Original article

Clinicopathological features and outcome of type 3 gastric neuroendocrine tumours

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Background: With the widespread use of endoscopy, small and low-grade type 3 gastric neuroendocrine tumours (NETs) are increasingly being detected. The clinicopathological features, biological behaviour and appropriate treatment strategy for these NETs remain unclear.

Methods: Patients with biopsy-proven gastric NET and a normal fasting serum gastrin level were identified from a prospectively maintained database. Clinicopathological features and long-term outcome of local resection for type 3 NETs were reviewed retrospectively and compared according to tumour grade.

Results: Some 32 patients with type 3 gastric NETs were included (25 patients with NET grade G1, 5 with G2 and 2 with G3). Pathological tumour size was 2·0 cm or less in 30 patients. All tumours were well differentiated, even G3 lesions, and all tumours but one were confined to the submucosal layer. G1 NETs were significantly smaller and had a significantly lower lymphovascular invasion rate than G2 and G3 NETs. Twenty-two patients with a G1 NET without lymphovascular invasion were treated with wedge or endoscopic resection. After a median follow-up of 59 (range 6–102) months, no patient with a G1 NET of 1·5 cm or smaller developed recurrence and one patient with a G1 NET larger than 1·5 cm had recurrence in a perigastric lymph node. Among seven patients with a G2 or G3 NET, two had lymph node metastasis and one had liver metastases.

Conclusion: Low-grade type 3 gastric NET has non-aggressive features and a favourable prognosis. Wedge or endoscopic resection may be a valid option for patients with type 3 gastric G1 NET no larger than 1·5 cm without lymphovascular invasion.

Paper accepted 3 May 2018

Published online 12 June 2018 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10901

Introduction

Gastric neuroendocrine tumours (NETs) originating from the histamine-secreting enterochromaffin-like cells are increasingly being identified with the widespread use of endoscopy. The Surveillance, Epidemiology, and End Results (SEER) database in the USA and National Cancer Registry in England have shown a steady increase in the incidence of gastric NETs[1,2]. In the USA, gastric NETs accounted for 8·7 per cent of all gastrointestinal NETs between 1992 and 1999[2]. Gastric NETs are classified into three distinct subgroups, and as either gastrin-dependent or gastrin-independent. Type 1 and type 2 gastric NETs are related to the presence of hypergastrinaemia, whereas type 3 NETs develop independently of gastrin[3–7].

Type 3 gastric NETs occur sporadically without evidence of a predisposing condition, such as atrophic body gastritis or a gastrinoma that leads to hypergastrinaemia. In Western studies, type 3 gastric NETs have been large (over 2 cm) and high-grade tumours. They frequently showed aggressive features including lymphovascular invasion and tumour infiltration beyond the submucosal layer[3,4]. As they have high metastatic potential at presentation, the European Neuroendocrine Tumour Society (ENETS) consensus guidelines[4] recommend partial or total gastrectomy with lymph node dissection for all type 3 tumours, regardless of tumour size or depth of invasion. However, recent National Comprehensive Cancer Network (NCCN) guidelines and several authorities have proposed that small and low-grade type 3 gastric NETs might be treated by surgical wedge or endoscopic

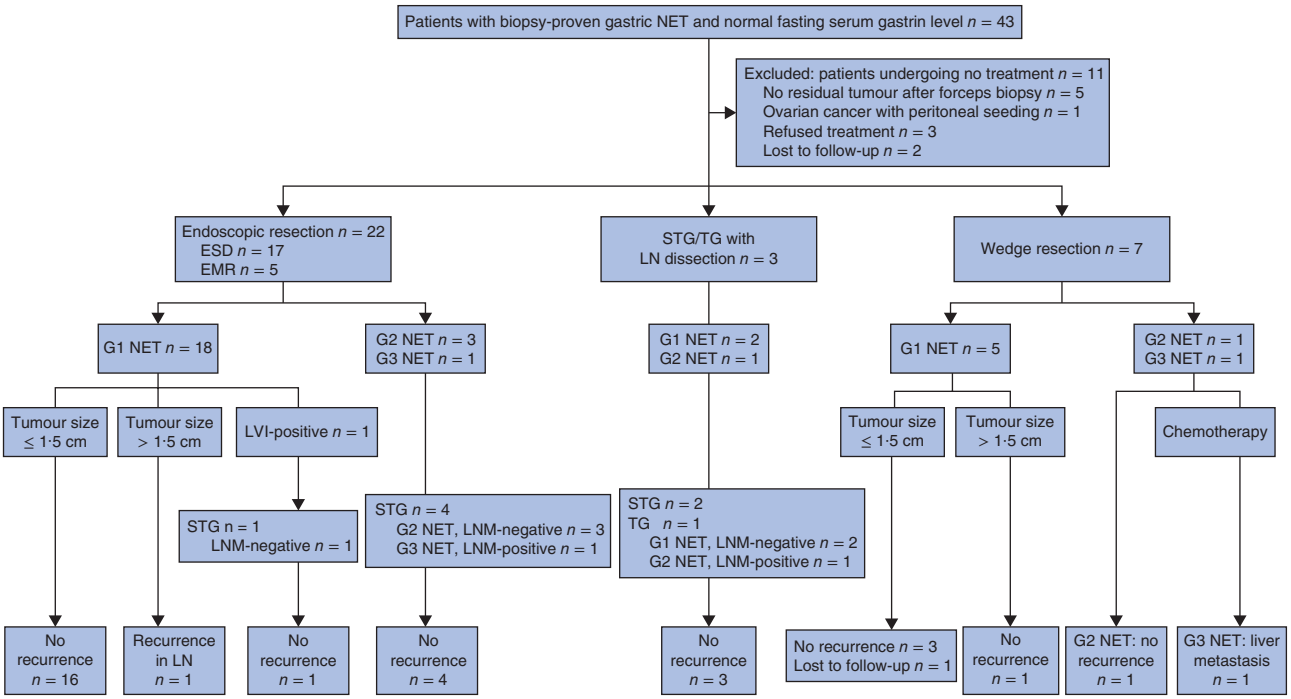

Fig. 1 Flow chart showing treatment and outcomes for enrolled patients who were diagnosed with biopsy-proven gastric neuroendocrine tumour (NET) and a normal fasting serum gastrin level. ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; STG, subtotal gastrectomy; TG, total gastrectomy; LN, lymph node; LVI, lymphovascular invasion; LNM, lymph node metastasis

resection[8,9]. The clinicopathological features and biological behaviour of small and low-grade type 3 gastric NETs remain unclear[10]. Two Korean studies[11,12] reported favourable outcomes after surgical wedge or endoscopic resection for type 3 gastric NETs smaller than 2 cm and confined to the submucosal layer. However, both studies had limitations as neither presented data on the gastrin levels or mitotic count and Ki-67 index, which are essential for determining tumour grade and risk of tumour progression.

The aim of this study was to evaluate the clinicopathological features and long-term outcomes of surgical wedge or endoscopic resection for low-grade type 3 gastric NETs according to the WHO 2010 classification[13,14].

Methods

An institutional database was used to identify consecutive patients who were diagnosed with biopsy-proven gastric NET and a normal fasting serum gastrin level (normal value less than 90 pg/ml) in Samsung Medical Centre between April 2005 and April 2014. No patient had Zollinger–Ellison syndrome or multiple endocrine neoplasia type 1. An endoscopic resection or wedge resection without lymphadenectomy is performed when patients show normal fasting serum gastrin levels and have a gastric NET of 2 cm or less on upper gastrointestinal endoscopy. For endoscopic resection, endoscopic mucosal resection (EMR) was performed until 2008 and endoscopic submucosal dissection (ESD) after 2008[15–17]. Subtotal or total gastrectomy with radical D2 lymph node dissection was indicated for gastric NETs larger than 2 cm or for tumours with lymphovascular invasion on forceps biopsy, regardless of tumour grade. Radical gastrectomy was also indicated for patients with concurrent gastric cancer when the cancer was beyond the expanded indication for endoscopic resection[18]. If the tumour was diagnosed as a G2 or G3 NET from the wedge or endoscopic resection specimen, additional treatment was generally recommended including subtotal or total gastrectomy with lymph node dissection. All patients underwent oesophagogastroduodenoscopy (OGD) and abdominal CT before treatment.

Clinical data, including demographic features, tumour characteristics and treatment outcomes, were obtained by review of medical records using the intranet resources of Samsung Medical Centre. All patients provided informed consent according to the institutional guidelines. The institutional review board

Table 1 Clinicopathological features of type 3 gastric neuroendocrine tumours

	G1 NET ($n = 25$)	G2 or G3 NET ($n = 7$)	P§
Age (years)*	53·5(10·8) (27–75)	50·4(8·9) (36–62)	0·494¶
Sex ratio (M : F)	16 : 9	7 : 0	0·149
Concomitant gastric adenocarcinoma			0·395
No	24	6	
Yes	1†	1‡	
Gastrin (pg/ml)*	49·2(17·4) (23·5–89·3)	47·8(13·9) (34·6–67·4)	0·842¶
Tumour site			0·632
Antrum	5	2	
Body or fundus	20	5	
Tumour shape			1·000
Elevated	25	7	
Flat or depressed	0	0	
No. of lesions			1·000
Single	25	7	
Multiple	0	0	
Differentiation			1·000
Well differentiated	25	7	
Poorly differentiated	0	0	
Tumour size (cm)*	0·8(0·6) (0·2–2·5)	1·5(0·9) (0·6–3·5)	0·027¶
Tumour depth			0·219
Mucosa or submucosa	25	6	
Subserosa	0	1	
Lymphovascular invasion			0·001
No	24	2	
Yes	1	5	

*Values are mean(s.d.) (range). †Patient underwent total gastrectomy; adenocarcinoma stage was pT2 N0 M0. ‡Patient underwent endoscopic submucosal dissections for both neuroendocrine tumour (NET) and adenocarcinoma; adenocarcinoma stage was pT1a Nx Mx. §Fisher's exact test test, except ¶Student's *t* test.

of Samsung Medical Centre approved the study protocol.

Histopathological evaluation

Processing of surgical or endoscopic resection specimens in Samsung Medical Centre has been described in detail elsewhere[15,19]. In the present study, diagnosis and grading of gastric NETs was done by two pathologists according to WHO 2010 classification: G1, mitotic count less than 2 per 10 high-power fields (HPFs) and/or Ki-67 index 2 per cent or less; G2, mitotic count 2–20 per 10 HPFs and/or Ki-67 index 3–20 per cent; and G3, mitotic count over 20 per 10 HPFs and/or Ki-67 index exceeding 20 per cent[13,14]. Immunohistochemical staining was undertaken using antibodies against chromogranin (1 : 400; Dako, Glostrup, Denmark), synaptophysin (1 : 200; Dako), Ki-67 (1 : 300; Dako) and phosphohistone 3 (1 : 500; Biocare Medical, Concord, California, USA). Non-tumour biopsy specimens were reviewed to evaluate the presence of atrophic body gastritis. Gastric atrophy was defined according to the updated Sydney System[20].

Wedge or endoscopic resection was judged as curative when all of the following pathological conditions were met: *en bloc* resection with negative lateral and vertical resection margins, well differentiated NET, tumour size 2 cm or less, tumour confined to the mucosal or submucosal layer, absence of lymphovascular invasion, and grade 1 according to the WHO 2010 classification.

Follow-up schedule

OGD was carried out 2 months after endoscopic resection to confirm healing of the artificial ulcer and to exclude the presence of residual tumour. Thereafter, OGD was performed along with biopsy and abdominal CT every 6 months for 3 years, and then annually for up to 5 years. For patients undergoing surgical resection, OGD and abdominal CT were undertaken at 3- and 6-month intervals for the first year and then annually thereafter[19]. Tumour recurrence was diagnosed if OGD along with biopsy revealed an intragastric NET lesion or abdominal CT showed radiological findings consistent with NET recurrence during follow-up.

Statistical analysis

Categorical variables were analysed using the χ^2 test or Fisher's exact test. Student's *t* test or the Mann–Whitney *U* test was used for analysis of continuous variables. Data on overall survival were obtained from the national registry of medical insurance. Overall survival was determined from the date of wedge or endoscopic resection to the date of death from any cause or to the censoring date of 30 April 2017. Survival rates were calculated using the Kaplan–Meier method. $P < 0{\cdot}050$ was considered statistically significant.

Results

Of 43 patients identified, 32 underwent surgical or endoscopic resection for biopsy-proven type 3 gastric NET and were included in the study (*Fig. 1*). Some 22 patients were treated with endoscopic resection and seven had wedge resection without lymphadenectomy. Three patients underwent subtotal gastrectomy or total gastrectomy with radical D2 lymph node dissection as initial treatment; one patient had a gastric lesion larger than 2 cm on OGD (G1

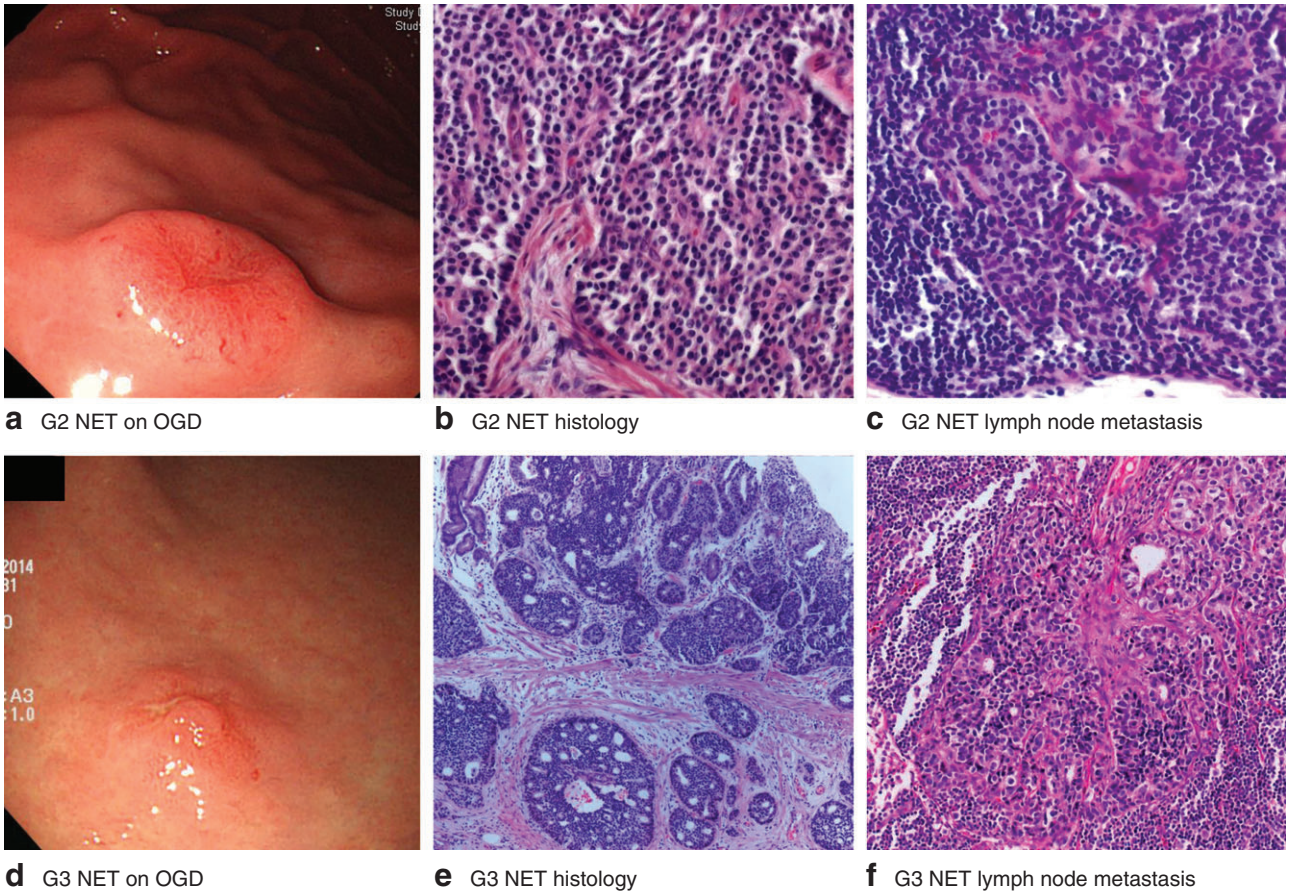

Fig. 2 Examples of type 3 gastric neuroendocrine tumours (NETs) with lymph node metastasis in the gastrectomy resection specimen. **a–c** G2 NET (patient 4 in *Table S1*, supporting information) 1·4 cm in size confined to the submucosal layer; this tumour showed lymphovascular invasion: **a** appearance of the lesion on oesophagogastroduodenoscopy (OGD) before treatment; **b** histology showing a primary well differentiated NET in the stomach (haematoxylin and eosin stain, original magnification × 40); **c** histology showing lymph node metastasis with NET cell infiltration (haematoxylin and eosin stain, original magnification × 40). **d–f** G3 NET (patient 6 in *Table S1*, supporting information) 1·2 cm in size confined to the submucosal layer; this tumour had lymphovascular invasion: **d** appearance of the lesion on OGD before treatment; **e** histology showing a primary well differentiated NET in the stomach (haematoxylin and eosin stain, original magnification × 4); **f** histology showing lymph node metastasis with NET cell infiltration (haematoxylin and eosin stain, original magnification × 40)

NET), one patient had a concurrent advanced gastric cancer confined to the muscularis propria layer (G1 NET) and one patient had lymphatic tumour emboli in the forceps biopsy specimen (G2 NET). Two patients with gastric NETs larger than 2 cm on OGD underwent wedge resection because they refused total gastrectomy (1 G1, 1 G3).

Table 1 summarizes the clinicopathological features of type 3 gastric NETs according to tumour grade. Twenty-five NETs were G1, five were G2 and two G3. All tumours were well differentiated, even G3 lesions, and all tumours but one were confined to the submucosal layer. Pathological tumour size was 1·0 cm or less in 20 patients, greater than 1·0 cm but no more than 2·0 cm in ten patients, and larger than 2·0 cm in two patients. No patient had lymph node or distant metastasis visualized on abdominal CT before treatment. Only one patient had a G1 NET showing lymphovascular invasion.

Forceps biopsy specimens were reviewed to identify whether there was a difference in tumour grade between biopsy specimens and endoscopic or surgical resection specimens. For G1 NETs, tumour grade in the initial forceps biopsy specimens was G1 in all 25 patients. Among five patients with G2 NETs, tumour grade in the initial forceps biopsy was G1 in four and G2 in one. For two patients with G3 NETs, the tumour grade in the initial forceps biopsy was G1 in one patient and G3 in the other. Biopsy

Table 2 Clinicopathological features and outcomes of treatment for type 3 gastric neuroendocrine tumour according to treatment modality

	Endoscopic resection† ($n = 22$)	Wedge resection ($n = 7$)	P§
Age (years)*	52·6(12·0) (27–75)	52·1(6·0) (42–58)	0·933¶
Sex ratio (M : F)	14 : 8	6 : 1	0·382
Concomitant gastric adenocarcinoma			1·000
No	21	7	
Yes	1	0	
Gastrin (pg/ml)*	48·0(16·9) (23·5–89·3)	51·0(16·7) (32·4–81·6)	0·687¶
Tumour site			0·147
Antrum	7	0	
Body or fundus	15	7	
Tumour size (cm)*	0·8(0·4) (0·2–1·6)	1·5(1·2) (0·2–3·5)	0·172¶
Tumour grade			0·612
G1 NET	18	5	
G2 or G3 NET	4	2	
Tumour depth			0·241
Mucosa or submucosa	22	6	
Subserosa	0	1	
Lymphovascular invasion			1·000
No	18	6	
Yes	4	1	
Resection margin			0·557
Negative	19	7	
Positive in LRM	0	0	
Positive in VRM	3‡	0	
Curative resection			0·642
Curative	16	4	
Non-curative	6	3	

*Values are mean(s.d.) (range). †Seventeen endoscopic submucosal dissections and five endoscopic mucosal resections. ‡One patient had endoscopic mucosal resection for a G1 neuroendocrine tumour (NET), and one patient each underwent endoscopic submucosal dissection for a G2 and G3 NET. LRM, lateral resection margin; VRM, vertical resection margin. §Fisher's exact test, except ¶Student's *t* test.

specimens of normal gastric mucosa from the body or fundus were available for 26 patients; none of these showed signs of atrophic gastritis.

Clinicopathological features of seven patients with G2 or G3 type 3 gastric NETs are described in detail in *Table S1* (supporting information). Lymphovascular invasion was present in five of seven patients. Two patients who underwent subtotal gastrectomy for a G2 or G3 NET showed lymph node metastasis (*Fig. 2*). One patient with a G3 NET refused total gastrectomy and underwent wedge resection with adjuvant chemotherapy. This patient developed liver metastases 48 months after resection.

Table 2 shows the clinicopathological features according to treatment (endoscopic resection *versus* wedge resection). The endoscopic resection group included 17 ESDs, four EMRs using the inject and cut technique, and one EMR by the cap technique[17].

Among 17 patients with a G1 NET treated with endoscopic resection alone (including 16 no larger than 1·5 cm in size), 16 underwent curative resection. One patient who underwent EMR by the cap technique showed involvement of the vertical resection margin. This patient was followed without additional treatment; follow-up OGD showed no residual tumour at the EMR site. Among the 17 patients who underwent endoscopic resection, only one had a CT finding consistent with recurrence (a 1·9-cm round enlarged perigastric lymph node without local disease) 68 months after curative ESD for a 1·6-cm G1 NET. No patient with a G1 NET no larger than 1·5 cm developed recurrence after curative endoscopic resection during a median follow-up of 59 (range 6–96) months (*Fig. 1*).

Of five patients with a G1 NET treated with wedge resection (including 4 with tumour 1·5 cm or smaller), four underwent curative resection. A patient who underwent non-curative resection met all the criteria for curative resection except for a tumour size of 2·5 cm. During a median follow-up of 70 (range 58–102) months, no recurrence developed after wedge resection (*Fig. 1*).

A total of eight patients (3 with G1 NET, 4 with G2 NET, 1 with G3 NET) underwent subtotal or total gastrectomy either as an initial or additional treatment. No patient with a G1 NET showed lymph node metastasis in the surgical specimens. None of these patients developed recurrence during follow-up (*Fig. 1*).

The 5-year overall survival rate was 96 per cent in 32 patients undergoing surgical or endoscopic treatment for type 3 gastric NET and there was no gastric NET-related death during the follow-up period.

Discussion

In the present study, low-grade type 3 gastric NETs showed favourable clinicopathological features and prognosis, in contrast to previous reports[3,4]. Twenty-five patients had G1 NETs and a G3 NET was found only in two patients. No recurrence was observed after curative surgical wedge or endoscopic resection for a type 3 G1 NET of 1·5 cm or smaller, which suggests that local resection is sufficient.

Two Korean studies reported similar findings. In a study of 16 patients, Kim and colleagues[11] reported that the mean size of type 3 gastric NETs was 1·2 cm and the majority of the tumours were confined to the submucosal layer. In

the study by Kwon and co-workers[12], the mean size of type 3 gastric NETs was 1·0 cm and all tumours were well differentiated. Lymphovascular invasion was found in only three of the 50 patients enrolled. An Italian study by Lahner *et al.*[10] reported a well differentiated gastric NET of low grade in a patient with a normal serum gastric level and without atrophic body gastritis. In the present study, all type 3 gastric NETs were well differentiated, even G3 tumours. As in the present study, well differentiated NETs with a high grade (WHO G3) have recently been described in the pancreas as a discrete entity, which is reflected in the WHO 2017 classification[21–24]. In the original Rindi classification, type 3 gastric NET was defined as a subtype of well differentiated gastric neuroendocrine neoplasm and poorly differentiated neuroendocrine carcinoma was classified in a different category[5–7,9,25]. In recent studies, however, type 3 gastric NETs have been regarded as neuroendocrine carcinoma, which is usually poorly differentiated[3,4,26]. Recent ENETS consensus guidelines[4] state that a further distinction among type 3 gastric neuroendocrine neoplasms may be appropriate.

In the present study, in contrast to G1 NETs, well differentiated type 3 G2 or G3 gastric NETs showed aggressive features and frequent metastases despite their small size and superficial depth. This implies that type 3 gastric NETs can be appropriately classified according to tumour grade based on mitotic count and Ki-67 index.

As well differentiated type 3 G2 or G3 gastric NETs showed frequent lymph node or distant metastasis in this study, additional radical gastrectomy with nodal dissection is indicated for these tumours, even if they are small. In contrast to those with G2 or G3 NETs, no patient with a G1 NET had lymph node or distant metastasis at presentation and no patient with a G1 NET of 1·5 cm or smaller developed recurrence after local resection. These favourable outcomes after wedge or endoscopic resection were consistent with the results of two Korean studies[11,12]. Based on these data, Kwon and colleagues[12] argued that endoscopic treatment could be considered an initial treatment for type 3 gastric NET smaller than 2 cm confined to the submucosal layer. However, neither study reported on gastrin levels or tumour grade, which is essential for risk stratification. In the present study, G2 or G3 NETs showed metastases despite their small size and superficial tumour depth, which underlines the importance of tumour grade in treatment selection. Tumour grade was underestimated in forceps biopsy specimens in five of seven G2 or G3 NETs. This underestimation might have resulted from the small size of biopsy specimens and limited numbers of HPFs that could be evaluated. In biopsy-proven G1 NET, therefore, the need for additional treatment after local resection should be determined based on pathological review of the endoscopic or surgical specimen.

This study was limited in that it was carried out at a single tertiary referral centre and had a retrospective design. Furthermore, the presence of atrophic body gastritis may have been missed as systematic mapping of biopsies from normal gastric mucosa was not performed. Although atrophic body gastritis is important in the classification of gastric NETs, raised levels of gastrin are usually diagnostic for type 1 or type 2 NETs[8]. As only patients with normal serum gastrin levels were included in the present study, it is unlikely that other types of gastric NET were included.

The present study showed that type 3 gastric NETs are a heterogeneous group. G1 NETs were over-represented and showed favourable clinicopathological features and prognosis, whereas G2 or G3 NETs had aggressive features and frequent metastases, despite their small size and superficial tumour depth. Surgical wedge or endoscopic resection is a valid option for patients with type 3 gastric G1 NET no larger than 1·5 cm if the tumour is confined to the submucosal layer and there is no lymphovascular invasion.

Acknowledgements

B.-H.M. and M.H. contributed equally to this work. K.-M.K. and J.J.K. are joint senior authors.
Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.