particular resection technique. Although ESD is more likely to result in complete resection, it is also more likely to be associated with complications. Endoscopic complications occurred not infrequently in d-NET patients, probably reflecting the anatomy of the duodenum, but most of these complications seemed to be effectively treated and were not fatal. Prospective randomised clinical trials to clarify the role of endoscopic resection and resection technique in d-NETs would however be helpful.

Conclusions

The quality of the data that currently informs management decisions in patients who have localised low grade gastric and duodenal NETs is very low. Evidence from a number of retrospective case series does however seem to suggest that less aggressive treatment approaches such as endoscopic surveillance or endoscopic resection with close follow up are safe and effective in many patients, especially those who have type I g-NETs. Similar approaches also appear to be appropriate in selected patients who have small, low grade, non-ampullary d-NETs. Type III g-NETs are potentially more serious and these tumours should therefore generally be resected unless they are metastatic. However some type III g-NET patients appear to be suitable for endoscopic resection or gastric wedge excision rather than needing to undergo a major gastric resection. Based on our findings and bearing in mind the weak level of evidence currently available, we have made some suggestions about the management of patients with localised type I g-NETs in Figure 4. However we feel that the evidence is currently insufficient to suggest similar algorithms for the management of type III g-NETs and d-NETs.

Prospective clinical trials or possibly large multi-centre registries with prospective detailed recording of patient/tumour characteristics and outcomes are however desperately needed to better inform the management of patients who have localised, low grade, non-functional g-NETs and d-NETs. Such studies will hopefully in future provide data that will permit personalisation of management approaches in this patient group.

Author contributions and Acknowledgments

KE and NH performed the literature review and extracted data from the papers that were chosen for inclusion. KE and DMP wrote the first draft of the manuscript. KE, NH and DMP revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript. The guarantor of this article is Prof DM Pritchard.

No external funding was received for this work. DMP has acted as a consultant for Ipsen and Advanced Accelerator Applications and has received research funding from Trio Medicines UK. Neither of the other authors has any conflicts of interest to declare.

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approach in a series of 8 patients. Case series. *International Journal of Surgery.* 2011;9(3):248-253.

FIGURE LEGENDS

Figure 1: Diagnostic algorithm for suspected g-NET. Patient assessment should include endoscopic, biochemical, histological as well as clinical assessment. All cases should be referred to specialist NET centre and discussed at a Multidisciplinary Team meeting for further management.

Figure 2: Endoscopic images of (A) Multiple type 1 g-NETs, (B) Solitary type III g-NET and (C) Solitary d-NET. Histological images demonstrating (D) Synaptophysin immunohistochemistry of type I g-NET, (E) Ki67 immunohistochemistry of same grade 1 type I g-NET and (F) Synaptophysin immunohistochemistry of atrophic gastric mucosa from same patient with type I g-NET demonstrating linear and nodular ECL cell hyperplasia.

Figure 3: PRISMA diagram depicting selection criteria for inclusion of articles for gastric and duodenal NETs.

Figure 4: Proposed management algorithm for patients with localised type-1 g-NETs.

TABLES AND FIGURES

Table 1: World Health Organisation classification and grading for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs.

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm²)	Ki-67% index*
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High†	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated‡	Variable‡	Variable‡	Variable‡

LCNEC, Large-cell neuroendocrine carcinoma; MiNEN, Mixed neuroendocrine–non-neuroendocrine neoplasm; NEC, Neuroendocrine carcinoma; NET, Neuroendocrine tumour; SCNEC, Small-cell neuroendocrine carcinoma.
* Mitotic rates are to be expressed as the number of mitoses/2 mm² as determined by counting in 50 fields of 0.2 mm² (i.e. in a total area of 10 mm²); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.
† Poorly differentiated NECs are not formally graded but are considered high-grade by definition.
‡ In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

Table 2: Classification of gastric neuroendocrine tumours according to type and general characteristics in endoscopic appearance, histology and prognostic indicators.

	Type I	Type II	Type III
Proportion, %	70–80	5–10	15-20
Gastric localisation	Corpus, fundus	Corpus, fundus, antrum	Antrum or corpus
Typical endoscopic and morphological characteristics	Often multiple (>60%), small (<1 cm); polypoid or submucosal	Often multiple, small (<1–2 cm); polypoid (sessile)	Single, large size (>2 cm); occasionally ulcerated
Associated disorders	Chronic atrophic gastritis and pernicious anaemia	Gastrinoma/Multiple endocrine neoplasia 1	Sporadic
Histology	Well differentiated (G1-G2)	Well differentiated (G1-G2)	Well differentiated, poorly differentiated or mixed endo/exocrine (G1,2,3 NET or NEC)
Fasting serum gastrin concentrations	↑	↑	Normal
Gastric pH	↑↑	↓	Normal
Risk of metastases (%)	2–5	10–30	50–100
Prognosis	Excellent	Very good	Poor

†Adapted from ENETS Consensus Guidelines[6]

Table 3: Patient and tumour characteristics of all studies describing Type I g-NETs including treatment methods.

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Multiple lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3/ UK)	Location (F/B/A/UK or O)	Endoscopic Surveillance	Endoscopic Treatment	Surgery	Follow up months (Median†, Mean‡)	Death/ Death related to disease	Local Recurrence
Chung et al[47], 2018	142	50:92	60.8‡(SD±14.3)	103(72.5)	14 ‡(SD±18)	89/26/0/27	9/93/17/23	-	X	X	32.4‡(SD±30)	-	-
Vanoli et al[29], 2018	123	45:78	64†	67(54)	4† (IQR:2-8)	111/11/1/0	0/117/6/0	-	79/123	44/123	87† (R:52-146)	0/1	-
Manfredi et al[33], 2017	84	30:54	55.8†(R:9.6-84.8)	30(36)	20†(R:2-45)	43/14/1/26	-	-	64/69§	4/69§	48† (R:0-543.6)	-	-
Campana et al[48], 2016	97#	38:59	59 ‡	97(100)	5†	56/33/0/8	0/97/0/0	13/97	45/97	3/97	30.5† (IQR: 12-64)	0	16
Sagatun et al[27], 2016	26#	7:19	59.5‡	19(73)	6‡	24/2/0/0	-	8/26	-	8/26	34†	6/1	-
Lee et al[49], 2016	17	7:10	57.5 ‡(SD±14.9)	-	9‡(SD±6)	5/12/0/0	-	-	X	X	14†(R:0-147)	-	0
Chen et al[50], 2015	56#	11:45	63.3†(R:37.2-89.4)	31(55)	3 †(R:0.8-25)	47/9/0/0	13/34/9/0	-	16/56	26/56	62.4†(R:2-205)	2/0	-
Sato et al[51], 2014	82	44:38	56†(R:24-79)	38(46)	5 †(R:1-45)	-	11/70/0/1	25/82	41/82	16/82	84†(R:0-240)	0	2
Kim et al[52], 2014	62	37:25	50†(R:40-68)	-	7.6 ‡(SD±4.1)	72/15/0/0¶	9/60/18/0¶		62/62	-	-	-	-
Uygun et al[53], 2014	22	11:11	51†(R:36-67)	17(77)	18 pts:<10, 4 pts:10-20	All lesions Ki 67<12%	-	-	22/22	-	84†(R:24-168)	-	4
Louthan et al[34], 2014	18	4:14	60†(R:41-74)	-	-	16/2/0/0	2/13/3/0	-	17/18	1/18	46.8†(R:6-204)	1/0	-
Thomas et al[54], 2013	111	29:82	58.5‡ (R:29-84, SD±12.7)	53(48)	7.9‡ (R:0.2-100 SD±12.1)	85/9/0/17	-	-	59/111	20/111	76†(R:12-384)	2/0	22
Merola et al[30], 2012	33	9:24	65†(R:23-81)	17(52)	5†(R:2-20)	-	-	-	33/33	-	46†(R:4-123)	0	21
Chen et al[37], 2012	15	5:10	48†(R:35-70)	5(33)	4.5†(R:2-8)	15/0/0/0	3/7/0/5	-	15/15	-	28‡(R:7-44)	0	2
Li et al[36], 2012	11	4:7	48‡(R:35-56)	2(18)	4.5†(R:3-6)	11/0/0/0	2/9/0/0	-	11/11		24†(R:12-40)	0	1
Endo et al[35], 2012	10	6:4	62.5†(R:54-72)	2(20)	5†(R:1-7)	6/4/0/0	-	1/10	2/10	7/10	48.5†(R:3-83)	3/0	-
Kim et al[26], 2010	22#	13:9	52.6†(R:32-71)	2(9)	15.9† (SD±12.8)	-	10/9/3/0	-	13/22	5/22	68‡ (SD±45)	0/1	2
Gladdy et al[55], 2009	65	11:54	58†(R:29-91)	53(82)	ES:5† (SD±1) SR:13†(SD±3)	-	-	-	46/65	19/65	ET 25†(R:1-157) SR:60†(R:1-176)	0	3
Safatle-Ribeiro et al[28], 2007	13#	4:9	62‡(R:45-79)	12(92)	7 pts:<10 5pys: 10-20	9/4/0/0	0/13/0/0	-	6/13	6/13	36†(R:7-107)	5/1	0

					1pt:>20								
Ravizza et al[56], 2007	11	6:5	61‡(R:45-72)	7(64)	all lesions<10	-	0/11/0/0	11/11	-	-	54†(R:9-136)	0	-
Dakin et al[57], 2006	18#	6:12	52‡(SD±11.6)	4(22)	-	-	-	-	-	10/18	-	-	-
Borch et al[58], 2005	51	13:38	66‡(R:39-86)	34(67)	10†(R:4-80)	-	-	3/51	26/51	22/51	65†(R:14-215)	20/1	1
Okada et al[59], 2005	5	1:4	52.6‡(R:42-62, SD± 7.5)	5(100)	5† (R:3-15 SD±4.9)	-	-	-	-	5/5	108.4†(R:4-144)	0	0
G1: Grade 1; G2: Grade 2; G3: Grade 3; F: fundus; B: body; A: antrum; -: data not reported in manuscript; UK: unknown; §: Treatment data available on 69 pts only; ¶: multiple tumours recorded; X: studies where details could not be extracted but did include this treatment option; #: Campana et al: 36 pts treated with somatostatin analogue (SSA); Sagatun et al: 10 pts treated with SSA; Chen et al: 30 patients treated with SSA; Thomas et al: 32 pts treated with SSA; Kim et al: 4 pts not treated due to either advanced disease or other malignancy; Safatle-Ribeiro et al: 1pt not treated due to advanced disease; Dakin et al: 8 pts treated with SSA												

Table 4: Studies describing endoscopic surveillance in Type I g-NETs.

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Multiple lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3/UK)	Location (F/B/A)	Depth of invasion (M/SM/MP/S/UK)	Follow up months (Median†, Mean‡)	Death/ Death related to disease	Recurrence (local/distant metastasis)
Campana et al[48], 2016	13	6:7	62†(IQR:50-65)	2pts<5 lesions, 11pts>5 lesions (100)	4.5†(IQR:3-10)	3/8/0/2	-	-	82†(IQR:34-120)	0	0
Sagatun et al[27], 2016	8	-	57.9‡(SEM:4.2)	8 (100)	5‡	8/0/0/0	-	0/0/0/0/8	34†	1/0	-
Sato et al[51], 2014	25	9:16	54†(R:24-79)	16 (64)	4†(R:2-13)	0/0/0/25	-	4/3/0/0/18	84†(R:0-204)	0	0
Ravizza et al[56], 2007	11	6:5	61‡(R:45-72)	7 (64)	all lesions<10	Ki-67:2.5%†	0/11/0	-	54†(R:9-136)	0	0
G1: grade 1; G2: grade 2; G3: grade 3; F: fundus; B: body; A: antrum; -: data not reported in manuscript; UK: unknown; M: mucosa; SM: submucosa, MP: muscularis propria, S: serosa											

Table 5: Studies describing tumour characteristics and follow up when utilising endoscopic treatment for Type I g-NETs.

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Multiple lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3/UK)	Location (F/B/A/UK or O)	Depth of invasion (M/SM/MP/S)	Endoscopic Treatment (Polypectomy /EMR/ESD)	Complications	Follow up months (Median†, Mean‡)	Death/ Death related to disease	Local Recurrence
Campana et al[48], 2016	45	14:31	61†(IQR:49-71)	45 (100)	5†(IQR:3-8)	28/16/0/1	0/45/0/0	-	45§	-	30.5† (IQR: 12-64)	0	11
Chen et al[50], 2015	30	-	-	-	-	-	-	-	30§	-	-	2/0	-
Kim et al[60], 2014	62	37:25	50†(R:40-68)	-	7.6‡(SD±4.1)	72/15/0/0¥	9/60/18/0¥	-	87(0/48/39)	14¶	-	-	-
Sato et al[51], 2014	41	28:13	57†(R:24-79)	26(63)	5†(R:1-23)	-	-	10/31/0/0	41 (0/30/11)	-	84†(R:0-240)	0	2
Uygun et al[53], 2014	22	11:11	51†(R:36-67)	17(77)	18pts<10 4pts:10-20	All lesions Ki 67%<12%	-	-	22 (0/22/0)	1¶	84†(R:24-168)	-	4
Louthan et al[34], 2014	17	-	-	-	-	-	-	-	17	-	46.8†(R:6-204)	1/0	-
Thomas et al[54], 2013	59	21:38	-	-	-	56/3/0/0	-	0/48/11/0	59	-	90.3†(SD±72.5)	2/0	5
Merola et al[30], 2012	33	9:24	65†(R:23-81)	17(52)	5†(R:2-20)	-	-	-	33 (18/15/0)	-	46†(R:4-123)	0	21
Chen et al[37], 2012	15	5:10	48†(R:35-70)	5(33)	4.5†(R:2-8)	15/0/0/0	3/7/0/5	5/10/0/0	15 (0/0/15)	0	28‡(R:7-44)	0	2
Li et al[36], 2012	11	4:7	48‡(R:35-56)	2(18)	4.5†(R:3-6)	11/0/0/0	2/9/0/0	1/10/0/0	11 (0/0/11)	0	24†(R:12-40)	0	1
Endo et al[35], 2012	2	1:1	65†(R:60-70)	0	3.5†(R:1-6)	2/0/0/0	-	1/1/0/0	2 (0/2/0)	-	43† (R:3-83)	1/0	0
Kim et al[26], 2010	13	-	-	-	-	-	-	-	13	-	-	-	-
Gladdy et al[55], 2009	46	39:7	59†(R:44-91)	42(91)	5†(SD±1)	-	-	0/46/0/0	46	0	25†(R:1-157)	0	0
Safatle-Ribeiro et al[28], 2007	6	1:5	62.5‡(R:48-83)	6(100)	3pts<10 3pts:10-20	4/2/0/0	0/6/0/0	-	6 (0/6/0)	-	30† (R:7-75)	3/0	0
Borch et al[58], 2005	26	-	-	-	-	-	-	-	26	-	-	1	0

G1: grade 1; G2: grade 2; G3: grade 3; -: data not reported in manuscript; UK: unknown; F: fundus; B: body; A:antrum; M: mucosa; SM: submucosa, MP: muscularis propria, S: serosa; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; §: No details regarding type of endoscopic procedure; ¥: multiple tumours described in some patients; ¶: Complications: Kim et al: Bleeding - 13 all managed endoscopically (5 EMR and 8 ESD), Perforation - 1 (ESD); Uygun et al: 1 perforation managed surgically

Table 6: Studies describing tumour characteristics and follow up during the surgical management of Type I g-NETs.

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Multiple lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3)	Location (F/B/A)	Depth of invasion (M/SM/MP/S)	Surgery (Wedge resection/ Antrectomy/ Sub or Total gastrectomy)	Follow up months (Median†, Mean‡)	Death/ Death related to disease	Local Recurrence
Sagatun et al[27], 2016	8	-	61.2‡(SEM:2.8)	8(100)	13.5‡(IQR:10.8)	-	-	-	8(0/0/8)	-	3/1	0
Sato et al[51], 2014	16	7:9	58.5†(R:39-76)	7(44)	6.5†(R:1-45)	-	-	5/10/1/0	16(0/4/12)	138†(R:0-228)	0	0
Thomas et al[54], 2013	20	-	-	-	31.9 ‡(SD±32.4)	-	-	-	20(0/2/18)	-	2/0	4
Endo et al[35], 2012	7	5:2	65†(R:54-72)	2(29)	5†(R:1-7)	3/4/0	-	0/7/0/0	7 (1/1/5)	48.5†(R:32-82)	3/0	0
Gladdy et al[55], 2009	19	4:15	58†(R:29-72)	8(42)	13†(SD±3)	-	-	-	19(7/6/6)	60†(R:1-176)	0	2
Safatle-Ribeiro et al[28], 2007	6	2:4	55‡(R:36-75)	5(92)	3 <10mm, 2:10-20mm, 1>20 mm	4/2/0	0/6/0	-	6(0/0/6)	91†(R:10-107)	1/0	0
Okada et al[59], 2005	5	1:4	52.6‡(SD±7.5, R:42-62)	5(100)	5†(SD±4.9, R:3-15)	-	-	0/5/0/0	5(0/0/5)	108.4† (R:4-144)	0	0

G1: grade 1; G2: grade 2; G3: grade 3; -: data not reported in manuscript; F: fundus; B: body; A: antrum; M: mucosa; SM: submucosa, MP: muscularis propria, S: serosa

Table 7: Patient and tumour characteristics, including patient management and follow up in Type III g-NETs

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Solitary Lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3/UK)	Location (F/B/A/ UK or other)	Depth of invasion (M/SM/MP/S/UK)	Endoscopic Treatment (EMR/ESD)	Surgery (Wedge resection/ Antrectomy/ Sub or Total gastrectomy)	LVI	Lymph node metastasis	Distant metastasis	Follow up months (Median†, Mean‡)	Death / Death related to disease	Recurrence
Vanoli et al[29], 2019	34	24: 10	59†	34(100)	20† (IQR:15-45)	15/10/9/0	0/32/2/0	0/13/21/0/0	8	26	-	11	10	-	-/13	-
Min et al[31], 2018	32	23:9	G1 53.5‡ (R:27-75) G2/3 50.4‡ (R:36-62)	32(100)	G1 8‡ (R:2-25, SD±6) G2/3 15‡ (R:6-35, SD±9)	25/5/2/0	0/25/7/0	0/31/1/0/0	22 (5/17)	10(7/0/3)	5	2	0	ER 59† (R:6-96) WR:70† (R:58-102)	1/0	2
Manfredi et al[33], 2017	52§	33:19	58† (R:19.3-81.4)	49(94)	20† (R:4-160)	10/26/0/16	-	-	15	17(0/0/17)	-	-	-	24† (R:0-177.6)	-	-
Louthan et al[34], 2014	7	5:2	66† (R:47-85)	-	-	0/3/4/0	4/3/0/0	-	0	1 (0/0/1)	-	2	6	46.8† (R:6-204)	7/6	-
Kwon et al[32], 2013	50	28:22	58.6‡ (R:25-85)	48(96)	33pts <10mm 17pts >10mm	-	8/38/4/0	0/49/1/0/0	50 (41/9)	0	3	0	0	46† (R:13-60)	0/0	0
Endo et al[35], 2012	12§	9:3	67† (R:46-79)	12(100)	30†(R:8-98)	3/2/7/0	-	2/4/1/5/0	1 (1/0)	9(0/0/9)	-	2	1	28.5† (R:1-122)	4/3	0
Chen et al[37], 2012	10	3:7	53.5† (R:40-82)	9(90)	15†(R:5-30)	7/3/0/0	1/7/1/1	0/10/0/0/0	10 (0/10)	0	0	0	-	27.5‡ (R:11-52)	-/0	0
Li et al[36], 2012	8	3:5	56‡ (R:35-71)	8(100)	16.5†(R:8-30)	6/2/0/0	1/5/1/1	0/8/0/0/0	8 (0/8)	0	0	-	-	27† (R:14-48)	0	0
Kim et al[26], 2010	16§	10:6	51.1† (R:25-64)	15(94)	11.7†(SD±5.1)	-	8/6/2/0	0/13/1/0/2	7	7(3/0/4)	-	0	0	68‡ (SD±45)	-/0	0
Safatle-Ribeiro et al[28], 2007	8§	4:4	60.5‡ (R:36-78)	8(100)	1pt<10mm 1pt: 10-20mm 6pts>20mm	0/1/7/0	0/5/3/0	-	-	5(0/0/5)	-	-	-	12† (R:6-144)	5/5	-

G1: grade 1; G2: grade 2; G3: grade 3; -: data not reported in manuscript; UK: unknown; F: fundus; B: body; A: antrum; M: mucosa; SM: submucosa, MP: muscularis propria, S: serosa; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; LVI: lymphovascular invasion, **§:** Manfred et al: Complete treatment data reported on only 38 pts, 32 of whom underwent invasive treatment options; Endo et al: 1/12 had palliative treatment on diagnosis; Kim et al: only 14/16 patients underwent invasive treatment options, Safatle-Rubeiro: only 5/8 patients underwent invasive treatment options

Table 8: Patient and tumour characteristics, including patient management in d-NETs, including study limitations.

Study	n	Sex (M:F)	Age (Median†, Mean‡)	Number of solitary lesions n (%)	Size mm (Median†, Mean‡)	Grade (G1/G2/G3/UK)	Location (D1/D2/ampullary/ D3-4/UK)	Endoscopic Surveillance	Endoscopic resection	Surgery	Study Limitations
Mahmud et al[44], 2019	33	21:12	57.7†(R:52.5-67.8)	33(100)	Polypectomy 10† (IQR: 2-4) EMR† 23 (IQR:6-12)	21/3/0/9	30/3/0/0/0	-	33/33	-	Includes functioning d-NETs
Fujimoto et al[61], 2019	10	7:3	55.5‡(R:39-82)	10(100)	All less than <13	10/0/0/0	6/4/0/0/0	-	10/10	-	All lesions <13mm
Khara et al[62], 2019	8	1:8	63†(R:34-79)	8(100)	6† (R:3-9)	8/0/0/0	8/0/0/0/0	-	8/8	-	All lesions <10mm
Massironi et al[40], 2018	108#	69:39	59.5†(R:18-87)	84(78)	12† (R:3-130)	71/21/4/12	44/24/38/0/2	-	16/108	57/108	Includes functioning d-NETs
Park et al[63], 2018	15	6:9	55.4‡(SD±11.6)	15(100)	6.6‡ (SD±-3.9)	-	12/3/0/0/0	-	15/15	-	
Oono et al[64], 2019	12	7:5	74†(R:55-84)	12(100)	9† (R:4-10)	11/1/0/0	11/1/0/0/0	-	12/12	-	All lesions <10mm
Hatta et al[46], 2017	49	35:14	63.9‡(SD±8.5)	43(88)	8‡ (SD±-3.9)	49/0/0/0	46/3/0/0/0	-	35/49	14/49	Size restriction <20mm, includes functional NETs
Weatherall et al[65], 2017	36	17:19	60†(R:46-89)	32(89)	10† (R:4-40)	20/10/0/6	32/4/0/0/0	-	8/36	28/36	Excludes ampullary, functional and high grade d-NETs
Iwasaki et al[66], 2017	6	3:3	59.5†(R:41.75-63.75)	5(83)	23† (IQR:14-40.5)	4/0/1/1	0/6/0/0/0	-	-	6/6	
Margonis et al[43], 2016	146	72:73~	63.2†(R:55-71 ER:63.5†(R:52-70.8) LR 63.4†(R:52-70.8) PD 63† (R:56-70)	-	12†(IQR:7-20) ER:7†(R:4-11) LR 13†(R:8-17) PD 20†(R:9-28)	113/13/3/17	98/0/16/9/23	-	39/146	107/146	Includes functioning d-NETs
Scherer et al[45], 2015	37	-	EBL 67.5‡ (SD±11.7) ER 58.3‡ (SD±14.5)	35(95)	EBL: max 6.7 (SD±2.1) ER: max 6.7 (SD±1.7)	31/0/0/8§	35/4/0/0/0§	-	37/37	-	All lesions <10mm
Shroff et al[67], 2015	30	16:14	59† (R:52.5-67.5) ER:58.7†(R:45-74) SR:58.3†(R:34-75)	30(100)	8.5†(R:4-19) ER:11.4‡(SD±-3.9) SR:7.7‡(SD±3.8)	-	23/7/0/0/0	-	20/30	10/30	All lesions<20mm
Untch et al[41], 2014	75	46:29	60†(R:36-83)	75(100)	17‡ (SD±13)	54/7/10/4	29/37/0/5/4	-	12/75	63/75	Includes ampullary and non-ampullary and functioning d-NETs
Kim et al[60], 2014	38	19:19	63†(R:38-79)	36(95)	All less than 10	38/0/0/0	34/7/0/0/0§	-	38/38	-	All lesions<10mm
Kim et al[38], 2013	14	8:6	61.5†(R:51.25-72)	14(100)	8† (IQR:6.25-10)	10/0/04	13/1/0/0/0	1/14	12/14	1/14	

Min et al[39], 2013	27	16:11	Surv:61† (R:42-81) ER:55.5† (R:32-73)	27(100)	Surv:4† (R:1-9) ER:7†(R:2-10)	-	27/0/0/0/0	13/27	14/27	-	Surveillance offered when no evidence of lymph node or regional metastases
Waisberg et al[68], 2013	20	8:12	66.4‡(R:43-88)	18(90)	11‡ (R:3-60)	-	15/4/0/1/0	-	15/20	5/20	Excludes ampullary and functional d-NETs
Ishido et al[69], 2010	11	8:3	57†	11(10)	9† (R:2-12)	11/0/0/0	9/2/0/0/0	-	3/11	8/11	Excludes ampullary and functional d-NETs
Nikou et al[70], 2010	8	3:5	56.5†(R:47.25-66.25)	8(100)	11† (IQR:9.5-17.25)	-	5/0/3/0/0	-	2/8	6/8	Includes ampullary and non-ampullary d-NETs
Zyromski et al[42], 2002	27	15:12	66†(R:43-86)	26(100)	ER: All less than <10 SR: 14† (IQR:10.5-32.5)	-	16/7/2/2/0	-	11/26	15/26	Includes functioning NETs and 1 patient who had no treatment
Witzigmann et al[19], 2002	12	9:3	55.4‡(R:41-72)	12(100)	10† (IQR:6-18.7)	-	5/2/6/0/0§	-	2/12	9/12	Includes ampullary and non-ampullary d-NETs and 1 patient who had chemotherapy only

G1: grade 1; G2: grade 2; G3: grade 3; -: data not reported in manuscript; UK: unknown; D1: 1st part of duodenum; D2: 2nd part of duodenum; D3-4: 3rd or 4th part of duodenum; §: Multiple tumours; #: Massironi et al: 35 pts underwent treatment with chemotherapy/PRRT/liver directed therapy; ~: 1 patient not accounted for in paper

Table 9: Treatment management and follow up in in d-NETs.

Study	n	Endoscopic Surveillance	Endoscopic Resection (Polypectomy/EMR/ESD/APC/EBL)	Surgery (LR/S-TG/PD-PDDD)	LVI	Lymph node metastasis	Distant metastasis	Endoscopic Complications	Surgical Complications	Follow up-months (Median†, Mean‡)	Deaths/ Deaths related to disease	Recurrence/ Progression
Mahmud et al[44], 2019	33	0	33(10/23/0/0/0)	-	-	0	0	2§	-	24‡(IQR:6.5-48.6)	3/0	Polypectomy:1 EMR:3
Fujimoto et al[61], 2019	10	0	10(0/10/0/0/0)	-	3	-	0	1§ /1¶	-	18.6†(R:6-52)	0/0	0
Khara et al[62], 2019	8	0	8(0/0/0/0/8)	-	-	0	0	0	-	51.5‡(R:25.4-67)	0/0	0
Park et al[63], 2018	15	0	15(0/15/0/0/0)	-	1	0	0	1§ / 1¶	-	26.1†(SD±20.7)	0/0	0
Oono et al[64], 2019	12	0	12(0/12/0/0/0)	-	-	0	0	1§	-	17‡(R:1-89)	0/0	0
Scherer et al[45], 2015	37	0	39*(0/16/0/0/23)	-	0/16	-	0	1§ /2¨	-	EBL:19†(SD±15.2)	0/0	2
Kim et al[60], 2014	38	0	37(0/37/0/0/0)	-	4	0	0	5§	-	17†(R:1-53)	0/0	0
Min et al[39], 2013	27	13	14(0/11/0/3/0)	-	0	0	0	2¶	-	Surv:37‡ (R:10-102) ER:40‡(R:14-129)	0/0	3
Iwasaki et al[66], 2017	6	0	-	6 (3/3/0)	2	3	0	-	-	51.6‡(R:4.8-130)	0/0	1
Massisoni et al[40], 2018	73	0	16(-)	57	-	37	17	-	-	76‡(R:7-211)	20/19	5
Hatta et al[46], 2017	49	0	35(0/29/6/0/0)	14 (5/6/3)	12	6	2	2¶	-	66.5‡(SD±48.2)	8/2	1
Weatherall et al[65], 2017	36	0	8(7/1/0/0/0)	28 (25/0/3)		5/19	0	-	-	25‡(R:9-139)	9/0	1
Margonis et al[43], 2016	146	0	39(-)	107 (57/0/50)	18	50/85	0	2	60	28‡(IQR:6.4-52)	-	26
Shroff et al[67], 2015	30	0	20(0/20/0/0/0)	10 (6/0/4)	1	0	0	1¶ / 1#	1¶ /1¤ /1¥	25.5‡(IQR:15.5-49.25)	0/0	5
Untch et al[41], 2014	75	0	12(0/12/0/0/0)	63(34/0/29)	-	23/44	0	-	-	27‡	-/4	11

Kim et al[38], 2013	14	1	12(0/12/0/0/0)	1(0/1/0)	0	0	0	1[§]	-	12[‡](IQR:3.25-51.5)	-	0
Waisberg et al[68], 2013	20	0	15(0/15/0/0/0)	5 (1/4/0)	0	-	0	-	-	39.6[†](R:3-96)	7/1	0
Ishido et al[69], 2010	11	0	3(0/3/0/0/0)	8 (4/3/1)	4	1	0	0	-	54[‡](R:6-201)	0/0	0
Nikou et al[70], 2010	8	0	2(2/0/0/0/0)	6 (3/0/3)	n-	3	1	0	-	51[†](R:18-115.2)	1/0	0
Zyromski et al[42], 2002	26	0	11(0/11/0/0/0)	15 (10/0/5)	2	2	-	-		ER:50.4[‡](R:18-96) SR:51.6[‡](R:18-270)	4/3	6
Witzigmann et al[19], 2002	11	0	2(0/2/0/0/0)	9 (3/1/5)	-	1	1	-	1[§] / 2[×]	68[†] (R:8-102)	2/0	0

EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; APC: argon plasma coagulation; LR: local resection; S/TG: sub/total gastrectomy; PD/PDDD: pancreaticoduodenectomy/pylorus preserving pancreaticoduodenectomy; Surv: Endoscopic surveillance; ER: endoscopic resection; SR: surgical resection; [®]: multiple tumours; -: data not reported in manuscript; Complications: § Bleeding ¶ perforation ~ abdominal pain # anaesthetic complication ¤ wound infection ¥ leak × pancreatic fistula

Figure 1

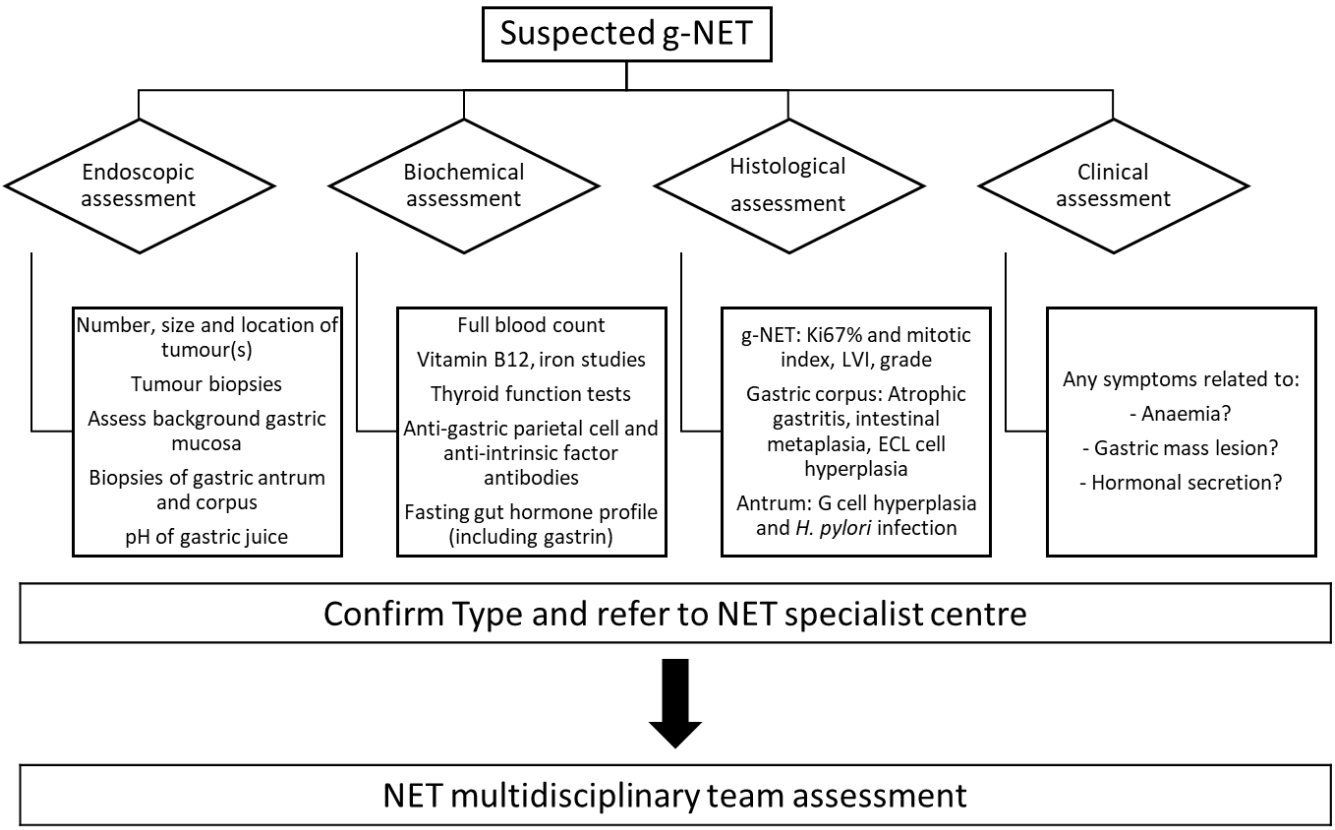

Suspected g-NET
Endoscopic assessment
Biochemical assessment
Histological assessment
Clinical assessment
Number, size and location of tumour(s)
Tumour biopsies
Assess background gastric mucosa
Biopsies of gastric antrum and corpus
pH of gastric juice
Full blood count
Vitamin B12, iron studies
Thyroid function tests
Anti-gastric parietal cell and anti-intrinsic factor antibodies
Fasting gut hormone profile (including gastrin)
g-NET: Ki67% and mitotic index, LVI, grade
Gastric corpus: Atrophic gastritis, intestinal metaplasia, ECL cell hyperplasia
Antrum: G cell hyperplasia and H. pylori infection
Any symptoms related to:
- Anaemia?
- Gastric mass lesion?
- Hormonal secretion?
Confirm Type and refer to NET specialist centre
NET multidisciplinary team assessment

Figure 2

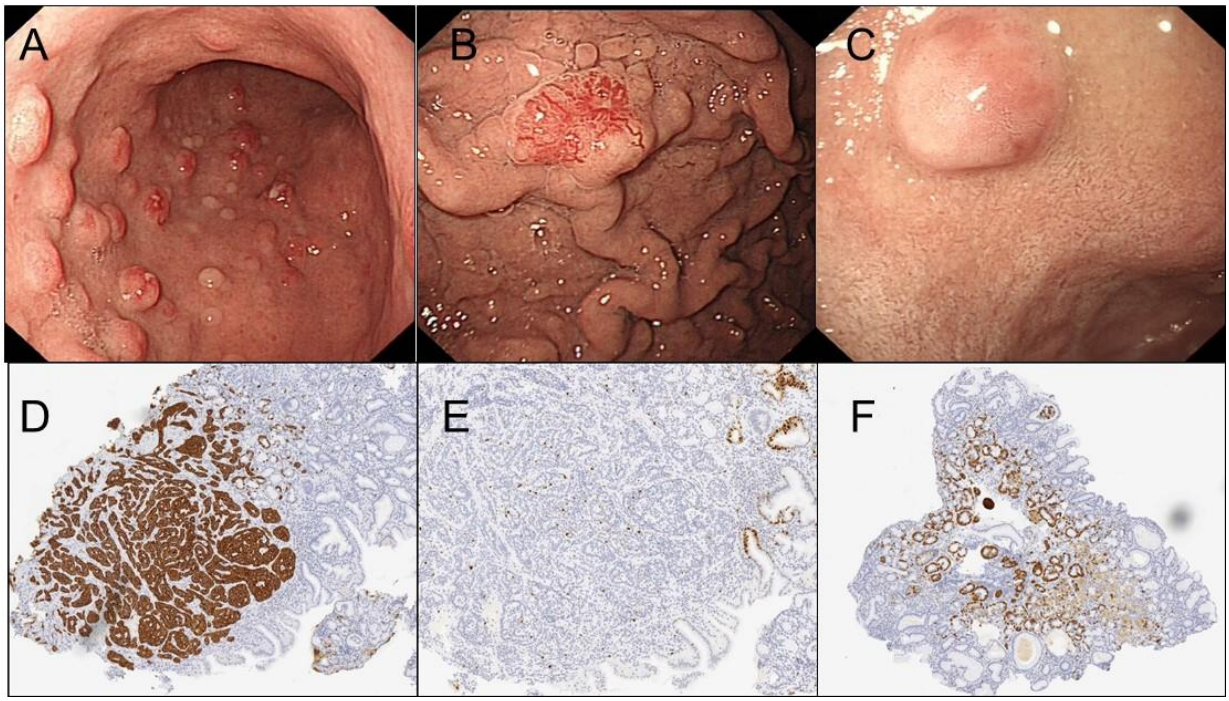


Figure 3

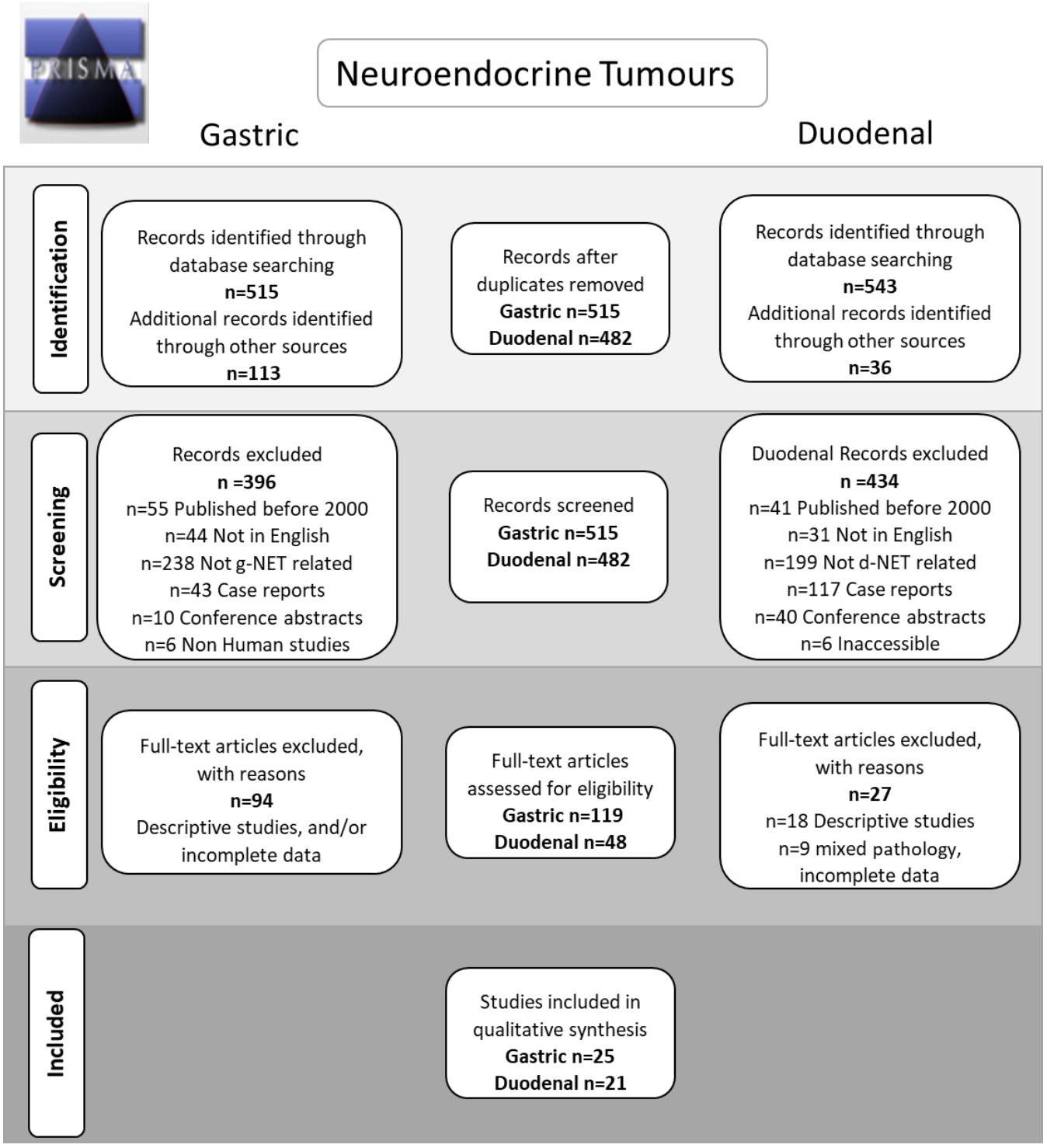
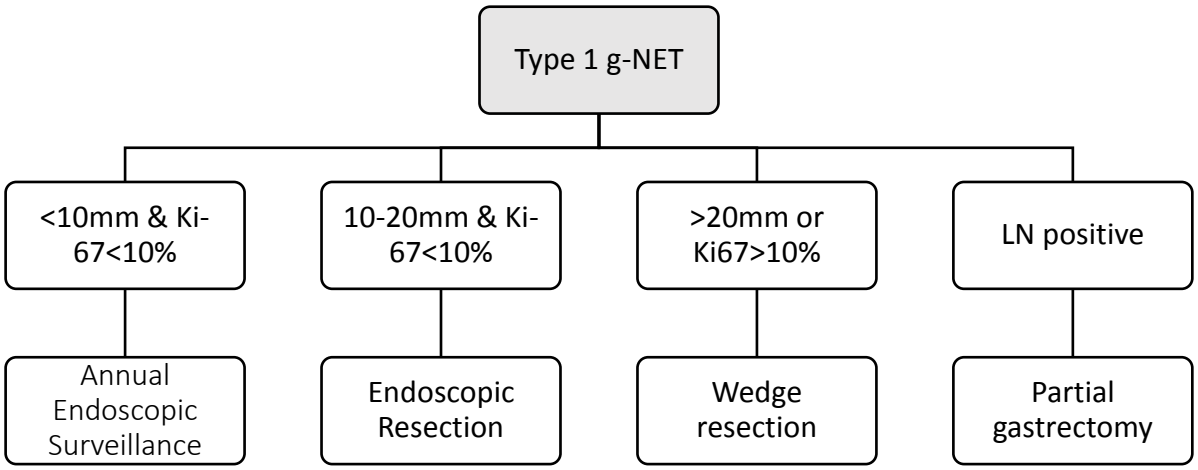

Neuroendocrine Tumours
Gastric
Duodenal
Identification
Records identified through database searching
n=515
Additional records identified through other sources
n=113
Records after duplicates removed
Gastric n=515
Duodenal n=482
Records identified through database searching
n=543
Additional records identified through other sources
n=36
Screening
Records excluded
n =396
n=55 Published before 2000
n=44 Not in English
n=238 Not g-NET related
n=43 Case reports
n=10 Conference abstracts
n=6 Non Human studies
Records screened
Gastric n=515
Duodenal n=482
Duodenal Records excluded
n =434
n=41 Published before 2000
n=31 Not in English
n=199 Not d-NET related
n=117 Case reports
n=40 Conference abstracts
n=6 Inaccessible
Eligibility
Full-text articles excluded, with reasons
n=94
Descriptive studies, and/or incomplete data
Full-text articles assessed for eligibility
Gastric n=119
Duodenal n=48
Full-text articles excluded, with reasons
n=27
n=18 Descriptive studies
n=9 mixed pathology, incomplete data
Included
Studies included in qualitative synthesis
Gastric n=25
Duodenal n=21

Figure 4


Type 1 g-NET
<10mm & Ki-67<10%
10-20mm & Ki-67<10%
>20mm or Ki67>10%
LN positive
Annual Endoscopic Surveillance
Endoscopic Resection
Wedge resection
Partial gastrectomy

SUPPLEMENTARY DATA

Literature Search strategy Gastric Neuroendocrine Tumours

PubMed and Medline databases were interrogated and search results from #23-26 were included.

Table 1

#	Database	Search term	Results
1	PubMed	(neuroendocrine tumo*r).af	172341
2	PubMed	(carcinoid).af	16848
3	PubMed	(NET).af	261783
4	PubMed	(1 OR 2 OR 3)	433287
5	PubMed	(gastric).af	389478
6	PubMed	(stomach).af	271788
7	PubMed	(5 OR 6)	390741
8	PubMed	(4 AND 7)	8378
9	PubMed	(endoscop*).af	239114
10	PubMed	(endoscopy).af	371044
11	PubMed	(endoscopic).af	423523
12	PubMed	(mucosal resection).af	3704
13	PubMed	(EMR).af	7290
14	PubMed	(submucosal dissection).af	3932
15	PubMed	(ESD).af	4233
16	PubMed	(polypectomy).af	4478
17	PubMed	(endoscopic ultrasound).af	21890
18	PubMed	(endoscopic surveillance).af	1272
19	PubMed	(gastrectomy).af	43076
20	PubMed	(antrectomy).af	948
21	PubMed	(9 OR 10 OR 11)	432584
22	PubMed	(12 OR 13 OR 14 OR 15 OR 16)	18137
23	PubMed	(8 AND 21 AND 22)	211
24	PubMed	(8 AND 17)	180
25	PubMed	(8 AND 18)	33
26	PubMed	(8 AND 19 AND 20)	29

Literature Search strategy Duodenal Neuroendocrine Tumours

PubMed and Medline databases were interrogated and search results from #24-27 included.

Table 2

#	Database	Search term	Results
1	PubMed	(neuroendocrine tumo*r).ti,ab	173041
2	PubMed	(carcinoid).ti,ab	16885
3	PubMed	(NET).ti,ab	263062
4	PubMed	(1 OR 2 OR 3)	435241
5	PubMed	(duoden*).ti,ab	87941
6	PubMed	(duodenum).ti,ab	64626
7	PubMed	(duodenal).ti,ab	115230
8	PubMed	(5 OR 6 OR 7)	120278
9	PubMed	(4 AND 8)	3138
10	PubMed	(endoscop*).ti,ab	240305
11	PubMed	(endoscopy).ti,ab	372658
12	PubMed	(endoscopic).ti,ab	425423
13	PubMed	(mucosal resection).ti,ab	3763
14	PubMed	(EMR).ti,ab	7390
15	PubMed	(submucosal dissection).ti,ab	3976
16	PubMed	(ESD).ti,ab	4266
17	PubMed	(polypectomy).ti,ab	4502
18	PubMed	(endoscopic ultrasound).ti,ab	22023
19	PubMed	(endoscopic surveillance).ti,ab	1279
20	PubMed	(duodenectomy).ti,ab	648
21	PubMed	(surgery).ti,ab	4530072
22	PubMed	(10 OR 11 OR 12)	434521
23	PubMed	(13 OR 14 OR 15 OR 16 OR 17)	18320
24	PubMed	(9 AND 22 AND 23)	101
25	PubMed	(9 AND 18)	160
26	PubMed	(9 AND 19)	4
27	PubMed	(9 AND 20 AND 21)	39