Comparison of relapse-free survival in gastric neuroendocrine carcinoma (WHO grade 3) and gastric carcinoma

Beom Su Kim, Young Soo Park, Jeong Hwan Yook and Byung-Sik Kim

Abstract

Background: We compared relapse-free survival (RFS) in gastric neuroendocrine carcinoma (WHO grade 3) and gastric carcinoma (GC). This is one of very few studies that compare the prognosis of poorly differentiated neuroendocrine carcinoma (WHO grade 3, G3 NEC) with that of GC.

Methods: Between 1996 and 2014, 63 patients were diagnosed with G3 NEC of the stomach and 56 with gastric neuroendocrine tumors (NETs) with GC at Asan Medical Center in Seoul, Korea. We also randomly selected 762 patients diagnosed with GC between 1999 and 2008.

Results: Patients with G3 NEC tumors that invaded the muscularis propria or shallower had poorer RFS than those with GC of the same type, while G3 NEC that invaded the subserosa or deeper had similar RFS to GC of that type. Patients diagnosed with G3 NEC with N0 or N2 had poorer RFS than the corresponding patients with GC, while those who had G3 NEC with N1 or N3 had similar RFS to the corresponding patients with GC. G3 NEC patients had poorer RFS than well-differentiated, moderately differentiated and poorly differentiated GC patients, while G3 NEC patients had similar RFS to that of those with signet ring cell carcinoma (SRC). In addition, patients with G3 NEC of stages I or IIa had poorer RFS than those with corresponding GC, while G3 NEC stage IIb or greater had similar RFS to the corresponding GC.

Conclusions: Non-advanced G3 NEC showed poorer RFS than GC excluding SRC, while advanced G3 NEC has a similar RFS to that of GC without SRC. Therefore, we recommend that patients with non-advanced G3 NEC of the stomach be given a more aggressive treatment and surveillance than those with non-advanced GC excluding SRC.

Keywords: grade 3 NEC, gastric carcinoma, neuroendocrine carcinoma, relapse-free survival, WHO classification

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Introduction

Neuroendocrine tumors (NETs) of the stomach are rare and comprise about 0.1–0.6% of all gastric cancers [Matsubayashi *et al.* 2000]. However, gastric NETs have increased in incidence [Modlin *et al.* 2003, 2004]. The World Health Organization (WHO) has proposed a classification of NETs of the digestive system based on the Ki-67 index (grade 1, ≤2%; grade 2, 3–20%; and grade 3, >20%) [Hamilton and Aaltonen, 2000]. As of now, NETs are classified into the following subclasses: NETs, grade 1 (carcinoid); atypical carcinoid tumors (well-differentiated neuroendocrine carcinomas), grade 2; poorly differentiated neuroendocrine carcinomas (small and large cell type), grade 3. Rindi and colleagues have presented the 'European Neuroendocrine Tumor Society (ENETS) TNM staging of foregut (neuro) endocrine tumors: a consensus proposal including a grading system based on Ki-67 index and mitosis' [Rindi *et al.* 2006], and Pape and colleagues have examined the prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [Pape *et al.* 2008]. Recently, ENETS published consensus guidelines for the standard of care in NETs: 'Towards a standardized approach to the diagnosis of GEP-NETs and

their prognostic stratification based on TNM classification' [Kloppel *et al.* 2009]. However, the American Joint Committee on Cancer (AJCC) (7th edition) proposed that high-grade neuroendocrine carcinomas and mixed glandular/well-differentiated NETs should be staged according to the guidelines used for staging carcinomas at that site [Edge *et al.* 2010]. Thus, the staging systems for NETs are not yet unified worldwide.

It is generally regarded that gastric neuroendocrine carcinomas (NECs) are extremely malignant because they have aggressive biological behavior and frequently metastasize to lymph nodes and the liver, even in the early stages of the disease [Matsui *et al.* 1991]. It has been suggested that angioinvasion, tumor size, clinicopathological type, mitotic index and Ki-67 labeling index are predictors of tumor malignancy and patient outcome [Rindi *et al.* 1999]. However, there have been only few reports supporting this view [Jiang *et al.* 2006; Kubota *et al.* 2012]. In addition, Kim and colleagues reported that the small cell type of gastric NEC did not have such extreme behavior [Kim *et al.* 2013]. We sought to find reports that compared gastric NEC (WHO grade 3, G3) with gastric carcinoma (GC) in terms of relapse-free survival (RFS), but were unable to find such studies. We therefore presumed that a study on RFS comparison in NEC/GC would be a valuable addition to the current clinical knowledge in gastric cancer.

Methods

Between 1996 and 2013, 63 patients were diagnosed with poorly differentiated G3 NEC of the stomach, and 56 were diagnosed as mixed type at the Asan Medical Center in Seoul, Korea. Mixed type was defined as NET mixed with GC. None of the tumors had metastasized and all were curatively resected. All tissues were reviewed by a pathologist and classified according to the WHO 2010 classification [Hamilton and Aaltonen, 2000]. We also selected 762 patients with GC according to the following criteria: availability of entire specimen; blood samples; full follow-up records; and records of genetic analysis between 1999 and 2008. None had distant metastases at diagnosis and all underwent curative resection. We used the AJCC (7th edition) TNM classification for these tumors [Edge *et al.* 2010].

We compared the basic clinical features and survival data for the G3 NEC *versus* mixed type pair,

for the G3 NEC *versus* GC pair, and for the GC *versus* the mixed type pair. RFS was defined as the time from resection to recurrence or last contact. We then evaluated clinical outcomes and RFS according to depth of invasion, nodal stage, AJCC TNM stages and histologic differentiation.

Numeric data are expressed as means with standard deviations, and compared using Student's *t*-test. Risk factors were analyzed using the chi-square test. Survival data were examined using the Kaplan–Meier method with the log-rank test. All statistical data were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) software; a *p* value below 0.05 was considered statistically significant.

This study received approval from Asan Medical Center's Institutional Review Board.

Results

Subgroup clinicopathologic analysis: grade 3 neuroendocrine carcinoma, mixed type and gastric carcinoma

All 63 G3 NEC patients had invasion of the submucosa or deeper, and only 2 (3.7%) of the 56 patients with mixed types showed confinement to the mucosal layer. However, 196 (25.6%) of the GCs were confined to the mucosal layer. There were distinctive clinicopathologic differences between G3 NEC and GC (Table 1): patients with G3 NEC were older than those with GC ($p < 0.05$), and they experienced more lymph node metastases, had higher stages and suffered more tumor recurrence than did the GC patients ($p < 0.05$). Patients of the mixed type were also older than those with GC ($p < 0.05$) and experienced more lymph node metastases and higher stages ($p < 0.05$). In addition, they had a higher proportion of poorly differentiated adenocarcinoma or signet ring cell carcinoma (SRCs) than the patients with GC ($p < 0.05$), while showing a lower proportion of well-differentiated adenocarcinoma ($p < 0.05$).

Figure 1 shows Kaplan–Meier estimates of RFS. Patients with G3 NEC had a lower survival rate than the other two groups ($p < 0.05$), who had similar RFS values ($p > 0.05$).

Adjuvant chemotherapy

We could not compare the adjuvant chemotherapy regimen between the three groups of tumors

Table 1. Subgroup clinicopathologic analysis; G3 NEC, mixed type, and GC.

Patient characteristics	G3 NEC (n = 63, %)	Mixed type (n = 56, %)	GC (n = 762, %)	p value
Age (year)	61.7 ± 9.1	60.2 ± 10.6	50.9 ± 12.1	$p < 0.05^{\dagger,\ddagger}$
Gender				NS
Male	48 (76.2)	40 (71.4)	517 (67.8)	
Female	15 (23.8)	16 (28.6)	245 (32.2)	
Tumor site (%)				$p < 0.05^{*,\dagger}$
Upper third	11 (17.5)	1 (1.8)	176 (23.1)	
Middle third	21 (33.3)	25 (44.6)	306 (40.2)	
Lower third	31 (49.2)	30 (53.6)	340 (44.7)	
Multiple	6 (9.5)	6 (10.7)	12 (1.6)	$p < 0.05^{\dagger,\ddagger}$
Adjuvant CTx	35 (55.6)	30 (53.6)	294 (38.6)	$p < 0.05^{\dagger,\ddagger}$
Tumor size (mm)	56.9 ± 28.7	59.9 ± 29.2	50.8 ± 33.3	$p < 0.05^{\ddagger}$
Differentiation				
Well-differentiated		1 (1.8)	78 (10.2)	$p < 0.05^{\ddagger}$
Moderately differentiated		14 (25.0)	180 (23.6)	NS
Poorly differentiated		32 (60.7)	339 (44.5)	$p < 0.05^{\ddagger}$
SRC type		3 (5.4)	149 (19.60)	$p < 0.05^{\ddagger}$
Others		4 (7.1)	16 (2.1)	$p < 0.05^{\ddagger}$
Lymphovascular invasion	55 (87.3)	44 (78.6)	266 (34.9)	$p < 0.05^{\dagger,\ddagger}$
Lymph node metastasis	40 (63.5)	36 (64.3)	314 (41.2)	$p < 0.05^{\dagger,\ddagger}$
Recurrence	24 (38.1)	13 (23.2)	121 (15.9)	$p < 0.05^{\dagger}$
T stage				$p < 0.05^{\dagger,\ddagger}$
1	9 (14.3)	7 (12.5)	350 (45.9)	
2	13 (20.6)	14 (25.0)	84 (11.0)	
3	27 (42.9)	27 (48.2)	155 (20.3)	
4	14 (22.2)	8 (14.3)	173 (22.8)	
Nodal stage				$p < 0.05^{\dagger,\ddagger}$
0	23 (36.5)	20 (35.7)	448 (58.8)	
1	14 (22.2)	15 (26.8)	93 (12.2)	
2	15 (23.8)	13 (23.2)	82 (10.8)	
3	11 (17.5)	8 (14.3)	139 (18.2)	
Stage				$p < 0.05^{\dagger,\ddagger}$
1	15 (23.8)	17 (30.3)	384 (50.4)	
2	22 (34.9)	20 (35.7)	151 (19.8)	
3	26 (41.3)	19 (40.0)	230 (30.2)	

G3 NEC, grade 3 neuroendocrine carcinoma; GC, gastric carcinoma; NS, non-specific; SRC, signet ring cell carcinoma.
*G3 NEC *versus* mixed type.
†G3 NEC *versus* GC.
‡Mixed type *versus* GC.

as a function of mucosal layer involvement because none of the G3 NEC was confined to the mucosa. We reviewed the adjuvant chemotherapy regimens administered for the patients. A total of 39 (61.9%) of the GC NEC patients received adjuvant chemotherapy and 21 (53.8%) of them received intravenous chemotherapy. A total of 37 (66.1%) of the mixed type patients received adjuvant chemotherapy, 14 (37.8%) received intravenous chemotherapy, and 14 received oral plus intravenous chemotherapy. For GC, 292 patients (38.3%) received adjuvant chemotherapy and 165 (56.5%) of them received oral plus intravenous chemotherapy. Regimens of oral chemotherapy or intravenous chemotherapy differed between G3 NEC and GC and between
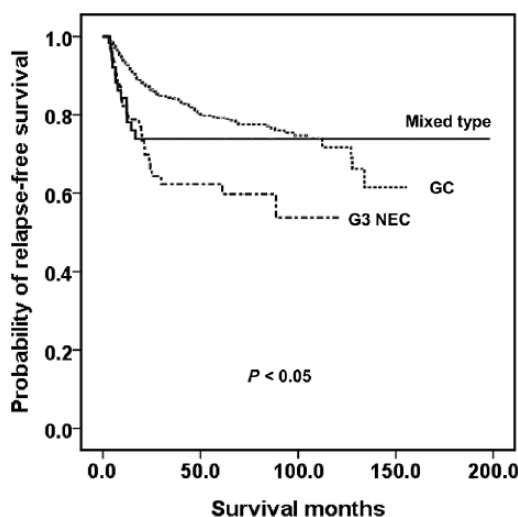
Figure 1. Kaplan–Meier curves for RFS in patients with grade 3 neuroendocrine carcinoma, mixed type or gastric carcinoma.

mixed type and GC. However, regimens of oral plus intravenous chemotherapy differed only between mixed type and GC. In stage 2 cancer, a similar proportion of patients in each group received chemotherapy. The route of chemotherapy administration differed between subgroups.

Matched-pair analysis according to depth of invasion

We analyzed the relation between clinicopathologic data and depth of invasions. For invasions reaching either the submucosa or the muscularis propria, the results were similar. In the submucosal layer, G3 NEC had more aggressive behavior, including lymph node metastasis and tumor recurrence, and poorer RFS than GC ($p < 0.05$). The mixed type also had poorer RFS than the GC. In the muscularis propria tumors, G3 NEC again exhibited more aggressive behavior, including lymphovascular invasion and tumor recurrence, and poorer RFS than the GC ($p < 0.05$), and the mixed types had poorer RFS than the GC as well. In the subserosal layer or beyond the subserosa, the results differed from those in the submucosa and muscularis propria: in the subserosal layer, there were no significant differences in lymph node metastasis and tumor recurrence between any groups ($p > 0.05$) and a similar trend was seen in the serosal layer.

Therefore, we divided the cases into two groups. Group 1 (Table 2) contained tumors invading the

submucosa or muscularis propria; group 2 (Table 3) contained tumors invading the subserosa or beyond the subserosa. The G3 NEC in group 1 had more aggressive behaviors, including lymphovascular invasion, lymph node metastasis and tumor recurrence, than did the GC ($p < 0.05$). They also had poorer RFS than the mixed type and GC (Figure 2a), which had similar RFS (Figure 2a) ($p > 0.05$). In contrast, there were no statistically significant differences in surgical outcomes including lymph node metastasis and recurrence between the various types in group 2 (Figure 2b) ($p > 0.05$)

RFS according to nodal group, histologic differentiation and TNM stage

We evaluated RFS according to nodal stage. In N0 and N2, G3 had poorer RFS than the other two groups ($p < 0.05$), between which there was no difference in RFS ($p > 0.05$). However, in N1 and N3, there was no difference in RFS between any groups ($p > 0.05$). We evaluated RFS according to the histologic differentiation of the GC. G3 NEC had poorer RFS than well-differentiated, moderately differentiated or poorly differentiated GC (Figure 3a–c, $p < 0.05$). However, the RFS was similar to that of SRC GC (Figure 3d, $p < 0.05$). We also evaluated RFS according to TNM stage. In stage I, G3 NEC and the mixed type had poorer survival than GC ($p < 0.05$), but there was no difference in RFS between G3 NEC and mixed type ($p > 0.05$). In stage IIa, G3 NEC had poorer survival than the other two groups ($p < 0.05$), but there was no difference in RFS between G3 NEC and mixed type and between mixed type and GC ($p > 0.05$). In stage IIb, IIIa, IIIb or IIIc there was no difference in RFS between any groups ($p < 0.05$). Therefore, we divided the stages into two groups: stage I and IIa in group 1; and stage IIb through to IIIc in group 2. The G3 NEC in group 1 had poorer survival than the mixed type and GC (Figure 4a, $p < 0.05$), and there was no difference in survival between mixed type and GC ($p > 0.05$). In group 2 there was no difference in RFS between any of the types (Figure 4b, $p > 0.05$).

Discussion

The WHO and ENET grading systems according to Ki-67 index/mitosis have been validated for the foregut and particularly for pancreatic neuroendocrine neoplasm (NEN)s (PanNENs), and their biological relevance and power to discriminate

Table 2. Matched-pair analysis according to depth of invasion in submucosa or muscularis propria.

Patient characteristics	G3 NEC (n = 22, %)	Mixed type (n = 19, %)	GC (n = 238, %)	*p* value
Age (year)	63.8 ± 7.5	62.1 ± 8.7	53.3 ± 12.1	$p < 0.05^{\dagger,\ddagger}$
Gender				$p < 0.05^{\ddagger}$
Male	13 (59.1)	8 (42.1)	170 (71.4)	
Female	9 (40.9)	11 (57.9)	68 (28.6)	
Tumor site (%)				$p > 0.05$
Upper third	1 (4.5)	0	27 (11.1)	
Middle third	8 (36.4)	9	106 (44.5)	
Lower third	13 (59.1)	10	105 (44.1)	
Multiple	3 (13.6)	2 (10.5)	2 (0.8)	$p < 0.05^{\dagger,\ddagger}$
Adjuvant CTx	5 (22.7)	2 (10.5)	31 (13.1)	$p > 0.05$
Tumor size (mm)	40.5 ± 22.1	50.1 ± 24	38.7 ± 20.0	$p < 0.05^{\ddagger}$
Lymphovascular invasion	20 (90.9)	13 (68.4)	65	$p < 0.05^{\dagger,\ddagger}$
Lymph node metastasis	11 (50.0)	6 (31.6)	60 (27.3)	$p < 0.05^{\dagger}$
Recurrence	6 (27.3)	1 (5.3)	12 (5.0)	$p < 0.05^{\dagger}$

G3 NEC, WHO grade 3 neuroendocrine carcinoma; GC, gastric carcinoma.
*G3 NEC *versus* mixed type.
†G3 NEC *versus* GC.
‡Mixed type *versus* GC.

Table 3. Matched-pair analysis according to depth of invasion in subserosa or deeper.

Patients characteristics	G3 NEC (n = 41, %)	Mixed type (n = 35, %)	GC (n = 328, %)	*p* value
Age (year)	60.5 ± 9.8	59.2 ± 11.7	50.5 ± 12.6	$p < 0.05^{\dagger,\ddagger}$
Gender				$p < 0.05^{\dagger,\ddagger}$
Male	35 (85.6)	31 (88.6)	217	
Female	6 (14.6)	4 (11.4)	111	
Tumor site (%)				$p < 0.05^{*,\ddagger}$
Upper third	10 (24.4)	1 (2.9)	58 (17.7)	
Middle third	13 (31.7)	14 (40.0)	134 (40.9)	
Lower third	18 (43.9)	20 (57.1)	136 (41.4)	
Multiple	3 (7.3)	3 (8.6)	5 (1.5)	$p < 0.05^{\dagger,\ddagger}$
Adjuvant CTx	30 (73.2)	28 (80.0)	262 (79.9)	$p > 0.05$
Tumor size (mm)	65.5 ± 28.3	66.9 ± 29.5	71.1 ± 35.3	$p > 0.05$
Lymphovascular invasion	35 (85.4)	31 (88.6)	193 (58.8)	$p < 0.05^{\dagger,\ddagger}$
Lymph node metastasis	29 (70.7)	30 (85.7)	247 (75.3)	$p > 0.05$
Recurrence	18 (43.9)	12 (34.3)	105 (32.0)	$p > 0.05$

G3 NEC, WHO grade 3 neuroendocrine carcinoma; GC, gastric carcinoma.
*G3 NEC *versus* mixed type.
†G3 NEC *versus* GC.
‡Mixed type *versus* GC.

among prognostic groups has been widely confirmed [Ekeblad *et al.* 2008; Fischer *et al.* 2008; Pape *et al.* 2008; La Rosa *et al.* 2009; Scarpa *et al.* 2010]. However, the TNM stages of the AJCC and ENET have not yet been unified. In the AJCC (7th edition), the T categories for GC, NEC and adenocarcinoma with NET are: T1 – tumor invading the mucosa or submucosa;
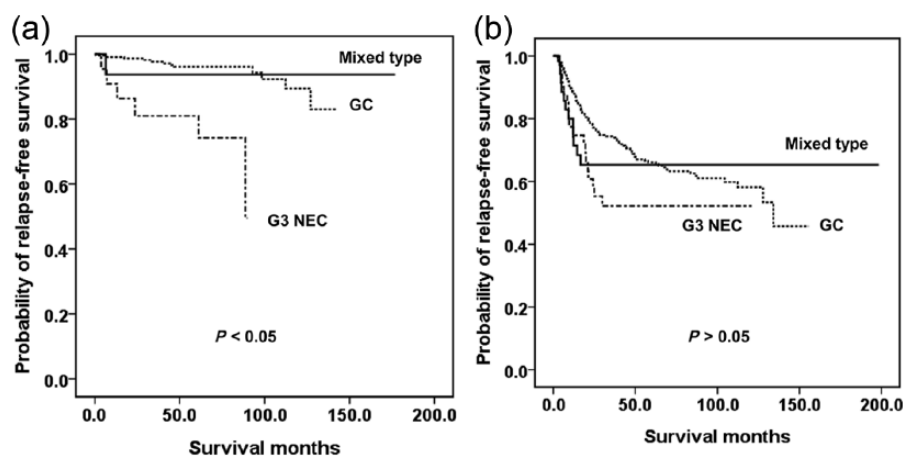
Figure 2. Kaplan–Meier survival curves for relapse-free survival of (a) tumors invading the submucosa or muscularis propria; and (b) tumors invading the subserosa or deeper.
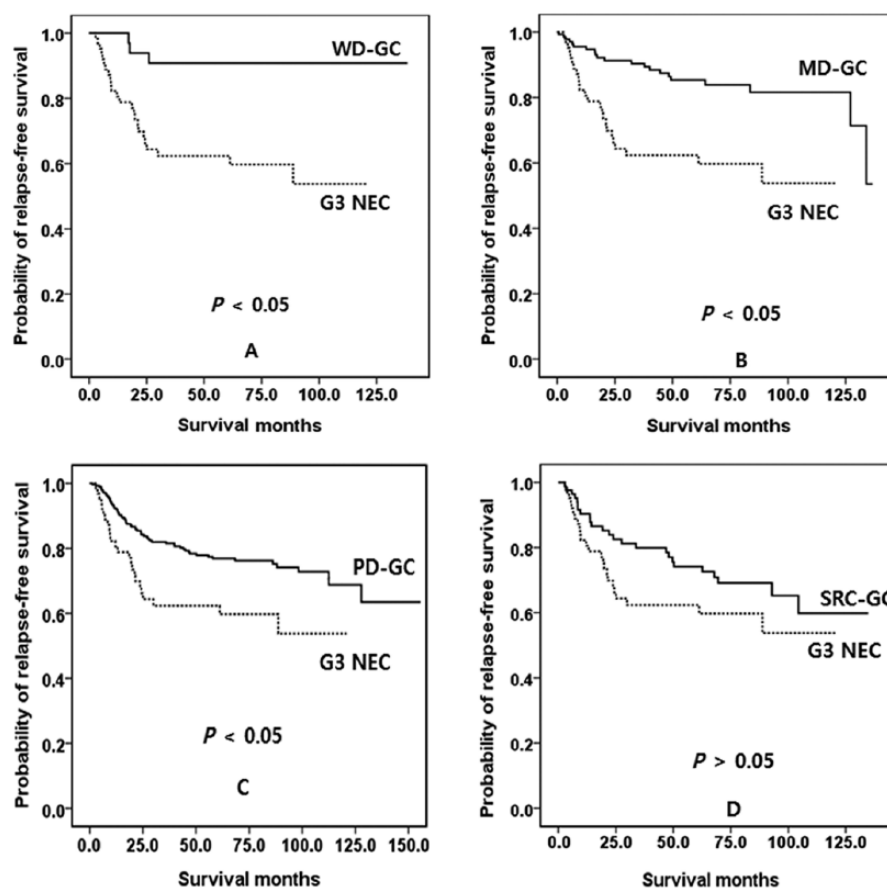

Figure 3. Kaplan–Meier survival curves for RFS, according to histologic differentiation of the GC. (a) Well-differentiated GC *versus* G3 NEC. (b) Moderately differentiated GC *versus* G3 NEC. (c) Poorly differentiated GC *versus* G3 NEC. (d) SRC type GC *versus* G3 NEC.
G3 NEC, WHO grade 3 neuroendocrine carcinoma; GC, gastric carcinoma; MD, moderately differentiated; PD, poorly differentiated; RFS, relapse-free survival; SRC, signet ring cell carcinoma; WD, well-differentiated.

T2 – tumor invading the muscularis propria; T3 – tumor invading the subserosa; and T4 – tumor penetrating the serosa or invading adjacent structures. In contrast, the T categories for gastric
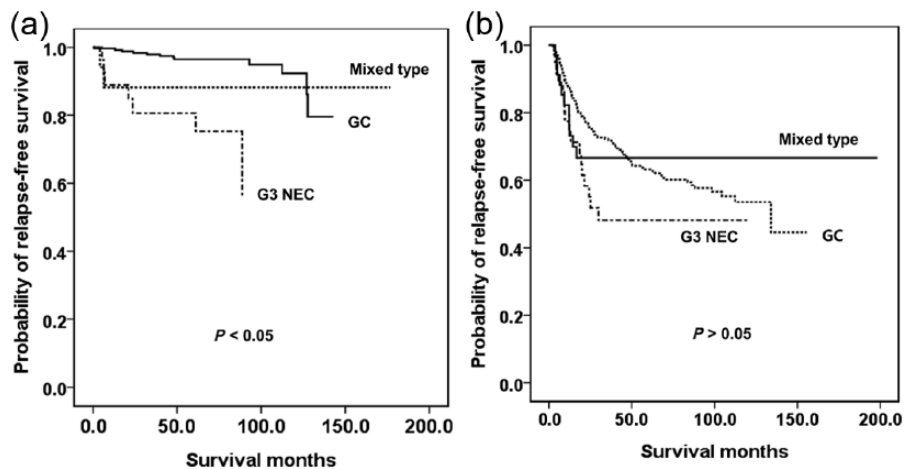
Figure 4. Kaplan–Meier survival curves for RFS. (a) AJCC stage I or IIa. (b) AJCC stage IIb or IIIa–c. G3 NEC, WHO grade 3 neuroendocrine carcinoma; GC, gastric carcinoma.

NET are defined as: T1 – tumor invading the lamina propria or submucosa and 1 cm or less in size; T2 – tumor invading the muscularis propria or >1 cm in size; T3 – tumor penetrating the subserosa; and T4 – tumor invading serosal or other organs or adjacent structures [and for any T, add (m) for multiple tumors]. In contrast, ENET TNM stage is uniform for all gastric NET or NEC, unlike GC TNM stage. In this study we evaluated the TNM stage uniformly according to the AJCC (7th edition) definitions of GC, NEC, and adenocarcinoma with NET.

Gastric NET frequently contains an adenocarcinoma component [Waldum *et al.* 1998; Nishikura *et al.* 2003], and it has been proposed that gastric NET is derived predominantly from endocrine precursor cell clones arising in earlier adenocarcinoma components that transform into endocrine tumors during rapid clonal expansion [Nishikura *et al.* 2003]. A category of mixed adeno-neuroendocrine carcinoma (MANEC) was recently proposed on the grounds that WHO 2010 did not define cases with both neuroendocrine and non-neuroendocrine components [La Rosa *et al.* 2012]. In addition, there are no studies that support the 30% rule for the definition of MANEC. Thus, WHO 2010 classification is likely to be correct in the light of the evidence for the MANEC definition [Rindi *et al.* 2014]. Kim and colleagues reported that the neuroendocrine features of GC appeared to be correlated with clinicopathologic parameters such as high stage and high frequency of regional lymph node metastasis [Kim *et al.* 2011]. In our study, we could not establish the

exact proportions of each component. Therefore, we defined NETs with any proportions of adenocarcinoma as a mixed type.

Recently, Park and colleagues evaluated the clinicopathologic features of GCs with neuroendocrine differentiation (NED) and found no significant difference in the survival rate between NEC and GC with 10–30% of NED [Park *et al.* 2014]. They therefore proposed that GCs with ≥10% NED should be differentiated from conventional adenocarcinomas. They also recommended that the ≥10% NED cut-off may be useful in practice and may serve as an informative parameter for predicting patient outcomes and establishing optimal therapeutic guidelines for GCs with NED.

Several studies have already shown that NEC of the stomach has a poor prognosis [La Rosa *et al.* 2011; Ishida *et al.* 2013]. However, there are few reports that have evaluated the prognostic significance of neuroendocrine components of GC [Jiang *et al.* 2006; Kubota *et al.* 2012]. In addition, Kim and colleagues reported that the small cell type of gastric NECs did not have such extreme behavior [Kim *et al.* 2013], and Kubota and colleagues reported that early detection and curative operations are essential for improving the prognosis of gastric NEC [Kubota *et al.* 2012].

Our study has the following limitations. NETs of the stomach are very rare; therefore, the statistical power of this study was limited by the relatively small number of patients. Recently, WHO 2010

defined MANEC as requiring >30% of each component. However, as mentioned above, we could not determine the exact proportions of the components, so we defined NETs with any portion of adenocarcinoma as mixed type. Another weakness is the lack of data on the expression of neuroendocrine markers in the control group. In addition, various adjuvant chemotherapy regimens were administered for patients in each type of tumor and the regimens differed widely among subgroups. Our study may also be prone to selection bias because the patients were selected according to the following criteria: availability of entire specimen, blood samples, full follow-up records, and records of genetic analysis.

In conclusion, even though the number of patients with GC NEC was very small and different adjuvant chemotherapy regimens were administered, our results show that G3 NEC has a worse prognosis than GC. G3 NEC tumors that invade only as far as the muscularis propria have poorer RFS than the corresponding cases of GC, while those that invade the subserosa or deeper have similar RFS to GC. Therefore, non-advanced G3 NEC of the stomach requires more aggressive treatment and surveillance than does GC, excluding the SRC type.

Ethical standards
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or its alternative was obtained from every patient in the study.

Funding

Conflict of interest statement
The authors declare that there is no conflict of interest.

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