Is Local Excision Sufficient in Selected Grade 1 or 2 type III Gastric Neuroendocrine Neoplasms?

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Abstract

Purpose

Type III gastric neuroendocrine neoplasms (g-NENs) have historically been regarded as aggressive tumours, hence current guidelines advocate radical surgery with lymph node dissection. Data on the roles of endoscopic or less extensive surgical resections are more limited. The aim of our study is to evaluate the clinicopathological features and long-term outcomes of patients undergoing endoscopic or limited surgical resection for localised grade 1 or 2 type III g-NENs when compared to radical surgery.

Methods

Retrospective analysis of all patients diagnosed with a localised grade 1 or 2 type III g-NENs across six tertiary NEN centers between 2006-2019.

Results

Forty-five patients were diagnosed with a potentially resectable grade 1 or 2 type III g-NEN of whom 36 underwent either endoscopic or surgical resection. No statistically significant differences were found between the three resection groups in terms of patient age, tumour location, grade or size. Only tumour size was found to be significantly associated with poor clinical outcome (p=0.012) and ROC curve analysis identified tumour size >10mm as a negative predictor (AUC:0.8030, p=0.0021). Tumours >10mm were also more likely to be associated with lymph node metastases on imaging and histology (p=0.039 and p=0.026 respectively).

Conclusions

Localised grade 1 or 2 type III g-NENs had a good prognosis in this series. Tumour size >10mm was the most significant prognostic factor affecting patient outcome. Endoscopic resection or limited surgical resection is feasible and safe in small type III g-NENs which demonstrate favourable grade 1/2, well differentiated histology.

Keywords: Neuroendocrine tumour, carcinoid, endoscopy, surgery

Declarations

Funding

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Conflicts of Interest

DMP has acted as a consultant for Ipsen, Advanced Accelerator Applications and Laboratoire Mayoly Spindler and has received research funding from Trio Medicines UK.

SGG has received research support from Novartis and Ipsen and honoraria from Novartis, Ipsen, Pfizer, and Lexicon.

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None of the other authors have any conflicts of interest to declare.

Availability of data and material

Data available on request from the authors

Authors' contributions

DMP and CT conceived and designed the study. KE, LK, MT, AV, KO, MSK, RS identified patients and extracted clinical data. MSK, RS, DM, SGG, GK, NH oversaw project at their centre. KE performed the analysis and with DMP wrote the first draft of the manuscript. KE, DMP and CT revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript. The guarantor of this article is Dr Christos Toumpanakis.

Ethics approval

No ethical approval was required for this retrospective study. Each individual institution sought and was granted local approval by their respective Research and Audit Departments.

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Introduction

Gastric neuroendocrine neoplasms (g-NENs) are increasingly being identified with the use of upper gastrointestinal endoscopy and multiple studies have suggested that they account for approximately 7% of all digestive NENs [1]. Gastric NENs are classified into three distinct types [2,3] and these types have very different and distinct disease biology. Types I and II g-NENs are associated with high concentrations of plasma gastrin, tend to be well differentiated tumours and usually have a good long-term prognosis [3,4].

Historically, type III g-NENs represent <20% of all gastric NENs [5] and have been considered to be sporadic, gastrin independent, large tumours (over 2cm), presenting at a higher grade (usually G3) [6,7] and having greater metastatic potential and poorer prognosis. They frequently demonstrate more aggressive features of poor differentiation, lymphovascular invasion (LVI) and tumour infiltration beyond the submucosal layer [8]. Due to their more aggressive behaviour, surgical resection, in the form of a partial or total gastrectomy with lymph node (LN) dissection, remains the recommended treatment according to the ENETS consensus guidelines [4]. However, recent National Comprehensive Cancer Network (NCCN) guidelines [9] have proposed that endoscopic resection may be sufficient for small (<10mm), superficial, low grade type III g-NENs or wedge resection can be considered if there is no evidence of lymphadenopathy on endoscopic ultrasound (EUS).

Gastric NEN grading is based on the most recent World Health Organisation classification, taking into consideration tumour differentiation, mitotic count and Ki-67% proliferation index [10]. Although tumour grade has been shown to be the strongest negative prognostic factor in digestive NENs from the pancreas and jejunum-ileum [11-13], its role in gastric NENs remains less clear due to a lack of robust data. A recent systematic review suggested that the majority of type III g-NENs diagnosed in the modern day have a lower grade than historically reported [2]. Moreover, tumour size is reported by international guidelines to be one of the most relevant factors affecting patient management, with tumours of larger size warranting a more aggressive therapeutic approach and a more intensive surveillance programme [14,4,9].

Only a few previous studies have explored the roles of endoscopic resection [15] and/or gastric wedge resection [16,17] as curative treatments for certain type III g-NENs and these have reported favourable outcomes.

Aim

To evaluate the clinicopathological features and long-term outcomes of patients undergoing local excision and in particular endoscopic or limited surgical resection, for localised grade 1 or 2 type III g-NENs when compared to radical surgery.

Materials and Methods

Patient selection

We performed a multicenter retrospective analysis of all consecutive patients diagnosed with a localised low grade type III gastric neuroendocrine neoplasm (g-NEN) across six tertiary centers (four in the UK, one in Greece and one in Israel) between November 2006 and January 2019 and identified patients using institutional databases. Inclusion criteria were: histologically confirmed type III g-NEN with normal fasting plasma gastrin concentration; no evidence of Multiple Endocrine Neoplasia (MEN)-1 on clinical, biochemical and imaging criteria; no evidence of atrophic gastritis on background gastric biopsies and negative anti gastric parietal cell and/or intrinsic factor antibodies; grade 1 or 2 well differentiated tumours; localised disease on endoscopic, cross-sectional and/or functional imaging; details available about all interventional procedures; regular endoscopic follow-up at a NEN Unit or at a Gastroenterology department linked to a NEN Unit. Exclusion criteria were: grade 3 neuroendocrine tumours or neuroendocrine carcinomas; evidence of non-regional lymph nodes (that would not be included in the surgical resection margin) and distant metastases at diagnosis; incomplete follow up.

Clinical data, including demographics features, tumour characteristics and treatment outcomes were obtained through medical records locally. No ethical approval was required for this study, but local approvals from respective Hospital Audit Departments were granted.

Indications for the treatment modality that was advocated varied between institutions. Endoscopic resection was performed in some patients who had a type-III g-NEN of up to two centimeters in diameter with a Ki-67 index of <10%. For the patients treated with surgery, a limited surgical resection was defined as a gastric wedge resection without lymphadenectomy and radical surgery as a subtotal or total gastrectomy with D2 lymph node dissection. All patients underwent oesophagogastroduodenoscopy (OGD) and abdominal CT scan as part of the staging process prior to treatment. Endoscopic ultrasound and functional imaging in the form of ^{68}Ga DOTA-

peptide PET/CT or ^{111}In-Octreotide scan and/or ^{18}F-FDG PET/CT were undertaken according to local protocols. Histological tumour grade was based on the most recent WHO classification [18]. Grade 2 tumours were subdivided into those which were low G2 (Ki-67 index 3-10%) and high G2 (Ki-67 index 11-20%). Follow-up was undertaken again according to local protocols. All cases were discussed and treatment planned at the local NEN multidisciplinary team meeting.

Statistical Analysis

Ordinary one-way ANOVA was used for continuous variables and Kruskal-Wallis test for non-normally distributed data for comparisons between treatment groups. A composite negative endpoint was defined to identify patients who had a poor clinical outcome and was considered to have occurred if any of the following events were observed: tumour-related death, presence of metastases and evidence of recurrence on follow-up. Logistic regression was used to identify possible predictors of this negative endpoint. Receiver operating characteristic (ROC) curve analysis was used to identify the cut-off for tumour size as a predictor of presence of the composite endpoint. A comparison between subgroups was carried out using the Fisher exact test for non-continuous variables. Differences were considered significant at $p < 0.05$. Statistical analysis was performed using GraphPad Prism version 8.4.0 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

Results

Cohort characteristics

Six centers contributed to this project (Figure 1). We identified 45 patients who had grade 1 or 2 and potentially resectable type III g-NENs and they had a median age of 56 years (IQR:46-67) (Table 1, Supplementary Fig 1). Initial management included 3 patients who underwent medical management due to patient choice and/or significant comorbidities. Six additional patients who had very small polyps appear to have been successfully treated by avulsion biopsy at the time of initial diagnostic OGD (median tumour size 3mm (IQR:3-5mm)). These six patients underwent yearly endoscopic follow up as well as CT or MRI imaging with no evidence of recurrence during a median follow up of 55 months (IQR:4-114 months). The remaining 36 patients underwent either planned endoscopic resection or planned surgical resection (wedge resection/radical surgery) based on local management protocols (Figure 1). All 36 patients had a CT scan and 7 of these scans demonstrated evidence of locoregional lymph node metastasis. Endoscopic ultrasound was performed in 15 of the patients who underwent

a planned resection, including 9 of the 10 cases who underwent endoscopic resection. None of these EUS examinations showed evidence of lymph node metastases. EUS was not performed in 21 patients who underwent a planned resection, but it was not clinically indicated in the 7 patients who demonstrated lymph node metastases on CT scan or in a further 7 patients who had lesions ≥20mm in diameter, suggesting that they should have a surgical resection from the outset. Functional imaging (either ^{68}Ga DOTA-peptide PET/CT or ^{111}In-Octreotide scan and/or ^{18}F-FDG PET/CT) was performed in 21 (58%) of the patients who underwent a planned resection. 15 examinations showed somatostatin receptor positive disease and the single ^{18}F-FDG PET/CT scan was tracer inavid. Only one functional imaging scan showed evidence of nodal metastases, but these were also detected by CT scan. Median follow up for the group that underwent resection was 62 months (IQR:14-93). Overall, two tumour recurrences were noted, and no NEN related deaths were recorded during the entire follow up period.

Clinicopathological features

The majority of tumours were located in the gastric body in all patient groups (Table 1, Supplementary Fig 1). Most tumours in this series (87%) were less than 20mm in diameter and nearly 50% were between 10 and 20mm (median 12mm, IQR:8-20mm, R:1-80mm). 91% of patients had a Ki-67 index <10% (median 3%, IQR:2-5%, R:1-15%). In the patients who underwent tumour resection, no statistically significant differences were found between the three resection groups in terms of patient age, tumour location, grade or size.

Factors corelated with negative endpoint

Gender, age at diagnosis, tumour grade, Ki-67% and tumour location were not associated with the composite negative endpoint on univariate analysis by logistic regression. Only tumour size was found to be a significantly associated with poor clinical outcome (p=0.012, OR:0.9, 95% CI:0.8-0.97). When ROC curve analysis was performed, a tumour cut off size of 10mm was identified as a negative predictor of poor clinical outcome (AUC:0.8030, p=0.0021, Figure 2). Tumour size was also significantly associated with the composite negative outcome using a multivariate logistic regression model (p=0.0055, OR:0.85, 95% CI:0.74-0.94) (Table 2). When comparing groups based on tumour size; tumours larger than 10mm were more likely to have lymph node metastases on imaging and histology (p=0.039 and p=0.026 respectively) and were also more likely to be

associated with the composite negative endpoint. Tumours measuring more than 12mm were also significantly more likely to demonstrate lymphovascular invasion (LVI) (Table 3).

Management of tumour recurrences

During follow up, two patients demonstrated tumour recurrence. The first patient had an 11mm G2 tumour (Ki-67 index 5%) and was originally treated by endoscopic resection. He presented 48 months later with a local recurrence. Functional imaging also demonstrated small metastatic lesions in the left lobe of the liver. The patient underwent a laparoscopic subtotal gastrectomy, liver metastatectomy and cholecystectomy. He is alive, but with residual stable liver disease after 56 months of follow-up and is currently receiving long acting somatostatin analogue injections. Apart from tumour size >10mm, no other adverse features were indentified on histology. The second patient had a 40mm G2 tumour (Ki-67 index 7%) and underwent a wedge resection with final histology being T2N1M0. Liver metastases were detected 96 months post operatively and the patient underwent a metastatectomy. He remains alive and free of radiological evidence of NEN 36 months after liver resection.

Discussion

Type III g-NENs are rare, sporadic tumours that are not associated with any underlying gastric mucosal abnormality or hypergastrinaemia. In some historic published cohorts, more than 70% of type III gastric NENs were larger than 10 mm at the time of diagnosis, and these tumours tended to infiltrate the muscularis propria and/or be angioinvasive, thus accounting for the high rate of metastases found at presentation (75%)[19,20]. The current gold standard of treatment for localised type III gastric NENs is therefore surgical resection with lymphadenectomy [4]. However, a less radical approach has been proposed in specific circumstances and recent studies have investigated the role of less aggressive surgical techniques and endoscopic resection in selected groups of patients [15-17].

Kwon *et al* [15] evaluated the long-term outcomes following endoscopic resection in 50 patients with type III g-NENs and concluded that tumours fulfilling certain criteria could initially be successfully managed endoscopically. These criteria were: size less than 20mm, depth of invasion confined to the submucosal layer and no evidence of LVI. All patients underwent EUS as part of tumour assessment. Although LVI was noted in larger tumours, there was no statistically significant difference between different tumour size groups and all patients who had LVI

underwent further operation. However, the study used CT scans for staging and EUS was only used to determine the depth of tumor invasion rather than lymph node status. Min e*t al* [16] also suggested recently that surgical wedge or endoscopic resection were valid treatment options for patients who had grade 1 type III g-NENs no larger than 15mm if the tumour was confined to the submucosal layer and there was no evidence of LVI. A recent retrospective multicenter study in Japan [17] also investigated the suitability of endoscopic resection in grade 1 and 2 type III g-NENs and suggested in that endoscopic resection may be an alternative treatment for <10mm grade 1 tumours that were confined to the mucosa or submucosa.

Criteria for selecting patients for endoscopic or local resection (without formal lymph node dissection) have now been accepted for managing early gastric adenocarcinomas using endoscopic mucosal resection or laparoscopic wedge resection[21,22] and for selected NENs at other sites such as the appendix (by simple appendectomy) [23] and rectum (through transanal excision) [24]. These criteria have been developed by defining those subgroups of tumors which are associated with a low rate of lymph node metastasis.

In our study we have evaluated the clinicopathological features of a cohort of patients who had localised grade 1 or 2 type III g-NENs and have demonstrated that these patients had an excellent overall prognosis. We showed that tumour size was the single most significant prognostic factor affecting patient outcome, irrespective of Ki-67 index, gender, age and tumour location. A tumour cut off size of >10mm was identified as being more likely to be associated with LN metastases, not only on pre-operative imaging, but also on post-operative histology. Furthermore, tumours >10mm in diameter were more likely to be associated with the composite negative endpoint of tumour recurrence, disease progression or death.

Tumour size, degree of tumour infiltration or layer of origin within the stomach wall, and presence or absence of metastatic loco-regional lymph nodes are best assessed using EUS [25]. The utilisation of EUS to determine the depth of invasion, but most importantly the presence of lymph node metastases is important for risk stratification [26] and further management. EUS has been used extensively in diagnosing gastroenteropancreatic NENs with high sensitivity (87.2%) and specificity (98%) [27,28] and has been incorporated as part of the diagnostic algorithm in both pancreatic and rectal NENs [24,29] in the current ENETS guidelines. In our series 9/10 patients undergoing endoscopic resection were staged with EUS. All tumours were between 6-20mm and they all demonstrated no evidence of LN metastases.

Furthermore, in our study, we also identified six patients who were treated apparently successfully by avulsion biopsy at the time of initial diagnostic OGD. These patients all had small tumours (<7mm) that were confined to the muscularis mucosa. Only one patient had a grade 2 tumour (Ki-67 9%), but as that lesion was only 3mm in diameter and the patient had significant co-morbidities of type 2 diabetes mellitus and chronic kidney disease stage 5 and was receiving renal replacement therapy, endoscopic surveillance was deemed more appropriate than further resection. Although these patients should ideally have undergone formal planned endoscopic resection rather than avulsion biopsy, there was no macroscopic evidence of residual tumour during follow up OGD, hence they were placed in an endoscopic surveillance programme. Annual OGDs and imaging in the form of MRI or CT scan have not identified any recurrences in any of these six patients. Although we do not propose that avulsion/ strip biopsy is intentionally used to treat type III g-NENs, it is important to recognise that in certain cases successful resection may be achieved in this way.

Our findings are in keeping with the recent systematic review by Exarchou *et al* [2] highlighting that low grade histology is associated with good prognosis and recognising the role of limited surgical resection and endoscopic management. Based on our findings and the current literature, we are in a position to propose an algorithm for the management of localised low grade, well differentiated type III g-NENs (Figure 3). Overall, all type III g-NENs should be assessed at baseline by endoscopy to determine size and location and by histology to establish grade and differentiation. CT scan and functional imaging tests are needed for accurate staging and evaluation of locoregional and metastatic disease. All patients who have evidence of lymph node or (resectable) distant metastases on imaging or grade 3 Ki-67 proliferation index or poor differentiation on histology should undergo definitive surgical resection if feasible and their management is outside the remit of this article.

For G1 and G2 type III g-NENs, tumour size and LN status appear to the major factors which should influence management. The management of patients who have either small (<10mm) tumours or large (>20mm) tumours appears to be more easily defined. Most patients with tumours <10mm in size can be effectively managed initially be endoscopic resection. In the event of adverse histology margins, further endoscopic management or salvage wedge resection should subsequently be undertaken. Similarly, it is reasonably clear from the published series that type III g-NENs >20mm should be treated with radical surgery, given the increased risk of metastases.

We however propose that for tumours measuring 10-20mm, EUS should play a pivotal role in the assessment. If EUS shows no evidence of regional LN metastases, then patients can undergo a wedge resection. In the event of adverse histology such as an increase in grade in the resection specimen compared to the original biopsy, evidence of LVI, or invasion into the submucosal layer, radical surgery remains a subsequent option without compromising oncological outcome. If EUS demonstrates probable or definite metastatic LNs then radical surgery is advised at the outset.

Our study has some limitations, primarily related to its design. It is a retrospective, observational, multicenter, non-randomised study. Although each case was discussed at the local NEN specialised multidisciplinary team meeting, each center had a different protocol for the assessment and management of type III g-NENs; therefore criteria for choosing a given therapeutic approach could not be standardised across all centers. Furthermore, even with the contribution of six centers, we only recruited 45 patients over a 13-year period. However, this is a rare tumour type and we only included patients who had localised grade 1 and 2 tumours in our study protocol as we were interested specifically in evaluating the effectiveness of endoscopic and limited surgical resection options. Even Hirawasa *et al* [17] only identified 144 patients during a 28 year study period in a study which covered the whole of Japan. Therefore; in spite of the relatively small study population, our series is one of the largest in the published literature and confirms recent observations from Japan in a Western population.

In conclusion, we have identified that a cut off size of 10mm in type III g-NENs appears to predict a negative long-term outcome. Furthermore, definitive treatment by endoscopic resection or limited surgical resection is feasible and safe in type III g-NENs which demonstrate favourable low grade and well differentiated histology and small size (<10mm). Tumours 10-20mm warrant further assessment with EUS for risk stratification before considering the most appropriate mode of resection.

References

1. Dasari, A., Shen, C., Halperin, D., Zhao, B., Zhou, S., Xu, Y., Shih, T., Yao, J.C.: Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol **3**(10), 1335-1342 (2017). doi:10.1001/jamaoncol.2017.0589
2. Exarchou, K., Howes, N., Pritchard, D.M.: Systematic review: management of localised low-grade upper gastrointestinal neuroendocrine tumours. Aliment Pharmacol Ther **51**(12), 1247-1267 (2020). doi:10.1111/apt.15765
3. Burkitt, M.D., Pritchard, D.M.: Review article: Pathogenesis and management of gastric carcinoid tumours. Aliment Pharmacol Ther **24**(9), 1305-1320 (2006). doi:10.1111/j.1365-2036.2006.03130.x
4. Delle Fave, G., O'Toole, D., Sundin, A., Taal, B., Ferolla, P., Ramage, J.K., Ferone, D., Ito, T., Weber, W., Zheng-Pei, Z., De Herder, W.W., Pascher, A., Ruszniewski, P., Vienna Consensus Conference, p.: ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology **103**(2), 119-124 (2016). doi:10.1159/000443168
5. Basuroy, R., Srirajaskanthan, R., Prachalias, A., Quaglia, A., Ramage, J.K.: Review article: the investigation and management of gastric neuroendocrine tumours. Aliment Pharmacol Ther **39**(10), 1071-1084 (2014). doi:10.1111/apt.12698
6. La Rosa, S., Inzani, F., Vanoli, A., Klersy, C., Dainese, L., Rindi, G., Capella, C., Bordi, C., Solcia, E.: Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol **42**(10), 1373-1384 (2011). doi:10.1016/j.humpath.2011.01.018
7. Postlewait, L.M., Baptiste, G.G., Ethun, C.G., Le, N., Cardona, K., Russell, M.C., Willingham, F.F., Kooby, D.A., Staley, C.A., Maithel, S.K.: A 15-year experience with gastric neuroendocrine tumors: Does type make a difference? Journal of Surgical Oncology **114**(5), 576-580 (2016). doi:https://dx.doi.org/10.1002/jso.24369
8. Rindi, G., Luinetti, O., Cornaggia, M., Capella, C., Solcia, E.: Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology **104**(4), 994-1006 (1993). doi:10.1016/0016-5085(93)90266-f
9. Shah, M.H., Goldner, W.S., Halfdanarson, T.R., Bergsland, E., Berlin, J.D., Halperin, D., Chan, J., Kulke, M.H., Benson, A.B., Blaszkowsky, L.S., Eads, J., Engstrom, P.F., Fanta, P., Giordano, T., He, J., Heslin, M.J., Kalemkerian, G.P., Kandeel, F., Khan, S.A., Kidwai, W.Z., Kunz, P.L., Kuvshinoff, B.W., Lieu, C., Pillarisetty, V.G., Saltz, L., Sosa, J.A., Strosberg, J.R., Sussman, C.A., Trikalinos, N.A., Uboha, N.A., Whisenant, J., Wong, T., Yao, J.C., Burns, J.L., Ogba, N., Zuccarino-Catania, G.: NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw **16**(6), 693-702 (2018). doi:10.6004/jnccn.2018.0056
10. Nagtegaal, I.D., Odze, R.D., Klimstra, D., Paradis, V., Rugge, M., Schirmacher, P., Washington, K.M., Carneiro, F., Cree, I.A., Board, t.W.C.o.T.E.: The 2019 WHO classification of tumours of the digestive system. Histopathology **76**(2), 182-188 (2020). doi:10.1111/his.13975
11. Pape, U.F., Berndt, U., Muller-Nordhorn, J., Bohmig, M., Roll, S., Koch, M., Willich, S.N., Wiedenmann, B.: Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer **15**(4), 1083-1097 (2008). doi:10.1677/ERC-08-0017
12. Panzuto, F., Boninsegna, L., Fazio, N., Campana, D., Pia Brizzi, M., Capurso, G., Scarpa, A., De Braud, F., Dogliotti, L., Tomassetti, P., Delle Fave, G., Falconi, M.: Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. J Clin Oncol **29**(17), 2372-2377 (2011). doi:10.1200/JCO.2010.33.0688
13. Panzuto, F., Campana, D., Fazio, N., Brizzi, M.P., Boninsegna, L., Nori, F., Di Meglio, G., Capurso, G., Scarpa, A., Dogliotti, L., De Braud, F., Tomassetti, P., Delle Fave, G., Falconi, M.: Risk

factors for disease progression in advanced jejunoileal neuroendocrine tumors. Neuroendocrinology **96**(1), 32-40 (2012). doi:10.1159/000334038
14. Kulke, M.H., Anthony, L.B., Bushnell, D.L., de Herder, W.W., Goldsmith, S.J., Klimstra, D.S., Marx, S.J., Pasieka, J.L., Pommier, R.F., Yao, J.C., Jensen, R.T., North American Neuroendocrine Tumor, S.: NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas **39**(6), 735-752 (2010). doi:10.1097/MPA.0b013e3181ebb168
15. Kwon, Y.H., Jeon, S.W., Kim, G.H., Kim, J.I., Chung, I.K., Jee, S.R., Kim, H.U., Seo, G.S., Baik, G.H., Choi, K.D., Moon, J.S.: Long-term follow up of endoscopic resection for type 3 gastric NET. World Journal of Gastroenterology **19**(46), 8703-8708 (2013).
16. Min, B.-H., Hong, M., Lee, J.H., Rhee, P.-L., Sohn, T.S., Kim, S., Kim, K.-M., Kim, J.J.: Clinicopathological features and outcome of type 3 gastric neuroendocrine tumours. **105**(11), 1480-1486 (2018).
17. Hirasawa, T., Yamamoto, N., Sano, T.: Is endoscopic resection appropriate for type 3 gastric neuroendocrine tumors? Retrospective multicenter study. Dig Endosc **33**(3), 408-417 (2021). doi:10.1111/den.13778
18. Nagtegaal, I.D., Odze, R.D., Klimstra, D., Paradis, V., Rugge, M., Schirmacher, P., Washington, K.M., Carneiro, F., Cree, I.A., Board, W.H.O.C.o.T.E.: The 2019 WHO classification of tumours of the digestive system. Histopathology **76**(2), 182-188 (2019). doi:10.1111/his.13975
19. Rindi, G., Bordi, C., Rappel, S., LaRosa, S., Stolte, M., Solcia, E.: Gastric carcinoids and neuroendocrine carcinomas: Pathogenesis, pathology, and behavior. World Journal of Surgery **20**(2), 168-172 (1996). doi:DOI 10.1007/s002689900026
20. Delle Fave, G., Kwekkeboom, D.J., Van Cutsem, E., Rindi, G., Kos-Kudla, B., Knigge, U., Sasano, H., Tomassetti, P., Salazar, R., Ruszniewski, P., Conference, B.C.: ENETS Consensus Guidelines for the Management of Patients with Gastroduodenal Neoplasms. Neuroendocrinology **95**(2), 74-87 (2012). doi:10.1159/000335595
21. Hyung, W.J., Cheong, J.H., Kim, J., Chen, J., Choi, S.H., Noh, S.H.: Application of minimally invasive treatment for early gastric cancer. J Surg Oncol **85**(4), 181-185; discussion 186 (2004). doi:10.1002/jso.20018
22. Gotoda, T.: Endoscopic resection of early gastric cancer. Gastric Cancer **10**(1), 1-11 (2007). doi:10.1007/s10120-006-0408-1
23. Pape, U.F., Niederle, B., Costa, F., Gross, D., Kelestimur, F., Kianmanesh, R., Knigge, U., Öberg, K., Pavel, M., Perren, A., Toumpanakis, C., O'Connor, J., Krenning, E., Reed, N., O'Toole, D.: ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). In: Neuroendocrinology 2016, pp. 144-152. S. Karger AG
24. Ramage, J.K., De Herder, W.W., Delle Fave, G., Ferolla, P., Ferone, D., Ito, T., Ruszniewski, P., Sundin, A., Weber, W., Zheng-Pei, Z., Taal, B., Pascher, A.: ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. In: Neuroendocrinology 2016, pp. 139-143. S. Karger AG
25. Attili, F., Capurso, G., Vanella, G., Fuccio, L., Delle Fave, G., Costamagna, G., Larghi, A.: Diagnostic and therapeutic role of endoscopy in gastroenteropancreatic neuroendocrine neoplasms. Dig Liver Dis **46**(1), 9-17 (2014). doi:10.1016/j.dld.2013.04.007
26. Zilli, A., Arcidiacono, P.G., Conte, D., Massironi, S.: Clinical impact of endoscopic ultrasonography on the management of neuroendocrine tumors: lights and shadows. Digestive and Liver Disease **50**(1), 6-14 (2018). doi:10.1016/j.dld.2017.10.007
27. Kim, M.K.: Endoscopic ultrasound in gastroenteropancreatic neuroendocrine tumors. Gut and Liver **6**(4), 405-410 (2012). doi:10.5009/gnl.2012.6.4.405
28. Puli, S.R., Kalva, N., Bechtold, M.L., Pamulaparthy, S.R., Cashman, M.D., Estes, N.C., Pearl, R.H., Volmar, F.H., Dillon, S., Shekleton, M.F., Forcione, D.: Diagnostic accuracy of endoscopic

ultrasound in pancreatic neuroendocrine tumors: a systematic review and meta analysis. World J Gastroenterol **19**(23), 3678-3684 (2013). doi:10.3748/wjg.v19.i23.3678
29. Falconi, M., Eriksson, B., Kaltsas, G., Bartsch, D.K., Capdevila, J., Caplin, M., Kos-Kudla, B., Kwekkeboom, D., Rindi, G., Kloppel, G., Reed, N., Kianmanesh, R., Jensen, R.T., Vienna Consensus Conference, p.: ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology **103**(2), 153-171 (2016). doi:10.1159/000443171

Tables

Table 1: Overall and Treatment group characteristics						
	All patients	Avulsion Biopsy Treated	Resected patients	*Total/Subtotal Gastrectomy*	*Wedge Resection*	*Endoscopic Resection*
n	45	6	36	10	16	10
Age, years **Median** **IQR, R**	 56 47-67, 25-80	 62 57-65, 29-67	 54 45-66,25-77	 57 47-70, 34-77	 54 46-64, 32-75	 54 44-65, 25-69
Sex, n (%) **Male** **Female**	 24 (53) 21 (47)	 1 (17) 5 (83)	 20 (56) 16 (44)	 5 (50) 5 (50)	 9 (56) 7 (44)	 6 (60) 4 (40)
Tumour Size, mm **Median** **IQR, R**	 12 8-20,1-40	 3 3-5, 1-7	 14 9-20,6-40	 16.5 12-21,8-40	 13 9-25,6-40	 10 8-15,7-20
Tumour Site, n (%) **Antrum** **Body** **Fundus**	 3 (7) 36 (80) 6 (13)	 0 (0) 5 (83) 1 (17)	 2 (6) 29 (81) 5 (14)	 1 (10) 8 (80) 1 (10)	 1 (6) 13 (81) 2 (13)	 0 (0) 8 (80) 2 (20)
Tumour Grade, n (%) **G1- Ki-67 <3%** **Low G2- Ki-67 3-10%** **High G2- Ki-67 11-20%** **Unknown**	 22 (49) 19 (42) 3 (7) 1 (2)	 0 (0) 5 (83) 1 (17) 0 (0)	 15 (42) 17 (47) 3 (8) 1 (3)	 4 (40) 5 (50) 1 (10) 0 (0)	 6 (38) 7 (44) 2 (13) 1 (6)	 5 (50) 5 (50) 0 (0) 0 (0)
Staging, n (%) **EUS** **CT scan** **^{68}Ga DOTA PET/CT or ^{111}In Octreoscan** **^{18}F-FDG PET/CT**	 17 (38) 45 (100) 25 (56) 2 (4)	 0 (0) 6 (100) 1 (17) 0 (0)	 15 (42) 36 (100) 21 (21) 1 (1)	 1 (10) 10 (100) 5 (50) 0 (0)	 5 (31) 16 (100) 10(63) 1 (6)	 9 (90) 10 (100) 6 (60) 0 (0)
Follow up, months **Median** **IQR, R**	 56 14-86,4-290	 55 19-82, 4-114	 62 14-92,6-290	 77 73-117, 34-179	 62 20-96,6-290	 23 12-54,6-258
Recurrence, n (%)	2 (4)	0 (0)	2 (6)	0 (0)	1 (6)	1 (10)
G1: grade 1; G2: grade 2; p>0.05 for all comparators						

Table 2: Factors associated with negative endpoint			
Factor	**OR**	**95% CI**	**p value**
Univariate analysis			
Male gender	0.8333	0.2171-3.187	0.7871
Age at diagnosis	1.005	0.9584-1.054	0.8186
Tumour Size	0.8913	0.8040-0.9667	**0.012**
Grade	0.3760	0.1191-1.049	0.0722
Ki-67%	0.9114	0.7555-1.098	0.3117
Location	1.612	0.3574-8.697	0.5444
Multivariate analysis			
Male gender	0.5471	0.07966-3.355	0.5156
Age at diagnosis	1.009	0.9451-1.079	0.7758
Tumour Size	0.8509	0.7431-0.9388	**0.0055**
Ki-67%	0.9298	0.7531-1.149	0.4804
Location	2.018	0.3706-14.11	0.4338

Negative endpoint was considered to have occurred if any of the following events were observed: tumour-related death, presence of metastases and evidence of recurrence on follow-up.

Table 3: Size and negative outcome factors									
Size (mm)	**<10**	**>10**	**p value***	**<12**	**>12**	**p value**	**<14**	**>14**	**p value**
LN metastases on imaging Yes No	0 16	7 22	**0.040**	0 19	7 19	**0.016**	0 7	26 12	**0.001**
LN metastases on histology Yes No	0 8	11 13	**0.029**	1 10	10 11	**0.050**	1 14	10 7	**0.003**
LVI *Yes* *No*	1 9	9 12	0.106	1 11	9 10	**0.046**	3 13	7 8	0.135
Composite Negative Endpoint *Yes* *No*	0 16	12 17	**0.004**	2 16	10 17	0.086	2 24	10 9	**0.0014**
LN: Lymph node; LVI: lymphovascular invasion; *Fisher's exact									

Figure Legends

Fig. 1. Cases per centre and initial management.

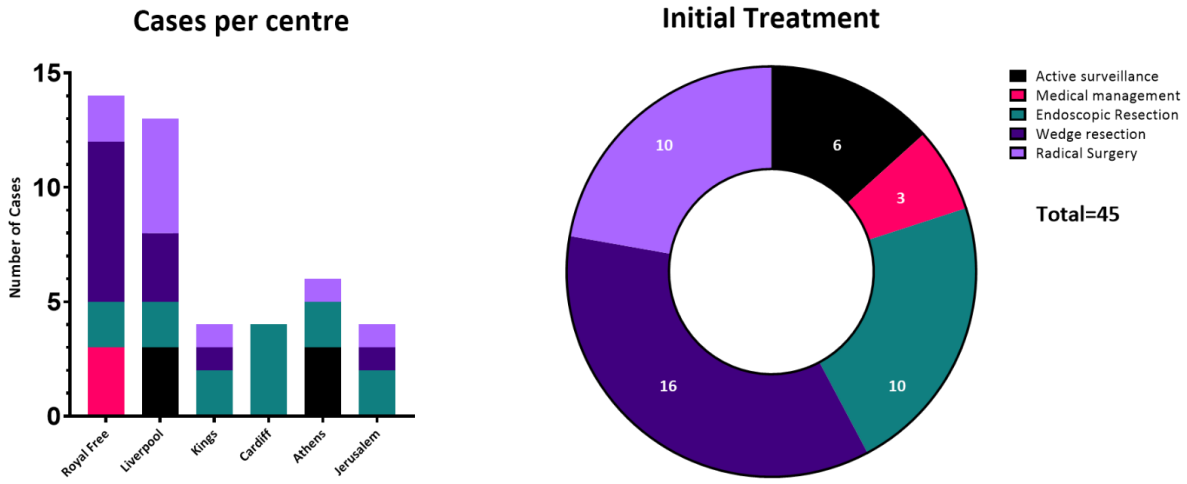


Fig. 2. Receiver operating characteristic (ROC) curve analysis of size of Type 3 NEN as negative outcome predictor. The cut off was 10mm.

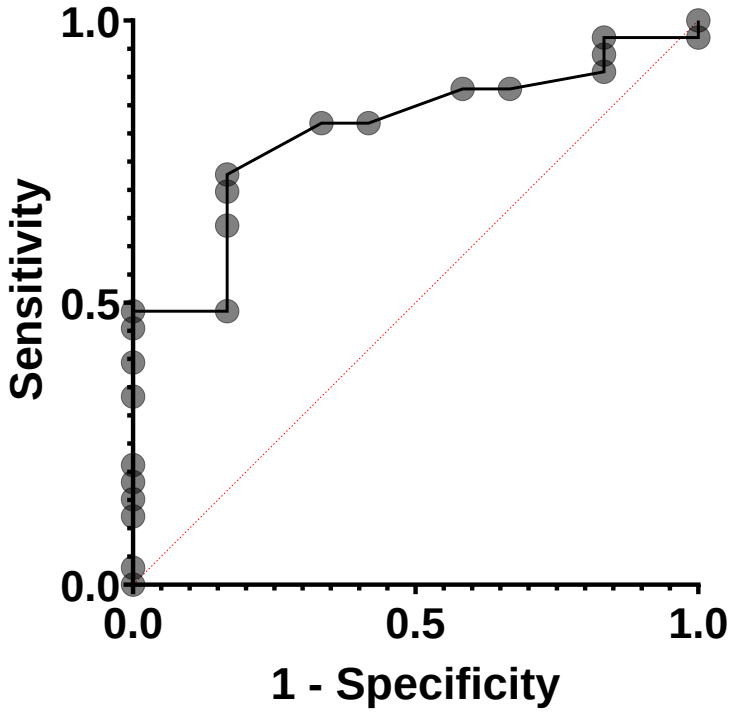
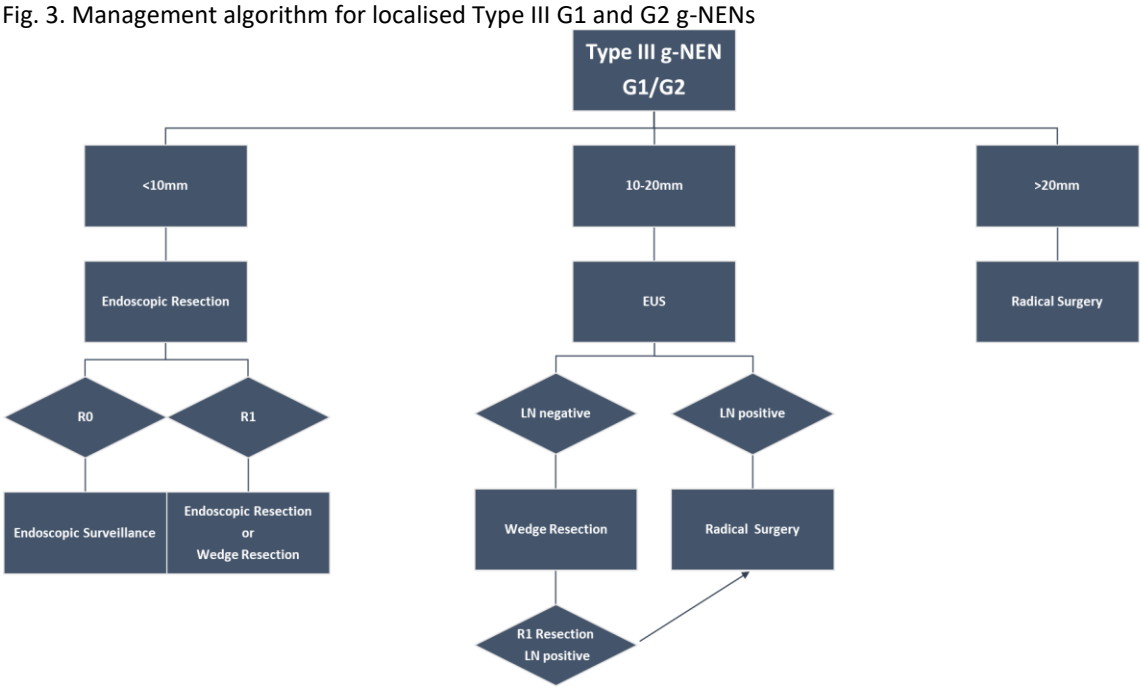


Fig. 3. Management algorithm for localised Type III G1 and G2 g-NENs



Supplementary Material

Fig. 1: Flow diagram of Type III g-NEN patients