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Gastric Endocrine Carcinoma: A New Look at a Rare Tumor From Cases in Japan

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Objective: We evaluated the clinicopathologic factors associated with gastric neuroendocrine carcinoma (NEC) in patients who underwent surgical resection. Gastric NEC is rare, accounting for only about 0.6% of all malignant gastric tumors. Neither its pathogenesis nor its treatment has been fully established.

Methods: We assessed 10 patients with gastric NEC who underwent surgical resection in our hospital between September 2007 and June 2019.

Results: The patients consisted of 9 men and 1 woman, aged 63 to 78 years. The tumors were localized in the upper region (n = 5), middle region (n = 3), and lower region (n = 2). The macroscopic types were evaluated as 0-IIc (n = 3), 1 (n = 3), 2 (n = 1), 3 (n = 2), and 4 (n = 1). The stages were ascertained as IA (n = 3), IIB (n = 3), IIIA (n = 2), IIIB (n = 1), and IIIC (n = 1). Radical resection was performed in all the patients. After surgery, relapse-free survival was achieved in 6 patients. The mean postoperative survival time was 63.5 months. On immunostaining, 6 patients were positive for CD56, and all were positive synaptophysin and chromogranin A. Of the 10 patients, standard-type adenocarcinoma was concomitantly present in 6.

Conclusions: Some patients with surgically resected gastric NEC survived over a long period, suggesting the usefulness of radical resection. In future studies, the pathogenesis of gastric NEC should be fully clarified, and therapeutic strategies must be further developed.

Key words: Neuroendocrine carcinoma – Radical resection – Gastric NEC

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Gastric neuroendocrine carcinoma (NEC) is rare, accounting for only approximately 0.6% of all malignant gastric tumors. Its malignancy level is high, and lymph node and liver metastases are commonly observed. However, to our knowledge, neither the classification nor the pathogenesis and treatment of gastric NEC has been fully established. In this study, we evaluated the clinicopathologic factors associated with gastric NEC in patients who had undergone surgical resection in our hospital.

Patients and Methods

We assessed 10 patients with gastric NEC who were diagnosed in accordance with the 2010 WHO classification in our hospital between September 2007 and June 2019. For the clinicopathologic factors, we evaluated the age, sex, tumor site, macroscopic type, stage, prognosis, immunohistochemical reactions (neuroendocrine markers: CD56, synaptophysin, chromogranin), and presence or absence of standard-type adenocarcinoma.

Results

The patients consisted of 9 men and 1 woman whose ages ranged from 63 to 78 years (median: 72 years). The tumor sites included the upper region (n = 5), middle region (n = 3), and lower region (n = 2). The macroscopic types were evaluated as 0-IIc (n = 3), 1 (n = 3), 2 (n = 1), 3 (n = 2), and 4 (n = 1). In accordance with the 8th edition of the regulations for the management of gastric cancer (UICC-TNM), the stages were evaluated as IA (n = 3), IIB (n = 3), IIIA (n = 2), IIIB (n = 1), and IIIC (n = 1). The characteristics of the 10 patients are shown in Table 1.

Histopathologically, all 10 patients were diagnosed as having gastric NEC in accordance with the 2010 World Health Organizaiton classification. Of the 10 patients assessed, lymphatic invasion was noted in 8 and venous invasion in 6. On immunostaining, 6 patients were positive for CD56, and all were positive for synaptophysin and chromogranin A. Furthermore, standard-type adenocarcinoma was concomitantly present in 7 of the 10 patients (Table 2).

Surgery was performed in all 10 patients in whom R0 resection was considered possible. Proximal, distal, or total gastrectomy was selected in accordance with the tumor site. R0 resection was possible in all 10 patients. Other organs were concomitantly resected in 3 of the 10 patients. Of these 3 patients, total gastrectomy, D2 dissection, and splenectomy were performed separately in 2, and total gastrectomy, D2 dissection, distal pancreatectomy, and splenectomy were carried out in 1. Postoperative relapse-free survival was achieved in 7, of whom postoperative adjuvant chemotherapy was performed in 4. Overall, the median relapse-free survival time was 56.5 months, and the mean postoperative survival time was 63.5 months (Table 3).

Table 1 Patient characteristics

Background	n = 10
Sex	
Male	9
Female	1
Age	
Median (range)	72 (63–78)
Tumor location	
U	5
M	3
L	2
Tumor type	
0	3
1	3
2	1
3	2
4	1
5	0
15th JCGC stage	
I	3
II	3
III	4
IV	0
Initial treatment	
Operation	10
Chemotherapy	0

JCGC, Japan Classification of Gastric Carcinoma; L, lower; M, middle; U, upper.

Discussion

Gastric NEC is rare, accounting for only approximately 0.6% of all malignant gastric tumors.[1–4] It usually has a poor prognosis with lymph node and liver metastases. Apparently, neither its pathogene-

Table 2 Immunohistochemical findings

Pathological features	n = 10	
Lymphatic vessel invasion	(+/−)	8/2
Blood vessel invasion	(+/−)	6/4
Cell type	(Small/large)	4/6
Coexistence of adenocarcinoma	(+/−)	6/4
Neuroendocrine markers		
CD56	(+/−)	6/4
Synaptophysin	(+/−)	10/0
Chromogranin	(+/−)	10/0

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Table 3 Characteristics of the resected cases (n = 10)

Case	Treatment	Curability	pStage	Recurrence	Postoperative survival (mo)	Prognosis	Cause of death
1	TG	R0	IIB	—	79.5	Alive	—
2	TG	R0	IA	—	90.4	Alive	—
3	TG	R0	IIB	Liver	37.3	Dead	Cancer
4	DG	R0	IIIB	—	74.1	Alive	—
5	TG+S+DP	R0	IIIC	LN[a]	65.9	Alive	—
6	TG+S	R0	IIB	—	110.4	Alive	—
7	DG	R0	IA	—	24.1	Dead	Cancer
8	TG	R0	IIIA	Peritoneum	3.4	Dead	Cancer
9	TG+S	R0	IIIA	—	97.1	Alive	—
10	PG	R0	IA	—	58.7	Alive	—

DG, distal gastrectomy; DP, distal pancreatectomy; PG, proximal gastrectomy; S, splenectomy; TG, total gastrectomy.
[a]LN 16a2: positive.

sis nor treatment has been fully established. NEC is classified as a subtype of neuroendocrine neoplasm (NEN) in accordance with the revision of the 2010 World Health Organization classification.[5] NEN is classified into NEC and neuroendocrine tumors (NET) on the basis of the clinical prognosis and biological kinetics (Table 4).

In many cases, NEC is derived from ductal adenocarcinoma as a preceding lesion. This may be because NEC differentiates from standard-type adenocarcinoma in its inner area, leading to deciduation of the standard-type adenocarcinoma because of the more rapid proliferative capacity of the tumorous NEC.[6] If the proliferation of NEC in the deep layer results in deciduation of the adenocarcinoma area in the superficial layer, the cancer nest may be composed of NEC alone. Therefore, it is difficult to make a definitive diagnosis of this disease using biopsy. In fact, the preoperative diagnosis rate is reportedly only 30%.[6,7] Of our 10 patients with gastric NEC, 7 patients also had standard-type adenocarcinoma. Furthermore, a preoperative diagnosis of NEC could only be made in 5 (50%) of the 10 patients who underwent radical resection. In addition to the difficulty of making a preoperative diagnosis, marked lymphovascular invasion and remote metastasis from NEC in the early stage may contribute to a poor prognosis.[3,8,9]

Table 4 Classification of neuroendocrine neoplasms

2010 WHO classification	Grading		
	Grade	Mitotic rate	Ki-67 index
NET G1	G1	<2	≤2
NET G2	G2	2–20	3–20
NEC	G3	>20	>20

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumors; WHO, World Health Organization.

The treatment of NEC involves typical surgery described in the regulations for the management of gastric cancer, which is routinely combined with adjuvant chemotherapy.[10,11] However, no specific treatment guidelines or chemotherapeutic regimens have been established to date. In the National Comprehensive Cancer Network guidelines, treatment in accordance with small cell lung cancer is recommended. In the European Neuroendocrine Tumor Society guidelines, Cisplatin (CDDP) + Etoposide (ETP) therapy is recommended. In Japan, CDDP + Irinotecan (CPT-11) and S-1 + CDDP therapies are frequently selected.[3,12] Furthermore, the response rate for a 3-drug combination therapy (Carboplatin [CBCDA] + ETP + CPT-11) involving a taxane in patients with gastrointestinal NEC was reportedly 53%, and the median exacerbation-free survival time was 14.5 months. However, in Japan, the doses of the 3 drugs to be recommended have not yet been established.[13]

Concerning surgery, resection is the first-choice procedure if possible. However, chemotherapy is selected because of rapid progression in many patients. In the present study, relapse-free survival was achieved in 6 of the 10 patients who underwent resection. However, periaortic lymph node metastasis was detected in 1 patient 3.3 months postoperatively. In contrast, remote metastasis is already present at the time of diagnosis in most patients with NEC. Therefore, chemotherapy is performed as a primary treatment in many cases.

Recently, the efficacy of monotherapy with a standard drug for advanced/recurrent gastric cancer (*i.e.*, S-1[14] or S-1+CDDP combination therapy[14]) in such patients has been reported. Of our patient

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Table 5 Reported surgical and chemotherapeutic treatments and prognoses of patients with gastric neuroendocrine carcinoma

Author	Year	Age (yr)	Sex	Surgery	Chemotherapy	pStage	Prognosis
Kusaka *et al*[18]	1998	77	Male	TG	ND	ND	60 mo alive
Kitazawa *et al*[19]	2000	55	Male	DG	Tegafur suppository	IIA	147 mo alive
Shirado *et al*[20]	2006	28	Male	DG, Hepatectomy	5′ DFUR, DOX, MMC, 5FU, CDDPia FP	IV	90 mo alive
Endo *et al*[21]	2012	70	Male	DG	—	IIB	87 mo alive
Okimoto *et al*[22]	2014	70	Male	TG	S-1	IB	66 mo alive
Kagawa *et al*[23]	2014	54	Female	—	CPT-11/CDDP, CPT-11/CBDCA	IV	63 mo alive

CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; DG, distal gastrectomy; DOX, doxorubicin; ia, intra-arterial; MMC, mitomycin C; mo, months; ND, not documented; pStage, based on the Japanese Classification of Gastric Carcinoma (15th edition); TG, total gastrectomy; 5′DFUR, 5′-deoxy-5-fluorouridime; 5FU, fluorouracil

series, 1 patient with periaortic lymph node metastasis occurring 5.4 months postoperatively received an S-1–based regimen. This treatment led to a favorable outcome, with a follow-up period of 60.5 months after the start of chemotherapy. These results suggest the usefulness of S-1 for NEC treatment.

The guidelines for the management of gastric cancer indicated that preoperative chemotherapy for advanced gastric cancer should be indicated for the following: (1) patients with locally advanced, resectable gastric cancer in whom the risk of relapse is high, requiring micrometastasis control, and (2) patients in whom R0/R1 surgery is possible, although lymph node metastasis is present, or patients with markedly advanced cancer (*e.g.*, type 3/4 large gastric cancer) requiring down-staging.[14] In contrast, other studies regarding preoperative chemotherapy for gastrointestinal NEC indicated that 50% of patients with remote metastasis responded to CDDP + CPT-11 therapy, with a median survival time of 15.8 months.[15,16] However, preoperative chemotherapy has not yet been established, and it is difficult to review preoperative chemotherapy regimens in a small number of patients with NEC. Data from a large number of patients must be accumulated by conducting a multicenter collaborative study. Of our patient series, preoperative chemotherapy was not performed in any patient.

It was previously reported that ≥50% of NEC patients died within 1 year and that the mean survival time ranged from 9.3 to 15 months.[17] When searching for reports in the literature using the keywords "stomach" and "neuroendocrine carcinoma" in the Medical Central Journal (1983–2019, excluding meeting records), 192 patients were identified. Of these, only 6 patients survived for ≥5 years. Of these 6 patients, surgery was performed in 5 patients, surgery alone was carried out in 2 patients, and postoperative adjuvant chemotherapy was administered in 4 patients (Table 5) .[18–23] In all of these 6 patients, including those with liver metastasis, radical resection was performed. This suggests that radical resection contributes to the prognosis regardless of the presence or absence of systemic chemotherapy.

Of the 10 patients with gastric NEC who underwent resection in our hospital, relapse-free survival was achieved in 6 patients with favorable results. In these patients who underwent resection, the interval until relapse was short. This implies that a short interval period should be established between examinations, and postoperative follow-up must be carefully performed.

Recently, the usefulness of postoperative chemotherapy has also been reported.[24] However, in patients with NEC, early lymphovascular invasion and remote metastasis through rapid progression, as well as the absence of an effective secondary treatment, may contribute to a poor prognosis. Several studies have shown that the prognosis of patients with NEC was poorer than that of patients with standard-type adenocarcinoma, although there was no significant difference.[24–26] In the future, the pathogenesis of NEC should be fully clarified by accumulating data from a larger number of patients, and therapeutic strategies should be further developed or newly established.

Conclusions

Of the 10 patients with gastric NEC who underwent surgical resection in our hospital, long-term survival was achieved in some patients, suggesting the usefulness of radical resection. The pathogenesis of gastric NEC should be fully clarified in future studies by accumulating data from a larger number of patients. Therapeutic strategies should also be further developed or newly established.

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