ANTICANCER RESEARCH *39*: 2233-2238 (2019)
doi:10.21873/anticanres.13339

Five-year Recurrence-free Survival After Surgery Followed by Oral Chemotherapy for Gastric Cancer With Portal Vein Tumor Thrombosis

YASUSHI YOSHIDA[1], TORU BEPPU[1], KOICHI KINOSHITA[1], NOBUTAKA SATO[1], SHINICHI AKAHOSHI[1], HIDEAKI YUKI[2], SEIYA SAITO[3], MITSUHIKO KITAOKA[4] and JIRO NASU[3]

Departments of [1]Surgery and [2]Radiology, Yamaga City Medical Center, Kumamoto, Japan; Departments of [3]Surgery and [4]Pathology, Kumamoto Chuo hospital, Kumamoto, Japan

Abstract. *Gastric cancer with portal vein tumor thrombosis (GC-PVTT) is a rare condition with a very poor prognosis. A 64-year-old man with GC-PVTT was admitted to our hospital. His carcinoembryonic antigen level was slightly elevated (17.4 ng/ml). Upper gastrointestinal endoscopy showed a type-2 gastric lesion (45 mm × 40 mm) in the gastric antrum. The PVTT originated from the main gastric tumor and continued to the superior mesenteric vein. Fluorodeoxyglucose-positron emission tomography showed high uptake both by the main tumor and PVTT. A distal gastrectomy with D2 lymphadenectomy was performed with simultaneous removal of the PVTT. Pathological examination showed a poorly differentiated adenocarcinoma with neuroendocrine differentiation. Adjuvant chemotherapy with S-1 was administered for 1 year. The patient survived for >5 years with no recurrence. Surgical gastrectomy and complete removal of the PVTT followed by S-1 chemotherapy could be a treatment option that offers improved long-term survival for patients with GC-PVTT.*

Gastric cancer with portal vein tumor thrombosis (GC-PVTT) is a rare condition that is treated with chemotherapy and/or surgery; however, its prognosis is very poor (1-12). Both the role of chemotherapy and surgery for patients with GC-PVTT has yet to be established. Recently, several reports have suggested that gastrectomy with removal of the PVTT in combination with perioperative chemotherapy may be beneficial in selected cases (3-12). In East Asians, S-1 (TS-1; Taiho Pharmaceutical) is widely administered as an adjuvant therapy for patients who have undergone curative resection for locally advanced gastric cancer (13, 14).

Herein, we present a case involving an advanced GC-PVTT patient who survived for >5 years without recurrence. The patient underwent distal gastrectomy with removal of the PVTT that extended to the superior mesenteric vein (SMV) trunk followed by adjuvant chemotherapy with S-1.

Correspondence to: Toru Beppu, MD, Ph.D., F.A.C.S. Department of Surgery, Yamaga City Medical Center, 511 Yamaga, Kumamoto, 861-0593, Japan. Tel: +81 968442185, Fax: +81 968442420, e-mail: tbeppu@yamaga-mc.jp

Key Words: Gastric cancer, portal vein tumor thrombosis, recurrence-free survival, surgery, oral chemotherapy.

Case Report

A 64-year-old man was referred to our hospital because of epigastric pain. Physical examination showed no abnormality. Laboratory testing gave slightly abnormal results: aspartate aminotransferase, 75 IU/l; alanine aminotransferase, 77 IU/l; blood sugar, 189 mg/dl; and HbA1c, 6.9%. Carcinoembryonic antigen was slightly elevated 17.4 ng/ml (normal range, ≤5.0 ng/ml), whereas carbohydrate antigen 19-9 and serum α-fetoprotein were within the normal range. Upper gastrointestinal endoscopy showed a type 2 gastric lesion (45 mm × 40 mm) in the gastric antrum (Figure 1). The pathological diagnosis of biopsy specimens revealed a poorly differentiated adeno-carcinoma. On T2-weighted magnetic resonance imaging, a PVTT with hyperintensity spreading from the gastroepiploic vein to the SMV trunk was observed (Figure 2). Abdominal computed tomography (CT) showed the main tumor and PVTT. Three-dimensional CT angiography clearly showed PVTT *via* the gastrocolic trunk (Figure 3). Fluorode-oxyglucose-positron emission tomography showed abnormal uptake both of the main tumor and PVTT (Figure 4). The diagnostic images did not show distant metastasis or peritoneal dissemination; therefore, surgical intervention was selected as an initial therapy. In February 2014, we performed an open distal gastrectomy with D2 lymphadenectomy and Roux-en-Y reconstruction. The main tumor was egg sized and had distinct serosal invasion. Lymph node, liver, and peritoneal metastases were not detected during surgery. The non-invasive PVTT occupied an area from the right gastroepiploic vein to the SMV. Initially, the SMV was clamped up- and down-stream

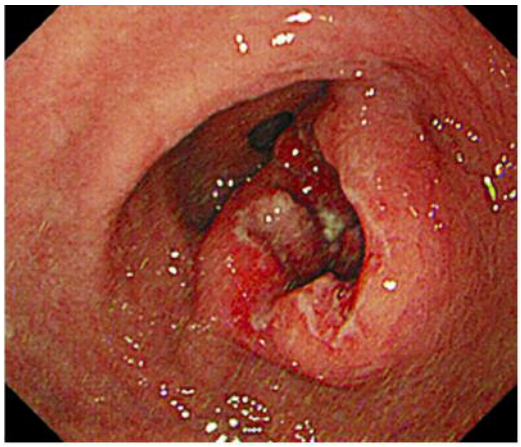

Figure 1. *Upper gastrointestinal endoscopy. A lesion suspected of being a type 2 gastric cancer is shown in the gastric antrum.*

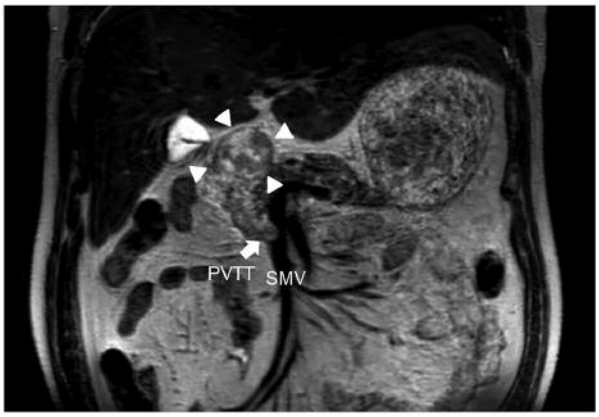

Figure 2. *T2-weighted magnetic resonance imaging (coronal image). A mixed intensity tumor is shown in the gastric antrum (arrow head), and the portal vein tumor thrombosis has spread from the gastroepiploic vein to the superior mesenteric vein trunk (arrow).*

at the point where the PVTT protruded into the SMV, and the PVTT was completely removed followed by minimal portal vein wall resection (Figure 5A). The defect of the portal vein was closed by using a transverse continuous suture with 5-0 Prolene® (Figure 5B). The operative time was 403 min, the blood loss amount was 780 g, and no blood product was needed. Macroscopically, the resected specimen appeared to show complete removal of the main tumor and the PVTT (Figure 6). Pathological examination of the resected specimen showed a poorly differentiated adenocarcinoma with neuroendocrine differentiation (Figure 7). By immunostaining, obvious staining of chromogranin A and synaptophysin was observed. AFP immunostaining was negative, and no hepatoid features were identified. Ki67 was positive in 20% to 30% of the tumor cells. The final pathological tumor stage according to the Union for International Cancer Control TNM Classification of Malignant Tumors, 8th Edition (15) was stage IIIA [pT4a, pN2 (5/38), and pM0]. In the postoperative course, the patient developed delayed gastric emptying, but he promptly recovered after receiving medication and was discharged from the hospital on postoperative day 25. Adjuvant chemotherapy with S-1 was started on the 52nd postoperative day and continued for 1 year. S-1 therapy was administered orally at a dose of 120 mg/day for 14 days, followed by a 7-day drug-free interval. Obvious side effects to delay the chemotherapy were not observed. The patient is alive without recurrence after 5 years at this writing.

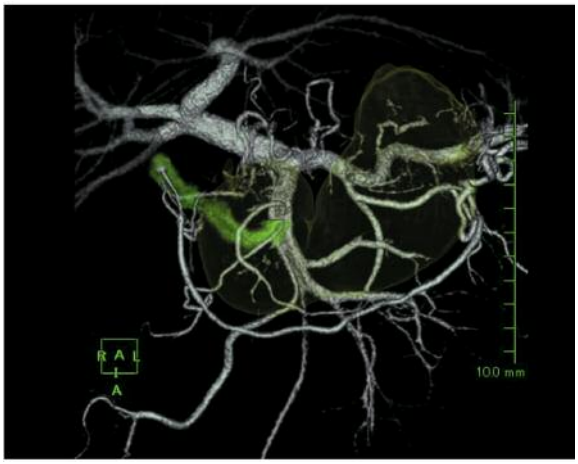

Figure 3. *Three-dimensional computed tomography image of portal vein tumor thrombosis (green color). Flow of the superior mesenteric vein is good, and there are no collateral veins.*

Discussion

To our knowledge, this is the first case of a GC-PVTT patient who lived >5 years without recurrence. He was treated with distal gastrectomy and surgical excision of PVTT followed by 12 months of adjuvant chemotherapy with S-1. The previous largest series of GC-PVTT cases (n=51) found that the median survival time was 5.4 months, and the 5-year survival rate was <10% with only one actual 5-year survivor (2). Surgical removal of the PVTT was not performed for all patients. Female sex and hepatic mass type of the PVTT were defined as independent poor prognostic factors. When the PVTT appeared to originate from the hepatic mass, it was classified as the hepatic mass type. In that cohort, operations for gastric cancer and systemic chemotherapy were performed for 12 (23.5%) and 43 (84.3%) patients, respectively; however, 'operations for gastric cancer' and 'application of chemotherapy' were not determined as prognostic factors.

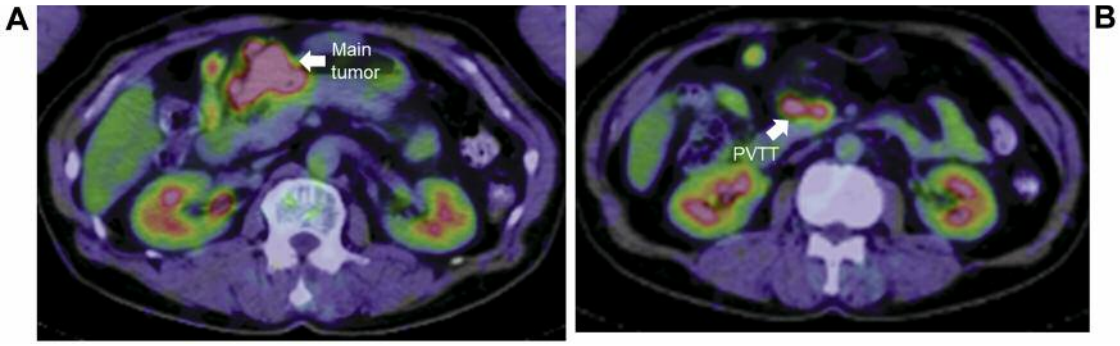

Figure 4. *Fluorodeoxyglucose-positron (FDG) emission tomography. A. Main tumor. B. Portal vein tumor thrombosis (PVTT). The main tumor and PVTT showing abnormal uptake of FDG. The maximum standardized uptake values of the main tumor (arrow) and PVTT (arrow head) are 9.9 and 6.9, respectively.*

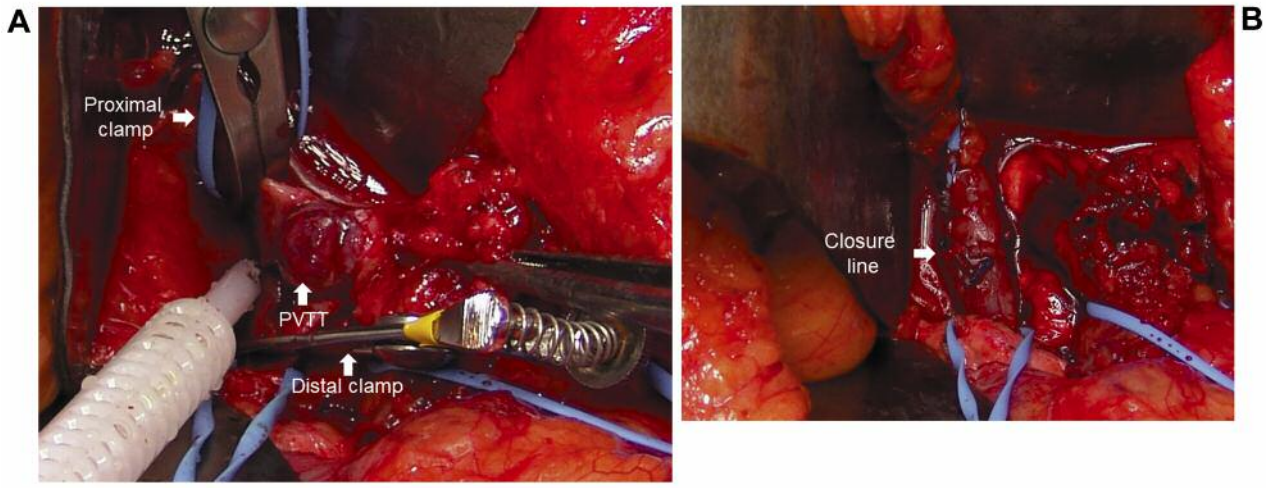

Figure 5. *Intraoperative findings. A. Excision of portal vein tumor thrombosis (PVTT). B. Post-suturing of the superior mesenteric vein (SMV) wall. The PVTT has been completely removed with partial resection of the SMV wall followed by closure of the incision site.*

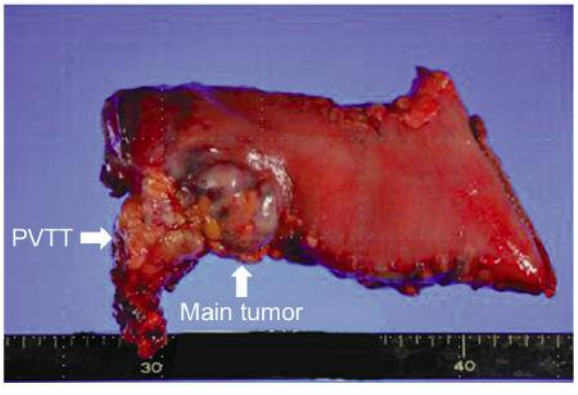

Figure 6. *Macroscopic appearance of the resected specimen. Macroscopic appearance of the resected specimen clearly showing the main tumor and connected portal vein tumor thrombosis.*

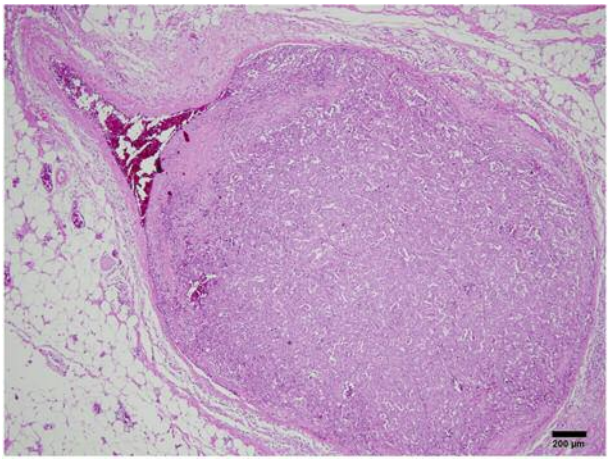

Figure 7. *Pathological findings of the resected specimen [portal vein tumor thrombosis (PVTT)]. Hematoxylin and eosin staining of the PVTT indicates a poorly differentiated adenocarcinoma without invasion to the portal vein wall.*

Table I. *Gastric cancer patients with portal vein tumor thrombosis undergoing surgery.*

REF number	Publication year	Age (year)/ Gender	Pathology (differentiation)	Serum AFP	Liver metastasis	Surgical method
3	1996	68/M	ADC (Moderate)	Normal	No	PD + PVTT removal
4	1998	70/F	ADC (Unknown)	Normal	No	TG + DP + SP + PVTT removal
5	2002	83/F	ADC (Moderate)	Normal	No	TG
6	2003	72/M	ADC (Poor)	High	No	TG + DP + SP + PVTT removal
7	2012	53/M	ADC (Well)	NA	No	TG + SP + PVTT removal
8	2013	56/M	ADC (Well)	NA	Yes	DG + liver resection
9	2015	63/M	ADC (Poor)	High	No	TG
10	2016	78/M	ADC (Moderate)	Normal	No	TG + SP + PVTT removal
11	2017	71/M	ADC (Moderate)	Normal	No	TG + SP
12	2018	61/M	ADC (Moderate)	NA	No	TG + PVTT removal
Our case	2019	64/M	ADC (Poor, neuroendocrine feature)	Normal	No	DG + PVTT removal

Surgical intent	Induction chemotherapy	Adjuvant chemotherapy	Chemotherapy after recurrence	Months/outcome/ recurrence
Curative	No	No	No	12/alive/disease-free
Curative	No	5-FU + CDDP	No	15/alive/disease-free
Palliative	No	No	No	4/dead
Curative	No	S-1	No	20/alive/disease-free
Curative	S-1 + CDDP	S-1	No	6/alive/disease-free
Curative#	S-1 + CDDP	S-1 + Paclitaxel	No	44/alive/disease-free
Curative#	S-1 + CDDP	S-1	No	48/alive/disease-free
Curative	No	S-1	No	49/dead/disease-free
Palliative	No	S-1	FOLFOX→Doxifluridine→FOLFIRI	82/alive/with disease
Palliative	No	Paclitaxel + Carboplatin	No	22/alive/with disease
Curative	No	S-1	No	60/alive/disease-free

REF: Reference; AFP: alpha-fetoprotein; meta: metastasis; ADC: adenocarcinoma; NA: not available; PD: pancreatoduodenectomy; PVTT: portal vein tumor thrombosis; TG: total gastrectomy; DP: distal pancreatectomy; SP: splenectomy; DG: distal gastrectomy; S-1: Tegafur/Gimeracil/Oteracil; CDDP: cisplatin; 5-FU: 5- fluorouracil l; FOLFOX: fluorouracil plus leucovorin with oxaliplatin; FOLFIRI: fluorouracil plus leucovorin with irinotecan. Curative# means the disappearance of PVTT after induction chemotherapy.

GC- PVTT is known to be an aggressive phenotype with poor prognosis accompanied by high levels of AFP and a high incidence of liver metastasis (9, 16). PVTT is considered to be an early step in liver metastasis because metastasis is established when cancer cells are released from the primary tumor. However, formation of PVTT need not always represent the first step toward liver metastasis. It has been reported that an aggressive approach followed by appropriate chemotherapy may delay the recurrence and prolong the survival time for patients with no liver metastasis (3).

In our case, PVTT showed expanded growth even in the pathological findings, and a small portion existed in the SMV trunk. Therefore, we were able to easily remove the PVTT without simultaneous resection of the extensive SMV wall. The SMV wall was primarily closed subsequently. Intraoperative assessments, including intraoperative ultrasonography, are very useful to determine the extent of portal vein resection. In cases with invasive growth of PVTT, simultaneous resection of the portal vein wall is required. In a previous case with SMV invasion by a PVTT, pancreatoduodenectomy was applied (3).

A literature review showed 11 GC-PVTT patients who were treated with surgical intervention, including our case (Table I) (3-12). Among them, 5 patients survived for >3 years; all were males, and 4 were diagnosed as having moderately to poorly differentiated adenocarcinomas. One of those 5 patients was AFP-positive and the other showed liver metastasis. Gastrectomy was performed for all patients, and the PVTT was removed in 2 patients. In the other 2 patients, PVTT disappeared by induction chemotherapy with S-1 + cisplatin; therefore, no surgical treatment of the PVTT was needed. Adjuvant chemotherapy, including S-1, was administered to all 5 patients. Among the 3-year survivors, only 2 patients survived for >5 years, and our patient is the only recurrence-free survivor as of this report. The other 5-year survivor was treated with total gastrectomy without PVTT removal followed by adjuvant therapy of S-1. Aggressive chemotherapy, including fluorouracil plus leucovorin with oxaliplatin (termed FOLFOX) and fluorouracil plus leucovorin with irinotecan (termed FOLFIRI) (11), was additionally performed for recurrences.

On the other hand, in GC-PVTT patients treated with chemotherapy alone, there has been only 1 other report of a 5-year survivor (2). A 67-year-old male GC-PVTT patient without liver metastasis was treated with systemic chemotherapy and lived for 7 years; however, the details of his chemotherapy regimen are unknown.

Previous studies have reported on the effectiveness of chemotherapy for GC-PVTT; however, the regimens used differed across the studies, and the theoretical basis for the use of these regimens has not been described (1-4, 5-7, 9-12). In the current case, we selected S-1 as an adjuvant chemotherapy. As described in the Japanese guidelines (17), S-1 has been a key drug in adjuvant chemotherapy for advanced gastric cancer and was reported to be more effective for the undifferentiated type of gastric cancer than for the differentiated type (13). Presently, more effective adjuvant chemotherapies of capecitabine plus oxaliplatin and S-1 plus docetaxel are available (18, 19).

The long recurrence-free survival of our patient can be possibly explained by the following reasons. First, R0 resection of the primary tumor and complete extirpation of PVTT was achieved. The patient showed normal AFP-level and had no liver metastasis. Second, the patient was male and the PVTT did not originate from the hepatic mass. Third, adjuvant chemotherapy with S-1 may also have contributed to the long-term recurrence-free survival.

In conclusion, gastrectomy together with complete removal of PVTT followed by S-1 chemotherapy could be a treatment option that offers improved long-term survival for patients with GC-PVTT. Accumulation of more cases in which this treatment approach is used are needed to confirm our speculation.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Conception and design: Y. Yoshida, T. Beppu; Acquisition of data: Y. Yoshida, S. Saito; Writing, review, and/or revision of the manuscript: All Authors; Supervision: T. Beppu.

References

1 Saitoh H, Boku N, Ohtsu A, Hironaka S, Miyamoto S, Hamamoto Y, Ohkuwa M and Yoshida S: Five-year survivor with liver metastasis from gastric cancer successfully treated with systemic chemotherapy. Gastric Cancer *3*: 106-109, 2000. PMID: 11984720.

2 Eom BW, Lee JH, Lee JS, Kim MJ, Ryu KW, Choi IJ, Cho SJ, Lee JY, Rhee J, Nam BH and Kim YW: Survival analysis of gastric cancer patients with tumor thrombus in the portal vein. J Surg Oncol *105*: 310-315, 2012. PMID: 21898415. DOI: 10.1002/jso.22083

3 Sugawara Y, Konishi T, Hiraishi M, Ishizaki Y and Makuuchi M: Portal tumor thrombi due to gastric cancer. Hepatogastroenterology *43*: 1000-1005, 1996. PMID: 8884328.

4 Furui J, Enjyoji A, Okudaira S, Takayama K and Kanematsu T: Successful surgical treatment of gastric cancer with a tumor thrombus in the portal and splenic veins: report of a case. Surg Today *28*: 1046-1050, 1998. PMID: 9786577.

5 Tanaka A, Takeda R, Mukaihara S, Hayakawa K, Takasu K, Terajima H, Yamaoka Y and Chiba T: Tumor thrombi in the portal vein system originating from gastrointestinal tract cancer. J Gastroenterol *37*: 220-228, 2002. PMID: 11931537.

6 Yamaguchi M, Midorikawa T, Saitoh M, Kadokura S, Miyagawa K, Sanada Y and Kumada K: Tumor thrombus in the splenic vein originated from gastric carcinoma that produced alpha-fetoprotein. Hepatogastroenterology *50*: 1693-1696, 2003. PMID: 14571819.

7 Ishigami S, Arigami T, Okubo K, Sasaki K, Kurahara H, Uenosono Y, Okumura H, Owaki T, Kijima Y, Ueno S and Natsugoe S: Successful treatment of advanced gastric adenocarcinoma with portal tumor thrombosis by total gastrectomy following CDDP and S-1 therapy. Clin J Gastroenterol *5*: 230-233, 2012. PMID: 26182326. DOI: 10.1007/s12328-012-0307-4

8 Orii T, Karasawa Y, Kitahara H, Yoshimura M and Okumura M: Long-term survival after sequential chemotherapy and surgery for advanced gastric cancer. Int J Surg Case Rep *4*: 976-980, 2013. PMID: 24070832. DOI: 10.1016/j.ijscr.2013.07.031

9 Nakao S, Nakata B, Tendo M, Kuroda K, Hori T, Inaba M, Hirakawa K and Ishikawa T: Salvage surgery after chemotherapy with S-1 plus cisplatin for α-fetoprotein-producing gastric cancer with a portal vein tumor thrombus: a case report. BMC Surg *15*: 5, 2015. PMID: 25591731. DOI: 10.1186/1471-2482-15-5

10 Sato S, Nagai E, Taki Y, Watanabe M, Takahashi M, Kyoden Y, Ohata K, Kanemoto H, Oba N, Taku K, Suzuki M and Takagi M: A long-surviving case of gastric cancer with main portal vein tumor thrombus after surgical resection and postoperative S-1 therapy. Clin J Gastroenterol *9*: 233-237, 2016. PMID: 27318995. DOI: 10.1007/s12328-016-0665-4

11 Oh SD, Oh SJ, Suh BJ, Shin JY and Park JK: Long-term survival of a patient with adenocarcinoma of the esophagogastric junction with a portal vein tumor thrombosis who underwent palliative total gastrectomy: A case report. Case Rep Oncol *10*: 916-922, 2017. PMID: 29279692. DOI: 10.1159/000481430

12 Özcan B, Çevener M, Kargı A, Özdoğan M and Gürkan A: Isolated superior mesenteric vein tumor thrombus in a patient with gastric cancer. Case Rep Surg *2018*: 3648436, 2018. PMID: 29780653. DOI: 10.1155/2018/3648436

13 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A and Arai K; ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med *357*: 1810-1820, 2007. PMID: 17978289. DOI: 10.1056/NEJMoa072252

14 Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T and Ohashi Y: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol *29*: 4387-4393, 2011. PMID: 22010012. DOI: 10.1200/JCO.2011.36.5908

15 AJCC Cancer Staging Manual. 8th edition. Springer-Verlag; New York, 2017.

16 Inoue M, Sano T, Kuchiba A, Taniguchi H, Fukagawa T and Katai H: Long-term results of gastrectomy forα-fetoprotein-producing gastric cancer. Br J Surg *97*: 1056-1061, 2010. PMID: 20632272. DOI: 10.1002/bjs.7081

17 Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer *20*: 1-19, 2017. PMID: 27342689. DOI: 10.1007/s10120-016-0622-4.

18 Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S and Bang YJ; CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open label, randomised phase 3 trial. Lancet Oncol *15*: 1389-1396, 2014. PMID: 25439693. DOI: 10.1016/S1470-2045(14)70473-5

19 Fujitani K, Tamura S, Kimura Y, Tsuji T, Matsuyama J, Iijima S, Imamura H, Inoue K, Kobayashi K, Kurokawa Y, Shimokawa T, Tsujinaka T and Furukawa H: Three-year outcomes of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy. Gastric Cancer *17*: 348-353, 2014. PMID: 23736741. DOI: 10.1007/s10120-013-0273-7

Received March 15, 2019
Revised March 27, 2019
Accepted March 28, 2019