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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 NETs.

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, nonfunctional, 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, nonfunctional, 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.

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1 | 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.

2 | 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 and multiple neuroendocrine neoplasia type I. 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 NET 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.

2.1 | 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.

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 mm^2)[a]	Ki-67% index[a]
NET, G1	Well differentiated	Low	<2	<3%
NET, G2	Well differentiated	Intermediate	2-20	3%-20%
NET, G3	Well differentiated	High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High[b]	>20	>20%
NEC, large-cell type (LCNEC)	Poorly differentiated	High[b]	>20	>20%
MiNEN	Well or poorly differentiated[c]	Variable[c]	Variable[c]	Variable[c]

Abbreviations: LCNEC, large-cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-nonneuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCNEC, small-cell neuroendocrine carcinoma.

[a]Mitotic rates are to be expressed as the number of mitoses/2 mm^2 as determined by counting in 50 fields of 0.2 mm^2 (ie in a total area of 10 mm^2); 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.

[b]Poorly differentiated NECs are not formally graded but are considered high grade by definition.

[c]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. Adapted from ENETS Consensus Guidelines.[6]

	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 to 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

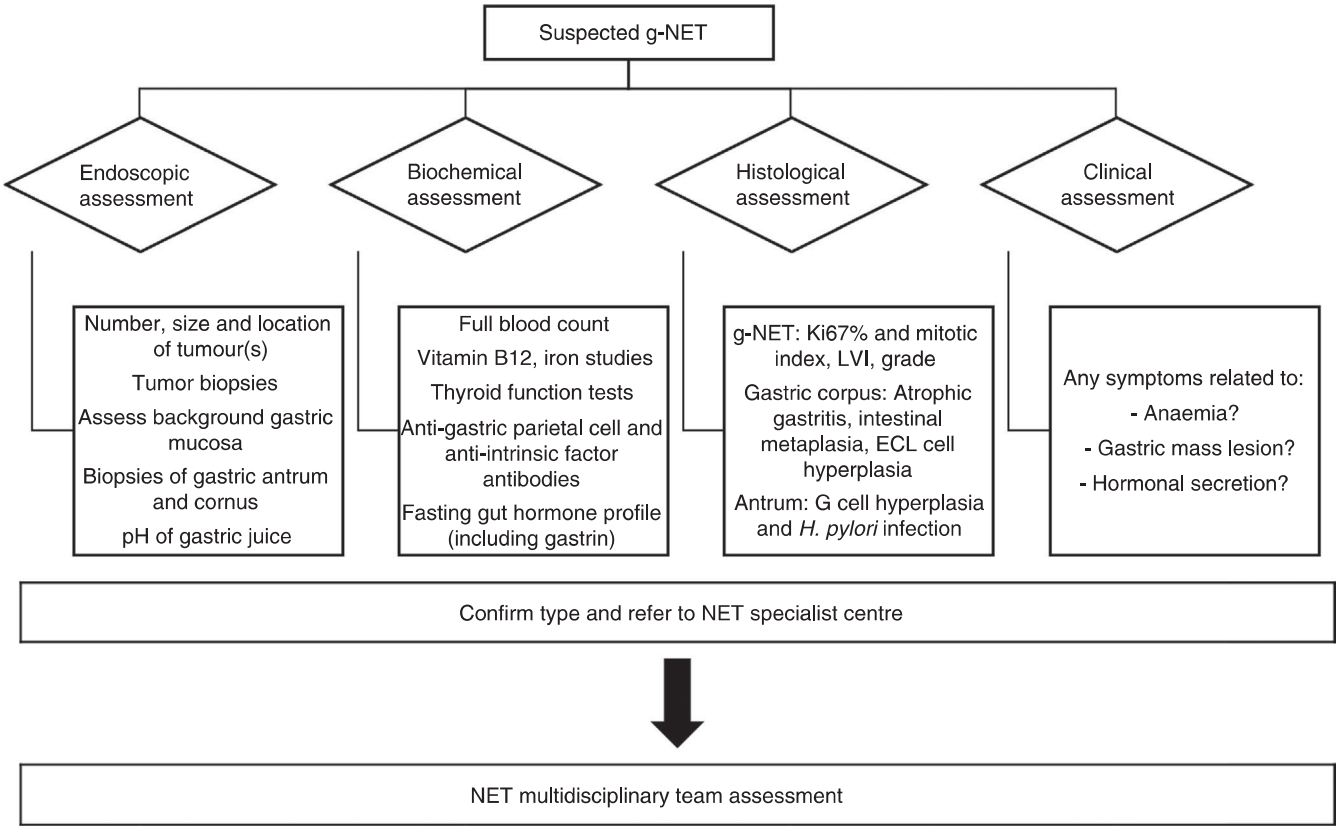

FIGURE 1 Diagnostic algorithm for suspected g-NET. Patient assessment should include endoscopic, biochemical, histological as well as clinical assessment. All cases should be referred to specialist NET centre and discussed at a Multidisciplinary Team meeting for further management

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 nonfunctional or nonsecretory 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 >10 mm 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 is typical within the tumour and diffuse linear and/or micronodular ECL-cell hyperplasia may also be present in the unaffected background corpus mucosa (Figure 2D,F).[12-15] Determination of the Ki-67 proliferation index establishes the tumour grade (Figure 2E).[15,16]

2.2 | 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 <10 mm in diameter. Endoscopic resection is suggested for lesions >10 mm 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.

3 | DUODENAL NEUROENDOCRINE TUMOURS

Duodenal neuroendocrine tumours (d-NETs) are heterogeneous. They can be classified into functional and nonfunctional tumours based on clinical presentation and hormone secretion and include duodenal gastrinomas; duodenal somatostatinomas; duodenal gangliocytic paragangliomas; poorly differentiated neuroendocrine carcinomas and nonfunctioning d-NETs (which do not give rise to a clinical hormonal syndrome).[17] Nonfunctioning 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

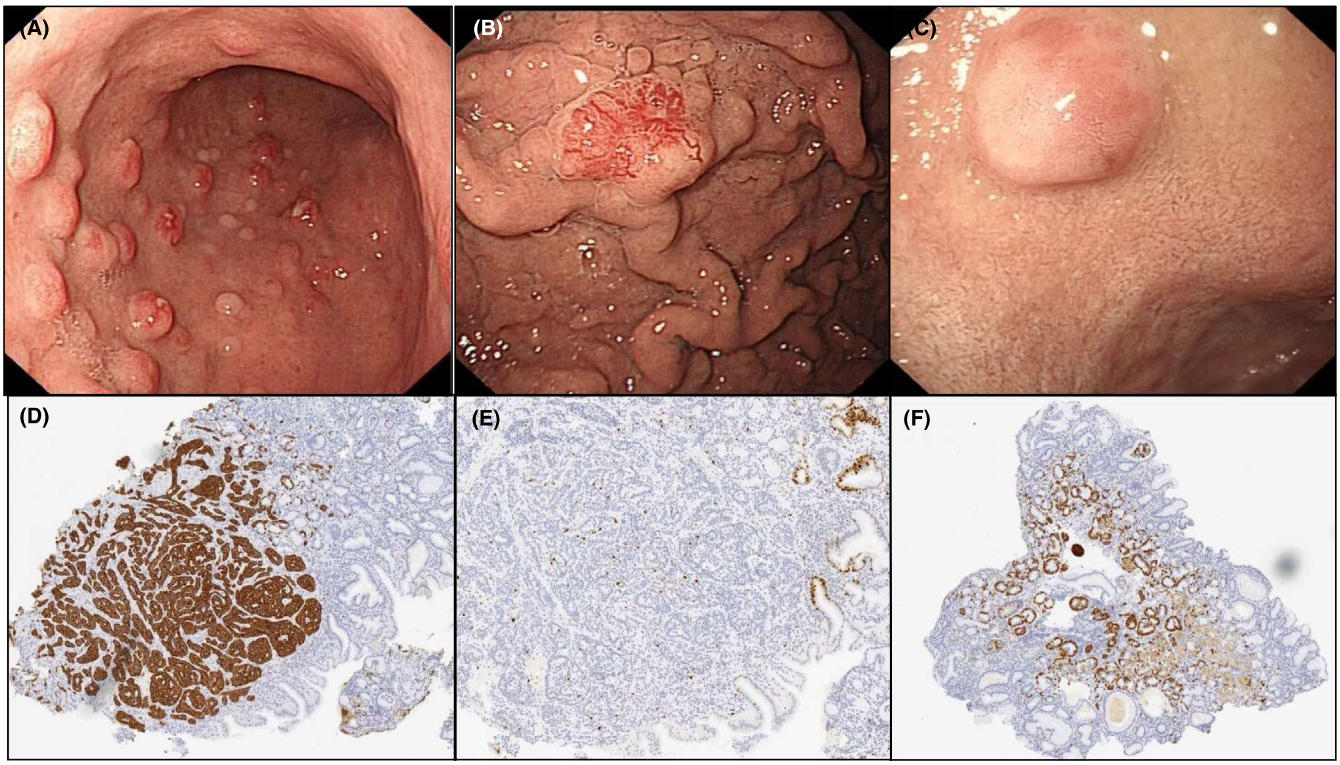

FIGURE 2 Endoscopic images of (A) Multiple type I g-NETs, (B) Solitary type III g-NET and (C) Solitary d-NET. Histological images demonstrating (D) Synaptophysin immunohistochemistry of type I g-NET, (E) Ki67 immunohistochemistry of same grade 1 type I g-NET and (F) Synaptophysin immunohistochemistry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

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.

3.1 | 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 >10 mm in diameter, high grade and ampullary lesions.

3.2 | 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, nonfunctional 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.

4 | 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, nonfunctional 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.

5 | 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 Tables S1 and S2 for Pubmed MESH terms) (Figure 3).

5.1 | Inclusion and exclusion criteria

All relevant studies from 2000 to 2019 inclusive that were published in English were considered. Exclusion criteria were nonhuman 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.

6 | RESULTS

6.1 | Type I gastric NETs

Twenty-three nonrandomised 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 fifth or sixth 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 <10 mm) 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 (60 mm),[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

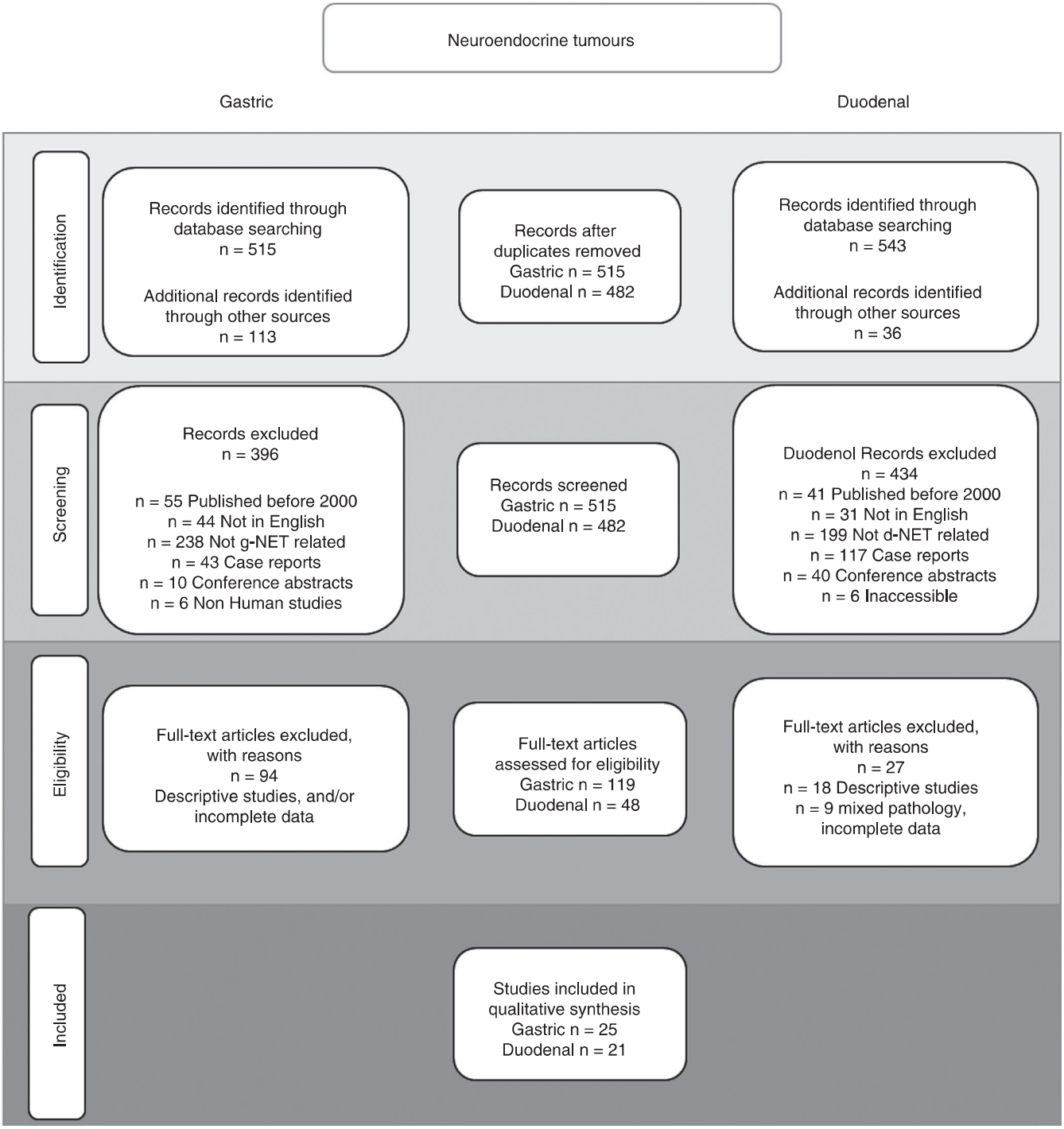

FIGURE 3 PRISMA diagram depicting selection criteria for inclusion of articles for gastric and duodenal NETs

resection was low but significant (74/544 patients [13.6%] in those studies that reported recurrence).

6.2 | 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 3 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 <10 mm 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.

TABLE 3 Patient and tumour characteristics of all studies describing type I g-NETs including treatment methods

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

(Continues)

TABLE 3 (Continued)

Study	n	Sex (M:F)	Age (Median[a], Mean[b])	Multiple lesions, n (%)	Size mm (median[a], Mean[b])	Grade (G1/G2/G3/UK)	Location (F/B/A/UK or O)	Endoscopic surveillance	Endoscopic treatment	Surgery	Follow-up months (Median[a], Mean[b])	Death/death related to disease	Local recurrence
Ravizza et al[56]	11	6:5	61[b] (R:45-72)	7 (64)	All lesions < 10	—	0/11/0/0	11/11	—	—	54[a] (R: 9-136)	0	—
Dakin et al[57]	18[d]	6:12	52[b] (SD ± 11.6)	4(22)	—	—	—	—	—	10/18	—	—	—
Borch et al[58]	51	13:38	66[b] (R:39-86)	34(67)	10[a] (R :4-80)	—	—	3/51	26/51	22/51	65[a] (R:14-215)	20/1	1
Okada et al[59]	5	1:4	52.6[b] (R:42-62, SD ± 7.5)	5 (100)	5[a] (R:3-15 SD ± 4.9)	—	—	—	—	5/5	108.4[a] (R :4-144)	0	0

Note: G1: Grade 1; G2: Grade 2; G3: Grade 3; F: fundus; B: body; A: antrum; —: data not reported in manuscript; UK: unknown.

[c]Treatment data available on 69 pts only.

[d]Multiple tumours recorded; X: studies where details could not be extracted but did include this treatment option.

[e]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[a], Mean[b])	Multiple lesions n (%)	Size mm (Median[a], Mean[b])	Grade (G1/G2/G3/UK)	Location (F/B/A)	Depth of invasion (M/SM/MP/S/UK)	Follow-up months (Median[a], Mean[b])	Death/death related to disease	Recurrence (local/distant metastasis)
Campana et al[48]	13	6:7	62[a] (IQR:50-65)	2pts < 5 lesions, 11pts > 5 lesions (100)	4.5[a] (IQR: 3-10)	3/8/0/2	—	—	82[a] (IQR: 34-120)	0	0
Sagatun et al[27]	8	—	57.9[b] (SEM:4.2)	8 (100)	5[b]	8/0/0/0	—	0/0/0/0/8	34[a]	1/0	-
Sato et al[51]	25	9:16	54[a] (R: 24-79)	16 (64)	4[a] (R: 2-13)	0/0/0/25	—	4/3/0/0/18	84[a] (R:0-204)	0	0
Ravizza et al[56]	11	6:5	61[b] (R: 45-72)	7 (64)	All lesions < 10	Ki-67:2.5%[b]	0/11/0	—	54[b] (R: 9-136)	0	0

Note: 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[a], Mean[b])	Multiple leslies, n (%)	Size mm (Median[a], Mean[b])	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[a], Mean[b])	Death/death related to disease	Local recurrence
Campana et al,[48] 2016	45	14:31	61[a] (IQR: 49-71)	45 (100)	5[a] (IQR:3-8)	28/16/0/1	0/45/0/0	–	45[b]	–	30.5[a] (IQR: 12-64)	0	11
Chen et al,[50] 2015	30	–	–	–	–	–	–	–	30[b]	–	–	2/0	–
Kim et al,[60] 2014	62	37:25	50[a] (R:40-68)	–	7.6[c] (SD ± 4.1)	72/15/0/0[d]	9/60/18/0[d]	–	87(0/48/39)	14[e]	–	–	–
Sato et al,[51] 2014	41	28:13	57[a] (R: 24-79)	26 (63)	5[a] (R :1-23)	–	–	10/31/0/0	41 (0/30/11)	–	84[a] (R :0-240)	0	2
Uygun et al,[53] 2014	22	11:11	51[a] (R: 36-67)	17 (77)	18pts < 10 4pts:10-20	All lesions Ki 67%<12%	–	–	22 (0/22/0)	1[e]	84[a] (R :24-168)	–	4
Louthan et al,[34] 2014	17	–	–	–	–	–	–	–	17	–	46.8[a] (R: 6-204)	1/0	–
Thomas et al,[54] 2013	59	21:38	–	–	–	56/3/0/0	–	0/48/11/0	59	–	90.3[a] (SD ± 72.5)	2/0	5
Merola et al,[30] 2012	33	9:24	65[a] (R :23-81)	17 (52)	5[a] (R: 2-20)	–	–	–	33 (18/15/0)	–	46[a] (R: 4-123)	0	21
Chen et al,[37] 2012	15	5:10	48[a] (R: 35-70)	5 (33)	4.5[a] (R:2-8)	15/0/0/0	3/7/0/5	5/10/0/0	15 (0/0/15)	0	28[b] (R :7-44)	0	2
Li et al,[36] 2012	11	4:7	48[b] (R: 35-56)	2 (18)	4.5[a] (R: 3-6)	11/0/0/0	2/9/0/0	1/10/0/0	11 (0/0/11)	0	24[a] (R:12-40)	0	1
Endo et al,[35] 2012	2	1:1	65[a] (R: 60-70)	0	3.5[a] (R:1-6)	2/0/0/0	–	1/1/0/0	2 (0/2/0)	–	43[a] (R:3-83)	1/0	0
Kim et al[26]	13	–	–	–	–	–	–	–	13	–	–	–	–

(Continues)

TABLE 5 (Continued)

Study	n	Sex (M: F)	Age (Median[a], Mean[b])	Multiple leslies, n (%)	Size mm (Median[a], Mean[b])	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[a], Mean[b])	Death/ death related to disease	Local recurrence
Gladdy et al,[55]	46	39:7	59[a] (R: 44-91)	42 (91)	5[a] (SD ± 1)	–	–	0/46/0/0	46	0	25[a] (R:1-157)	0	0
Safatle-Ribeiro et al[28]	6	1:5	62.5[b] (R:48-83)	6 (100)	3pts < 10 3pts:10-20	4/2/0/0	0/6/0/0	–	6 (0/6/0)	–	30[a] (R:7-75)	3/0	0
Borch et al[58]	26	–	–	–	–	–	–	–	26	–	–	1	0

Note: 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.

[c]No details regarding type of endoscopic procedure.

[d]Multiple tumours described in some patients

[e]Complications: Kim et al: Bleeding—13 all managed endoscopically (5 EMR and 8 ESD), Perforation—1 (ESD); Uygun et al: 1 perforation managed surgically.

6.3 | 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 >10 mm 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 EMR, but 76 patients underwent 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 <5 mm 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% to 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.

6.4 | 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 45 mm being recorded in one patient. However, this series also included several patients who had type I g-NETs that measured <10 mm in diameter (including a few patients who even had 1–2 mm 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

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[a], Mean[b])	Multiple leslies, n (%)	Size mm (Median[a], Mean[b])	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[a], Mean[b])	Death/death related to disease	Local recurrence
Sagatun et al[27]	8	—	61.2[b] (SEM:2.8)	8 (100)	13.5[b] (IQR: 10.8)	—	—	—	8(0/0/8)	—	3/1	0
Sato et al[51]	16	7:9	58.5[a] (R: 39-76)	7 (44)	6.5[a] (R:1-45)	—	—	5/10/1/0	16(0/4/12)	138[a] (R:0-228)	0	0
Thomas et al[54]	20	—	—	—	31.9[b] (SD ± 32.4)	—	—	—	20(0/2/18)	—	2/0	4
Endo et al[35]	7	5:2	65[a] (R: 54-72)	2 (29)	5[a] (R: 1-7)	3/4/0	—	0/7/0/0	7 (1/1/5)	48.5[a] (R:32-82)	3/0	0
Gladdy et al[55]	19	4:15	58[a] (R:29-72)	8 (42)	13[a] (SD ± 3)	—	—	—	19 (7/6/6)	60[a] (R: 1-176)	0	2
Safatle-Ribeiro et al[28]	6	2:4	55[a] (R: 36-75)	5 (92)	3 < 10 mm, 2:10-20 mm, 1> 20 mm	4/2/0	0/6/0	—	6 (0/0/6)	91[a] (R: 10-107)	1/0	0
Okada et al[59]	5	1:4	52.6[b] (SD ± 7.5, R: 42-62)	5 (100)	5[a] (SD ± 4.9, R: 3-15)	—	—	0/5/0/0	5(0/0/5)	108.4[a] (R: 4-144)	0	0

Note: 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[a], Mean[b])	Solitary lesions, n (%)	Size mm (Median[a], Mean[b])	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[a], Mean[b])	Death/Death related to disease	Recurrence
Vanoli et al,[29] 2019	34	24:10	59[a]	34 (100)	20[a] (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	: 9	G1 53.5[b] (R:27-75) G2/3 50.4[b] (R:36-62)	32 (100)	G1 8[b] (R:2-25, SD ± 6) G2/3 15[b] (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[a] (R:6-96) WR:70[a] (R:58-102)	1/0	2
Manfredi et al,[33] 2017	52[§]	33:19	58[a] (R:19.3-81.4)	49(94)	20[a] (R: 4-160)	10/26/0/16	—	—	15	17(0/0/17)	—	—	—	24[a] (R: 0-177.6)	—	—
Louthan et al,[34] 2014	7	5:2	66[a] (R:47-85)	—	—	0/3/4/0	4/3/0/0	—	0	1 (0/0/1)	—	2	6	46.8[a] (R: 6-204)	7/6	—
Kwon et al,[32] 2013	50	28:22	58.6[b] (R:25-85)	48 (96)	33pts < 10 mm 17 pts > 10 mm	—	8/38/4/0	0/49/1/0/0	50 (41/9)	0	3	0	0	46[a] (R: 13-60)	0/0	0
Endo et al,[35] 2012	12[c]	9:3	67[a] (R:46-79)	12 (100)	30[a] (R: 8-98)	3/2/7/0	—	2/4/1/5/0	1 (1/0)	9(0/0/9)	—	2	1	28.5[a] (R: 1-122)	4/3	0
Chen et al,[37] 2012	10	3:7	53.5[a] (R:40-82)	9 (90)	15[a] (R: 5-30)	7/3/0/0	1/7/1/1	0/10/0/0/0	10 (0/10)	0	0	0	—	27.5[b] (R:11-52)	—/0	0
Li et al,[36] 2012	8	3:5	56[b] (R:35-71)	8 (100)	16.5[a] (R: 8-30)	6/2/0/0	1/5/1/1	0/8/0/0/0	8 (0/8)	0	0	—	—	27[a] (R: 14-48)	0	0
Kim et al,[26] 2010	16[c]	10:6	51.1[a] (R:25-64)	15 (94)	11.7[a] (SD ± 5.1)	—	8/6/2/0	0/13/1/0/2	7	7(3/0/4)	—	0	0	68[b] (SD ± 45)	—/0	0
Safatle-Ribeiro et al,[28] 2007	8[c]	4:4	60.5[b] (R:36-78)	8 (100)	1pt < 10 mm 1 pt: 10-20 mm 6pts > 20 mm	0/1/7/0	0/5/3/0	—	—	5(0/0/5)	—	—	—	12[a] (R:6-144)	5/5	—

Note: 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.

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

(Continues)

TABLE 8 (Continued)

Study	n	Sex (M:F)	Age (Median[a], Mean[b])	Number of solitary lesion, n (%)	Size mm (Median[a], Mean[b])	Grade (G1/G2/G3/UK)	Location (D1/D2/ampullary/D3-4/UK)	Endoscopic surveillance	Endoscopic resection	Surgery	Study limitations
Untch et al[41]	75	46:29	60[a] (R:36-83)	75 (100)	17[b] (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]	38	19:19	63[a] (R:38-79)	36 (95)	All less than 10	38/0/0/0	34/7/0/0/0[c]	—	38/38	-	All lesions <10 mm
Kim et al[38]	14	8:6	61.5[a] (R:51.25-72)	14 (100)	8[a] (IQR:6.25-10)	10/0/04	13/1/0/0/0	1/14	12/14	1/14	
Min et al[39]	27	16:11	Surv:61[a] (R:42-81) ER:55.5[a] (R:32-73)	27 (100)	Surv:4[a] (R:1-9) ER:7[a] (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]	20	8:12	66.4[b] (R:43-88)	18(90)	11[b] (R:3-60)	—	15/4/0/1/0	—	15/20	5/20	Excludes ampullary and functional d-NETs
Ishido et al[69]	11	8:3	57[a]	11 (10)	9[a] (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]	8	3:5	56.5[a] (R:47.25-66.25)	8(100)	11[a] (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]	27	15:12	66[a] (R: 43-86)	26 (100)	ER: All less than < 10 SR: 14[a] (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]	12	9:3	55.4[b] (R: 41-72)	12 (100)	10[a] (IQR: 6-18.7)	—	5/2/6/0/0[c]	—	2/12	9/12	Includes ampullary and non-ampullary d-NETs and one patient who had chemotherapy only

Note: G1: grade 1; G2: grade 2; G3: grade 3; -: data not reported in manuscript; UK: unknown; D1: 1st part of duodenum; D2: second part of duodenum; D3-4: third or fourth part of duodenum.

[c]Multiple tumours.

[d]Massironi et al: 35 pts underwent treatment with [c]hemotherapy/PRRT/liver directed therapy.

[e]One 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[a], Mean[b])	Deaths/deaths related to disease	Recurrence/progression
Mahmud et al[44]	33	0	33 (10/23/0/0/0)	—	—	0	0	2[c]	—	24[b] (IQR:6.5-48.6)	3/0	Polypectomy:1 EMR:3
Fujimoto et al[61]	10	0	10 (0/10/0/0/0)	—	3	—	0	1[c]/1[d]	—	18.6[a] (R: 6-52)	0/0	0
Khara et al[62]	8	0	8 (0/0/0/0/8)	—	—	0	0	0	—	51.5[b] (R:25.4-67)	0/0	0
Park et al[63]	15	0	15 (0/15/0/0/0)	—	1	0	0	1[c]/1[d]	—	26.1[a] (SD ± 20.7)	0/0	0
Oono et al[64]	12	0	12(0/12/0/0/0)	—	—	0	0	1[c]	—	17[b] (R:1-89)	0/0	0
Scherer et al[45]	37	0	39®(0/16/0/0/23)	—	0/16	—	0	1[c]/2[e]	—	EBL:19[a] (SD ± 15.2)	0/0	2
Kim et al[60]	38	0	37(0/37/0/0/0)	—	4	0	0	5[c]	—	17[a] (R:1-53)	0/0	0
Min et al[39]	27	13	14(0/11/0/3/0)	—	0	0	0	2[d]	—	Surv:37[b] (R:10-102) ER:40[b] (R:14-129)	0/0	3
Iwasaki et al[66]	6	0	—	6 (3/3/0)	2	3	0	—	—	51.6[b] (R:4.8-130)	0/0	1
Massisoni et al[40]	73	0	16 (–)	57	—	37	17	—	—	76[b] (R:7-211)	20/19	5
Hatta et al[46]	49	0	35 (0/29/6/0/0)	14 (5/6/3)	12	6	2	2[d]	—	66.5[b] (SD ± 48.2)	8/2	1
Weatherall et al[65]	36	0	8 (7/1/0/0/0)	28 (25/0/3)		5/19	0	—	—	25[b] (R:9-139)	9/0	1
Margonis et al[43]	146	0	39 (–)	107 (57/0/50)	18	50/85	0	2	60	28[b] (IQR:6.4-52)	-	26
Shroff et al[67]	30	0	20 (0/20/0/0/0)	10 (6/0/4)	1	0	0	1[c]/1[f]	1[d]/1[g]/1[h]	25.5[b] (IQR:15.5-49.25)	0/0	5
Untch et al[41]	75	0	12 (0/12/0/0/0)	63(34/0/29)	—	23/44	0	—	—	27[b]	–/4	11
Kim et al[38]	14	1	12 (0/12/0/0/0)	1(0/1/0)	0	0	0	1[c]	—	12[b] (IQR:3.25-51.5)	—	0
Waisberg et al[68]	20	0	15 (0/15/0/0/0)	5 (1/4/0)	0	—	0	—	—	39.6[a] (R:3-96)	7/1	0
Ishido et al[69]	11	0	3(0/3/0/0/0)	8 (4/3/1)	4	1	0	0	—	54[b] (R:6-201)	0/0	0
Nikou et al[70]	8	0	2(2/0/0/0/0)	6 (3/0/3)	n–	3	1	0	—	51[a] (R:18-115.2)	1/0	0
Zyromski et al[42]	26	0	11(0/11/0/0/0)	15 (10/0/5)	2	2	—	—		ER:50.4[b] (R:18-96) SR:51.6[b] (R:18-270)	4/3	6
Witzigmann et al[19]	11	0	2(0/2/0/0/0)	9 (3/1/5)	—	1	1	—	1[c]/2[i]	68[a] (R:8-102)	2/0	0

Note: 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: [c]Bleeding, [d]perforation, [e]abdominal pain, [f]anaesthetic complication, [g]wound infection, [h]leak, [i]pancreatic fistula.

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 to 138 months.

6.5 | Type III gastric NETs

Ten nonrandomised 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. Two hundred and twenty-nine patients were included, of whom 63% were male. Most tumours were diagnosed in the sixth 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. Eighty-seven per cent 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]

6.6 | Duodenal NETs

Twenty-one nonrandomised 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 (eg 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 nonfunctional 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 10 mm, although a wide range of diameters from 1 mm to 130 mm 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 third or fourth 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 (<10 mm 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 to 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.

Three hundred and eighty-two 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 <15 mm 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]

7 | DISCUSSION

Our review highlights a current lack of high-quality evidence to inform the optimal management of patients who have localised, low-grade, nonfunctional gastric and duodenal NETs. All the studies that we identified during this systematic literature review were retrospective and nonrandomised 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.

7.1 | 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 <10 mm 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

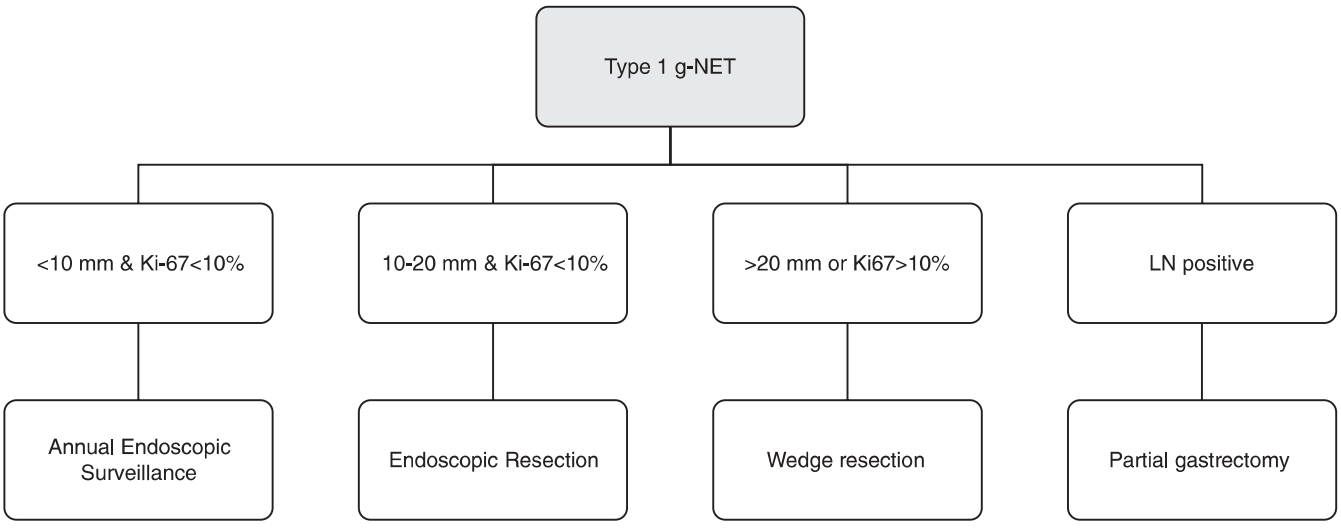

FIGURE 4 Proposed management algorithm for patients with localised type I g-NETs

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.

7.2 | 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 (<20 mm), 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.

7.3 | d-NETs

The d-NETs identified in this systematic review were heterogeneous. For example, the largest series reported by Massironi[40] and Margonis et al[43] included functioning and ampullary tumours as well as nonfunctional 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, nonfunctional 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.

8 | 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, nonfunctional g-NETs and d-NETs. Such studies will hopefully in future provide data that will permit personalisation of management approaches in this patient group.

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AUTHORSHIP

Guarantor of the article: Prof DM Pritchard.

Author contributions: 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.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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