



## Case report

# Primary gastric choriocarcinoma: two case reports and a pooled analysis of 53 cases

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### Abstract

**Primary gastric choriocarcinoma (PGC) is a rare tumor. In total, approximately 140 cases of PGC have been reported in the international medical literature. However, the clinical behavior, tumor characteristics, and prognostic parameters of PGC have not been clearly described. We conducted a pooled analysis to clarify the tumor characteristics and prognostic parameters in 53 patients with PGCs, including 2 patients treated at our hospital. The following variables were examined as potential prognostic factors: (1) sex, (2) age, (3) depth of invasion, (4) size, (5) histology, (6) nodal metastasis, (7) distant lymph node metastasis, (8) synchronous liver metastasis, (9) residual tumor, and (10) chemotherapy (not given or given). Univariate and multivariate analyses showed that the presence of residual tumor and synchronous liver metastasis and the absence of chemotherapy were significantly associated with an increased hazard rate (HR) of short overall survival (OS). Pooled analysis, including the two patients with PGC treated at our facility, demonstrated that the presence of a curative operation and chemotherapy, and the absence of synchronous liver metastasis were the strongest indicators of a favorable clinical course in patients with PGC.**

**Key words** Choriocarcinoma · Stomach · Prognosis

### Introduction

Primary gastric choriocarcinoma (PGC) is a rare tumor that is reported to account for approximately 0.08% of all gastric cancers [1]. Most PGCs have been reported to possess an adenocarcinoma component of variable extent, and pure PGC is especially rare [2–4].

In the English-language medical literature, approximately 30 PGC cases have been reported to date. While the clinicopathological characteristics or prognostic pa-

rameters of PGCs were described in some of these reports, most of the conclusions were unreliable because of the small number of PGC cases analyzed.

In the present study, we conducted a pooled analysis of 53 PGC cases, including 2 patients treated at the National Cancer Center Hospital East (NCCHE), to clarify the tumor characteristics and prognostic parameters of patients with PGC.

### Case reports

#### Case 1

A 74-year-old man complaining of loss of appetite and loss of body weight, for 9 months, visited the NCCHE. Laboratory data showed anemia (RBC,  $369 \times 10^4/\text{mm}^3$ ; hemoglobin [Hb], 8.4 g/dl; hematocrit [Hct], 28.5%), hypoalbuminemia (serum albumin, 3.0 g/dl), and high serum carcinoembryonic antigen (CEA; 31.2 ng/ml; normal, 0–5 ng/ml).

A gastrointestinal X-ray examination revealed an ulcerated lesion with a distinct elevation occupying the lower third of the stomach and invading the duodenum. The lesion was endoscopically diagnosed as a gastric cancer, and a biopsy specimen taken from its margin revealed well-differentiated tubular adenocarcinoma. A computed tomography (CT) scan and echography showed no evidence of liver metastasis at this time.

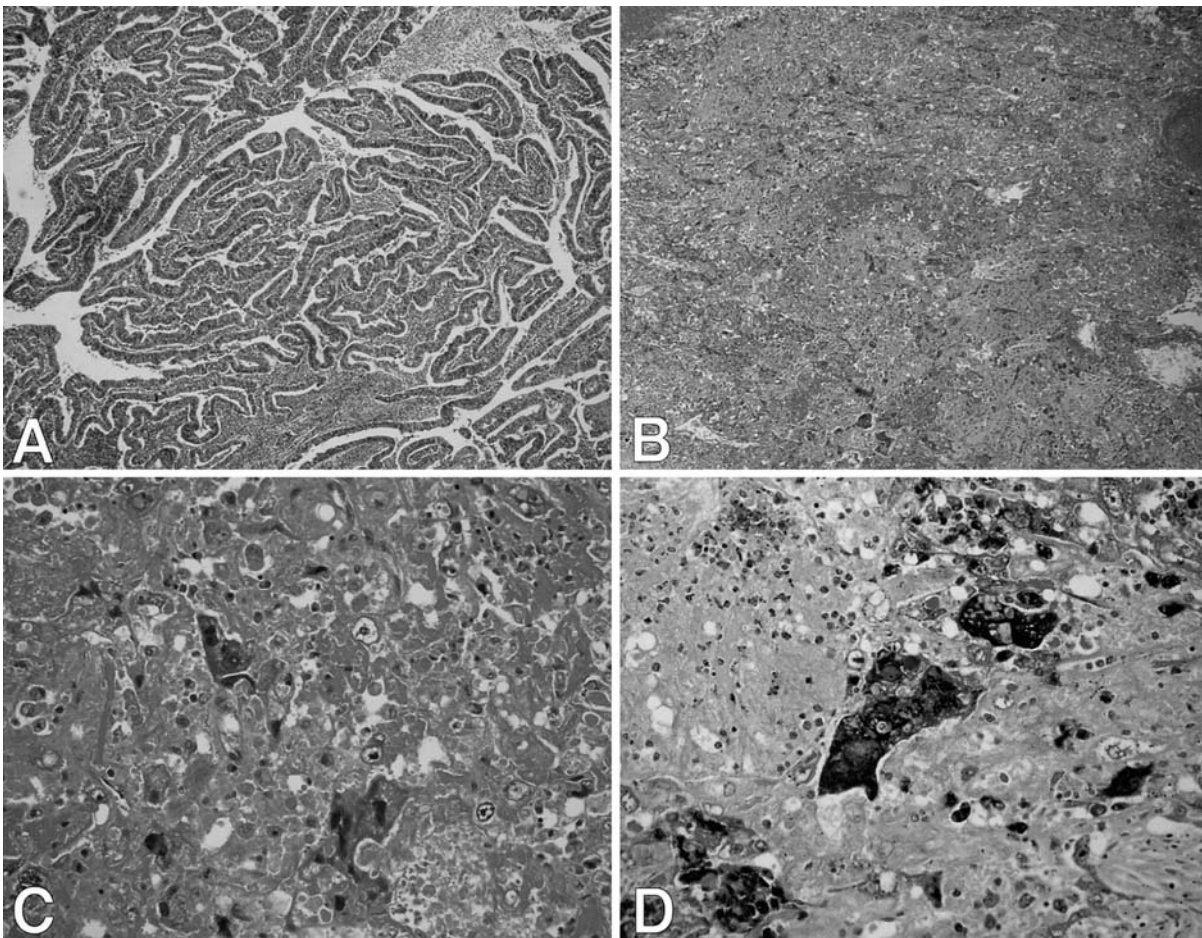
A radical subtotal Billroth II gastrectomy with lymph node dissection, omentectomy, and partial resection of the pancreatic head was performed. Macroscopically, no signs of liver metastasis or retroperitoneal invasion were observed.

The resected tumor was  $11.5 \times 8.5 \times 5.0$  cm in size. The tumor had extended to the serosa (T3) and had directly invaded the duodenum. A metastasis was found in one of the supragastric lymph nodes (N1). Grossly, the tumor was fungating (Fig. 1). Histologically, the tumor



**Fig. 1.** Photograph of the tumor shows a large ulcerative tumor with a hemorrhagic central protrusion

had two components. The first component was a moderately differentiated tubular adenocarcinoma, accounting for approximately 80% of the entire tumor (Fig. 2A). The remaining 20% of the tumor was a pleomorphic carcinoma with several syncytiotrophoblastic giant cells and hemorrhage; the histological features of this component were very suggestive of a choriocarcinoma (Fig. 2B,C). A gradual transition between the two components was observed, and the second component consisted mainly of a protruding lesion. The single nodal metastasis was composed only of tubular adenocarcinoma cells. Positive immunohistochemical staining for the beta subunit of human chorionic gonadotropin (HCG; rabbit polyclonal antibody for HCG, diluted 1:200; Dako, Copenhagen, Denmark) was observed only in the choriocarcinoma-like component (Fig. 2D). Thus, this component was diagnosed as a choriocarci-



**Fig. 2A–D.** Photomicrographs of the surgical specimen. **A** Adenocarcinomatous component. **B** Choriocarcinomatous component, consisting of syncytiotrophoblasts and cytotrophoblasts with marked hemorrhage. **C** Choriocarcinomatous component with syncytiotrophoblastic giant cells. **D** Immunohistochemical staining for the beta subunit of human chorionic gonadotropin ( $\beta$ -HCG) in the choriocarcinomatous component. **A** and **B** H&E,  $\times 85$ ; **C** H&E,  $\times 340$ ; **D**  $\times 340$

**Table 1.** Clinicopathological features of operated primary gastric choriocarcinoma in the Japanese and world literature

Case no.	Report year	Age (years)	Sex	Location	Size (cm)	Histology	Depth (involved organ) <sup>b</sup>	LN metastasis	Distant metastasis <sup>a</sup>	Residual tumor classification <sup>a</sup>	Chemotherapy	Prognosis	Cause of death	Reference no.
1	2004	74	M	AM	11	Ade > Cho	T3	+	None	R0	-	5 Years 4 months, alive	-	-
2	2004	64	M	M	7	Ade > Cho	T2	+	HEP	R0	CDDP, CPT11	6 Months, death	Hepatic failure	-
3	2002	69	M	MC	18	Cho > Ade	T4 (pancreas)	+	HEP	R2	-	27 Days, death	Hepatic failure	7
4	2002	68	M	MA	12	Cho > Ade	T4 (pancreas)	+	None	R0	MMC, CDDP, 5FU	4 Years 6 months, death	Lung disease	8
5	2000	26	F	NM	3	Cho	NM	NM	PUR	R0	MTX, ACD, CPA,	1 Years 9 months, alive	-	9
6	1998	64	M	M	5	Cho > Ade	T3	+	None	R0	5FU, CDDP	6 Months, death	Hepatic failure	10
7	1997	49	F	NM	NM	Ade, Cho	T4 (pancreas)	-	HEP	R0	NM	45 Days, death	Hepatic failure	11
8	1997	58	M	CM	8	Cho	T4 (pancreas)	NM	None	R0	CDDP, VP16	6 Months, death	NM	12,13
9	1997	71	M	C	NM	Ade, Cho	T4 (pancreas)	NM	HEP	R2	+	79 Days, death	Hepatic failure	14
10	1997	66	F	M	NM	Ade, Cho	T2	+	HEP	R2	+	36 Days, death	Hepatic failure	15
11	1997	39	F	M	3	Ade, Cho	NM	NM	HEP	R2	+	5 Months, death	NM	16
12	1997	71	M	MA	8	Ade, Cho	T2	-	HEP	R2	-	22 Days, death	Bleeding	17
13	1996	63	M	M	4	Ade, Cho	T2	+	None	R0	-	6 Months, death	Hepatic failure	18
14	1995	74	M	A	6	Cho > Ade	T2	+	LYM	R2	MTX (PR)	4 Months, alive	-	19
15	1994	63	F	C	4.5	Ade > Cho	T2	+	None	R0	MTX, ACD	88 Days, death	DIC	20
16	1994	46	F	A	4.5	Ade > Cho	T2	+	None	R0	5FU	1 Years 2 months, death	Liver and lung metastasis	21
17	1994	57	M	A	7	Ade > Cho	T2	+	LYM	R2	MTX, CPA, ACD	5 Months, death	Peritonitis	22
18	1993	45	M	M	7	Cho > Ade	T4 (pancreas, liver)	+	HEP, LYM	R2	HA, 5FU, MMC, epiADM (PR) → CDDP, VP16	9 Months, death	Multiple metastasis carcinomatosa	23
19	1992	57	M	MA	8	Ade > Cho	T4 (colon)	+	None	R0	5FU, OK432 → 5FU, CDDP (PR)	1 Years 10 months, alive	-	24
20	1991	74	F	A	7.5	Cho > Ade	T4 (duodenum)	+	None	R0	-	5 Months, death	Hepatic and renal failure	25
21	1990	79	M	C	9	Cho	T3	+	HEP, LYM	R2	5FU	43 Days, death	Hepatic failure	26
22	1990	77	M	M	6	Ade, Cho	T3	-	None	R0	-	3 Months, death	Renal failure	12
23	1990	83	M	A	5	Cho	T2	+	None	R0	-	1 Years 9 months, alive	-	25
24	1989	66	M	AM	14	Cho	T3	+	None	R0	-	22 Days, death	Respiratory failure	20
25	1988	53	M	C	NM	Cho	T4	+	N0	R0	MTX, ACD, CPA → VP16 (PR)	5 Months, alive	-	20

26	1988	62	M	M	A	10	Ade, Cho	NM	+	None	R0	CDDP, CPA (PR)	9 Months, death	Chronic heart failure	27
27	1987	63	M	CM	A	9.8	Cho > Ade	T3	+	LYM	R0	-	3 Months, death	Respiratory failure	20
28	1987	55	M	AM	A	NM	Cho	T4 (pancreas)	+	LYM	R2	5FU, MTX, CPA	4 Months, death	Cachexia	28
29	1987	32	M	M	A	NM	Ade > Cho	T3	NM	HEP	R2	MTX, ACD, CDDP	2 Months, death	Bleeding	26
30	1986	55	M	A	A	NM	Cho	T4 (pancreas)	+	LYM	R2	5FU, MTX, OK432	16 Weeks, death	Bleeding	14
31	1985	61	M	MA	A	14	Cho	T3	+	LYM	R2	MTX, ACD, CPA (PR)	5 Months, death	Hepatic failure	20
32	1985	70	F	M	A	2	Cho	T2	NM	HEP	R2	MTX, ACD	16 Days, death	Bleeding	29
33	1985	70	F	A	A	10	Cho > Ade	T3	+	LYM	R2	5FU, MMC	5 Months, death	Bleeding	30
34	1985	64	M	M	A	5.5	Cho > Ade	T3	+	HEP	R2	MMC, MTX, HA, 5FU	21 Days, death	Bleeding	23
35	1985	69	F	A	A	3	Cho > Ade	NM	+	HEP	R2	MTX, CPA, ACD	6 Months, death	Hepatic failure	20
36	1985	66	F	A	A	NM	Ade > Cho	T2	+	None	R0	-	4 Months, death	Liver and LN metastasis	28
37	1984	62	M	A	A	8	Cho > Ade	T4 (colon)	+	LYM	R2	-	2 Months, death	NM	26
38	1984	64	M	A	A	7.6	Cho, Ade	T2	+	HEP	R2	HA:5FU, MMC, MTX	55 Days, death	DIC	14
39	1982	55	F	M	A	14	Cho > Ade	T3	+	PER	R2	-	4 Months, death	NM	1
40	1982	42	M	C	C	5	Ade > Cho	T4 (pancreas)	+	PER	R2	-	3 Months, death	NM	2
41	1982	63	M	C	C	4	Cho	T2	+	HEP, LYM	R2	-	42 Days, death	Peritonitis	28
42	1981	68	M	A	A	2.5	Cho	T2	+	HEP	R2	-	20 Days, death	carcinomatosa	31
43	1981	67	F	A	A	17	Cho, Ade	T4 (colon)	NM	HEP, PUL	R2	-	10 Days, death	Shock	3
44	1981	56	F	C	C	3.5	Cho, Ade	T2	-	None	R0	Cytosan, ACD	4 Months, death	Hepatic failure	3
45	1980	60	M	AM	A	6.5	Cho > Ade	T4 (pancreas)	+	HEP, LYM	R2	MTX, ACD	80 Days, death	Cachexia	24
46	1977	66	M	M	M	3	Cho	T2	-	None	R0	-	55 Days, death	Hypoglycemia	31
47	1977	45	M	AM	A	7.5	Ade > Cho	T3	+	HEP, PER	R2	5FU, MTX, ACD	84 Days, death	Cachexia	32
48	1976	68	F	C	C	8	Cho	T3	+	HEP, PUL	R2	-	18 Days, death	Bleeding	4
49	1973	73	M	M	M	NM	Cho > Ade	T3	+	HEP	R2	5FU, MTX	46 Days, alive	-	26
50	1972	45	M	A	A	NM	Cho	NM	+	HEP, PER	R2	VCR, EX, CO → VCR, MTX (PR) → ADM	6 Months, death	Multiple metastasis	4
51	1970	47	F	A	A	5	Cho	T2	+	HEP, PUL	R2	-	18 Days, death	Bleeding	4
52	1966	47	M	A	A	4.5	Cho, Ade	T2	-	None	R0	-	3 Months, death	Bleeding	31
53	1960	77	M	M	C	7	Cho, Ade	T3	+	HEP	R2	-	25 Days, death	Pneumonia	33

NM, not mentioned; C, upper third; M, middle third; A, lower third; Ade, adenocarcinoma; Cho, choriocarcinoma; L.N, lymph node; HA, intrahepatic artery injection; PR, partial response; DIC, disseminated intravascular coagulation  
<sup>a</sup> TNM-UICC, 1997 [34]

noma. Based on these findings, the tumor was diagnosed as a moderately differentiated tubular adenocarcinoma with a choriocarcinoma component.

In case 1, the preoperative, 2-week postoperative, and 6-month postoperative HCG levels were 1055, 44.7, and less than 0.5 mIU/ml, respectively (normal range, <0.5 mIU/ml). The patient's postoperative course was uneventful, and he remains recurrence-free 64 months after the operation.

### Case 2

A 64-year-old man visited our hospital for a routine medical examination. Laboratory data showed erythema (RBC,  $700 \times 10^4/\text{mm}^3$ ; Hb, 16.0 g/dl; Hct, 51.2%; WBC,  $17\,000/\text{mm}^3$ ; platelets [Plt],  $54 \times 10^4/\text{mm}^3$ ) and a high serum alpha-fetoprotein (AFP) value (2307.2 ng/ml; normal, <9.5 ng/ml). Neither gynecomastia nor abdominal abnormalities were recognized. A chest X-ray showed no abnormal shadows.

A gastrointestinal X-ray examination revealed an ulcerated mass occupying the upper third of the stomach. The mass was endoscopically diagnosed as a gastric cancer, and a biopsy specimen taken from an elevated lesion at the tumor margin revealed a moderately differentiated tubular adenocarcinoma. A CT scan showed regional lymph node swelling and metastases in the lateral segment of the liver.

A radical total gastrectomy, with lymph node dissection, splenectomy, and partial hepatic resection was performed. At the time of the operation, a macroscopic examination showed no metastatic tumors in the retroperitoneal area.

The resected tumor was  $7.0 \times 7.0$  cm in size. The tumor had extended to the subserosa (T2), and six regional lymph node metastases were identified (N1). Grossly, the tumor showed macroscopic features consistent with a type-3 lesion. Histologically, the tumor was composed of a well-differentiated tubular adenocarcinoma and a carcinoma with pleomorphic features. The former component accounted for approximately 90% of the entire tumor. The latter component contained syncytiotrophoblastic giant cells and hemorrhage; the histological features of this component were consistent with a choriocarcinoma. The hemorrhagic component of this tumor was composed only of choriocarcinoma-like tumor cells. All six nodal metastases were composed of tubular adenocarcinoma cells. Because positive immunohistochemical staining for the beta subunit of HCG was observed only in the choriocarcinoma-like component, this component was diagnosed as a choriocarcinoma. Based on these findings, the tumor was diagnosed as a well-differentiated tubular adenocarcinoma with a choriocarcinoma component.

In case 2, the preoperative and 2-week postoperative HCG levels were 246.9 and 2.3 mIU/ml, respectively. The patient's immediate postoperative course was uneventful, and he was treated with combination chemotherapy consisting of cisplatin (CDDP) and carboplatin (CPT-11) [5,6], as for AFP-producing gastric cancer. However, multiple liver metastases were detected 1 month after the operation, and his serum AFP level increased to 2307.2 ng/ml. The patient died 6 months after the operation.

## Reported PGC cases and pooled analysis

### Cases and methods

We retrospectively collected all the reported PGC cases and chose all operated cases (curative or noncurative) with a clear postoperative prognosis. Fifty-three cases of PGC have been documented previously [1–4,7–33] including the 2 cases reported here. All cases were classified according to the pTNM classification [34]. Measurement of the overall survival (OS) periods began at the time of surgery. Death due to gastric cancer was the only endpoint considered for the purpose of this study. The OS curves were drawn using the Kaplan-Meier method, and differences between the curves were compared using log-rank tests. The Cox proportional hazards regression model was used to estimate the multivariate hazard risk (HR) of tumor death (with a 95% confidence interval [CI]). The following variables were examined as potential prognostic factors: (1) sex, (2) age (<64 years or  $\geq 64$  years), (3) depth of invasion (T2 or T3, T4), (4) size (<7 cm or  $\geq 7$  cm), (5) histology ([adenocarcinoma > choriocarcinoma] or [choriocarcinoma > adenocarcinoma]), (6) regional lymph node metastasis (negative or positive), (7) distant lymph node metastasis (negative or positive), (8) synchronous liver metastasis (absent or present), (9) residual tumor after operation (absent or present), and (10) chemotherapy (not given or given). The cutoff values for size and age in this study were the median values for the patients in the pooled analysis. The variables associated with a significant increase in the HR of tumor death in the univariate analysis were entered into the multiple regression analysis, using the step-down method.

### Results of pooled analysis

Clinicopathological and follow-up data from the patients are presented in Table 1. Thirty-seven men and 16 women were included in the analysis (M/F ratio, 2.3:1). The mean age of the men was 62.4 years (median, 63 years; range, 32–83 years) and that of the women was 54.8 years (median, 63 years; range, 26–74 years). In the

51 previously reported patients, the PGC was most frequently located in the lower third of the stomach (41%; 21/51), followed by the middle third (37%; 19/51) and the upper third (22%; 11/51); the location frequently coincided with the location of the gastric adenocarcinoma [4]. The tumor sizes ranged from 2 to 18 cm (mean, 7.0 cm) in diameter, and nearly all the tumors were accompanied by macroscopic hemorrhage or necrosis. Thirty-seven patients (70%) had PGCs that exhibited an adenocarcinoma component. Most patients with PGC had metastatic lesions at the time of operation. The rates of lymph node, liver, peritoneal, and lung metastases were 87% (40/46), 45% (24/53), 23% (12/53), and 8% (4/53), respectively. Denominators indicate numbers of patients for whom the parameter was mentioned. The percentages of patients with a choriocarcinoma component in the lymph node and liver were 63% (19/30) and 96% (24/25), respectively. All patients with PGC had invasion beyond the muscularis propria (T2–T4). Postoperatively, residual tumor was found in 31 of the 53 patients (58%), because of distant metasta-

sis. The most frequent cause of death was hepatic failure because of tumor metastasis (29%; 12/41), followed by the bleeding of primary or metastatic tumors (24%; 10/41). Only 8% (4/53) of the PGC cases were diagnosed correctly by endoscopic biopsy.

On univariate and multivariate analyses, the presence of synchronous liver metastasis, the presence of residual tumor after operation, and the absence of chemotherapy were significantly associated with a short OS (Table 2). On the univariate analysis, the other parameters showed no significant association with a short OS. The OS curves are shown in Fig. 3A–C. Of the 53 patients, 10 died less than 1 month postoperatively (19%; Table 1).

## Discussion

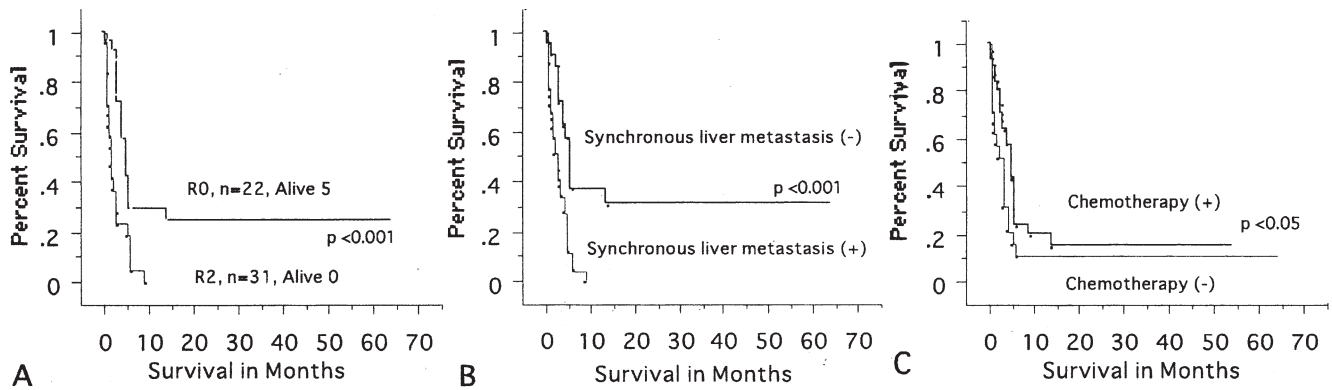
Davidsohn [35] first described PGC in 1905, and approximately 140 cases have been reported in the international medical literature to date. However, most of

**Table 2.** Univariate and multivariate analyses for overall survival (OS) periods (days) in PGC patients

Parameter	Univariate				Multivariate	
	No.	Rec (%)	<i>P</i> value <sup>a</sup>	HR	95% CI	Cox <i>P</i> value
Chemotherapy	52					
Given	31	24 (77)	0.037	4.4	1.0	Referent
Not given	21	18 (86)				
Residual tumor after operation	53					
Absent	22	14 (64)	<0.001	3.3	1.0	Referent
Present	31	29 (94)				
Synchronous liver metastasis	53					
Absent	29	20 (69)	<0.001	3.0	1.0	Referent
Present	24	23 (96)				
LN metastasis	46					
Negative	6	5 (83)	0.162			
Positive	40	32 (80)				
Age	53					
High ( $\geq 64$ years)	26	20 (77)	0.394			
Low (<64 years)	27	23 (85)				
Histology	42					
Chorio > adeno	32	25 (78)	0.411			
Adeno > chorio	10	8 (80)				
Sex	53					
Male	36	27 (75)	0.425			
Female	17	16 (94)				
Distant LN metastasis	53					
Negative	41	32 (78)	0.499			
Positive	12	11 (92)				
Depth	48					
T2	18	15 (83)	0.888			
T3, 4	30	25 (83)				
Size	43					
Small (<7 cm)	20	16 (80)	0.968			
Large ( $\geq 7$ cm)	23	19 (83)				

Rec, recurrence; HR, hazard ratio; CI, confidence interval; LN, lymph node; chorio, choriocarcinoma; adeno, adenocarcinoma

<sup>a</sup>*P* values are based on the log-rank test



**Fig. 3A–C.** Overall survival curves of patients with primary gastric choriocarcinoma (PGC). **A** Residual tumor after operation (absent or present);  $P < 0.001$ . **B** Synchronous liver metastasis (absent or present);  $P < 0.001$ . **C** Chemotherapy (given or not given);  $P < 0.05$

the cases were presented as single case reports or small series, and no studies have precisely examined the prognostic parameters for patients with PGCs. The clinicopathology and prognostic factors of PGCs also have yet to be elucidated. This prompted us to perform a pooled analysis of PGC cases to identify the biological characteristics of PGCs and establish prognostic clinicopathological parameters.

Several studies have indicated that the pathogenesis of PGC can be explained as the dedifferentiation of malignant adenocarcinoma tissue to the level of the embryonal ectoderm, retaining the ability to form trophoblasts [20,36]. Liu et al. [37] reported, with a comparative genomic hybridization and fluorescence in situ hybridization study, that PGC genetically possessed characteristics of both adenocarcinoma and gestational choriocarcinoma. In fact, the clinical features of gastric choriocarcinoma are similar to those of gastric adenocarcinoma; the mean age, male-female ratio, and tumor location all parallel those of primary gastric adenocarcinoma [27]. In the present two patients, the PGCs were accompanied by adenocarcinoma and exhibited a gradual transition from adenocarcinoma to choriocarcinoma components. These observations strongly suggest that the PGCs in the present patients originated from pre-existing gastric adenocarcinomas.

PGC is often diagnosed as adenocarcinoma because of the coexistence of adenocarcinoma and choriocarcinoma. That is why our patients were preoperatively diagnosed as having adenocarcinoma from endoscopic biopsy specimens. Only 8% (4/53) of the PGC cases were diagnosed correctly by biopsy.

Using univariate and multivariate analyses, our results demonstrated that synchronous liver metastasis, residual tumor after surgery, and the absence of chemotherapy were significant prognostic parameters of a short OS. One of the main characteristics of the PGC

patients was early death after operation because of hepatic failure, brought on by tumor metastasis, and bleeding of the primary or metastatic tumors. Of the ten patients who died within 1 month after operation, nine (90%) had synchronous liver metastasis. In the present report, case 2 died of liver metastasis in spite of receiving a curative operation and chemotherapy. The presence of synchronous liver metastasis at the time of operation may represent an advanced metastatic state and may be associated with a poor clinical course in PGC patients. We suggest that a palliative gastrectomy should never be performed in such patients, as it is likely that the patients would die soon after such a procedure. Regional and distant lymph node metastases, which are potent prognostic factors for many tumors, were not significant prognostic parameters in the present study. Therefore, PGCs with a high metastatic potential, especially to the liver, may have the highest malignant potential among PGCs with tumor metastasis. Our case 1 has survived for 5 years and 4 months since receiving a curative operation. There is no established regimen of chemotherapy for PGC. Based on these clinicopathological findings, we speculated that a combination of R0 resection and adequate chemotherapy may contribute to the long-term survival of PGC patients.

The present study suggests that PGC is a highly aggressive tumor that is often associated with liver metastasis. Curative resection, appropriate chemotherapy, and the absence of synchronous liver metastasis are favorable prognostic factors for patients with PGC.

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