

# A successful treatment for metastatic liver tumors from endocrine carcinoma of the stomach

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**Abstract.** Endocrine carcinomas (ECs) of the stomach reveal prominently aggressive behavior and have poor prognoses. Optimal treatments for gastric ECs have not been established because of the rarity of EC. In general, patients with gastric ECs die within a year of diagnosis in spite of surgical resections and subsequent chemotherapies. Liver metastases are the most common cause of death in gastric ECs, and their control is very important for improving the poor prognosis associated with the disease. In the present report, we describe a case in which a subject with stomach EC was diagnosed at an early stage. However, multiple liver metastases occurred soon after curative surgical resection and were treated via hepatic arterial infusion (HAI) with a combination of cisplatin and 5-fluorouracil. Consequently, the tumors almost completely disappeared. HAI therapy is a useful treatment for multiple metastatic liver tumors from gastric ECs devoid of metastases in other organs. Previously published therapies used to treat ECs of the stomach, including the ones used in the current case, are also discussed herein.

## Introduction

Endocrine carcinomas (ECs) can arise in any gastrointestinal (GI) tract, however, their occurrence is infrequent (1). ECs of the stomach account for only 0.1 to 0.9% of all gastric carcinomas (2,3), and reveal prominently aggressive behavior, which differ from conventional gastric carcinomas (1,4). In general, EC patients have very poor prognoses in spite of surgical resections and subsequent chemotherapies, and die within a year of diagnosis (1,4,5). However, with the occurrence of new anti-cancer agents and improvements in interventional treatments (6), the number of long-term survivors with gastric ECs has increased. In the current study, we

describe a case in which a subject with stomach EC, had multiple metastatic liver tumors which disappeared almost completely after hepatic arterial infusion (HAI) chemotherapy with the continuous administration of cisplatin (CDDP) and 5-fluorouracil (5-FU). In the 'Discussion', the previously reported treatments for ECs of the stomach are also reviewed.

## Case report

Despite the lack of abdominal symptoms, a 76-year-old woman displayed a polypoid lesion on a screening barium meal study. A subsequent upper gastrointestinal endoscopy revealed an early-stage gastric carcinoma (a superficially spreading-type carcinoma with a protruding region) in the lesser curvature of the stomach body (Fig. 1). A total gastrectomy with a regional lymph node (LN) dissection was performed, and postoperative pathological findings showed well-, and in some parts moderately-differentiated tubular adenocarcinomas with no LN metastases. According to the UICC TNM classification, the clinical stage was T1, N0, M0, and stage IA. Two months after the surgical resection, multiple liver tumors lacking swollen LNs were disclosed on an abdominal computed tomographic (CT) scan (Fig. 2A). No other tumors presented as primary foci in any other tissue except the liver. Biopsied specimens from the liver tumors revealed poorly differentiated carcinomas, which showed solid growth without glandular components. Additional histological examinations disclosed positive immunostaining for cytokeratin, the epithelial membrane antigen (EMA) and the neural cell adhesion molecule (NCAM) in the liver tumors, while an electron microscopic study showed multiple dense-cored granules in the cytoplasm of the poorly differentiated carcinoma cells (Fig. 3A), suggesting that they were ECs. Re-examinations of the microscopic findings of the resected stomach defined poorly differentiated carcinomas, which revealed solid growth with gland-like structures, in a small area inside of extensively distributed tubular adenocarcinomas (Fig. 3B). Histological examinations also revealed positive responses for cytokeratin, EMA, NCAM and small electron-dense granules in the poorly differentiated carcinoma cells of the stomach. Under the diagnosis that the multiple liver tumors were metastases from composite type gastric ECs, intensive chemotherapy using HAI (20 mg CDDP for 1 h and 250 mg 5-FU for 4 h, on days 1 to 5) via a subcutaneously implanted port, was performed for 3 continuous weeks, and

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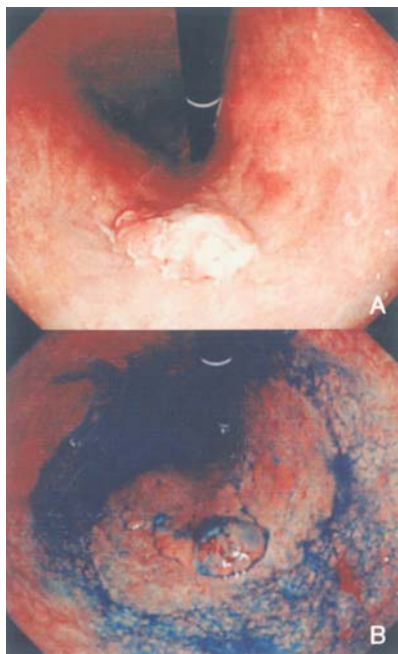


Figure 1. An upper gastrointestinal endoscopy revealed a superficially spreading-type tumor with a protruding region in the lesser curvature of the stomach body (A). After spraying with indigo dye, a widespread tumor with a mildly elevated margin became clear (B).

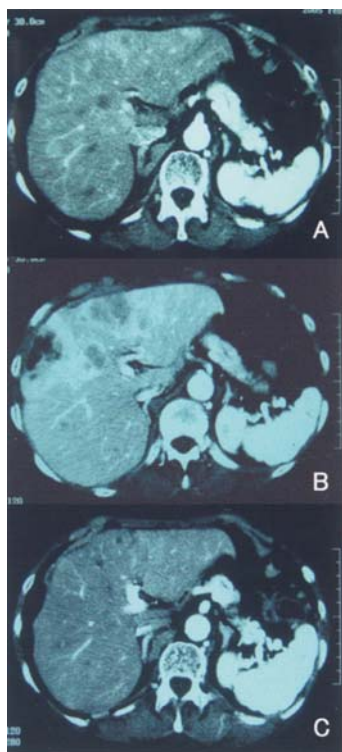


Figure 2. Multiple liver tumors were revealed in the arterial phase of a dynamic computed tomographic scan (A), which became massive before the start of chemotherapy using hepatic arterial infusion. (B). After the end of the first round of chemotherapy, the massive liver tumors almost completely disappeared, and no new lesions were visible (C).

subsequently discontinued due to drug toxicity, nausea and vomiting. Even though the multiple liver tumors were growing to a large size before the start of chemotherapy (Fig. 2B),

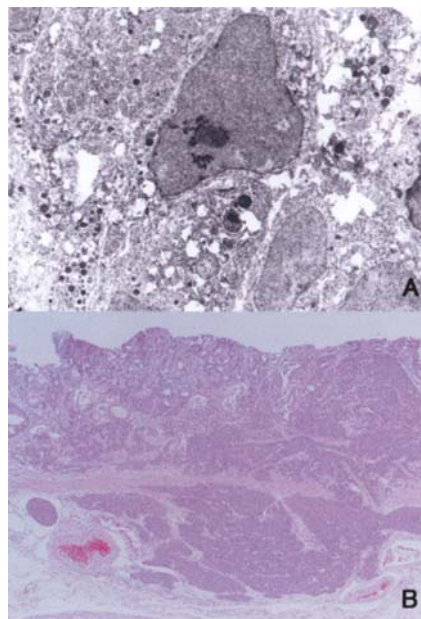


Figure 3. In electron microscopic examinations, poorly differentiated carcinomas in the liver showed multiple dense-cored granules in the cytoplasm of the tumor cells (A) (x4000). Poorly differentiated carcinomas were revealed with solid growth and gland-like structures, underlying widely distributed well-differentiated tubular adenocarcinomas in the stomach (B) (H&E, x40).

these tumors disappeared almost completely 2 weeks after the end of the HAI therapy (Fig. 2C). Soon, the patient was discharged and was followed-up in an outpatient clinic. She underwent HAI therapy with the administration of 20 mg CDDP and 250 mg 5-FU, once a week. However, 3 months following her hospital discharge, recurrences of liver tumors and new metastatic lesions, including those in the lung, pubic bone and para-aortic LNs, were disclosed on CT scans of the chest, abdomen and pelvis. A second round of chemotherapy using 80 mg S-1 on days 1 to 28, and the intravenous administration of 30 mg CDDP on days 7, 14, 21, and 28, was started immediately. Unfortunately, the diffuse liver tumor recurrences progressed, and the subject's condition worsened. She developed jaundice, and died of liver failure 10 months after surgery.

The patient had provided informed consent for liver biopsies, which were carried out to histologically type the tumors, in order to decide upon subsequent therapy.

## Discussion

Bleak prognoses associated with stomach ECs are caused by prominent propensities for carcinomic metastases, which originate in the bottom of the gastric glands, spreading into the lymphatic and/or blood vessels even during the early stage of the disease (4,7). An optimal treatment for gastric ECs has not been established because of the rarity of the disease. However, in general, operable cases can undergo surgical resections of the invaded organs, followed by intensive chemotherapy. In cases with metastatic brain tumors, which are a common cause of death in gastric ECs, cranial radiation can be employed. The clinicopathological characteristics and the chemotherapeutic regimen for gastric ECs are summarized in



## SPANDIDOS PUBLICATIONS Clinicopathological characteristics and chemotherapeutic regimen in 36 reported cases with gastric endocrine carcinoma.

Case no.	Year	Age/sex	Stage	Adeno-carcinoma component	Chemotherapeutic regimen	Response	Concomitant treatment	Site of metastasis or recurrence	Status	Follow-up (month)	Refs.
1	1988	74/M	LD (early)	Yes	5-FU/OK432	PD	TG	Liver	DOD	6	(7)
2	1990	42/M	ED	No	i) CPA/DXR/VCR ii) CDDP/VP16	PR PD	PG, gastro- jejunostomy	Liver, LN	DOD	10	(11)
3	1991	59/M	LD (early)	No	MMC/oral tegafur	ND	SG	None	Alive, NED	20	(4)
4	1991	72/M	LD (early)	Yes	MMC/oral tegafur	ND	TG	None	Alive, NED	13	(4)
5	1991	59/M	LD (early)	Yes	CDDP/DXR	ND	SG, RT	Liver, lung, brain, LN	DOD	18	(4)
6	1991	57/M	LD (advanced)	No	MMC/oral tegafur	ND	TG	Liver	DOD	5	(4)
7	1991	58/M	LD (advanced)	No	MMC/oral tegafur	ND	TG	Liver	DOD	9	(4)
8	1991	59/M	LD (advanced)	No	MMC/oral tegafur	ND	SG	Liver, lung, brain, LN	DOD	11	(4)
9	1991	73/F	LD (advanced)	No	MMC/oral tegafur	ND	TG	Liver	DOD	9	(4)
10	1991	67/F	LD (advanced)	No	MMC/oral tegafur	ND	SG	Liver, lung, brain, bone, LN	DOD	6	(4)
11	1991	71/M	LD (advanced)	No	MMC/oral tegafur	ND	SG	Liver	DOD	10	(4)
12	1991	54/M	LD (advanced)	Yes	MMC/oral tegafur	ND	SG, RT	Liver, lung, brain, LN	AWD	18	(4)
13	1991	73/M	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	Liver	DOD	8	(4)
14	1991	79/M	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	Liver, lung, brain, LN	DOD	13	(4)
15	1991	64/M	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	Liver	DOD	8	(4)
16	1991	74/F	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	None	Alive, NED	6	(4)
17	1991	81/F	LD (advanced)	Yes	MMC/oral tegafur	ND	SG, RT	Liver, lung, brain, skin, LN	DOD	22	(4)
18	1991	76/F	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	Liver, lung, skin, LN	DOD	6	(4)
19	1991	69/M	LD (advanced)	Yes	MMC/oral tegafur	ND	SG	Liver	DOD	7	(4)
20	1994	69/M	ED	No	5-FU/EPI using HAI/ tegafur uracil/OK432	PD	TG	Liver	AWD	8	(17)
21	1997	31/M	ED	ND	CDDP/CPA/EPI/ VP16/VCR	CR	PBSCT	Bone	Alive, NED	14	(18)
22	1997	54/M	LD (advanced)	ND	i) CPA/DXR/VP16 ii) Carboplatin/MTX, CPA/DXR/VP16 iii) VCR/chlorambucil/ dexamethasone	CR NC or PD PD	None RT (for stomach)	None	DOD	23	(19)
23	1998	70/F	ED	Yes	CDDP/VP16/DXR	CR	DG, hepatectomy	Liver	Alive, NED	26	(8)
24	1998	71/M	ED	Yes	CDDP/VP16/DXR	CR	DG	Peritoneum, para-aortic LN	DOD	18	(8)
25	1999	54/M	LD (advanced)	No	CDDP/VP16	PR	TG, splenectomy	Liver, lung	DOU	7	(20)
26	2003	58/M	ED	No	CDDP/VP16/5-FU	PR?	TG, splenectomy, hepatectomy, pancreatectomy	Liver, pancreas, colon, spleen, peritoneum	DOD	8	(21)
27	2003	48/M	ED	No	Carboplatin/VP16	PR?	TG, esophago- jejunostomy	Liver, colon, kidney	DOD	7	(22)
28	2004	73/M	ED	ND	i) CDDP/irinotecan ii) CDDP/VP16	PR CR	TG (for adeno- carcinoma)	Liver	Alive, NED	≥24	(3)
29	2004	64/M	ED	ND	CDDP/VP16	PR	RT	Brain	DOD	9.2	(23)
30	2004	75/M	ED	ND	CDDP/S-1	PR	None	Liver	DOD	14	(24)
31	2004	76/F	ED	No	i) Neoadjuvant CDDP/VP16 ii) PTX	PR PD	TG	Liver, diaphragma, clavicular and para-aortic LN	DOD	7	(25)

Table I. Continued.


Case no.	Year	Age/sex	Stage	Adeno-carcinoma component	Chemotherapeutic regimen	Response	Concomitant treatment	Site of metastasis or recurrence	Status	Follow-up (month)	Refs.
32	2005	52/M	LD (advanced)	No	CDDP/VP16		TG	None	Alive, NED	36	(26)
33	2005	72/M	LD (advanced)	Yes	Neoadjuvant; carboplatin/ EPI/VP16/5-FU	PR	TG, splenectomy	Para-aortic LN	DOU	43	(2)
34	2005	60/M	ED	ND	i) CDDP/5-FU ii) CDDP/irinotecan iii) S-1/irinotecan	PD PR PR	None	Liver, pancreas	AWD	8	(27)
35	2006	69/M	ED	ND	i) S-1/PTX ii) CDDP/irinotecan iii) CDDP/VP16	PR NC NC	Jejunostomy, RT	Pancreas, adrenal gland, brain, LN	AWD	21	(28)
36	2006	28/F	ED	No	i) CDDP/VP16/ doxifluridine ii) DXR/MMC/5-FU/ lipiodol iii) CDDP using HAI iv) CDDP/5-FU	ND ND PR CR	PG, hepatectomy	Liver	AWD	≥84	(9)

ED, extensive disease (spread of disease beyond locoregional boundaries); LD, limited disease (limited in stomach including regional LN metastasis); ND, not described; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; OS, overall survival; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; DOU, died of unknown cause; SG/TG/PG/DG, subtotal/total/partial/distal gastrectomy; RT, radiotherapy to brain; PBSCT, peripheral blood stem cell transplantation; hepatectomy, including lobectomy, segmentectomy and tumor resection; CDDP, cisplatin; 5-FU, 5-fluorouracil; CPA, cyclophosphamide; DXR, doxorubicin; EPI, epirubicin; MMC, mitomycin C; VCR, vincristine; PTX, paclitaxel.

Table I, based on previously reported literature. Similar to the current case and case 1, even early-stage cases reveal metastases soon after surgical resection (7). Therefore, even if the gastric EC is in the early stage, postoperative adjuvant chemotherapy should always be administered. While the anti-cancer agents used in chemotherapy for gastric ECs vary, platinum-based chemotherapies have been used in many cases, and occasionally excellent responses have been obtained (3,8,9). Since there are biological similarities between stomach ECs and small cell lung carcinomas (SCLCs), chemotherapeutic regimens for SCLCs have often been applied towards stomach ECs. A combination of CDDP and VP16, which is a standard regimen for extensive SCLCs (10), demonstrates a high response against gastric ECs. In contrast to SCLCs, ECs of the stomach are often accompanied by a non-small cell component, such as an adenocarcinoma or a squamous cell carcinoma (4,5,11). Therefore, careful attention should be paid to the choice of anti-cancer agents for composite-type gastric ECs, as chemosensitivities vary for each carcinoma cell type. Moreover, the beneficial responses after chemotherapy are mostly short and transient, and may be followed by another chemotherapeutic regimen.

In the current case, as the first recurrence was limited to the liver and the recurrent hepatic tumors progressed very quickly, HAI therapy was chosen, which led to the almost complete disappearance of the massive tumors. While a few documented cases with liver metastases treated by HAI therapy using CDDP have resulted in favorable responses (9), there are no reports showing almost complete responses after HAI therapy. In Japan, HAI chemotherapy with the continuous

low-dose administration of CDDP and 5-FU (low-dose FP) (12) is frequently used to treat advanced, unresectable and multinodular forms of hepatocellular carcinoma (HCC). HAI with low-dose FP achieved more beneficial therapeutic results for these HCCs than transcatheter arterial chemoembolization (13,14). In addition to its own effect, CDDP amplifies the cell-killing effect of 5-FU, and the combination of CDDP and 5-FU, is widely used in chemotherapy for esophageal, colorectal and ovarian carcinomas. Unlike the intravenous high-dose administration of chemotherapeutic agents, HAI therapy through an implanted port can deliver anti-cancer agents in high concentrations directly to the liver, thereby decreasing the therapy's adverse effects. In contrast, a combined administration of 5-FU, epirubicin and mitomycin C (FEM) through HAI has been established for the treatment of liver metastases from gastric carcinomas (15). FEM chemotherapy using HAI resulted in favorable responses against these metastatic liver tumors. Histologically, these stomach lesions are highly differentiated carcinomas, such as papillary, well-, and moderately-differentiated adenocarcinomas, in more than half of these cases. In contrast, advanced HCCs, which can be managed by HAI with low-dose FP, are composed of moderately to poorly differentiated carcinomas in most cases (16). For the above-mentioned reasons, we selected HAI therapy with low-dose FP, which proved to be a useful option to regionally treat metastatic liver tumors from gastric ECs. Unfortunately, in the present case, soon after the almost complete disappearance of the multiple liver tumors, extended and aggressive recurrences occurred, followed by liver failure and subsequent death in spite of systemic

 SPANDIDOS PUBLICATIONS. Nevertheless, there is no doubt that the HAI prolonged the patient's survival period.

In conclusion, we reported a case in which a subject with stomach EC, developed metastatic liver tumors, which were successfully treated by HAI therapy with low-dose FP. We reviewed previously published therapies for gastric ECs, and emphasized the importance of positive and intensive therapy even in cases of early-stage disease. Cumulative reports in the future are necessary to improve the bleak prognosis of gastric ECs.

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### References

- Brenner B, Tang LH, Klimstra DS, *et al*: Small-cell carcinomas of the gastrointestinal tract: A review. *J Clin Oncol* 22: 2730-2739, 2004.
- Nakamura Y, Otani S, Otaka M, *et al*: Gastric small cell carcinoma with marked response to neoadjuvant chemotherapy. *Int J Clin Oncol* 10: 348-352, 2005.
- Hosokawa A, Shimada Y, Shirao K, *et al*: Long-term survivor of gastric small cell carcinoma. *Hepatogastroenterology* 51: 1567-1570, 2004.
- Matsui K, Kitagawa M, Miwa A, *et al*: Small cell carcinoma of the stomach: A clinicopathologic study of 17 cases. *Am J Gastroenterol* 86: 1167-1175, 1991.
- Kusayanagi S, Konishi K, Miyasaka N, *et al*: Primary small cell carcinoma of the stomach. *J Gastroenterol Hepatol* 18: 743-747, 2003.
- Tanemura H, Ohshita H, Kanno A, *et al*: A patient with small-cell carcinoma of the stomach with long survival after percutaneous microwave coagulating therapy (PMCT) for liver metastasis. *Int J Clin Oncol* 7: 128-132, 2002.
- Fukuda T, Ohnishi Y, Nishimaki T, *et al*: Early gastric cancer of the small cell type. *Am J Gastroenterol* 83: 1176-1179, 1988.
- Hirama K, Tsuchida H, Matsumoto K, *et al*: Two cases of gastric small cell carcinoma responding to postoperative chemotherapy with modified EAP regimen. *J Jpn Soc Clin Surg* 59: 983-989, 1998.
- Shirado A, Uto H, Kusumoto K, *et al*: A case of gastric endocrine cell carcinoma with liver metastasis showing rapid growth during pregnancy and marked reduction by systemic chemotherapy after delivery. *Nippon Shokakibyo Gakkai Zasshi* 103: 827-832, 2006.
- Noda K, Nishiwaki Y, Kawahara M, *et al*: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 346: 85-91, 2002.
- Hussein AM, Otrakji CL and Hussein BT: Small cell carcinoma of the stomach. Case report and review of the literature. *Dig Dis Sci* 35: 513-518, 1990.
- Ando E, Yamashita F, Tanaka M, *et al*: A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 79: 1890-1896, 1997.
- Okuda K, Tanaka M, Shibata J, *et al*: Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. *Oncol Rep* 6: 587-591, 1999.
- Sumie S, Yamashita F, Ando E, *et al*: Interventional radiology for advanced hepatocellular carcinoma: comparison of hepatic artery infusion chemotherapy and transcatheter arterial lipiodol chemoembolization. *Am J Roentgenol* 181: 1327-1334, 2003.
- Kumada T, Arai Y, Itoh K, *et al*: Phase II study of combined administration of 5-fluorouracil, epirubicin and mitomycin-C by hepatic artery infusion in patients with liver metastases of gastric cancer. *Oncology* 57: 216-223, 1999.
- Sugihara S, Nakashima O, Kojiro M, *et al*: The morphologic transition in hepatocellular carcinoma - a comparison of the individual histological features disclosed by ultrasound-guided fine-needle biopsy with those of autopsy. *Cancer* 70: 1488-1492, 1992.
- Masuyama K, Oonishi Y, Sawataishi M, *et al*: A case of small cell carcinoma of the stomach with multiple liver metastases. *Gan To Kagaku Ryoho* 21: 2338-2340, 1994.
- Sakai K, Nomura H, Nogami T, *et al*: A case of complete remission of gastric endocrine cell carcinoma with multiple bone metastasis by combination chemotherapy and high-dose chemotherapy with autologous peripheral blood stem cell transplantation. *Gan To Kagaku Ryoho* 24: 2277-2280, 1997.
- O'Byrne KJ, Cherukuri AK, Khan MI, *et al*: Extrapulmonary small cell gastric carcinoma. A case report and review of the literature. *Acta Oncol* 36: 78-80, 1997.
- Futagami F, Asano K, Matsumura A, *et al*: A case of small cell carcinoma of the stomach with multiple liver and lung metastases successfully treated by combined chemotherapy with cisplatin and etoposide. *Gan To Kagaku Ryoho* 26: 149-152, 1999.
- Hosoya Y, Nagai H, Koinuma K, *et al*: A case of aggressive neuroendocrine carcinoma of the stomach. *Gastric Cancer* 6: 55-59, 2003.
- Chaudhary UB, Taksey JD, Johnson RD, *et al*: Small-cell cancers, and an unusual reaction to chemotherapy: Case 3. Small-cell carcinoma of the stomach. *J Clin Oncol* 21: 2441-2442, 2003.
- Kim JH, Lee S-H, Park J, *et al*: Extrapulmonary small-cell carcinoma: a single institution experience. *Jpn J Clin Oncol* 34: 250-254, 2004.
- Shimada M, Iwase H, Iyo T, *et al*: A case of complete response in a primary lesion treated by combined chemotherapy of TS-1 and CDDP for small cell carcinoma of the stomach with liver metastasis. *Gan To Kagaku Ryoho* 31: 593-596, 2004.
- Hasegawa K, Maruyama M, Takashima I, *et al*: A case of gastric endocrine cell carcinoma with neck lymph node metastasis resected after neoadjuvant chemotherapy. *Gan To Kagaku Ryoho* 31: 1935-1938, 2004.
- Namikawa T, Kobayashi M, Okabayashi T, *et al*: Primary gastric small cell carcinoma: report of a case and review of the literature. *Med Mol Morphol* 38: 256-261, 2005.
- Kato T, Sato K, Tamahashi N, *et al*: A case of small cell carcinoma of the stomach. *Gan To Kagaku Ryoho* 32: 1473-1475, 2005.
- Saeki H, Anegawa G, Masuda T, *et al*: A case of inoperable gastric small cell carcinoma effectively treated by chemotherapy and radiotherapy. *Gan To Kagaku Ryoho* 33: 977-979, 2006.