A rare case of colorectal metastasis found 8 years and 10 months after gastrectomy for advanced gastric cancer: A case report and literature review

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Abstract. Colorectal metastasis from gastric cancer is rare and may develop several years after gastric cancer surgery. Therefore, colonoscopic findings provide useful diagnostic information. The present report describes a case of gastric cancer colon metastasis diagnosed 8 years and 10 months after gastrectomy for advanced gastric cancer. A 64-year-old male patient underwent gastrectomy in December 2010 and received chemotherapy for 4 years and 10 months after the surgery. Subsequently, the patient was diagnosed as having colorectal cancer by computed tomography in February 2019. Colonoscopy revealed linitis plastica-like colon stenosis; however, biopsy pathology did not reveal any findings indicating malignancy. Right hemicolectomy was performed, and pathological examination revealed colon metastasis from gastric cancer. The patient received chemotherapy but died of peritoneal carcinomatosis 1 year and 8 months after the colectomy. According to literature, colorectal metastasis from gastric cancer is often attributed to hematogenous metastasis and often exhibits characteristic macroscopic features. Treatments, such as chemotherapy for gastric cancer and/or colorectal resection, are considered effective for gastric cancer colorectal metastasis.

Introduction

Colorectal metastases from gastric cancer rarely occur without dissemination or direct infiltration and may be found several years after gastrectomy (1-4). Metastasis patterns, diagnosis, and treatment are being investigated from reported cases. In colon metastasis not originating from infiltration of gastric cancer, endoscopic findings often reveal multiple polypoid or linitis plastica-like lesions due to submucosal development (5). There are case reports (2,4,6) of long-term survival following surgical treatment and chemotherapy for recurrent lesions, and it is highly possible that treatment will contribute to improving the prognosis. We aimed to examine the characteristics of solitary colorectal metastasis from gastric cancer by evaluating our case and other reported cases to improve the medical treatment of colorectal metastasis from gastric cancer.

Case report

Patient background, onset and course. A 64-year-old man underwent distal gastrectomy for gastric cancer in December 2010. He had a history of hypertension (which was well controlled with antihypertensive medication) and hyperlipidemia (total cholesterol was 150 mg/dl on antihyperlipidemic medication). The pathological diagnosis was poorly differentiated adenocarcinoma (Fig. S1), type 2, Se, ly +, v +, n +, T4a N1 M0-stage IIIa (according to the 7th edition UICC) (Fig. 1). Postoperative adjuvant chemotherapy with tegafur/gimeracil/oteracil potassium (S-1) was administered in two courses. Computed tomography (CT) in May 2011 revealed peritoneal carcinomatosis; therefore, chemotherapy with docetaxel was administered, given the recurrence. Subsequently, chemotherapy was changed to bi-weekly paclitaxel therapy, and complete remission (CR) was achieved. Contrast-enhanced CT scan taken in December 2014 showed no recurrent lesions, and chemotherapy was discontinued at the patient's request. Thereafter, he remained under outpatient observation for stage IV gastric cancer follow-up. After completion of chemotherapy in December 2014, tumor markers were measured once every 3 months, CT and ultrasonography were performed once every 6 months, and gastrofiberscopy was performed once a year. In February 2019, the patient complained of discomfort in the right abdomen, and a CT scan showed wall thickening from the ascending colon to the transverse colon (Fig. 2). A colonoscopy revealed stenosis and mucosal edema from the hepatic flexure of the transverse colon to the ascending colon; diverticula in the ascending colon was also detected. Biopsy

pathology showed no malignant findings. Positron emission tomography-CT examination (Fig. 3) showed accumulation of fluorodeoxyglucose, and colorectal diverticulitis, potential dissemination, and peritoneal carcinomatosis were further diagnosed. The laparoscopic examination showed no ascites, recurrence, or disseminated lesions. No colectomies were performed since there was no obstruction, and no diagnosis of colon cancer was made. Appendectomy was performed, and a white induration in the peritoneum was biopsied; both specimens were submitted for pathological diagnosis, but no malignant findings were observed. A CT scan conducted in October 2019 (Fig. 4) showed worsening of the wall thickening of the ascending colon. Furthermore, carcinoembryonic antigen levels increased to 23.7 ng/ml. Colonoscopy revealed extensive stenosis in the transverse colon, and the biopsy showed no findings indicating malignancy (Fig. 5). Despite these results, right hemicolectomy was performed in November 2019 based on a diagnosis of transverse colon cancer. Gross findings of the resected specimen (Fig. 6) showed a linitis plastica-like tumor that was 20x60 mm in size, extending from the ascending to the transverse colon; the extent of mucosal infiltration was unclear. The pathological diagnosis was poorly differentiated adenocarcinoma, type 4, Se, ly0, v0, Pn1b, BD3, n0, and Cy0, T4a N0 M0-stage IIb (according to the 8th edition UICC). Microscopic findings (Fig. 7) showed atypical cells that infiltrated and proliferated in a cord-like or individual-cell manner with a fibrous stroma and that the spread extended to all layers. Tumor cells were AE1/AE3 positive, cytokeratin (CK)7 positive, CK20 negative, and caudal type homeobox 2 (CDX2) negative on immunostaining (Fig. 8), and gastric cancer recurrence was diagnosed. Thereafter, S-1, oxaliplatin chemotherapy → ramucirumab, paclitaxel chemotherapy → nivolumab chemotherapy → irinotecan chemotherapy → docetaxel chemotherapy were administered; however, the patient died of peritoneal carcinomatosis in July 2021.

Analysis method from case reports. To investigate the characteristics of colon metastasis from gastric cancer, we performed a literature search of English abstracts published on colon metastasis and gastric cancer in the Cochrane Library and PubMed databases. The data were obtained directly from case reports searched in the literature and the present case. We did not acquire any patient cohort data during this study. From the previous case reports, we extracted data on the following factors: age, sex, gastric cancer pathology, macroscopic feature of gastric cancer, other metastatic sites besides the colorectum, metastatic site in the colorectum, chemotherapy after the diagnosis of colorectal metastasis, and prognosis. We tested for significant differences in each factor between the synchronous (n=13) and metachronous (n=24) gastric cancer colonic metastasis case groups. The prognosis after diagnosis of colon metastasis between the two groups was determined.

Statistical analysis. Categorical data were represented as n (%). Continuous data were described as mean ± standard deviation (SD). To compare 13 syncronous and 24 metacronous colon metastasis case groups, Fisher's exact test was used to determine significant differences between covariates for gastric cancer pathology, macroscopic features, recurrent colon tumor macroscopic features, other metastatic sites

Figure 1. Macroscopic findings of the excised stomach. The resected specimen had the appearance of a type 2 gastric cancer.

besides the colorectum, metastatic site in the colorectum, and chemotherapy after the diagnosis of colorectal metastasis. Continuous data for age were analyzed by unpaired t-test. Prognosis was analyzed using Kaplan-Meier survival curve and log-rank test. Estimated mean survival, estimated median survival, and their respective standard errors (SE) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Japan, Ltd., Tokyo, Japan). A two-sided P-<0.05 was considered significant.

Discussion

We described the case of a patient with stage IV gastric cancer who underwent chemotherapy and achieved CR. He was found to have developed colorectal metastases 8 years and 10 months after gastrectomy and died 1 year and 8 months after undergoing a right hemicolectomy.

Regarding cancer metastasis from other organs to the gastrointestinal tract, the most reported metastatic site is the colorectum, followed by the stomach and duodenum (7). The proportion of metastatic lesions from other organs in colorectal cancer is considered to be approximately 1%; however, it may be slightly higher at postmortem (7). In addition, the detection of colorectal metastases is thought to increase a greater awareness of the need to follow up on primary tumors (7). The most common primary organs of colorectal metastases are the lung, ovary, mammary gland, prostate, kidney, and skin (7). The incidence of multiple primary cancer after gastric cancer surgery is 2.0-7.6% (8), and colorectal cancer often occurs. In a single institutional report of secondary primary colorectal carcinoma in Asia (9), 17 of 1,031 resected colorectal cancers had metastasized from other sites. Of the 17 cases, six and five were breast and gastric cancers, respectively. The incidence of gastric cancer is high in East Asia (9). Genes are involved in the carcinogenic mechanism, but in cancers that occur in multiple organs, it is important to know whether they are metastases or multiple individual cancer occurrences. Classification of a cancer as metastatic or second primary cancer is essential. The criteria for multiple secondary tumors (MPCs) are reported by Warren and Gates
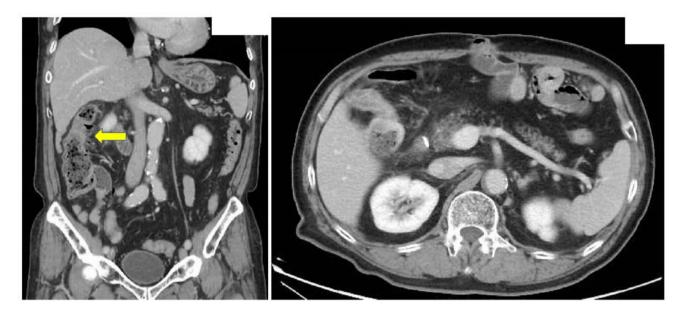
Figure 2. Contrast-enhanced computed tomography examination. Marked wall thickening was observed from the ascending to the transverse colon (arrow).

Figure 3. Positron emission tomography-computed tomography examination. Fluorodeoxyglucose accumulation was observed from the ascending colon to the transverse colon.

in 1932 (10). According to them, 'each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded'. Malignant lesions with characteristics other than these are treated as metastases. Evidence of such metastasis to distant organs is confirmed from pathological features;

however, recent determinations using immunostaining are believed to have increased accuracy. Immunohistochemical staining is effective in determining whether the lesions are of the same origin; this is reportedly effective in demonstrating metastasis (11,12). Immunohistochemical markers are useful in diagnosing metastatic adenocarcinoma with increased sensitivity and specificity to determine the primary site (12,13). The staining pattern of CDX2, CK7, and CK20 reveals whether the metastasis is gastric or colorectal (12). CDX2 is a homeobox gene that encodes a gut-specific transcription factor and is expressed in the epithelial cell nuclei of the intestine from the duodenum to the rectum. AE1/AE3 stains almost all epithelial cells. Gastric cancer is generally CK7-positive and CK20-negative, while colon cancer is generally CK7-negative and CK20-positive. Our findings revealed a similar pattern (CK7-positive and CK20-negative) of immunohistochemical staining. However, immunohistochemical staining does not aid in determining whether rare cancers in multiple organs occur due to the same gene.

In our case, the patient achieved CR from stage IV gastric cancer after chemotherapy, and CT scan revealed colon metastasis 8 years and 10 months postoperatively. To investigate the characteristics of colon metastasis from gastric cancer, we summarized the reported cases of gastric cancer colon metastasis. Synchronous colorectal metastases differ from metachronous; we found 24 metachronous (1-4,6,14-29) (Table I) and 13 synchronous cases (5,25,30-40), as classified and listed in Table II. Several reports have set the boundary between synchronous and metachronous metastases as diagnosed after 2 months, 6 months, and 1 year from the primary diagnosis. Our report is based on the Surveillance Epidemiology and End Results approach, which has the largest number of cases of metachronous cancer. According to this classification (41), metachronous cancer is defined as cancer of other organs diagnosed ≥2 months after the first cancer.

CT is reportedly effective in diagnosing metastasis to the colorectum after gastric cancer surgery. It has a very high rate of detection, especially when a helical CT outcome is interpreted
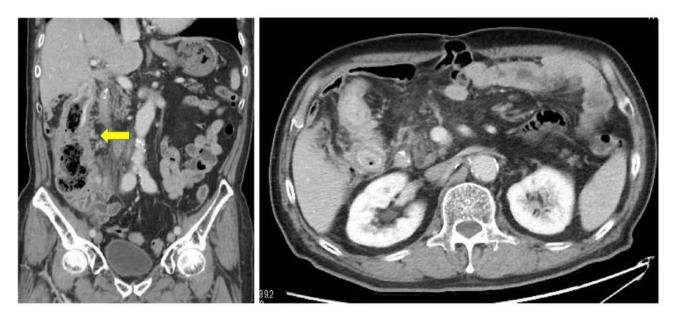
Figure 4. Contrast-enhanced computed tomography examination. Marked wall thickening was observed from the ascending colon to the transverse colon (arrow).
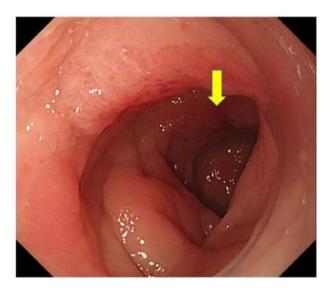

Figure 5. Colonoscopic findings. Colonoscopy showed stenosis in the transverse colon (arrow).

Figure 6. Macroscopic findings of the excised colon. The resected specimen had the appearance of a linitis plastica-like type 4 colon cancer with wall thickening and whitish induration.

by a radiologist (42). Most of the reported cases of gastric cancer and colorectal metastasis were diagnosed by CT and endoscopy. Diagnostic colonoscopy was performed in almost all cases for both metachronous and synchronous colon metastases, and the findings were polypoid or linitis plastica-like. In many of the reviewed cases, the biopsy results obtained using colonoscopy were not described, and no malignant findings were reported (17,19,24,25,28,29) (Tables I and II). In our case, more than 8 years had passed since the gastric cancer surgery, and no malignant findings were obtained upon examination. Therefore, the large intestine was not resected during the second laparoscopic surgery, and the diagnosis of colon metastasis was slightly delayed. Endoscopic biopsy diagnosis may be ineffective in colorectal metastasis due to the presence of metastatic lesions under the mucosa (42). Even if no malignant findings are revealed by biopsy, resection is a better option when it is feasible based on the diagnostic imaging.

Similar to a previous report (42), most of the colon metastases from gastric cancer (Tables I and II) are poorly differentiated and signet ring cell adenocarcinomas. In general, when the tissue is intestinal, the metastases are often hematogenous, whereas when it is poorly differentiated (diffuse type), the metastases are often lymphatic/disseminated (43). It is assumed that there is a mechanism responsible for the many hematogenous metastases of poorly differentiated adenocarcinoma to the colorectum from gastric cancer. Poorly differentiated and signet ring cell adenocarcinomas are rare primary colorectal cancers, and metastasis from gastric cancer should be considered when biopsy results by colonoscopy show such findings (1).

Sonoda *et al* (5) divided and investigated the metastatic pathways of colorectal metastasis from gastric cancer without peritoneal carcinomatosis, as follows: i) metastatic pathway
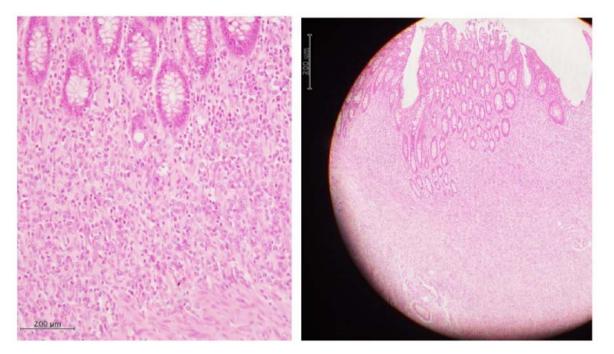
Figure 7. Hematoxylin and eosin staining of the colon. Cancer cells proliferated submucosally and partially invaded the mucosa, and the left image is a magnified version of the image on the right [magnification, x40 (right)/x100 (left)].
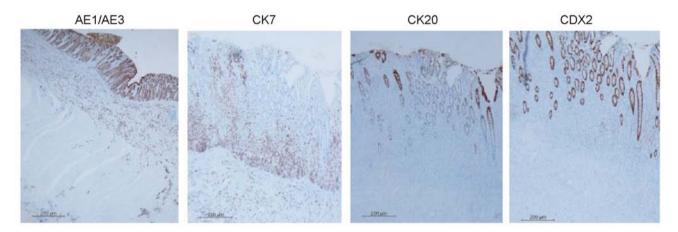

Figure 8. Immunostaining of the colon. Tumor cells were stained AE1/AE3-positive, CK7-positive, CK20-negative and CDX2-negative (magnification, x100; scale bar, 200 μm). CDX2, caudal-type homeobox protein 2; CK, cytokeratin.

from the gastrointestinal lumen; ii) lymphatic metastasis; and iii) hematogenous metastasis. According to them, there are many metastases from the gastrointestinal lumen, but the route is not considered in each report. Lymphatic metastasis to the colorectum, other than the transverse colon, is unlikely, and as reported by Noji et al (2), metastasis to the colorectum from the ovary or disseminated lesion is also possible. In this report (Tables I and II), many cases show macroscopic findings that cause submucosal infiltration, and many do not show malignant findings on the mucosal surface. Since metastasis from the gastrointestinal tract often presents with mucosal lesions and is often transplanted to the anastomotic stapler site, it is considered that the frequency of gastric cancer metastasis to the colon via the gastrointestinal tract is extremely low. Lymphatic metastasis is unlikely in colonic metastasis from a site distant from the stomach without dissemination,

and therefore, hematogenous metastasis is mostly considered. Cancer stem cells are involved in carcinogenesis and metastasis, and their markers are attracting attention in research. It is known that CD44 and G-protein coupled receptor 5 (LGR5) are closely related to gastric cancer (44,45). Although these were not investigated in the case reported in our study, we believe that evaluating these markers will be useful in future research on colorectal metastasis from gastric cancer.

There are cases in which signet ring cell adenocarcinoma of the mammary gland (46,47) and small-cell carcinoma of the lung present with metastases to the colon (48) with submucosal infiltration. In addition, cases in which signet ring cell adenocarcinoma of the sigmoid colon and rectum metastasized to the stomach (49,50), and poorly differentiated adenocarcinoma of the mammary gland metastasized to the stomach (51,52) with submucosal invasion have been reported. In many reports,

Table I. Cases of metachronous gastric cancer colorectal metastasis.

First author/s, year	No.	Age, years	Sex	N	Et	PGT					SCM				RCT		Outcome	(Refs.)
						MF	Stage	LNM	Pathology	CTX	OMS	BP	Pathology	MF	DFI, months	CACO		
Ogiwara et al, 1994	1	53	F	JPN	UN	IIc+III (advanced)	UN	Yes	Por	UN	D,S: none	Por	UN	Pol	132	UN	UN	(1)
Tanakaya et al, 2004	2	68	M	JPN	UN	Type IV	IIIA	Yes	Sig, Por	UN	IC: none	AC	Sig, Por	Pol	96	UN	Death 16 Mo after SS	(14)
Tseng et al, 2004	3	74	M	UN	UN	UN	UN	Yes	UN	UN	S,R: UN	AC	AC	Pol	108	Yes	Death 6 Mo after SS	(15)
Pace et al, 2009	4	77	M	ITA	UN	Type II or III	IIIA	Yes	Sig, Mod	Yes	A:none	Por	Por, Sig	UN	15	UN	UN	(16)
Lim et al, 2011	5	43	F	KOR	UN	Type III	II	Yes	Por	UN	R:none	NDM	Por	LPL	34	FOL-FOX	Alive 14 Mo after SS	(17)
Mayumi et al, 2013	6	74	M	JPN	UN	Type III	IV	No	Por	1st, S-1; 2nd, S-1, CDDP; 3rd, CPT	T: ovary	UN	Por	Type II	38	1st, CPT; 2nd, PTX	Death 28 Mo after SS	(18)
											T:intestine	UN	Por	UN	49	Capecitabine, CDDP	Death 17 Mo after 3rd Sur	
Watanabe et al, 2013	7	63	M	JPN	UN	Type II	IIB	No	Mod	TS-1	T:Per	NDM	Mod-Por	Type II	34	Yes	Alive 15 Mo after SS	(19)
Noji et al, 2014	8	61	M	JPN	UN	UN	II	No	Por, Sig	UN	T:LN	UN	Por, Sig	UN	108	Refused	Alive 17 Mo after SS	(2)

Table I. Continued.

First author/s, year	No.	Age, years	Sex	N	Et	PGT					RCT						Outcome	(Refs.)
						MF	Stage	LNM	Pathology	CTX	SCM: OMS	BP	Pathology	MF	DFI, months	CACO		
Noji et al, 2014	9	46	F	JPN	UN	UN	IIIA	Yes	Sig	Yes	R: ovary, LN	UN	Mod, Por	Pol	108	Yes	Alive 24 Mo after SS	(2)
Oh et al, 2014	10	69	F	USA	UN	Type II or III	II	Yes	Por	1st, FOL FOX; 2nd, ECX	S:UN	Por	No resections	Type II or III	47	1st, FOL FOX; 2nd, FOL FIRI	UN	(20)
Tomita et al, 2015	11	70	F	JPN	UN	Type IV	IIIA	Yes	Sig	S-1	T:UN	NDM	Sig	UN	33	S-1	Death 37 Mo after SS	(21)
											A:Per	UN	No resections	UN	47	S-1, DOC	Death 23 Mo after 3rd Sur	
Fujimoto et al, 2016	12	58	F	JPN	UN	0-IIc+ IIa	Ia	No	Por, Sig	1st, S-1; 2nd, S-1, CDDP, RTX	S: ovary	UN	Por, Sig	0-IIc	28	S-1, DOC	Alive 30 Mo after SS	(6)
Ikeda et al, 2016	13	69	F	JPN	UN	0-IIc	Ib	Yes	Por, Sig	No	T:LN	None	Por, Sig	SMTL	47	Refused	Death 7 Mo after SS	(22)
Uemura et al, 2016	14	64	M	JPN	UN	0-I	Ia	No	W	No	R:LN	W	W	Pol	24	UN	Alive 6 Mo after SS	(23)

Table I. Continued.

First author/s, year	No.	Age, years	Sex	N	Et	MF (PGT)	Stage	LNM	Pathology (PGT)	CTX	SCM: OMS	BP	Pathology (RCT)	MF (RCT)	DFI, months	CACO	Outcome	(Refs.)
Higuchi et al, 2018	15	55	M	JPN	UN	Type III	IV	Yes	Mod	S-1	C:none	NDM	Mod-Por	SMTL	10	FP	Death 20 Mo after SS	(24)
Higuchi et al, 2018	16	59	M	JPN	UN	Type IV	IIIB	Yes	Tub, Por	S-1	T:UN	Por. Sig	Por. Sig	LPL	23	S-1	Death 25 Mo after SS	(24)
Su et al, 2018	17	78	M	TW	UN	Advanced GC	IIIB	UN	Por	FOLFOX	R, T:UN	UN	Por	Type II	18	UN	Death 6 Mo after SS	(25)
Mizuguchi et al, 2018	18	60'	M	JPN	UN	Type III	IIB	Yes	Tub, Por	S-1	A: LN	Por	Tub, Por	LPL	26	None	Death 6 Mo after SS	(26)
Elghali et al, 2019	19	62	M	TUN	UN	UN	IB	No	Sig	No	T: LN	UN	Sig	UN	96	Yes	UN	(3)
Yang et al, 2020	20	57	M	CN	UN	UN	IIIA	Yes	Por, Sig	SOX	A: skin, LN	Por	Por. Sig	LPL	30	Yes	Death 9 Mo after SS	(27)
Okazaki et al, 2020	21	70	F	JPN	UN	UN	IV	UN	Por	SOX	C: none	NDM	Por	Pol	48	SOX	Alive 12 Mo after SS	(28)
Then et al, 2021	22	66	M	USA	UN	UN	UN	UN	UN	UN	T:UN	NDM	AC	UN	24	None	UN	(29)
Wang et al, 2021	23	42	M	CN	UN	UN	IIIA	Yes	Por	L-OHP, CF, 5-FU	RS: Per	UN	Por	Mass	70	PTX, CF, 5-FU	Death 76 Mo after SS	(4)

Table I. Continued.

First author/s, year	No.	Age, years	Sex	N	Et	MF	Stage	LNM	Pathology	CTX	SCM: OMS	BP	Pathology	MF	DFI, months	CACO	Outcome	(Refs.)
											S: LN	Por	Por	Pol	110	Epiru bicin, L-OHP, Capecita bine	Death 44 Mo after 3rd Sur	
											S LN	Por	Por	Mass	138	Suniti nib + S-1	Death 16 Mo after 4th Sur	
											S: LN	Por	Por	Mass	151	UN	Death 3 Mo after 5th Sur	
Present study	24	73	M	JPN	Asian	Type II	IIIA	Yes	Por	1st, S-1; 2nd, DOC; 3rd, PTX.	T: none	NDM	Por	LPL	118	1st, SOX; 2nd, RAM, PTX; 3rd, Niv; 4th, CPT; 5th, DOC	Death 20 Mo after SS	-

A, ascending colon; AC, adenocarcinoma; BP, biopsy pathology; C, caecum; CACO, chemotherapy after colectomy; CDDP, cisplatin; CF, folic acid; CN, China; CPT, irinotecan; CTX, chemotherapy; D, descending colon; DCM, diagnosis of colorectal metastasis; DFI, disease-free interval; DOC, docetaxel; DX, diagnosis; ECX, epirubicin, cisplatin and xeloda; Et, ethnicity; F, female; FOLFIRI, folic acid, 5-fluorouracil and irinotecan; FOLFOX, folic acid, 5-fluorouracil and oxaliplatin; FP, 5-FU, cisplatin; FU, fluorouracil; GC, gastric cancer; IC, ileo-cecal lesion; ITA, Italy; JPN, Japan; KOR, Korea; LN, lymph node; LNM, lymph node metastasis; LPL, linitis plastica-like lesion; L-OHP, oxaliplatin; M, male; MCS, metastatic colonic site; MF, macroscopic features; Mo, months; Mod, moderately differentiated adenocarcinoma; N, nationality; Niv, nivolumab; NDM, not detected malignancy; OMS, other metastatic site; Per, peritoneum; PGT, primary gastric tumor; Pol, polypoid lesion; Por, poorly differentiated adenocarcinoma; PTX, paclitaxel; R, rectum; RAM, ramucirumab; RCT, recurrent colon tumor; RS, remnant stomach; RTX, radiation therapy; S, sigmoid colon; SCM, site of colonic metastasis; Sig, signet ring cell carcinoma; SMTL, submucosal tumor like lesion; SOX, S-1, oxaliplatin; SS, second surgery; Sur, surgery; S-1, tegafur gimeracil oteracil potassium; T, transverse colon; Tub, tubular adenocarcinoma; TUN, Tunisia; TW, Taiwan; UN, unknown; USA, United States of America.

Table II. Cases of synchronous gastric cancer colorectal metastasis.

First author/s, year	No.	Age, years	Sex	N	Et	PGT Macroscopic features	Stage	Pathology	SCM: OMS	RCT BP	MF	CAC	Outcome	(Refs.)
Metayer et al, 1991	1	65	M	FR	UN	Type II or III	IV	Sig	C, T, S:UN	Sig	Pol	None	Death within a month after DX	(30)
Tomikashi et al, 2002	2	57	M	JPN	UN	Type III	IV	Por	All colon: bones	Por	Pol	FP	Alive 7 months after DX	(31)
Lee et al, 2004	3	41	M	TW	UN	Type IV	IV	Sig	T, D, S:WB, LN	Por, Sig	Pol	HDFL	Death 1 month after DX	(32)
Nakamura et al, 2008	4	86	F	JPN	UN	Type III	IV	Por, Sig	T:Per	Por, Sig	0-IIa+ IIc	None	Death 10 months after DX	(33)
Tural et al, 2012	5	74	F	TUR	UN	UN	IV	Well	R:none	Well	Pol	TCF	Alive several months after CTX	(34)
Reyes-Diaz et al, 2012	6	58	M	ES	UN	UN	IV	Sig	C, A, S, R:LN	Sig	UN	CDDP	Death 12 months after DX	(35)
Gao et al, 2014	7	80	M	CN	UN	Type II or III	IV	Por, Sig	A, T, D, S:UN	Sig	Pol	Xeloda	Death 3 months after DX	(36)
Lee et al, 2015	8	55	F	KOR	UN	0-IIc	IV	Sig	S, R: bone	Sig	Pol	FOL FOX	Alive >16 months after CTX	(37)
Patel et al, 2016	9	59	F	USA	CAU	UN	IV	Sig	A, T, S:LN	Sig	LPL	FOL FOX	Alive 1 months after surgery	(38)
Makker et al, 2016	10	60	F	UN	UN	Type I or II	IV	Sig	R:B, L, Pl	Por, Sig	Pol+ LPL	DCFL	Death 12 months after DX	(39)
Sonoda et al, 2017	11	81	M	JPN	Asian	Type III	IV	Por, Sig	T:Per	Por, Sig	0-IIa	UN	UN	(5)
Su et al, 2018	12	77	M	TW	UN	UN	IV	Por	R, T:UN	NDM	Pol	FOL FOX	Death 6 months after DX	(25)
Meheershahi et al, 2020	13	55	M	USA	UN	Type IV	IV	Por	S:UN	Por, Sig	Type II	UN	UN	(40)

A, ascending colon; B, bone; BP, biopsy pathology; C, caecum; CAC, chemotherapy after colectomy; CAU, Caucasian; CDDP, cisplatin; CN, China; CTX, chemotherapy; D, descending colon; DCFL, docetaxel, cisplatin, 5-fluorouracil, leucovorin; FU, fluorouracil; DX, diagnosis; ES, Spain; Et, ethnicity; F, female; FOLFOX, folic acid, 5-fluorouracil and oxaliplatin; FP, 5-FU, cisplatin; FR, France; HDFL, high-dose 5-fluorouracil and leucovorin; JPN, Japan; KOR, Korea; L, lung; LN, lymph node; LNM, lymph node metastasis; LPL, linitis plastica-like lesion; M, male; MF, macroscopic feature; N, nationality; NDM, no detected malignancy; OMS, other metastatic site; Per, peritoneum; PGT, primary gastric tumor; Pl, pleura; Pol, polypoid lesion; Por, poorly differentiated adenocarcinoma; R, rectum; RCT, recurrent colon tumor; S, sigmoid colon; Sig, signet ring cell carcinoma; SCM, site of colonic metastasis; T, transverse colon; TCF, docetaxel, cisplatin, 5FU; TUR, Turkey; TW, Taiwan; UN, unknown; USA, United States of America; Well, well differentiated adenocarcinoma; WB, whole body.

Table III. Comparison between patients with synchronous gastric cancer colorectal metastases and patients with metachronous gastric cancer colorectal metastases.

Variables	Synchronous colorectal metastases		Metachronous colorectal metastasis		P-value
	No.	Value	No.	Value	
Mean age ± SD, years	13	65.2±13.2	23	63.2±10.4	0.608[a]
Gastric cancer pathology, n (%)	13		22		>0.999[b]
Poorly differentiated		12 (92.3)		19 (86.4)	
Well-to-moderate differentiated		1 (7.7)		3 (13.6)	
Gastric cancer macroscopic features, n (%)	9		16		>0.999[b]
Early		1 (11.1)		3 (18.8)	
Advanced		8 (88.9)		13 (81.3)	
Recurrent colon tumor macroscopic features, n (%)	12		19		0.274[b]
Polypoid or early		9 (75.0)		10 (52.6)	
Advanced		3 (25.0)		9 (47.4)	
Other metastatic sites besides the colorectum, n (%)	9		18		0.201[b]
Yes		8 (88.9)		11 (61.1)	
No		1 (11.1)		7 (38.9)	
Metastatic site in the colorectum, n (%)	13		24		0.667[b]
Colon		8 (61.5)		18 (75.0)	
Rectum		2 (15.4)		3 (12.5)	
Colon and rectum		3 (23.1)		3 (12.5)	
Chemotherapy, n (%)	11		19		>0.999[b]
Yes		9 (81.8)		15 (78.9)	
No		2 (18.2)		4 (21.1)	

[a]Unpaired t test; [b]Fisher's exact test. Data are presented as mean ± SD or n (%). The number of cases differs for some variables due to unknown/missing data.

metastatic lesions from other organs that grow under the mucosa of organs of the gastrointestinal tract show polypoid or linitis plastica-like findings (46-52). In general, metastases from other organs to the gastrointestinal tract are often hematogenous, are thought to infiltrate submucosal lymphatics, and develop as linitis plastica (16,53). Regarding gastrointestinal metastasis from breast cancer, many are estrogen and progesterone receptor-positive, suggesting a relationship with chemocain (51). In addition, the metastasis is related to cancer-related adipocytes (54), and the relationship with submucosal and subserosal adipocytes of the gastrointestinal tract is also considered, although currently, it remains unclear. When tumor cell metastases occur submucosally, the smooth muscle acts as a barrier to tumor infiltration. Furthermore, it is thought that the tumor growth suppression mechanism of the muscle is involved in the growth and infiltration of cancer in the submucosa (55). In our case, colonic metastasis occurred at the same site as the colonic diverticulum. It has been reported (56) that the microbiome is involved in cancer development. In our case, metastasis of the microbiome is unlikely, considering that the metastasis

developed mainly in the submucosa. Furthermore, after cancer onset, the patient had achieved CR for a long time. In addition, in the referenced previous case report, the role of the microbiome was not mentioned; therefore, the relationship between metastasis and infection is unknown.

In cases of metastasis, it is possible that cancer lesions that have already metastasized before chemotherapy administration for gastric cancer may recur when chemotherapy is discontinued. Although patient prognosis has been extended due to advances in chemotherapy for advanced gastric cancer, there is no standard protocol for discontinuing chemotherapy for stage IV gastric cancer. Therefore, it is difficult to decide on the discontinuation of chemotherapy, as in the reported case.

In summary, a comprehensive study of published cases of gastric cancer colon metastasis, comparison between macroscopic classifications of gastric cancer, and these macroscopic features have not been reported. In our study, no differences were observed between the synchronous and metachronous metastasis groups. Similarly, there were no significant differences between the two groups in terms of sex, gastric

Table IV. Prognostic comparison between patients with synchronous and metachronous gastric cancer colorectal metastases.

Groups	Mean survival, months			Median survival, months		
	Estimated mean survival	SE	95% CI	Estimated median survival	SE	95% CI
Synchronous	8.37	1.73	4.98-11.77	10	4.88	0.43-19.57
Metachronous	22.90	3.33	16.36-29.43	20	4.55	11.07-28.93
Whole	19.11	2.84	13.53-24.69	20	4.88	10.44-29.56

Data are presented as estimated mean survival or estimated median survival, and their respective SE and 95% CI. Log-rank test P-value=0.0081. SE, standard error.

cancer pathology, macroscopic feature of gastric cancer, other metastatic sites besides the colorectum, metastatic site in the colorectum, and chemotherapy after the diagnosis of colorectal metastasis. In cases of metachronous colorectal metastases, the rate of early gastric cancer was higher, and the stage was considered lower than in cases of synchronous metastases. According to the characteristics of recurrence (Tables I and II), the stage of gastric cancer differs depending on the age at which gastric cancer develops; therefore, a comparison was made based on the age at which the metastasis to the colorectum was diagnosed (Table III). For synchronous and metachronous metastases, the mean age of patients was 65.2±13.2 years and 63.2±10.4 years, respectively, and there was no significant difference between the two groups (P=0.608). In metachronous cases, the period from the initial surgery for gastric cancer to the discovery of colorectal metastasis was 55.3±9.9 months, which is considered a long interval. The average ± standard error of prognosis after diagnosis of colorectal metastases was 22.90±3.33 months and 8.37±1.73 months for metachronous and synchronous colorectal metastases, respectively (Table IV). The prognosis for metachronous metastasis was significantly longer than for synchronous metastasis (P=0.008) (Fig. 9). According to this case, both synchronous and metachronous metastases were of stage IV, but the prognosis of synchronous metastases was shorter than the overall survival rate (57) of stage IV gastric cancer.

We found that metachronous colorectal metastasis from gastric cancer has a better prognosis than synchronous metastasis. First, the prognosis after gastric cancer surgery without MPC is better than with MPC. Synchronous MPC has a worse prognosis than metachronous MPC; however, when MPC occurs, the prognosis of metachronous colorectal metastasis deteriorates rapidly. This phenomenon has been reported as a reason for the treatment effect for gastric cancer in metachronous secondary primary cancer (58). Therefore, in gastric cancer metastasis, the therapy is expected to affect the colorectal metastasis.

In terms of prognosis after the diagnosis of colonic metastases, metachronous metastasis was associated with a favorable outcome when considering the reported case. The reasons for this are as follows: i) when metachronous gastric cancer has metastasized to the colorectum, the cancer lesions often remain localized or do not spread widely; ii) the effect of chemotherapy and resection on colonic metastases improves prognosis.
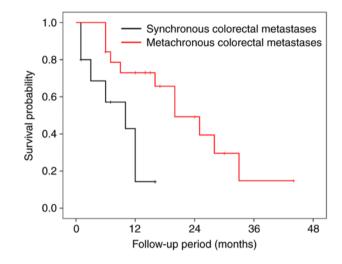

Figure 9. Kaplan-Meier survival curves according to the classification of onset time of colorectal metastases from 37 cases of gastric cancer collected from the database.

As reported by Mayumi *et al* (18) and Wang *et al* (4), long-term survival has been achieved in some cases by performing several resections and chemotherapy treatments for repeated recurrence. This suggests that surgical resection and chemotherapy may be effective for gastric metastasis to the colorectum.

The use of chemotherapy is based on the treatment guidelines of each country. In the reported cases, there were cases in which the prognosis was considered to have improved by administering chemotherapy using the same protocol or the same anticancer drug after recurrence due to colorectal metastasis (6,18,20,21,24). In cases of metachronous recurrence, if the chemotherapy protocol before recurrence was effective and the chemotherapy was discontinued, the same treatment should be considered first. However, it would be good to consider changing the protocol if lesion progression is observed.

Future research on the mechanisms of cancer metastasis and analysis of similar cases is expected to lead to findings that will guide the development of novel and rational treatment approaches. In particular, research advances involving biomarkers, immunohistochemistry, and liquid biopsies should be expected.

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Limitation: Since some case reports did not describe the stage and type of gastric cancer at the time of diagnosis or the pathological results of the endoscopic biopsy performed to diagnose colon metastasis, these items could not be statistically processed and examined.

In conclusion, colon metastases from gastric cancer may develop even after a prolonged period of treatment for gastric cancer and often result in polypoid, linitis plastica-like submucosal endoscopic findings. Such findings are similar to those of hematogenous colonic metastases from other organs. The results of biopsy pathology often show no malignant findings; however, poorly differentiated adenocarcinoma and signet ring cell carcinoma are common. When such findings are obtained, metastatic colorectal cancer should be suspected. It has been suggested that treatment for gastric cancer may have a therapeutic effect on gastric cancer colorectal metastasis and that resection and/or chemotherapy for gastric cancer metastases are effective.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SK, MI, SRY, HA, MO, FY and KE contributed to the study conception and design. Material preparation, data collection and analysis were performed by SK, SRY and HA. The first draft of the manuscript was written by SK, and all authors commented on previous versions of the manuscript. SK and MI confirm the authenticity of all the raw data. KE gave final approval of the version to be published. All authors have read and approved the final manuscript.

Ethics approval and consent for participate

Ethical review and approval were waived for this case report because of the retrospective nature of the published data.

Patient consent for publication

Written informed consent for publication was obtained from the patient antemortem.

Authors' information

SK is a member of the Japan Surgical Society, the Japanese Society of Gastroenterological Surgery, the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, the Japan Society of Clinical Oncology, and the Japanese Gastric Cancer Association.

Competing interests

The authors declare that they have no competing interests.

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