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Recurrence-Free Survival of a Hepatocellular Carcinoma Patient With Tumor Thrombosis of the Inferior Vena Cava After Treatment With Sorafenib and Hepatic Resection

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Sorafenib (Nexabar, Bayer, Berlin, Germany), one of multikinase inhibitors, can infrequently downstage advanced hepatocellular carcinoma (HCC). There are some reports that sorafenib in combination with other modalities, such as transcatheter arterial chemoembolization (TACE) or radiation therapy, could represent a bridge to surgery. We have observed a progressive HCC case with hepatic vein tumor thrombosis proceeding to the inferior vena cava (IVC-HVTT) convert to a state of feasible curative resection after a multidisciplinary treatment which included sorafenib. The patient underwent a successful resection in consequence of this therapy. A 45-year-old male with Hepatitis B Virus-associated chronic hepatitis was diagnosed as HCC with IVC-HVTT. To obtain oncological curative resection, we performed TACE, radiation therapy followed by administration of sorafenib (800 mg per day, total 72 g). The tumor including IVC-HVTT remarkably shrank, therefore, an

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extended posterior sectionectomy and total removal of the IVC-HVTT was successfully performed. The operation time was 736 minutes and the amount of intraoperative hemorrhage was 805 mL. No postoperative complication occurred. Adjuvant therapy with sorafenib was started four weeks after the operation and continued for 6 months (800 mg per day, total 144 g). The patient is alive without recurrence for about 4 years from the initial therapy. Multidisciplinary therapy including sorafenib, TACE, radiation, and hepatic resection may be an effective strategy to treat HCC patients with IVC-HVTT.

Key words: Hepatocellular carcinoma – Hepatic vein tumor thrombosis – Sorafenib transarterial chemoembolization – Hepatic resection

Hepatocellular carcinoma (HCC) with major hepatic vein tumor thrombosis proceeding to the inferior vena cava (IVC-HVTT) is a serious condition that can cause distant metastases or lethal pulmonary embolism.[1–3] Straightforward hepatectomy for such HCC patients often causes pulmonary metastases in early postoperative period and its prognosis is quite poor.[4–6] Therefore effective perioperative therapy has been required.[7]

We have already demonstrated the high tumor response of 3D conformal radiation therapy for patients with tumor thrombosis in major portal vein (PVTT) or IVC-HVTT.[8,9] Transarterial chemoembolization (TACE) has been a useful but palliative modality for HCC with excessive tumor thrombosis.[10] Sorafenib (Nexavar, Bayer, Berlin, Germany) is a molecular-targeted drug used in palliative treatment of advanced HCC patients in Child A and good performance status.[11,12] Although sorafenib monotherapy is effective for progressive HCC (extrahepatic spread or major vascular invasion), the radiologic response is not satisfactory.

We herein report a HCC patient with IVC-HVTT who was treated with multidisciplinary therapy, including hepatic resection and pre- and postoperative sorafenib administration.

Case Report

A 45-year-old male had been followed-up for hepatitis B virus (HBV)-associated chronic hepatitis for 10 years. A liver tumor was detected by a periodic abdominal ultrasonography. Abdominal dynamic CT demonstrated enhancement in the arterial phase and washout in the late phase. The tumor was solitary and 9.3 cm in diameter located in segment 6/7. IVC-HVTT was clearly detected from the right hepatic vein to the supradiaphragmatic IVC (Fig. 1). Tumor markers showed positive: α-fetoprotein (AFP), 670 ng/mL (normal range <7 ng/mL); AFP-L3, 27.8% (normal range <10%); and protein induced by vitamin K absence or antagonists-II (PIVKA-II), 577 mAU/mL (normal range <40 mAU/mL). Child-Pugh classification was A (5 points), and liver damage class was A. Eastern Cooperative Oncology Group performance status was 0. The HCC was considered as marginally resectable, but oncologically unresectable, because of the massive IVC-HVTT. We initially performed TACE targeting on the main tumor (cisplatin, 100 mg; 5-fluorouracil (5-FU), 1000 mg; and mytomycin C, 6 mg suspended in degradable starch microspheres (Spherex, Yakult, Tokyo, Japan),[13] followed by 3D conformal radiation therapy targeting on the IVC-HVTT[8,9] (total dose of 45 Gy). Then, sorafenib was started and continued for 3 months (800 mg/d, total 72 g). The tumor, including IVC-HVTT, responded remarkably to those multidisciplinary therapies; response rate was 45% according to RECIST criteria.[14] Tumor markers remarkably declined: AFP, 7.8; AFP-L3, 0; and PIVKA-II, 40. Because the cranial margin of IVC-HVTT shrank to subdiaphragmatic IVC (Fig. 2), we identified that curative resection can be performed from oncologic, technical, and liver functional aspects. HBV-DNA decreased from 6.1 log10 copies/mL to <2.1 log10 copies/mL by administration of entecavir for 6 months. Preoperative indocyanine green retention rate at 15 min (ICG R_{15}) was 10.5%, and uptake ratio of the liver to the liver plus heart at 15 min (LHL_{15}) in ^{99m}Tc-galactosylhuman serum albumin (GSA) scintigraphy was 0.912. Calculated %liver volume (%LV) and %functional

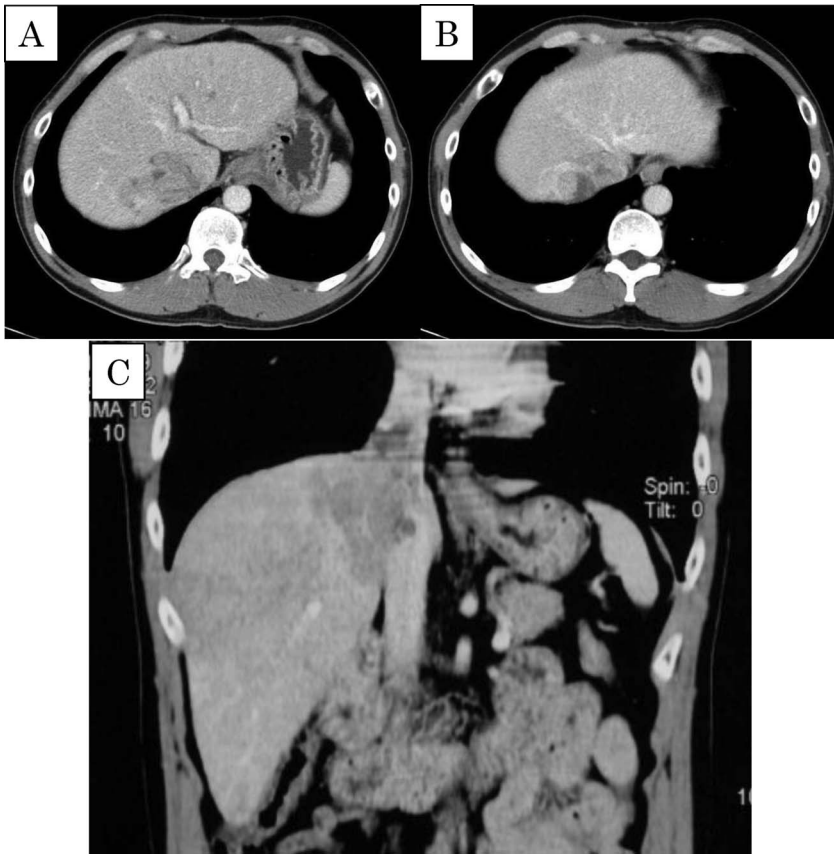

Fig. 1 Diagnostic imaging before initial therapy. (A) Portal phase, the height of the umbilical portion. (B) Portal phase, the height of the right hepatic vein confluence. (C) Venous phase, coronal scan.

liver volume (%FLV) with ^{99m}Tc-GSA scintigraphy single-photon emission computed tomography (SPECT)-CT fusion system was 17.6% and 21.9%,[15] respectively. A systematic extended right posterior sectionectomy was planned as a safe and curative hepatectomy and was proposed after 1 month cessation of sorafenib. Intraoperative ultrasonography demonstrated hypo-echoic lesion of confluent multinodular type. Contrast-enhanced ultrasonography using perflubutane microbubbles did not show early enhancement to the tumor including IVC-HVTT, and it suggested viabilities of HCC might almost disappear. The hepatic parenchymal resection was performed by anterior approach with the right-hemiliver clamping and hanging maneuver.[16] IVC was clamped at a caudal site of the common trunk of left and middle hepatic veins to prevent total hepatic ischemia. The extended posterior sectionectomy and the total removal of the IVC-HVTT were successfully completed (Fig. 3). The operation time was 736 minutes and the amount of intraoperative bleeding was 805 mL, and 1 unit of blood transfusion (280 mL) was performed. No postoperative complications were observed. He was discharged on 15 days after the operation. Adjuvant therapy with sorafenib was started at 4 weeks after the operation and continued for 6 months (800 mg/d, total 144 g). Few adverse events were observed. He is alive with no recurrence, approximately 4 years after the initial therapy, and 3 tumor markers were negative: AFP, 2.0; AFP-L3, 0; and PIVKA-II, 13. The clinical course is summarized in Fig. 4.

Discussion

HVTT is one of the independent poor prognostic factors in HCC patients who underwent hepatic resection.[2] The patients with IVC-HVTT survived no more than 2 years, and the survival rate was poorer than that for those with HVTT instead of IVC-HVTT (5-year survival: 0% versus 10%).[4] The prognosis of HCC with IVC-HVTT treated with surgical resection solely was dismal, with a mean postoperative survival time ranging from 7.3 to 8.4

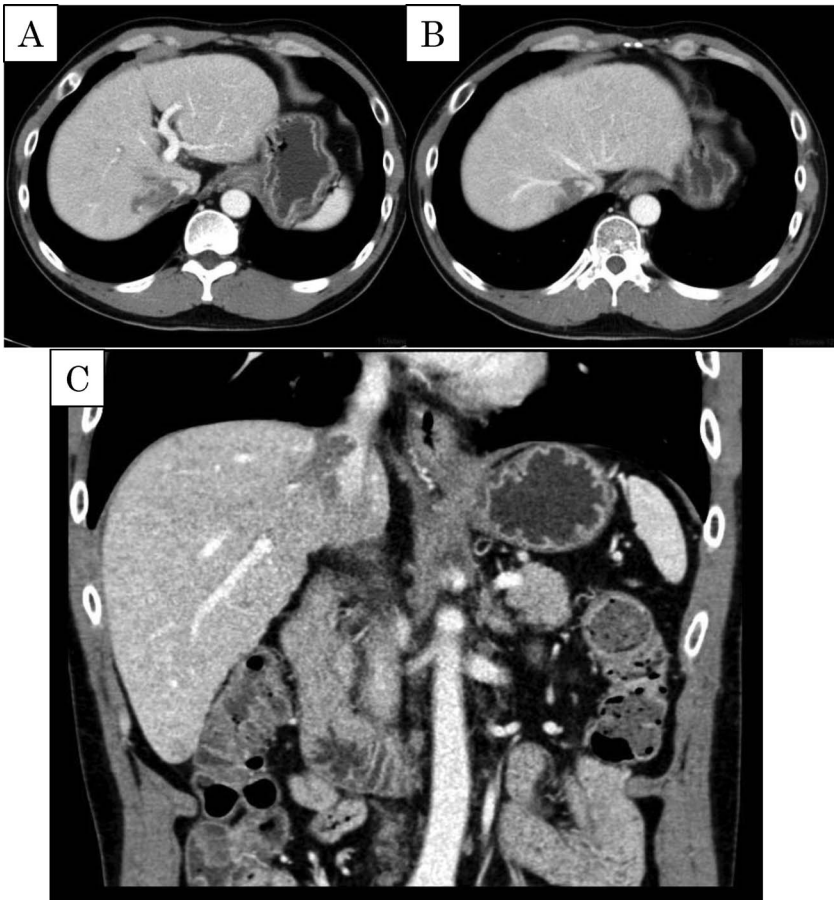

Fig. 2 Enhanced CT before hepatectomy (6 months after the initial therapy). (A) Portal phase, the height of the umbilical portion. (B) Portal phase, the height of the right hepatic vein confluence. (C) Venous phase, coronal scan.

months.[17,18] Hepatic resection for HCC with IVC-HVTT was acceptable only for the patients without PVTT.[19] Recently, there demonstrated an excellent therapeutic effect of 181 HCC patients with PV and/or IVC tumor thrombosis treated with external-beam radiation therapy (EBRT); EBRT was designed to focus on the tumor thrombi with or without primary intrahepatic tumors to deliver a median total conventional dose of 50 Gy (range, 30–60 Gy). HCC patients with IVC-HVTT treated with EBRT had a better response rate and longer survival than those with PVTT. The median survival was 17.4, and 8.5 months for patients with IVC-HVTT, and PV plus IVC-HVTT, respectively.[20]

It has been described that several HCC patients converted from unresectable to resectable condition using sorafenib monotherapy. Barbier *et al*[21] reported 2 patients of large HCCs with right PVTT and right HVTT. A right hepatectomy with removal of tumor thrombi was performed for each case. Histopathologic examination of main tumor showed 35% and 60% of tumor necrosis, and the right PVTT and right HVTT showed total necrosis. A surgical treatment was proposed 1 month after cessation of sorafenib. Irtan[22] described 2 patients of locally-advanced HCC with PVTT who showed histopathologic complete regression by sorafenib. Importantly, technical procedure was not altered by preoperative administration of sorafenib, and in particular, no significant bleeding occurred during pre- and postoperative course. Curtit *et al*[23] reported an advanced HCC patient who described pathologic complete response by sorafenib monotherapy. Although even sorafenib monotherapy can rarely downstage unresectable HCC to be resectable, the conversion rate was quite low. In Japan, Kudo *et al*[24] reported 15 complete remissions out of 3700 patients in May 2009.

There have already reported the usefulness of sorafenib in combination with other treatment

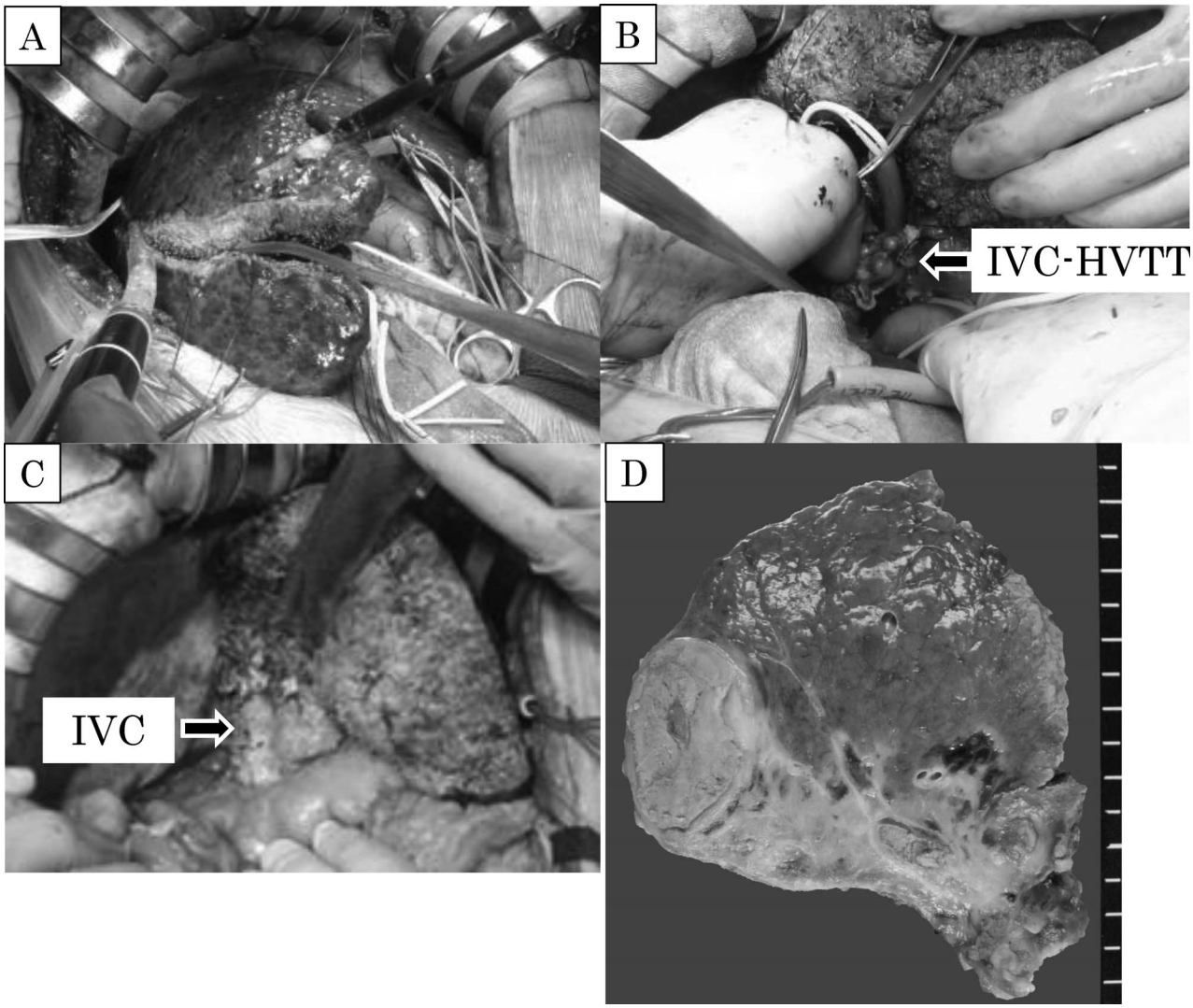

Fig. 3 Intraoperative findings and resected specimen. (A) Liver parenchymal dissection. (B) Removal of IVC-HVTT. (C) Post-hepatectomy. (D) Cut surface of the resected specimen.

modalities. TACE creates a hypoxic environment for the residual tumor cells.[25] This hypoxia stimulates those surviving cells to express vascular endothelial growth factor (VEGF), which can lead to neovascularization and reestablishment of the tumor's blood supply. Thus, an anti-angiogenesis agent like sorafenib, which can inhibit VEGF receptors, seems like a good choice for combination with TACE.25 During a median follow-up period of 21.4 weeks (range, 0.5–103 weeks), the addition of sorafenib prolonged time to progression [TTP; 6.3 versus 4.3 months; hazard ratio (HR) 0.60, $P = 0.004$] and median survival (7.5 versus 5.1 months; HR 0.61, $P = 0.009$) compared with TACE alone.[26]

The STORM study (http://clinicaltrials.gov/ct2/show/NCT00692770) was finished in 2014 and failed to indicate the survival benefits of sorafenib as an adjuvant treatment after potentially curative treatment (surgical resection or local ablation) for HCC. However the STORM study did not include patients with distinct vascular invasion. As we assessed this patient as a responder of sorafenib therapy preoperatively, sorafenib was administered 800 mg/d for 6 months as an adjuvant therapy.

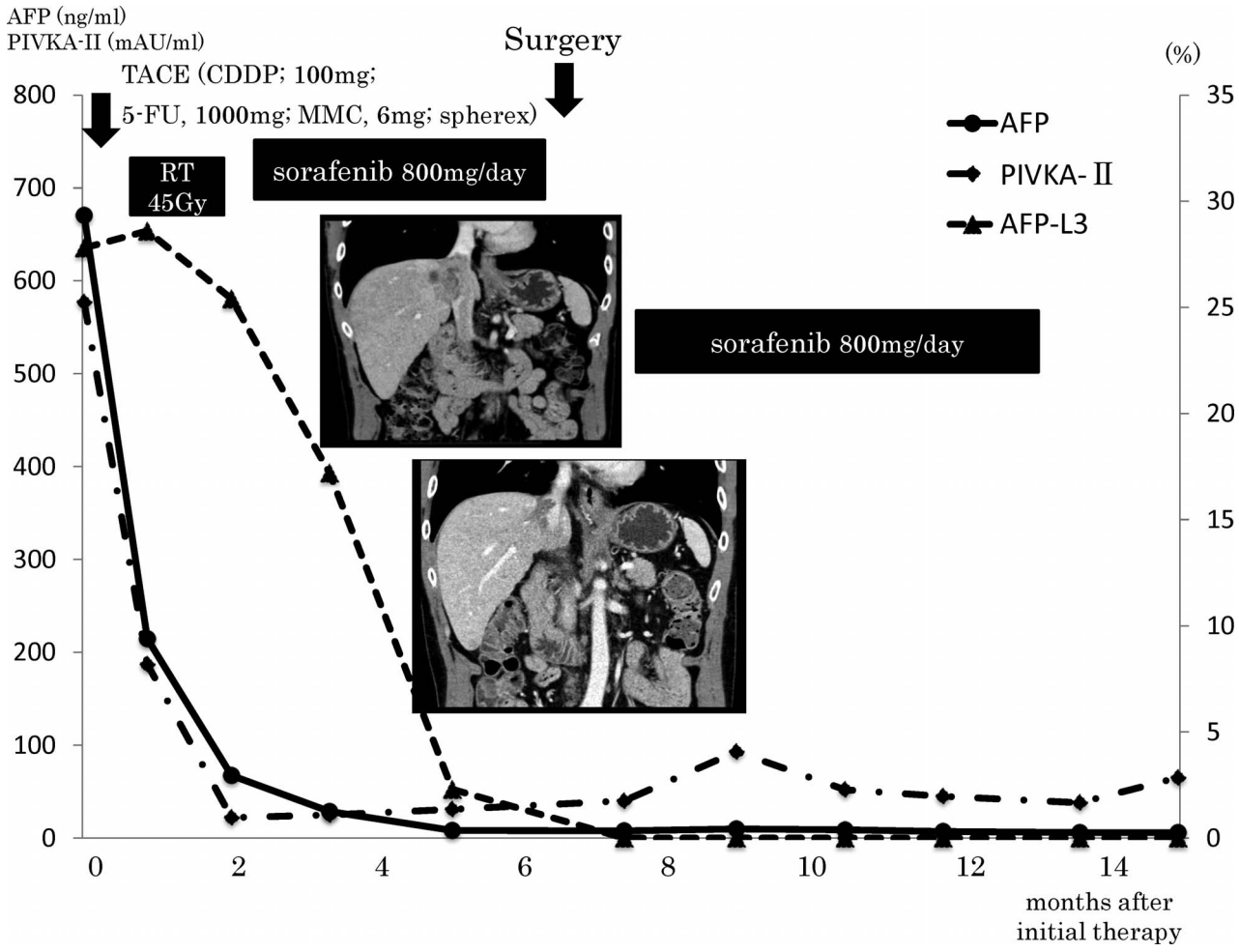

Fig. 4 Changes in tumor marker levels and timing of therapeutic modalities.

In conclusion, the multidisciplinary treatment consisting of sorafenib, TACE, radiation therapy, and hepatic resection may be an optimal therapeutic strategy for HCC with IVC-HVTT.

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