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Tumour type and size are prognostic factors in gastric neuroendocrine neoplasia: A multicentre retrospective study

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ABSTRACT

Background: Gastric neuroendocrine neoplasias (gNEN) are defined as type I if associated with atrophic body gastritis and type III when tumour is sporadic. This classification, together with grading and size, plays a crucial prognostic role. Nevertheless, the impact of these features on clinical outcome is not clear.
Aim: To identify factors predicting poor outcome.
Patients and methods: Analysis of type I and type III gNEN. A composite endpoint was defined if tumour-related death or metastases or angioinvasion were observed.
Results: 156 gNENs were evaluated: 137 (87.8%) type I and 19 (12.2%) type III. Among type I, 103 were G1 (75.2%) and 34 (24.8%) were G2. In type III group, 8 were G1 (42.1%), 10 were G2 (52.6%), and 1 was G3 (5.3%). Negative endpoint occurred in 18 patients including 10 type III and 8 type I. Male gender ($p = 0.032$), tumour type ($p = 0.003$) and size >10 mm ($p = 0.024$) were predictors for poor outcome, whereas Ki67 was not confirmed on multivariate analysis ($p = 0.192$). 5-yr survival rates in type I and type III were 100% and 76.2%, respectively ($p = 0.0002$).
Conclusions: Tumour size, tumour type and gender affect clinical outcome in gNENs. In contrast to NENs rising from other sites, Ki67 plays a less important role.

1. Background

Gastric neuroendocrine neoplasms (gNENs) are classified clinically according to the background gastric pathology in three major categories: type I when atrophic body gastritis (ABG) is present, type II if it is related to gastrinoma/MEN I, and type III when they are sporadic due to absence of related pathology [1].

This clinical classification plays a crucial role when analysing prognosis. In fact, type I gNENs are widely considered indolent diseases with negligible metastatic potential and almost 100% long-term survival, whereas type III are aggressive tumours with high risk of metastasis, significant mortality, and poor long-term clinical outcome. Type II represents the minority of gNENs (10%), with an intermediate aggressiveness compared with type I and type III, tumour-related mortality being approximately 20% [1].

As with other digestive NENs, according to the European Neuroendocrine Tumours Society (ENETS) grading system [2], these tumours may also be divided into three groups depending on Ki67 index value: G1 when Ki67 <2%, G2 when Ki67 is 3–20% and G3 when Ki67 is >20%. Although grading has shown to be the strongest negative prognostic factor in digestive NENs from pancreas and jejunum-ileum [3–5], its role in gastric NENs is less clear because of the lack of solid data focusing on this topic.

Tumour size is reported by international guidelines to be one of the most relevant factors affecting patient management, indicating

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the aggressive therapeutic approach and more intensive surveillance programmes [1,6,7]. However, relationships among tumour types, grading expressed by Ki67 and size to predict clinical outcome has not been investigated in depth. Furthermore, most of the papers on gNENs have been published with small series of patients, because of the well-known rarity of this disease.

The aim of this study was to identify risk factors predicting poor clinical outcome in patients with non-familial (type I and type III) gNENs.

2. Patients and methods

This was a retrospective analysis of prognostic factors and long-term survival in consecutive patients with non-familial (type I and type III) well-differentiated gastric NENs diagnosed by four Italian referral centres for NEN management, from January 2000 to January 2018. Inclusion criteria were as follows: age >18 years; histologically proven diagnosis of well-differentiated gastric NEN; and availability of clinical and pathological data useful to classify tumour type according to ENETS guidelines [1]. The minimal required data set included tumour size (measured by endoscopy), immunohistochemical Ki67 evaluation, multiple gastric antrum and body biopsy samples to assess the presence of ABG.

Data were obtained from the clinical and pathological charts collected at each participating centre where the initial diagnosis was done. A unique computerized datasheet was subsequently created, and data were analysed retrospectively.

Gastric NEN was classified basing on clinical classification as "type I" when ABG (either arisen from long-standing H. pylori infection or in the context of autoimmune gastritis) was diagnosed, basing on histological evidence of atrophy on biopsies performed in the gastric body confirming replacement of the parietal cell mass by atrophic and metaplastic mucosa; otherwise, the tumours were classified as "type III". Patients with gastrinoma/MEN I – associated gastric NEN (type II) were excluded from this study. Tumours were graded according to the ENETS grading system [2] into three categories: G1 (Ki67 $\leq$2%), G2 (Ki 67 = 3–20%), and G3 (KI67 >20%).

This study conforms to the declaration of Helsinki. Informed consent for data collection was obtained from all patients.

Actuarial survival probabilities were calculated by the Kaplan–Meier method and results were compared by the log rank test. A composite negative endpoint was defined to identify patients with poor clinical outcome and was considered to have occurred if any of the following events were observed at time of diagnosis or during follow-up: tumour-related death, presence of metastases or presence of angioinvasion documented by histological examination. Risk factors were expressed as hazard ratio (95% confidence interval). Logistic regression was used to identify possible predictors of negative endpoint. The multivariate model was constructed by the enter method. Receiver operating characteristic (ROC) curve analysis was used to identify the cut-off level for Ki-67 and tumour size as predictors of presence of the composite negative endpoint (tumour-related death or presence of metastases or presence of angioinvasion). In those patients with multiple tumours, the largest lesion was identified and included in the risk factor and ROC curve analysis. The distribution of continuous variables was reported as median and interquartile range (IQR; 25th–75th percentiles) or median and range, as specified. Pearson r correlation coefficient was calculated to assess correlation between variables. A comparison between the subgroups was carried out using the Fisher exact test or the chi-square test for non-continuous variables, whereas the Mann–Whitney U test was used to compare the continuous variables, as appropriate. A p value of <0.05 was considered statistically significant.

Table 1
Comparison between type I and type III gastric NENs.

Feature	Type I (n = 137)	Type III (n = 19)	p
Female gender	96 (70%)	13 (68.4%)	1.000
Median age (IQR)	58 yr (49–67)	59 (50–68)	0.520
Median tumor size (IQR)	5 mm (3–8)	15 mm (10–25)	<0.0001
Median tumor Ki67 (IQR)	2% (1–2)	3% (2–8.5)	0.001
G grading[a]			
NET G1	103 (75.2%)	8 (42.1%)	0.0008
NET G2	34 (24.8%)	10 (52.6%)	
NEC G3	–	1 (5.3%)	

[a] G grading according with ENETS [2].

3. Results

A total of 200 patients with gNEN were initially collected. Of these, 44 patients (22%) were excluded from the final analysis due to the lack of required data (Ki67 value or tumour size) (39 patients), or due to poorly differentiated tumour morphology (5 patients). Thus, 156 patients with gNEN, in which tumour size and Ki67 were available, were included in the final analysis. Median follow-up time was 35.5 months (IQR 17–69). Of these, 137 patients (87.8%) had ABG-associated type I gNENs, whereas the remaining 19 (12.2%) were sporadic type III gNENs (Table 1). Median age at the time of gNEN diagnoses was 58 yr (IQR 49–68). Among type I gNENs, 44 patients (33.6%) had multiple tumours, resulting in a total number of 171 tumour lesions. No type III gNEN patient had multiple tumours.

Overall, metastases were present in 10 patients (6.4%), specifically in 7/19 (36.8%, lymph nodes 6 patients, liver 4 patients) and 3/137 (2.2%, all lymph nodes) patients with type III and type I gNEN respectively (p < 0.0001). Histological examination revealed angioinvasion in 11 patients (7%), most of them with type I tumours (n = 7, 63.6%). A total of 3 patients (1.9%) died of disease during follow-up (2 type III gNENs, and 1 type I gNEN). As a result, a negative endpoint occurred in 18 patients (11.5%) including 10 type III (median Ki67: 3%, IQR 2–15) and 8 type I gNENs (median Ki67: 4%, IQR 1.5–6.5).

3.1. Grading and size according with tumour type

As far as grading is concerned, of 137 patients with type I gNENs, 103 were G1 (75.2%) and the remaining 34 tumours (24.8%) were G2 tumours. Among 19 type III gNENs, 8 were G1 (42.1%), 10 tumours were G2 (52.6%), and the remaining 1 was a G3 tumour (5.3%). A significant correlation between Ki67 proliferative index and tumour size was observed (r = 0.260, p = 0.0003).

When data were analysed comparing the total number of type I tumour lesions (n = 171) and the group of type III lesions (n = 19), the latter group including larger tumours, with median sizes 5 mm and 15 mm, respectively (p < 0.0001, Table 1). Most of type I lesions were <1 cm (150/171, 87.7%), whereas the majority of type III lesions were >1 cm (14/19, 73.7%). When ROC analysis was performed to identify the cut-off for Ki67 and tumour size as predictors for the negative endpoint, Ki67 >2% (AUC = 0.719, p = 0.002) and size >10 mm (AUC = 0.824, p < 0.001) were identified. In the subgroup of 171 type I gNENs, these features were observed in 37 (21.6%, Ki67 >2%) and 22 (12.9%, size >10 mm) tumours, respectively. Ki67 values distribution is showed in Fig. 1.

Male gender, tumour size and type, grading and Ki67 value were significantly associated with a negative endpoint on univariate analysis by logistic regression analysis. However, only gender, tumour type and size were significant risk factors for poor clinical outcome, whereas Ki67 value lost statistical significance on multivariate analysis (Table 2). In addition to 2% proposed by ENETS [2], the value of 5% was tested as possible cut-off level to predict

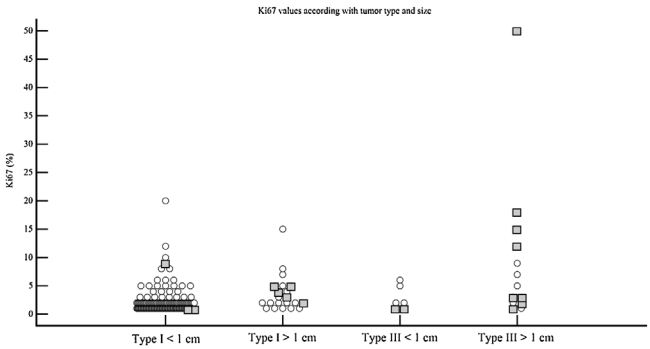

Fig. 1. Ki67 distribution according with tumour type and size. Square grey markers refer to patients in whom negative outcome occurred.

Table 2
Factors associated with negative endpoint.

Feature	OR	95%CI	p
Univariate analysis			
Male gender	3.41	1.25–9.30	0.016
Age at diagnosis[a]	1.00	0.96–1.04	0.720
Tumour type (III vs I)	17.91	5.67–56.54	<0.0001
Tumour size[a]	1.12	1.06–1.18	<0.0001
Tumor size >10 mm	13.70	4.43–42.33	<0.0001
Ki67[a]	1.26	1.10–1.45	0.0009
Ki67 >2%	5.20	1.86–14.53	0.0016
Multivariate analysis			
Male gender	4.17	1.12–15.51	0.032
Tumour type (III vs I)	9.29	2.09–41.16	0.003
Tumour size >10 mm	4.79	1.22–18.78	0.024
Ki67 >2%	2.32	0.65–8.27	0.192

Negative endpoint was considered to have occurred if any of the following events were observed: tumour-related death, presence of metastases or presence of angioinvasion documented by histological examination. Alternative Ki67 cut-off level 5% was also tested, however resulting not statistically significant by multivariate analysis (p = 0.562).

[a] For each increasing unit.

poor outcome. Similarly to 2%, also this alternative threshold was not significant by multivariate analysis (OR = 1.58, 95%CI 0.33–7.50, p = 0.562).

3.2. Therapeutic management

Most type I gNEN patients were treated by tumour endoscopic resection, chosen as the initial therapeutic approach in 113 patients (82.5%). Surgical gastric resection was performed in 5 patients (3.6%). A total of 19 patients (13.9%) with type I gNEN received somatostatin analogues; in this subgroup of patients, residual disease after initial endoscopic resection was observed in 14 patients, multiple tumours not suitable for radical endoscopic resection were found in 8 patients and recurrence after initial endoscopic resection occurred in 6 patients.

Among patients with type 3 gNEN, 9 (47.4%) were treated by gastrectomy, whereas in 6 patients (31.6%), tumours were removed by endoscopic resection. The remaining 4 patients (21%) were considered not suitable for tumour resection because of advanced disease. As far as medical treatment is concerned, 3 patients (15.8%) received somatostatin analogues, and 2 patients (10.5%) were treated with peptide receptor radionuclide therapy.

3.3. Tumour recurrence and survival

Among type I gNEN, 47 patients (34.3%) experienced tumour recurrence following initial tumour resection after a median

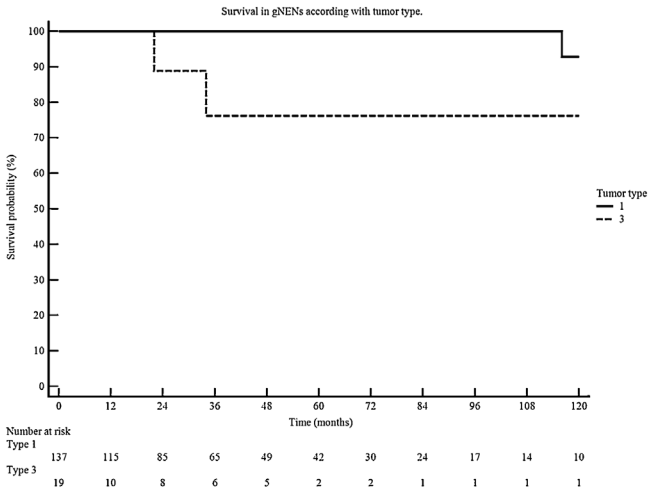

Fig. 2. Survival curves in type I (continuous line) and type III (dotted line). p < 0.0001.

follow-up period of 24 months (IQR 12–48 months). In this group of patients, median RFS was 86 months, and 2-yr RFS was 72.5%.

In the subgroup of type III gNEN, tumour recurrence was observed in only 3 patients (15.8%). Median RFS was not reached, and 2-yr RFS was 74.9%. No significant predictor for tumour recurrence was identified by univariate analysis: male gender, OR = 1.14, p = 0.672; tumour type III vs type I, OR = 0.61, p = 0.408; Ki67 >2%, OR = 1.04, p = 0.892; and tumour size >10 mm, OR = 1.20, p = 0.578).

Overall, 3 patients (1.9%) died of disease 22 months, 34 months and 116 months after initial diagnosis. Of these, 2 patients had type III gNEN, whereas the remaining one had type I G1 gNEN. This patient had initial diagnosis of G1 type I gNEN (size 12 mm), which underwent disease recurrence (G2, large tumour) 54 months after initial tumour resection, and died of disease 116 months after first gNEN detection. Mortality rates in type I and type III were 0.7% and 10.5%, respectively. Five-year survival rates in type I and type III gNENs were 100% and 76.2%, respectively (p = 0.0002) (Fig. 2). Median survival was not reached in either type I and type III gNENs.

4. Discussion

The present study showed that tumour size, tumour type and gender were the most powerful prognostic factors affecting clinical outcome in patients with gNENs, irrespective of tumour Ki67 value.

Although tumour type is a well-known negative feature in gNENs because of the varied biologies and more aggressive behaviour of sporadic type III compared with ABG-associated type I gNENs, prognostic role of size, proliferative index Ki67, and gender have not yet been established.

Ki67 is in general considered a pivotal marker predicting risk of recurrence and death in patients with GEP-NENs [3–5]. In fact, it is the rational basis for the grading system in digestive NENs, including gastric primaries [2]. However, its role in this specific group of patients, as for other primary sites such as the appendix [8,9], has not yet been established. In fact, conflicting results have been reported on this issue: in a multi-centre retrospective series of 20 patients with metastatic type I gNENs, it was reported that Ki67 widely ranged from 1% to 20% [10], thus suggesting that aggressive metastatic disease may occur also in tumours with very low proliferative index; in a recent large pathological series of gNENs, Ki67 was of limited prognostic value for type I tumours, whereas it proved effective for sporadic type III [11], again confirming its questionable prognostic role in the overall family of gNENs; Ki67 values ranging from 0.1% to 15% were also reported in another large series of 111 patients with type I gNENs who nevertheless

showed excellent log-term survival with no tumour-related death [12]. Conversely, tumour grading expressed by Ki67 significantly stratified gNENs into three subgroups with different survival in another large retrospective series, including 209 gNENs [13].

In the present study, Ki67 was not as effective as tumour type or size for predicting poor clinical outcome, as confirmed by multivariate analysis.

Tumour type was the primary criterion for prognosis and may be considered the key factor that drives physicians to plan treatment and follow-up in gNEN patients. Guidelines recommending planning therapeutic management of gNENs based on this factor suggest a conservative approach, including observation and endoscopic management in type I tumours and aggressive strategies comparable to those used in gastric non-endocrine cancers when faced with type III tumours [1]. Nevertheless, it should be considered that both type I and type III may be heterogeneous groups comprising different diseases with variable clinical behaviours according to other features. Although type III gNENs are usually characterized by large size and high Ki67 [1], it has been reported that even these tumours may be small, with low proliferative activity, and with non-aggressive behaviour during follow-up [14,15], thus suggesting there is not always strict correlations among tumour type, size and proliferative activity in these patients. The present paper confirms this hypothesis, because 42.1% of type III gNENs were G1 tumours with Ki67 <2%, and 26.3% were <1 cm. Conversely, large lesions with relatively high Ki67 were also observed in the group of type I tumours, as previously reported in other series [10,16]. Notably, no patients with G1 type III gNEN died during follow-up, thus resulting in a long-term survival in this subgroup of patients comparable to that observed in the type I gNEN subgroup. These findings suggest that planning gNEN therapeutic management based on tumour type only is insufficient, because other factors may impact tumour behaviour and prognosis.

Tumour size >10 mm is recommended by the ENETS guidelines as the cut-off diameter level to identify tumours with more aggressive behaviour, deserving radical resection, whereas an observational non-interventional approach was advocated for smaller lesions [1]. The present study highlights the prognostic role of tumour size, beyond tumour type and grading. In fact, size was an independent negative predictive factor for poor clinical outcome by multivariate analysis, and the cut-off size value showing the best discriminating ability was >10 mm, equal to the value proposed by the guidelines.

In terms of gender, other studies have reported worse clinical outcomes in males compared with females [17]. Male gender has also been reported as a risk factor in ABG patients for development of type I gNEN [18]; thereby suggesting possibly more aggressive behaviour in males than in females.

As previously recommended in series including mixed gastro-entero-pancreatic NENs, even in gNENs, an accurate prognosis assessment should be performed combining the prognostic roles of several factors [19,20], including tumour type, tumour size, gender, and as an additional less-relevant feature, the proliferative index Ki67.

Based on the findings of the present study, a simple step-by-step prognostic assessment of non-familial gNEN patients may be recommended (Fig. 3): (i) clinical evaluation to determine tumour type seeking ABG by performing multiple biopsy sampling of gastric fundus, body and antrum, as previously described [21]; (ii) assessing tumour size by endoscopic evaluation, to identify high risk tumour >1 cm; (iii) considering male gender as a generic negative prognostic factor; and (iv) considering Ki67 as potential additional negative factor.

The present study has some limitations, primarily related to the study design. Although data were collected by referral centres for the management of NENs, they were analysed retrospectively,

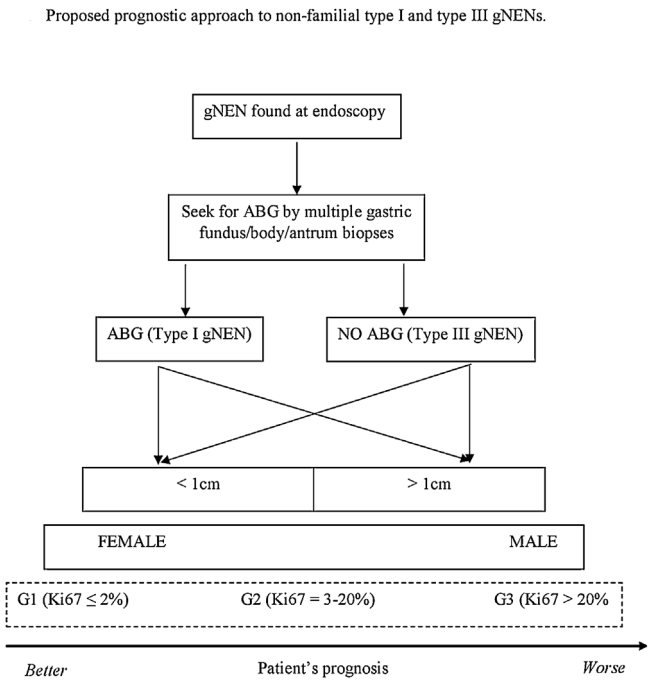

Fig. 3. gNEN: gastric neuroendocrine neoplasia. ABG: atrophic body gastritis. Grading according with ENETS [2].

and this represents an inherent limitation in terms of therapeutic management and follow-up programmes performed at each centre. The arbitrary choice to use a combined negative end-point including angioinvasion, developing of metastases and tumour-related death, may also affect risk factor analysis. Although angioinvasion may be considered a criterion of malignancy in NENs, as suggested by some studies, its role in gastric primaries is not well established [22–24]. Furthermore, a longer follow-up observation could improve the ability to detect unfavourable clinical outcomes in rare and indolent diseases such as gNENs. Finally, endoscopic procedures and histological diagnosis were not centralized, although they were performed in referral centres for NEN management, and this could reduce the reliability of some features, including number of detected tumour lesions at endoscopy and histological Ki67 assessment.

In conclusion, the present study shows that, in addition to tumour type, tumour size and patient gender are the most powerful prognostic factors in gNENs. Compared to NENs arising from other digestive sites (i.e., pancreas and jejunum-ileum), the proliferative index Ki67 plays a less important role in gNENs and should be considered as an additional minor prognostic factor in these patients.

Conflict of interest

None declared.

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