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【 CASE REPORT 】

Complete Response for Advanced Hepatocellular Carcinoma by Conversion Surgery Therapy Following a Good Response of Regorafenib Despite Rapid Progressive Disease with Sorafenib

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Abstract:

A 68-year-old man with hepatocellular carcinoma (HCC) visited his previous hospital due to abdominal pain and was diagnosed with ruptured HCC. Before visiting our hospital, he underwent HCC treatment at his previous hospital, but his tumors did not improve. Although he started treatment with sorafenib, the tumors rapidly grew. Subsequently, regorafenib was given, and the tumors shrank. After 22 months being treated with regorafenib, HCC reoccurred, with a new lung metastasis and a contrast-enhanced nodule on the peritoneal dissemination appearing. He underwent conversion surgery and survived for 4.5 years after his HCC was diagnosed.

Key words: hepatocellular carcinoma, regorafenib, conversion therapy

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide (1-3). In recent years, the prognosis of HCC has improved due to advances in imaging technology and therapeutic strategies. However, advanced HCC still has a poor prognosis.

Regorafenib is a molecular-targeted drug that inhibits angiogenic kinases and stromal RTKs (VEGFR1, 2 and 3; TIE 2, and PDGFR-beta) that promote tumor neovascularization, vessel stabilization, and lymphatic vessel formation and that play an important role in the tumor microenvironment (4). The RESORCE study proved that second-line treatment with regorafenib provides a survival benefit in patients with HCC after progression on sorafenib treatment (5). Since June 2017, regorafenib has been approved for clinical use as a second-line treatment for patients with advanced HCC after progression on sorafenib.

Although there have been some reports of conversion surgery for HCC performed after the use of sorafenib (6-9), there have been few reports of conversion surgery for HCC performed after the use of regorafenib as second-line chemotherapy (10).

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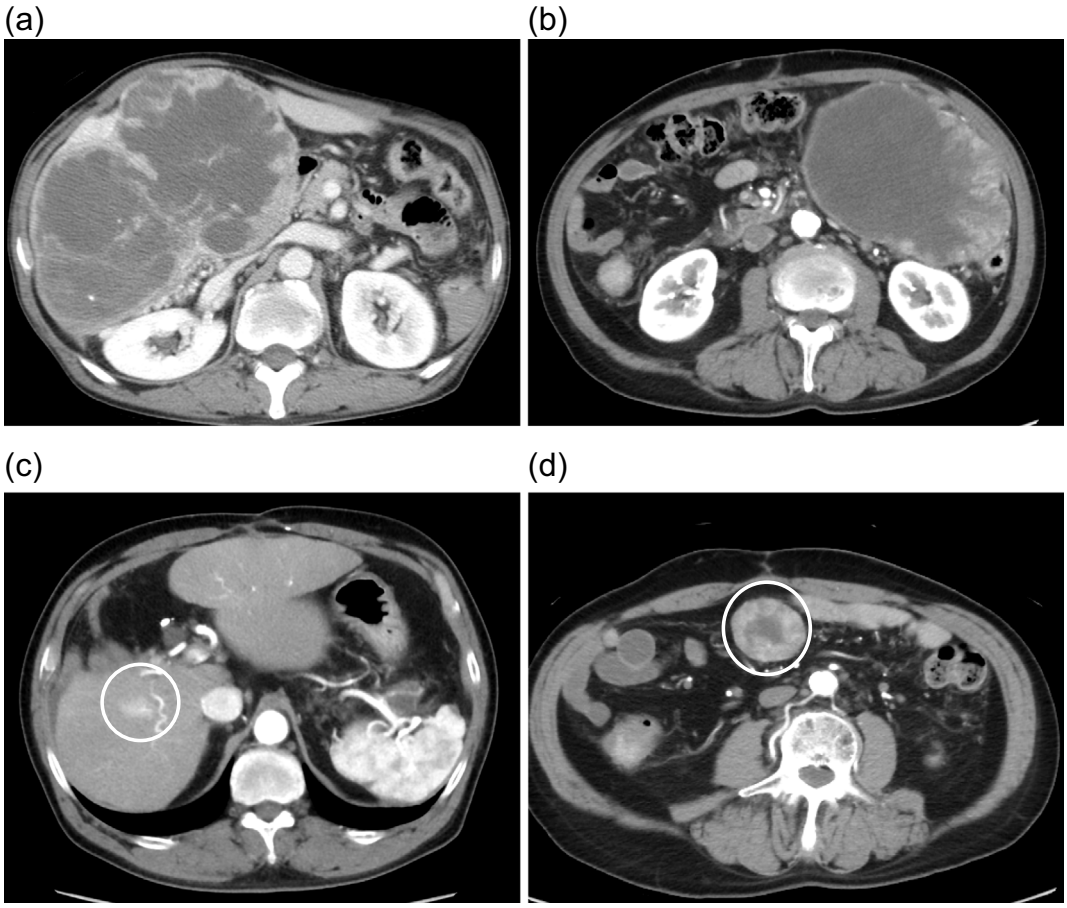


Figure 1. **(a) CT findings at the initial diagnosis. CT images from the patient's first visit to his previous hospital. (b) CT findings at six months after hepatectomy. Peritoneal dissemination appeared. (c) CT findings at seven months after resection of peritoneal dissemination. Recurrence of HCC appeared in liver segment 7. (d) CT findings at seven months after resection of peritoneal dissemination. Recurrence of peritoneal dissemination appeared.**

We herein report a case of advanced unresectable HCC that was treated successfully by conversion surgery following second-line chemotherapy with regorafenib.

Case Report

A 68-year-old man with a chronic hepatitis C infection had a medical history of hypertension and type 2 diabetes mellitus. The patient was urgently taken to a nearby hospital for rupture of HCC (Fig. 1a). He underwent emergency transcatheter arterial embolization (TAE) and subsequently underwent partial resection of liver segments 5 and subsegmentectomy of liver segment 6.

Six months after hepatectomy, the patient received emergency TAE again for peritoneal dissemination (Fig. 1b) at a nearby hospital and underwent omental nodule resection and partial descending colectomy. Seven months after the second surgery, computed tomography (CT) showed liver segment 7 recurrence of HCC with peritoneal dissemination (Fig. 1c, d). Transcatheter arterial chemoembolization (TACE) was performed for liver segment 7 HCC. One month after TACE, CT showed recurrence of intrahepatic HCC and lung metastasis.

The patient was admitted to our hospital for the further management of HCC. On admission, he was alert and conscious, with a height of 168 cm and weight of 76.9 kg. A physical examination showed no signs of anemia or jaundice. The abdomen was flat and soft, and the liver and spleen were not palpable. Laboratory tests revealed the following results: an alanine aminotransferase level of 91 IU/L (normal range 2-34 IU/L), an aspartate aminotransferase level of 49 IU/L (normal range 2-31 IU/L), a gamma-glutamyl transferase level of 37 IU/L (normal range 9-40 IU/L), an alkaline phosphatase level of 373 IU/L (normal range 35-105 IU/L), and a total bilirubin level of 0.9 mg/dL (normal range 0.50-1.20 mg/dL). The serum level of alpha-fetoprotein (AFP) was 17,034 ng/mL (normal range <10 ng/mL), that of des-gamma carboxyprothrombin (DCP) was 2,275 mAU/mL (normal range <40 mAU/mL), that of CEA was 4.5 μg/L (normal range 0-5.0 μg/L), and that of CA19-9 was 27 U/mL (normal range 0-27 U/mL). His Child-Pugh grade was A (Table).

The patient started taking 800 mg/day of sorafenib (standard dose) and showed no adverse events. Three months of sorafenib administration resulted in progressive disease (PD) based on the modified Response Evaluation Criteria in Solid

Table. **Laboratory Data.**

Complete blood count		**Blood chemistry**		**Tumor markers**	
WBC	6,960 /μL	T-Bil	0.9 mg/dL	T-AFP	17,034 ng/mL
RBC	5.68 ×10^6/μL	D-Bil	0.2 mg/dL	AFP-L3	0.5 %
HGB	18.7 g/dL	AST	49 U/L	DCP	2275 mAU/mL
HCT	54.2 %	ALT	91 U/L	CEA	4.5 ng/mL
PLT	18.9 ×10^4/μL	LDH	198 U/L	CA19-9	27 U/mL
		ALP	373 U/L		
Blood coagulation test		γGTP	37 U/L	**Liver functional reserve**	
PT AC	92 %	CH-E	209 U/L	Child-Pugh score	6 (A)
PT-INR	1.01	TP	8.6 g/dL	ALBI grade	1
APTT	30.2 sec	ALB	4.6 g/dL		
Fib	275.4 mg/dL	BUN	19.1 mg/dL		
FDP	0.5	Cre	0.8 mg/dL		
		NH_3	41 μmol/L		

WBC: white blood cells, RBC: red blood cells, HGB: hemoglobin, HCT: hematocrit, PLT: platelets, PT AC: prothrombin time activity, PT-INR: international normalized ratio of prothrombin time, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrinogen degradation products, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γGTP: gamma-glutamyl transferase, CH-E: cholinesterase, TP: total protein, ALB: albumin, BUN: blood urea nitrogen, Cre: creatinine, T-AFP: alpha-fetoprotein, AFP-L3: alpha-fetoprotein L3 isoform, DCP: des-gamma carboxyprothrombin, CEA: carcinoembryonic antigen, CA19-9: cancer antigen 19-9, ALBI: albumin-bilirubin

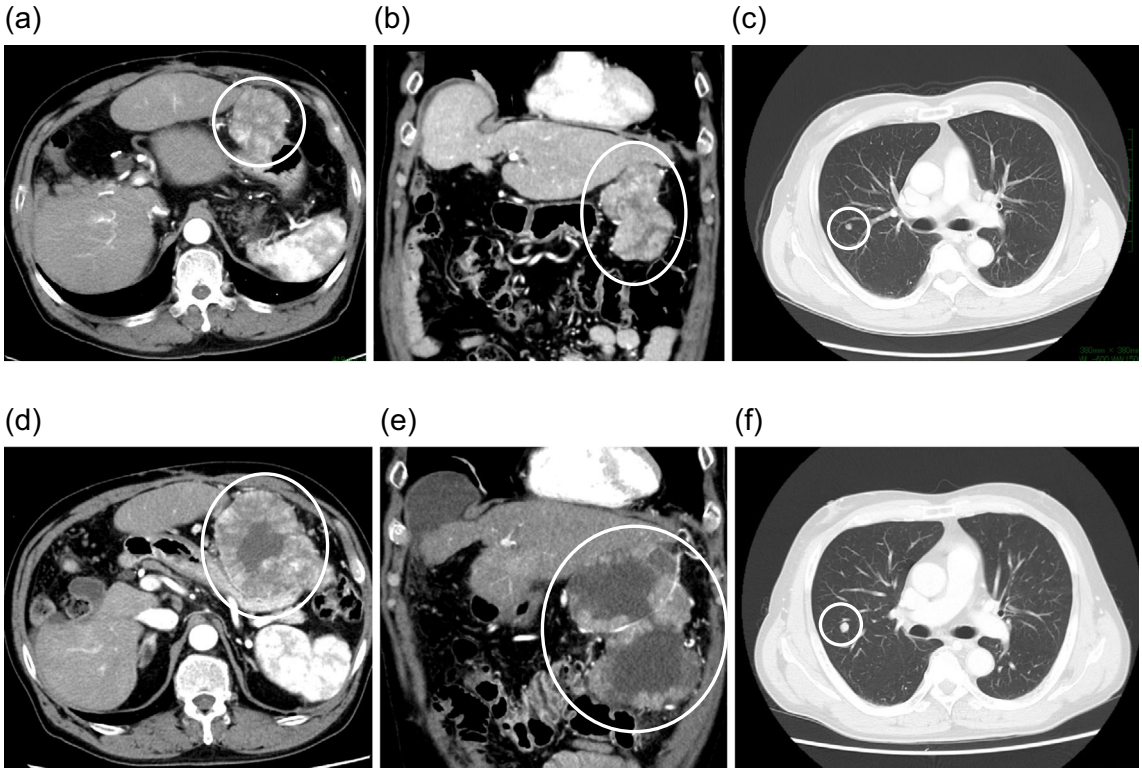


Figure 2. **Changes in lesions in the peritoneal dissemination and lung metastasis after sorafenib treatment. Tumor characteristics from the (a) horizontal, (b) frontal plane, and (c) chest CT before sorafenib treatment. CT findings after three months of sorafenib treatment. Peritoneal dissemination and lung metastasis had progressed. Tumor characteristics from the (d) horizontal, (e) frontal plane, and (f) chest CT.**

Tumors (mRECIST) (Fig. 2). Sorafenib was judged to be ineffective, so regorafenib was started as second-line chemotherapy. Regorafenib was started at a dose of 160 mg orally once daily on days 1-21 of each 28-day cycle. He developed

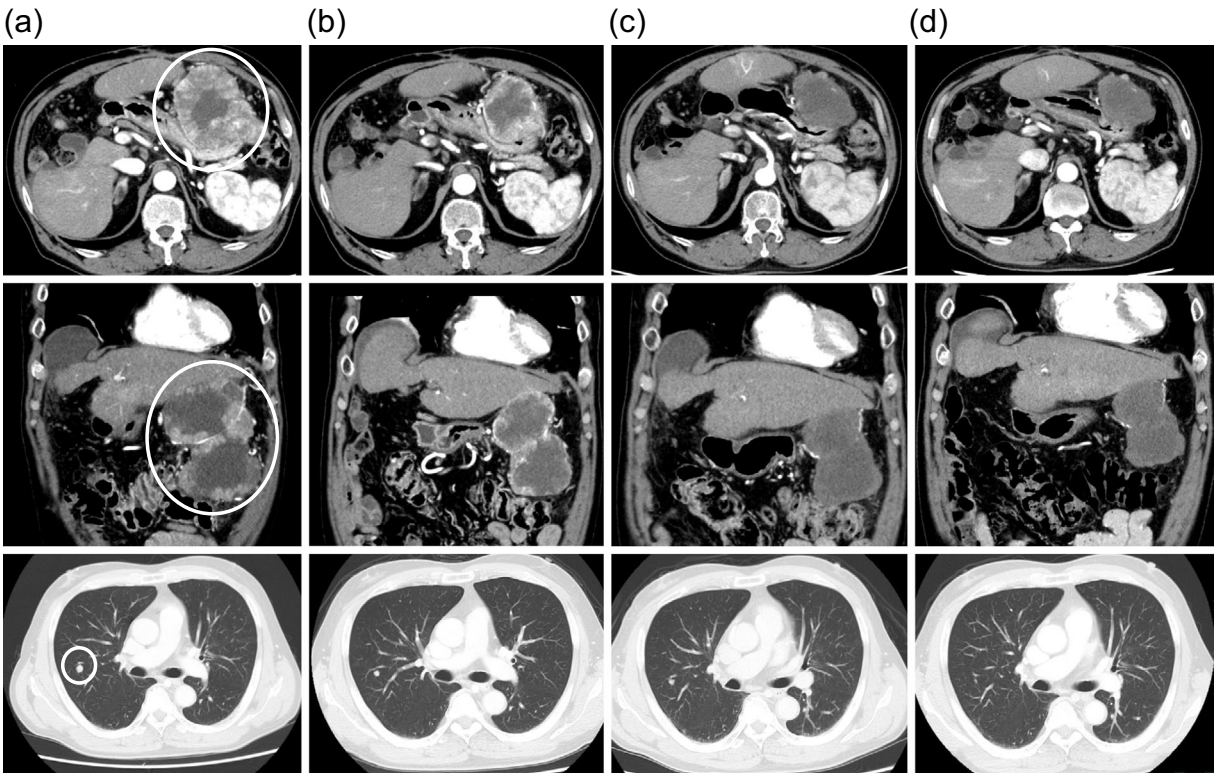


Figure 3. Changes in lesions in the peritoneal dissemination and lung metastasis after regorafenib treatment. Tumor characteristics from horizontal, frontal plane, and chest CT. CT findings (a) before regorafenib treatment, (b) after 1 month, (c) after 3 months, and (d) after 10 months of regorafenib treatment.

grade 3 hypophosphatemia as an adverse event of regorafenib. He started taking sodium dihydrogen phosphate monohydrate, and his hypophosphatemia improved. Nine months after starting regorafenib, he withdrew from regorafenib due to the appearance of grade 2 hand-foot syndrome. Ten days after the drug was withdrawn, he resumed regorafenib at a 80 mg orally once day, half the standard dose. After dose reduction, no adverse events appeared, so the dose of regorafenib was increased to 160 mg at 9 months after the dose was reduced.

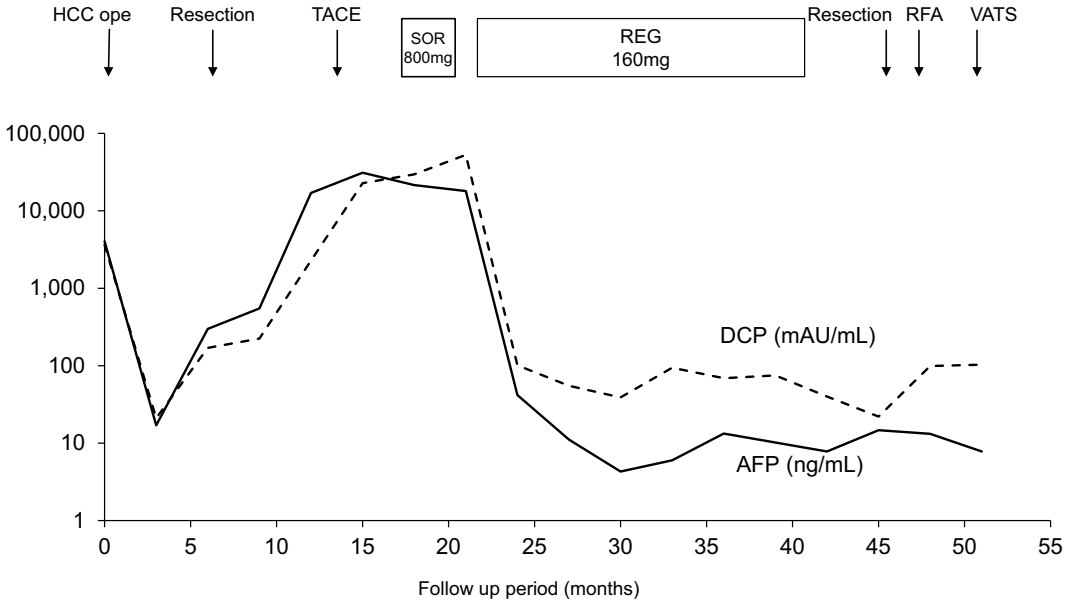
Ten months of regorafenib resulted in partial response (PR) based on the mRECIST (Fig. 3). The AFP levels decreased from a maximum of 47,050 ng/mL to 24.6 ng/mL, and the DCP levels decreased from a maximum of 56,171 mAU/mL to 38 mAU/mL (Fig. 4). Nineteen months after regorafenib treatment, he was treated for HCV with elbasvir and grazoprevir and achieved a sustained virological response (SVR) at 12 weeks post-treatment. Twenty-two months after regorafenib, CT showed a new lung metastasis and a contrast-enhanced nodule in the peritoneal dissemination that was 10 mm in size (Fig. 5a, b). Fluorodeoxyglucose-positron emission tomography (PET)/CT showed a hypermetabolic lesion in the peritoneal dissemination with a maximum standardized uptake value (SUV_{max}) of 5.6, while that of the right lung metastasis was 2.4 (Fig. 5c, d).

Surgical resection was performed for the peritoneal dissemination. The pathological result was metastasis of HCC (Fig. 6). Two months after the third surgery, CT showed liver segment 3 recurrence of HCC (Fig. 7a) and no change in the size of the lung metastasis. The HCC was a single nodule <20 mm in size and was treated with radiofrequency ablation (RFA) (Fig. 7b). The lung metastasis was treated with video-assisted thoracic surgery (VATS). Four years and six months have passed since the rupture of HCC, and the patient has survived because of these treatments.

Discussion

Ruptured HCC is associated with a poor survival compared to non-ruptured HCC, with a median overall survival of 8.9 and 28 weeks, respectively (10). We encountered a case of advanced unresectable HCC that was treated successfully by conversion surgery following a good response with regorafenib despite rapid progressive disease with sorafenib. Four years and six months have passed since the rupture of the HCC, and the patient has survived well because of conversion surgery, RFA and VATS.

In the RESORCE trial, the rate of PR + CR was 10.6%. There were 2 CR patients (1%) among the 379 patients. However, there is no information on these two patients. There has been only one report on treatment of HCC with hepatic vein tumor thrombosis protruding into the inferior vena cava using conversion surgery following chemotherapy



HCC: hepatocellular carcinoma, TACE: transcatheter arterial chemoembolization, SOR: sorafenib, REG: regorafenib, DAA: direct acting antiviral, RFA: radiofrequency ablation, VATS: video-assisted thoracic surgery

Figure 4. **Timeline of the therapeutic modalities and changes in levels of alpha-fetoprotein.**

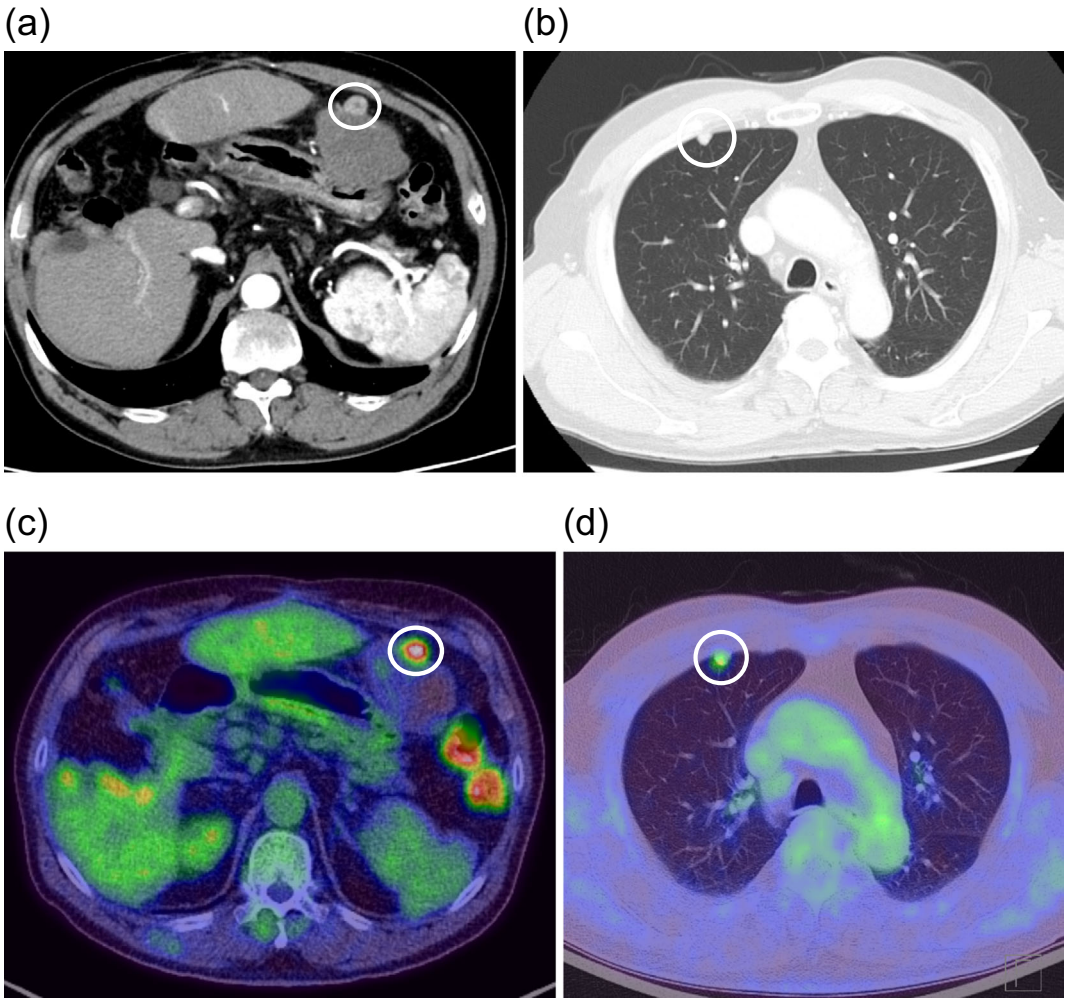


Figure 5. **CT and PET/CT findings after 22 months of regorafenib treatment. CT showed (a) a contrast-enhanced nodule in the peritoneal dissemination and (b) a new lung metastasis. PET/CT showed (c) a hypermetabolic lesion in the peritoneal dissemination with an SUV_{max} of 5.6, (d) while that of the right lung metastasis was 2.4.**

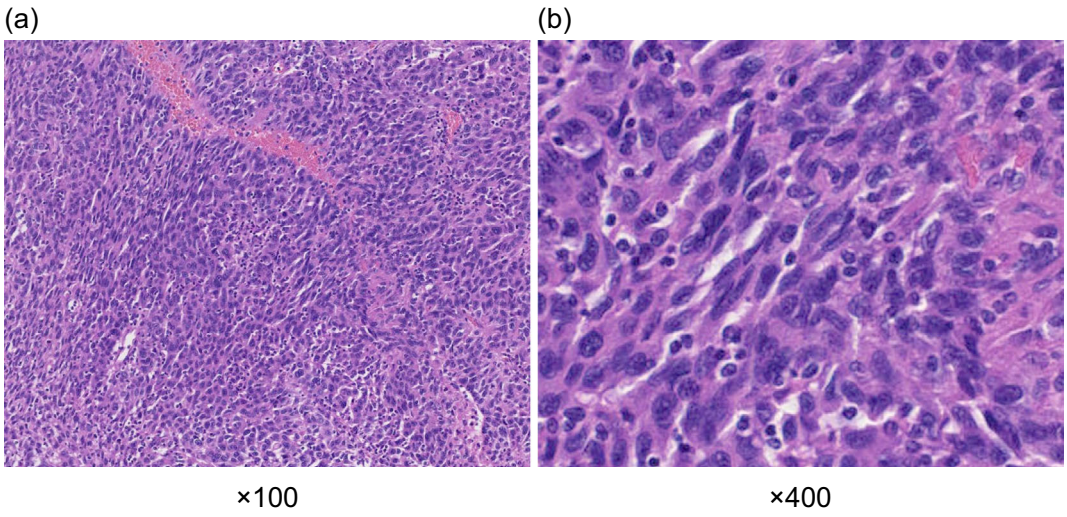


Figure 6. **Histological findings from the peritoneal dissemination. (a) Hematoxylin and Eosin (H&E) staining (×100), (b) H&E staining (×400).**

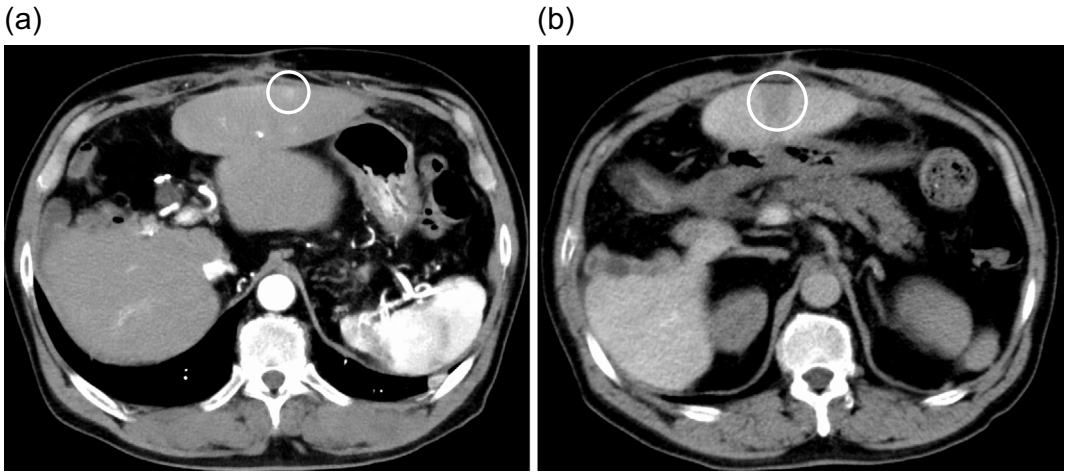


Figure 7. **(a) CT findings at two months after resection of the peritoneal dissemination. Recurrence of HCC appeared in liver segment 3. (b) CT findings after RFA treatment.**

with regorafenib (11). However, the patient started regorafenib due to tumor marker elevation, although the response of sorafenib was SD. The patient was not rapid PD of sorafenib like our patient.

Twelve patients with advanced unresectable HCC were treated successfully by conversion surgery following sorafenib (12). Furthermore, one patient with advanced unresectable HCC was treated successfully by conversion surgery following lenvatinib (13).

Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity (5). Although it is structurally related to sorafenib, the addition of a fluorine atom in the central phenyl ring might result in higher potency. It also induces apoptosis in hepatocytes (14). While the pharmacological activity of regorafenib is similar to that of sorafenib, the former has been shown to be effective in HCC that does not respond to sorafenib treatment (5). One of the underlying mechanisms that account for this difference in efficacy is the inhibition of tyrosine kinase with immuno-globulin-like and epidermal growth factor-like homology domain 2 (TIE2) activity by regorafenib and not sorafenib (4). TIE2 is a receptor expressed on vascular endothelial cells, activated by binding to angiopoietin 2 and contributes to angiogenesis. In addition, monocytes expressing TIE2 have been reported to have tumor angiogenic activity (15). The inhibition of TIE2 reduces TIE2-expressing monocytes in angiogenesis and HCC (16). Therefore, the sequential use from sorafenib to regorafenib is effective in patients with HCC that the influence of tumor vessel application by TIE2 is large.

In the present case, the patient was able to achieve PR following treatment with regorafenib. However, currently, there are no reports on factors influencing the efficacy of regorafenib in achieving PR. Wang et al reported 5 PR patients among 37 total but was unable to determine which factors influenced the efficacy of regorafenib administration for achieving PR (17). Furthermore, Ogasawara reported 44

patients treated with regorafenib but made no mention of how many achieved PR (18). While we have encountered 35 cases receiving regorafenib as a second-line treatment of HCC and examined the clinical factors influencing the efficacy of regorafenib, we have yet to draw any hard conclusions. Further studies on which factors most strongly influence the efficacy of regorafenib will need to be conducted in the future.

In conclusion, we reported a case of advanced HCC that was treated with conversion surgery after achieving a good response of regorafenib as second-line chemotherapy despite rapid progressive disease with sorafenib.

Author's disclosure of potential Conflicts of Interest (COI).
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