

Complete response to multidisciplinary therapy in a patient with primary gastric choriocarcinoma

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Abstract

Primary gastric choriocarcinoma is a rapidly growing neoplasm with an average survival of several months in untreated patients. Gastrectomy with lymph node dissection followed by chemotherapy is the treatment of choice. Regimens used for gastric adenocarcinoma are usually selected. However, median survival remains less than six months. In this case report, we describe a case of primary gastric choriocarcinoma with a clinical complete response to multidisciplinary treatment including surgery, chemotherapy, and radiofrequency ablation (RFA). The patient was originally referred for general malaise. Esophagogastroduodenoscopy demonstrated a large tumor occupying the fornix, and total gastrectomy with lymph node dissection was performed. Seven days later, multiple liver metastatic recurrences with high serum levels of beta-human chorionic gonadotropin (β -hCG) were recognized. Chemotherapy with a gonadal choriocarcinoma regimen consisting of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO), was initiated. After three cycles, serum β -hCG decreased markedly and the tumors disappeared. Six months later, multiple lung metastatic recurrences were found. After one cycle of EMA/CO, only

one nodule remained. Computed tomography-guided RFA was performed for this oligometastatic tumor. The patient has been alive with no evidence of disease for 10 years after the initial diagnosis. To the best of our knowledge, this patient with recurrent primary gastric choriocarcinoma has achieved the longest survival. The present case is the first report of choriocarcinoma metastatic to the lung successfully treated with RFA. From our retrospective analysis of recurrent or unresectable primary gastric choriocarcinoma, we propose that gonadal choriocarcinoma regimens can be considered as first-line for primary gastric choriocarcinoma.

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Key words: Primary gastric choriocarcinoma; Beta-human chorionic gonadotropin; Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine; Oligometastatic; Radiofrequency ablation

Core tip: We described a case of primary gastric choriocarcinoma with a complete response to multidisciplinary treatment including surgery, chemotherapy, and radiofrequency ablation (RFA). The patient has been alive with no evidence of disease for 10 years. To the best of our knowledge, this patient with recurrent primary gastric choriocarcinoma has achieved the longest survival. The present case is the first report of choriocarcinoma metastatic to the lung successfully treated with RFA. From our retrospective analysis of recurrent or unresectable primary gastric choriocarcinoma, we propose that gonadal choriocarcinoma regimens can be considered as first-line for primary gastric choriocarcinoma.

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INTRODUCTION

Choriocarcinoma typically occurs in females at the origin of the chorionic epithelium of the placenta, and is commonly related to gestation. The tumor is rapidly growing, widely metastasizing, and highly invasive of surrounding tissues. Gonadal choriocarcinomas are usually highly sensitive to various types of anti-cancer agents^[1].

Primary gastric choriocarcinoma is a type of non-gonadal choriocarcinoma that constitutes less than 1% of all gastric cancers^[2]. It was first described by Davidson in 1905, and there are currently approximately 140 reported cases worldwide^[3]. Most patients with primary gastric choriocarcinoma do not survive for even one year after surgery^[4]. Chemotherapy regimens used successfully for gonadal choriocarcinoma are not as effective for primary gastric choriocarcinoma^[5]. The prognosis is considerably worse than gastric adenocarcinoma^[4]. Primary gastric choriocarcinoma with liver metastases has the worst prognosis^[6].

We report a case of primary gastric choriocarcinoma successfully controlled by multidisciplinary therapy including surgery, chemotherapy, and radiofrequency ablation (RFA). The patient survived for approximately 10 years after initial diagnosis. To the best of our knowledge, the present case has the longest survival of recurrent primary gastric choriocarcinoma in the world.

CASE REPORT

A 65-year-old woman was referred to our clinic for general malaise and dizziness. She had no significant past medical history, and had never been hospitalized. On physical examination, the patient had pale skin due to anemia. Initial laboratory results were normal except for hemoglobin of 7.4 g/dL. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19 concentrations were within normal limits. Esophagogastroduodenoscopy demonstrated a large tumor from the fornix to the posterior wall of the upper body of the stomach, with a mixture of protruding and ulcerative lesions, as well as areas of hemorrhage. Biopsied specimens were interpreted as tubular adenocarcinoma with moderate differentiation. Abdominal computed tomography (CT) demonstrated wall thickening at the fornix with disappearance of adipose tissue at the gastrosplenic ligament, suggestive of penetration of the gastric serosa. There was no obvious evidence of metastasis to the lymph nodes or liver, or of peritoneal dissemination. Total gastrectomy with D2 lymphadenectomy was planned.

During laparotomy, the tumor showed invasion to the body of the pancreas, and metastasis to several adjacent lymph nodes was suspected. A 1 cm × 1 cm nodule was detected in the liver. Total gastrectomy with D3 lymph node dissection, distal pancreatectomy, splenectomy, and enucleation of the liver was performed, along with Roux-en-Y reconstruction.

Pathological findings

An elevated 10 cm × 8 cm tumor with surface ulceration

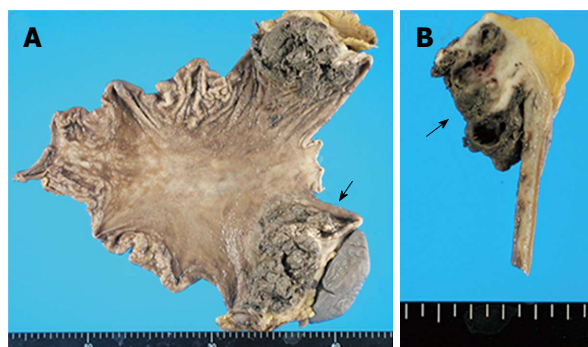


Figure 1 Gross appearance of the resected specimen. A: An elevated tumor with surface ulceration and hemorrhage was located in the fornix (arrow); B: On the cut surface of the specimen, there was a very large lobulated tumor, white to gray in color, with large areas of hemorrhage and necrosis (arrow).

and hemorrhage was located at the fornix (Figure 1A). On the cut surface of the specimen, there was a very large lobulated tumor, white to gray in color, with large areas of hemorrhage and necrosis (Figure 1B).

Microscopically, the tumor had two components (Figure 2A). The first component, with histological features suggestive of choriocarcinoma, consisted of unusually-shaped multinucleated giant cells, similar to syncytiotrophoblasts in a characteristic dimorphic plexiform pattern, associated with hemorrhage and necrosis (Figure 2B). The second component consisted of atypical mononucleated cells similar to intermediate trophoblasts in a solid and sheet growth pattern (Figure 2C). Immunohistochemically, the tumor cells in the first component were diffusely positive for β -human chorionic gonadotropin (hCG) (Figure 2D). Immunoreactivity was also seen for human placental lactogen (Figure 2E). The tumor cells in the second component were diffusely positive for β -hCG and placental alkaline phosphatase (Figure 2F and G). Immunoreactivity was also seen for CEA (Figure 2H). These findings are identical to the World Health Organization (WHO) classification of primary gastric choriocarcinoma based on clinicopathological criteria^[7]. Histologically, it showed an INF β growth pattern with invasion to the subserosa. Metastasis was detected in the lymph nodes along the short gastric vessels (no. 4SA) and at the right splenic hilum (no. 10). The liver nodule was also identified as a metastasis. The proximal and distal resection margins were clear. Peritoneal cytology was negative. The final classification was T3N1M1, stage IV, according to the Union for International Cancer Control guidelines.

Postoperative course and follow-up

The postoperative course was unremarkable. Serum β -hCG measured immediately after surgery was 12000 mIU/mL (normal range < 0.7 mIU/mL) (Figure 3). Seven days after surgery, multiple low-density lesions were detected in the liver on abdominal CT (Figure 4A and B). Recurrence was suspected and so systemic chemotherapy consisting of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) was initiated. After one cycle, the serum β -hCG concentration

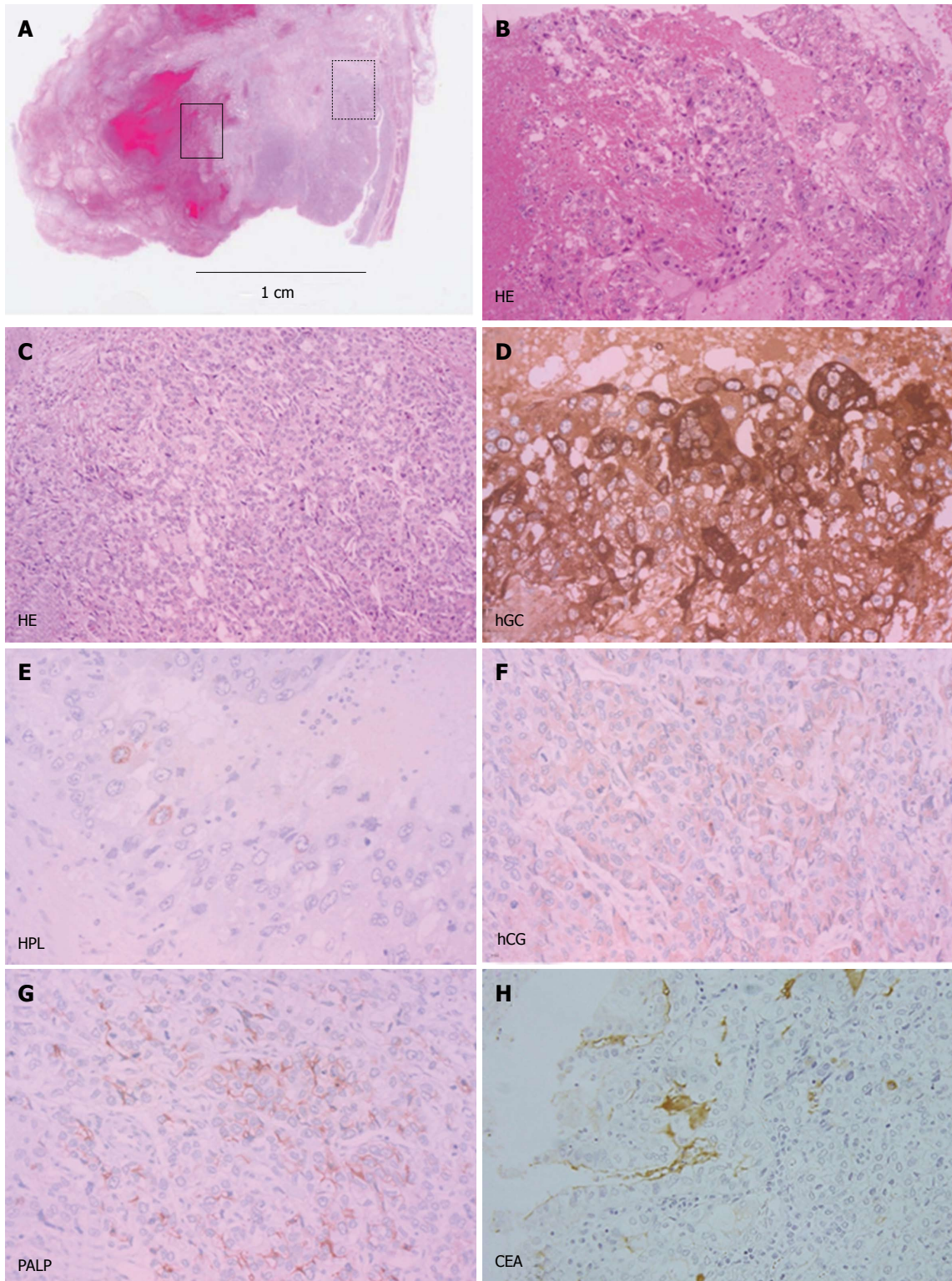


Figure 2 Pathological findings (hematoxylin/eosin staining and immunohistochemical staining). A: The tumor had two components, as indicated by small boxes with solid and dashed lines. Hematoxylin/eosin (HE) $\times 40$; B: In the area marked by a solid line in panel A, unusual multinucleated giant cells in a characteristic dimorphic plexiform pattern associated with hemorrhage and necrosis were observed. HE $\times 100$; C: Atypical mononucleated cells demonstrated a solid and sheet growth pattern in the area marked by a dashed line in panel A. HE $\times 100$; D, E: Tumor cells were diffusely positive for β -human chorionic gonadotropin (hCG) and focally positive for human placental lactogen (HPL) in the area marked by a solid line in panel A. HE $\times 200$; F, G: The tumor cells were positive for beta-human chorionic gonadotropin and placental alkaline phosphatase (PALP) in the area marked by a dashed line in panel A. HE $\times 200$; H: Immunoreactivity was focally positive for carcinoembryonic antigen (CEA). HE $\times 100$.

started to decrease and there was reduction in the size of the tumors on CT. After three cycles, the serum β -hCG

level was almost within normal limits and the tumors disappeared with a clinical complete response and no major

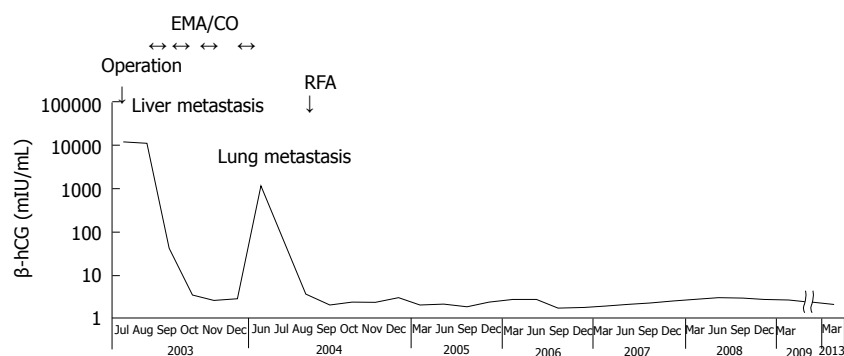


Figure 3 Tumor markers and chemotherapy. Seven days after surgery, metastatic recurrence in the liver was diagnosed. After starting etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO), serum beta-human chorionic gonadotropin (β -hCG) concentrations decreased. After three cycles, serum β -hCG levels decreased markedly to almost within normal limits and clinically the tumors showed a complete response. Six months later, there was a sudden elevation in serum β -hCG levels with the emergence of multiple nodules in both lung fields. Metastatic recurrence in the lung was diagnosed and EMA/CO was restarted. After one cycle, most tumors, except for one nodule in the left lower lobe, disappeared concomitantly with declines in serum β -hCG levels. Computed tomography-guided radiofrequency ablation (RFA) was performed for the oligometastatic tumor. The patient has been alive with no evidence of disease for nine years after RFA.

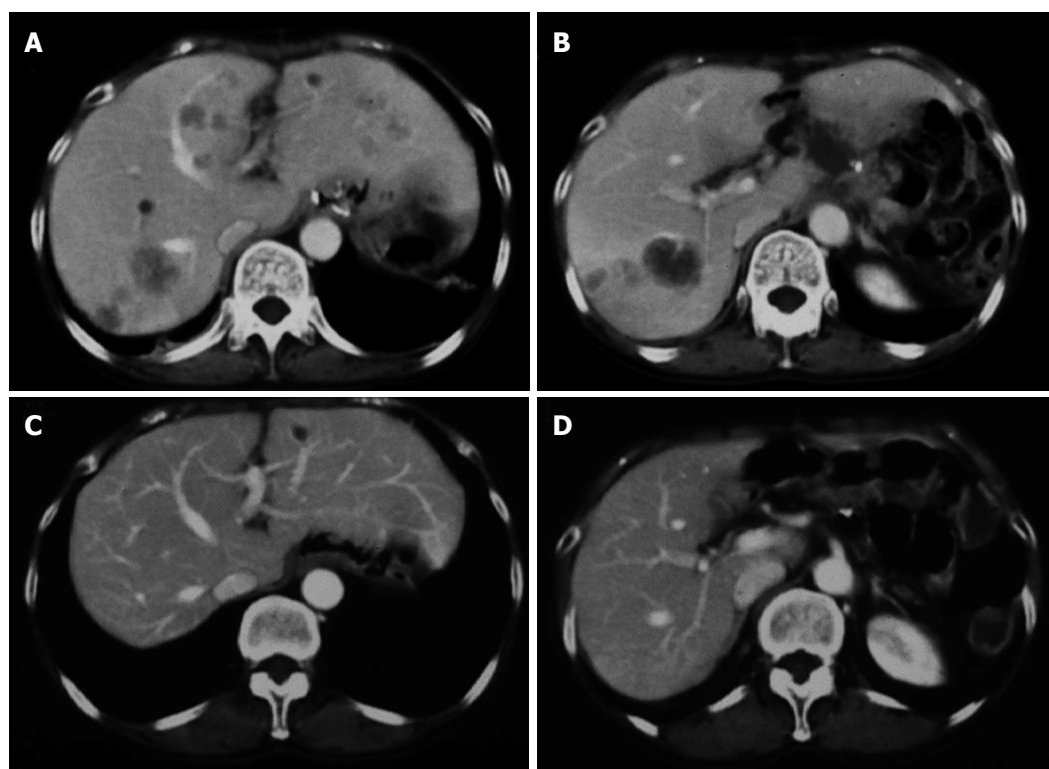


Figure 4 Computed tomography images before and after chemotherapy. A, B: Seven days after surgery, multiple low-density lesions were detected in the liver on abdominal computed tomography; C, D: After three cycles of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine, the tumors disappeared with a clinical complete response.

side effects (Figure 4C and D). Six months after surgery, there was a sudden elevation in the serum β -hCG level (1100 mIU/mL) and the emergence of multiple nodules in both lung fields on CT. Lung metastasis was diagnosed and EMA/CO was restarted. After one cycle, most tumors, except one nodule in the left lower lobe, disappeared along with decreases of serum β -hCG. CT-guided RFA was performed for oligo-recurrence. The patient remains alive with no evidence of disease for nine years after RFA treatment.

Pooled analysis of reported cases of recurrent or unresectable primary gastric choriocarcinoma treated with chemotherapy

We retrospectively collected all reported cases of recurrent or unresectable (including initially unresectable tumors treated with neoadjuvant therapy) primary gastric choriocarcinoma treated with chemotherapy with a clear postoperative prognosis in the English and Japanese literature after 1990 (Table 1)^[5,8-31]. Measurement of the overall survival (OS) period began at the time of initial

Table 1 Review of the English and Japanese literature for cases of recurrent or unresectable primary gastric choriocarcinoma treated with chemotherapy after 1990

| Cases | Authors | Age (yr)/sex | Type | Site of metastasis | Chemotherapy regimen | Response | Prognosis (mo) |
|-------|--|--------------|--------------|-----------------------|---|----------------|----------------|
| 1 | Present case | 65/F | Recurrent | Liver | EMA/CO | CR | 115 NED |
| 2 | Waseda <i>et al</i> ^[5] | 68/M | Unresectable | Liver | EP | CR | 24 NED |
| 3 | Shastri <i>et al</i> ^[8] | 44/M | Unresectable | Liver | BEP | Size reduction | 12 DOD |
| 4 | Shimuzu <i>et al</i> ^[9] | 43/F | Unresectable | Distant lymph nodes | TS-1/CDDP | Size reduction | 7 DOD |
| 5 | Yoon <i>et al</i> ^[10] | 62/M | Unresectable | Liver | 5-FU/USAN/L-OHP | Progression | 16 DOD |
| | | | | | PTX/CDDP | Progression | |
| | | | | | 5-FU/USAN/CPT-11 | Progression | |
| | | | | | BEP | Progression | |
| | | | | | EMA/CO | Progression | |
| | | | | | VIP | Progression | |
| 6 | Yoon <i>et al</i> ^[10] | 45/M | Unresectable | Liver | BEP | Progression | 12 DOD |
| | | | | | VIP | Progression | |
| | | | | | EMA/CO | Progression | |
| | | | | | 5-FU/USAN/CPT-11 | Progression | |
| 7 | Kanemura <i>et al</i> ^[11] | 79/M | Recurrent | No data | TS-1/PTX | Progression | 5 DOD |
| 8 | Yasumoto <i>et al</i> ^[12] | 76/F | Unresectable | Liver | 5-FU | Progression | 1 DOD |
| 9 | Mori <i>et al</i> ^[13] | 36/F | Recurrent | Brain and lung | EMA/CO | CR | 54 NED |
| 10 | Enokido <i>et al</i> ^[14] | 54/M | Unresectable | Liver | TS-1 | Progression | 3 DOD |
| 11 | Adachi <i>et al</i> ^[15] | 78/M | Unresectable | Liver | TS-1 | CR | 12 NED |
| 12 | Kishimoto <i>et al</i> ^[16] | 69/M | Recurrent | Liver | Epi-ADM/MMC (TACE) | Progression | 17 DOD |
| | | | | | 5-FU (HAI) | Progression | |
| | | | | | UFT | Progression | |
| 13 | Kawaguchi <i>et al</i> ^[17] | 60 M | Recurrent | Liver | MTX/BLM/CDDP/CPA | Progression | 5 DOD |
| 14 | Liu <i>et al</i> ^[18] | 36/F | Unresectable | Colon (infiltration) | BEP | Size reduction | 6 DOD |
| | | | | | VBL/IFM/CDDP | Progression | |
| 15 | Inaki <i>et al</i> ^[19] | 56/M | Recurrent | Liver | MAC (second-line after UFT as adjuvant) | Progression | 3 DOD |
| 16 | Bayhan <i>et al</i> ^[20] | 26/F | Recurrent | Lung | MAC | Size reduction | 18 NED |
| 17 | Satoh <i>et al</i> ^[21] | 58/M | Recurrent | Paraortic lymph nodes | VP-16/CDDP | Progression | 6 DOD |
| 18 | Kinoshita <i>et al</i> ^[22] | 74/M | Unresectable | Liver | MTX | Progression | 3 AWD |
| 19 | Imai <i>et al</i> ^[23] | 63/F | Recurrent | Liver | MA | Progression | 3 DOD |
| 20 | Fujimoto <i>et al</i> ^[24] | 57/M | Recurrent | Liver | MAC | Progression | 6 DOD |
| 21 | Ogura <i>et al</i> ^[25] | 45/F | Recurrent | Liver | 5-FU/MMC/Epi-ADM (HAI) | Size reduction | 10 DOD |
| | | | | | VP-16/CDDP | Progression | |
| 22 | Kan <i>et al</i> ^[26] | 67/M | Unresectable | Liver | 5'DFUR/CDDP | Size reduction | 10 DOD |
| | | | | | 5'DFUR/CDDP/VP-16 | Progression | |
| | | | | | MTX | Progression | |
| 23 | Saito <i>et al</i> ^[27] | 57/M | Recurrent | CEA elevation | 5-FU/CDDP (second-line after Tegafur as adjuvant) | SD | 12 AWD |
| 24 | Imatake <i>et al</i> ^[28] | 50/M | Unresectable | Liver | MMC/5-FU/lentinan | Progression | 2 DOD |
| 25 | Okada <i>et al</i> ^[29] | 57/F | Recurrent | hCG elevation | VAC | Progression | 7 DOD |
| 26 | Kobayashi <i>et al</i> ^[30] | 60/M | Unresectable | Liver | MTX/ADM (HAI) | Progression | 5 DOD |
| 27 | Masuda <i>et al</i> ^[31] | 79/M | Unresectable | Liver | UFT | Progression | 1.5 DOD |

M: Male; F: Female; USAN: Leucovorin; CDDP: Cisplatin; 5-FU: Fluorouracil; L-OHP: Oxaliplatin; CPT-11: Irinotecan; PTX: Paclitaxel; BLM: Bleomycin; CPA: Cyclophosphamide; VBL: Vinblastine; Epi-ADM: Epirubicin; IFM: Ifosfamide; VP-16: Etoposide; 5'DFUR: Doxifluridine; ACT-D: Actinomycin D; ADM: Adriamycin; VCR: Oncovin (vincristine); MMC: Mitomycin C; UFT: Tegafur-uracil; CEA: Carcinoembryonic antigen; β -hCG: β -human chorionic gonadotropin; NED: No evidence of disease; DOD: Died of disease; AWD: Alive with disease; CR: Complete response; SD: Stable disease; TACE: Transcatheter arterial chemoembolization; HAI: Hepatic arterial infusion; EMA/CO: Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine.

diagnosis. Death due to primary gastric choriocarcinoma was the only endpoint considered for the purpose of this study. OS curves were obtained using the Kaplan-Meier method, and differences were compared using the log-rank test. P values < 0.05 were considered significant.

Our search revealed 12 previous cases treated using gonadal choriocarcinoma regimens. 11 patients received first-line chemotherapy, of whom two had a complete response with etoposide and cisplatin (EP)^[5] and EMA/CO^[13], respectively (Table 1). The median survival of the patients treated with gonadal choriocarcinoma regimens used as the first-line was 9.5 mo compared to 5.0 mo in

patients treated with gastric adenocarcinoma regimens. Although the difference was not significant, treatment results showed a favorable prognosis with the gonadal choriocarcinoma regimen ($P = 0.1$) (Figure 5).

DISCUSSION

We report a rare case of primary gastric choriocarcinoma that showed a clinical complete response to multidisciplinary treatment, including surgery, chemotherapy, and RFA. The patient obtained nine years of disease-free survival. The present case represents the first report of cho-

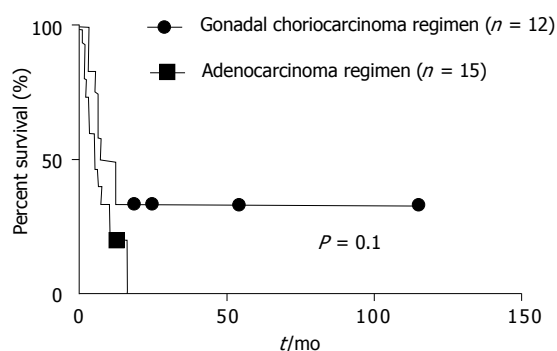


Figure 5 Overall survival with gonadal choriocarcinoma regimen and adenocarcinoma regimen. The median survival of patients treated with gonadal choriocarcinoma regimens used as the first-line was 9.5 mo compared to 5.0 mo in patients treated with gastric carcinoma regimens. Although this difference was not statistically significant, treatment results showed a favorable prognosis with gonadal choriocarcinoma regimens ($P = 0.1$).

riocarcinoma metastatic to the lung successfully treated with RFA. We propose that EMA/CO is useful as a first-line regimen for primary gastric choriocarcinoma.

Choriocarcinoma has been reported in extragonadal sites such as the lung, liver, breast, prostate, urinary bladder, nose, and gastrointestinal tract^[32]. Primary gastric choriocarcinoma is extremely rare. There are several theories on the histopathogenesis of primary gastric choriocarcinoma (*i.e.*, histological resemblance to choriocarcinoma, arising from a gonadal anlage displaced in the abdomen, a long delayed metastasis from a genital primary lesion, arising from gastric teratoma, and retro-differentiation of gastric carcinoma cells to embryonal ectodermal status with the ability to form trophoblasts)^[33,34]. In some cases, there is a combination of malignant cytotrophoblasts and syncytiotrophoblasts admixed with areas of typical glandular differentiation, which supports the retro-differentiation hypothesis^[35]. In recent years, Okada *et al.*^[33] described the possibility of normal gastric cells with the ability to produce hCG, which can directly develop into gastric choriocarcinoma. However, most authors favor the concept of retro-differentiation within an area of adenocarcinoma over primary gastric cells developing into choriocarcinoma due to the fact that less than 25% of cases are pure choriocarcinoma^[35]. In such cases, the more rapidly growing choriocarcinoma component seems to have replaced the adenomatous elements. In the present case, there was a component of adenocarcinoma, which was indicated by positive CEA immunohistological staining. This finding supports the hypothesis that primary gastric choriocarcinoma originates from pre-existing gastric adenocarcinoma.

Primary gastric choriocarcinoma is a rapidly growing neoplasm that has an average survival of only a few months in untreated patients^[6]. Gastrectomy with lymph node dissection followed by chemotherapy is the treatment of choice. Although some case reports and small studies have reported benefits from chemotherapy, a standard treatment has not been established due to the rarity of this tumor. Chemotherapy regimens usually

used successfully for gonadal choriocarcinoma, including MAC (methotrexate, actinomycin-D, cyclophosphamide), CHAMOCA (cyclophosphamide, hydroxycarbamide, doxorubicin, actinomycin D, methotrexate, melphalan, and vincristine), and EMA/CO are generally considered to have a lower success rate in the treatment of primary gastric choriocarcinoma^[5]. Several studies employed regimens used for gastric adenocarcinoma, such as a combination of fluorouracil and cisplatin or TS-1-based therapy, based on the concept that primary gastric choriocarcinoma develops from the retro-differentiation of gastric adenocarcinoma^[4,10,14,36]. However, despite recent advances in combination chemotherapy, median survival is still less than six months with these regimens. In our retrospective analysis, the median survival with gastric carcinoma regimens was 5.0 mo compared to 9.5 mo with gonadal carcinoma regimens. In the present case, we chose EMA/CO because it is the first-line regimen for high-risk gestational trophoblastic neoplasia due to its favorable effectiveness-to-toxicity ratio. EP, BEP (bleomycin, etoposide, cisplatin), or VIP (etoposide, ifosfamide, cisplatin) is used in refractory cases^[1]. In fact, the recurrent tumor showed a dramatic response to EMA/CO even with metachronous tumors in the lung. From our analysis and experience, EMA/CO can be considered a candidate for first-line treatment of recurrent or unresectable primary gastric choriocarcinoma.

RFA has been gaining popularity rapidly as a treatment for lung cancer^[37]. In recent years, RFA has been used to treat oligometastases and oligo-recurrences of metastatic lung cancer such as colorectal carcinoma, hepatobiliary carcinoma, renal cell carcinoma, and sarcoma^[37]. Oligometastasis and oligo-recurrence refer to the presence of one or a few metastatic or recurrent lesions with a controlled primary tumor^[38]. The International Registry of Lung Metastasis reported that the five-year OS of patients with complete resection of metastatic lung tumors was 36%, compared with 13% for patients without resection^[39]. Furthermore, for patients whose lung metastases were completely resected, survival depended on the number of tumors, *i.e.*, fewer metastatic lesions indicated better survival. Such data may provide the rationale for using local therapy including RFA for oligometastases and oligo-recurrences. In the present case, since the recurrent tumors in the liver and lungs were well-controlled by EMA/CO, we treated the oligometastatic tumor in the lung with RFA. The patient was disease-free for nine years without additional chemotherapy after RFA. The present case is the first successful case report of metastatic choriocarcinoma of the lung treated by RFA in the world.

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