

## A Surgically Treated Long-term Survivor of Hepatocellular Carcinoma with Tumor Thrombi in the Trunk of the Portal Vein

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### ABSTRACT

Prognosis of hepatocellular carcinoma (HCC) patients with tumor thrombi (TT) in the trunk of the portal vein (PV) has been extremely poor. There have been few reports of long-term survivors with such an advanced condition. In this article, the case of a 62-year-old woman of HCC, who survived for 6 years and 9 months after an operation, with TT in the trunk of the PV is described. The patient not only had a primary tumor of 4 cm in diameter with TT but also multiple intrahepatic metastases in the bilateral lobe of the liver. A palliative lateral segmentectomy with tumor thrombectomy through the incised left first branch of the PV was performed. Moreover, an intraoperative ethanol injection for residual intrahepatic metastatic tumors was performed subsequently. Hepatic arterial infusion of anti-cancer drug with Lipiodol, intraportal continuous infusion of 5-FU and percutaneous ethanol injection therapy were performed suitably during the follow-up periods. The patient survived for 6 years and 9 months after operation and died of hepatic insufficiency with cancer. In this case a patient who suffered from HCC with TT in the trunk of the PV was successfully treated by multimodality procedures including hepatic resection with tumor thrombectomy.

**Key words:** *Hepatocellular carcinoma, Tumor thrombi, Hepatic resection, Tumor thrombectomy*

Although recent advances in diagnostic modalities, such as abdominal computed tomography (CT) and ultrasound sonography (US), have made it possible to detect hepatocellular carcinoma (HCC) at an early stage resulting in improved prognoses of HCC patients<sup>9)</sup>, the majority of HCCs are found at an advanced stage marked by tumor thrombi (TT) in the major vasculatures and/or intrahepatic metastases. Moreover, the prognoses of such advanced HCC patients are still extremely poor, while multimodality treatments had been performed, and this has been considered a contraindication for hepatic resection<sup>11)</sup>. On the other hand, recently, the efficacy of hepatic resection to the patients with such advanced conditions on life prolongation were reported<sup>6,12)</sup>. Since 1986, we have actively performed hepatic resections on such advanced HCC patients<sup>4)</sup>. We report herein a case of a long-term surviving HCC patient, who had TT in the trunk of the portal vein (PV) and multiple intrahepatic metastases, after hepatic resection with tumor thrombectomy.

### CASE REPORT

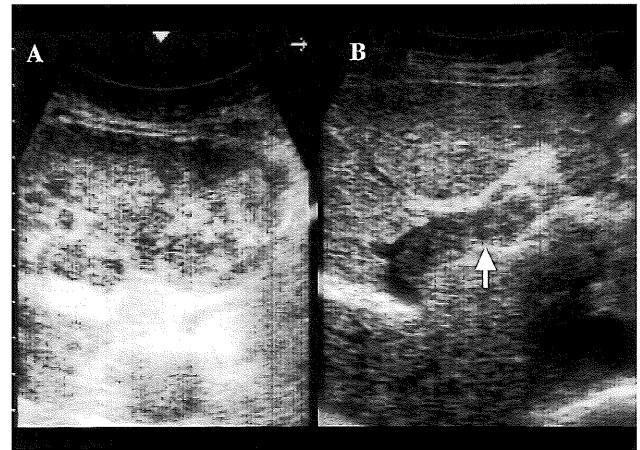
A 62-year-old woman was referred to the Second Department of Surgery, Hiroshima University, Hiroshima, Japan, with a complaint of mild right hypochondralgia, on July 19, 1989 and was hospitalized on August 25, 1989. Her past medical history revealed that she had undergone hysterectomy due to myoma uteri and subsequently laparotomies several times due to an adhesive ileus at the age of 33 years. Moreover, she had had cholecystectomy after a diagnosis of cholelithiasis 3 years earlier. It was uncertain whether she had received transfusion during her past hospitalizations. On admission, physical examination revealed that her liver could be palpated 3 or 4 finger breadths below the right costal margin and the xiphoid, although ascites and encephalopathy were not observed. The laboratory data on admission are summarized in Table 1. The serum albumin level was 3.0 g/dl, the indocyanine green retention rate at 15 min after injection 21.2%, the activity of prothrombin time 55%, and the serum total bilirubin level 0.5 mg/dl. These data indicat-

ed that her hepatic functional reserve corresponded to Child-Pugh grade B<sup>10)</sup> and Clinical Stage II<sup>14)</sup>.

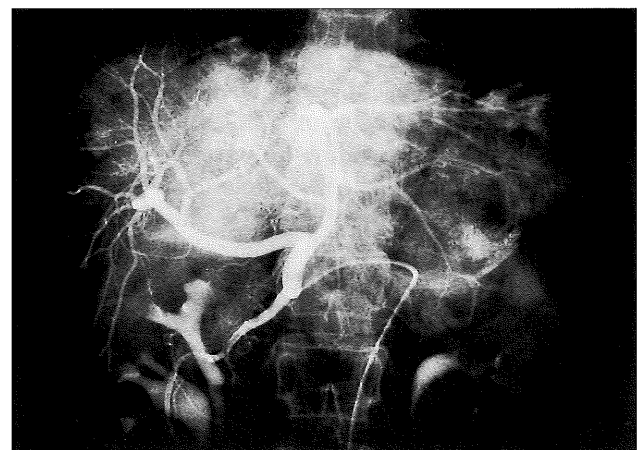
US disclosed an irregularly demarcated mass with an intratumoral mixed echo around 4 cm in diameter in the lateral segment and multiple high echoic or hypoechoic masses in the right lobe. Moreover, it was revealed that TT reached from the primary tumor to the trunk and the right first branch of the PV (Fig. 1). A hepatic arteriogram disclosed a hypervascular primary tumor and multiple tumor stains, which were suspected to be intrahepatic metastases, in the right lobe (Fig. 2). A portography, which was obtained by delayed phase of superior mesenteric arteriogram, disclosed a complete obstruction of the left first branch and an irregular defect in the right first branch of the PV (Fig. 3). Thereafter, a catheter was advanced into the proper hepatic artery and a transcatheter arterial infusion with iodized oil (Lipiodol: Andre Guerbet, France) (L-TAI) was performed. Four ml of Lipiodol mixed with 40mg of doxorubicin hydrochloride (Adrimycin: Adria, Dublin, Ohio, USA) was used for L-TAI. Moreover, a second L-TAI using 10 ml of Lipiodol mixed with 40 mg of Adriamycin was performed 8 days after the first L-TAI.

CT of the abdomen after 2 weeks of L-TAI disclosed a low-density area of around 4 cm in diameter in which partial deposition of Lipiodol was detectable and revealed that and TT, which filled the bilateral first branches and the trunk of the PV, were enhanced in the arterial phase (Fig. 4).

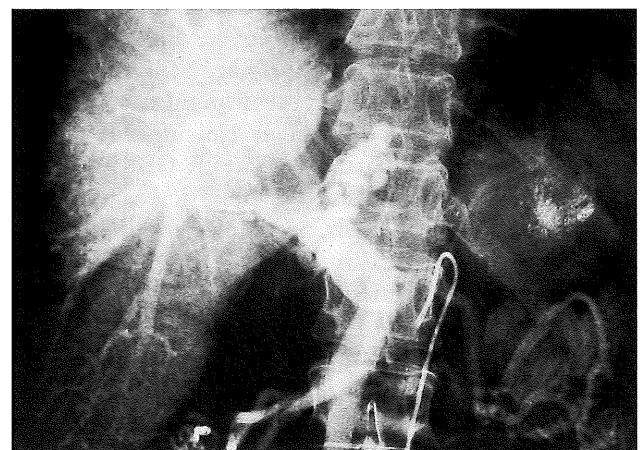
An operation was performed on October 19, 1989 following the diagnosis of HCC with TT of the



**Fig. 1.** Ultrasoundsonography revealed an irregularly demarcated primary tumor 4 cm in diameter with an intratumoral mixed echo pattern in the lateral segment of the liver (A) and tumor thrombi (arrow) which reached to the right first branch of the portal vein (B).



**Fig. 2.** A hepatic arteriogram revealed a hypervascular primary tumor and multiple intrahepatic metastases.

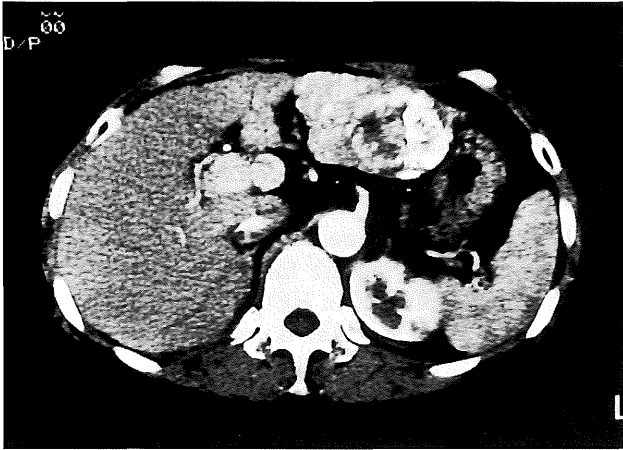


**Fig. 3.** A portography revealed a complete obstruction of the left first branch and a defect in the right first branch and trunk of the portal vein.

**Table 1.** Laboratory data on admission

WBC (/mm <sup>3</sup> )	8600	PT (%)	55
RBC (×10 <sup>4</sup> /mm <sup>3</sup> )	423	HPT (%)	49
Hb (g/dl)	14.0		
Ht (%)	42.4	ICG-R15 (%)	21.2
Plt (×10 <sup>4</sup> /mm <sup>3</sup> )	21.9		
TB (mg/dl)	0.5	HBs-Ag	(-)
TP (g/dl)	7.5	HBs-Ab	(+)
Alb (g/dl)	3.0	HCV-Ab	NE
AST (U/liter)	83		
ALT (U/liter)	59	αFP (ng/ml)	18874
LDH (U/liter)	359	DGP (AU/ml)	<0.06
Ch-E (U/liter)	147	CEA (ng/ml)	2.7
ALP (U/liter)	139		

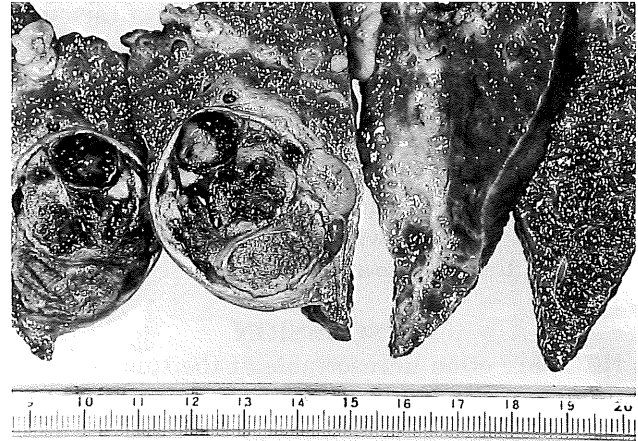
TB, Total bilirubin; TP, total protein; Alb, albumin; AST, aspartate-amino transferase; ALT, alanine-amino transferase; LDH, lactate dehydrogenase; Ch-E, cholinesterase; ALP, alkaline phosphatase; PT, prothrombin time; HPT, hepaplastin test; ICG-R15, indocyanine green retention at 15 min; HBs Ag, hepatitis B surface antigen; HBs Ab, hepatitis B surface antibody; HCV Ab, hepatitis C antibody; αFP, alpha-fetoprotein; DGP, des gamma carboxy prothrombin; CEA, carcinoembryonic antigen; NE, not examined



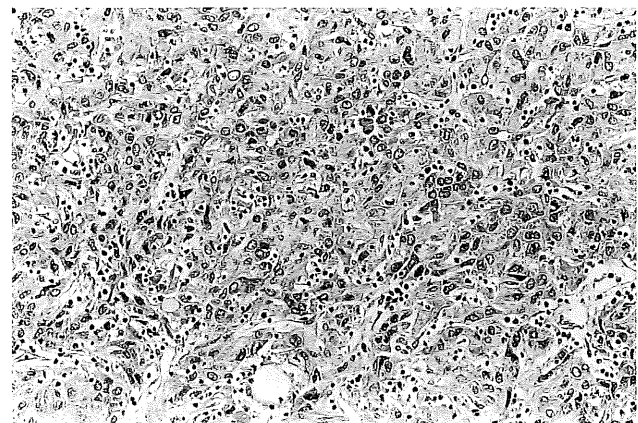
**Fig. 4.** Computed tomography taken 7 days after the first preoperative L-TAI revealed a primary tumor in which partial deposition of Lipiodol was detectable in the lateral segment, and tumor thrombi, which filled in the bilateral first branches and the trunk of the portal vein, was enhanced in the arterial phase.

bilateral first branch and the trunk of the PV. The abdomen was opened through a bilateral subcostal incision that was extended to the xyphoid. There was no ascites in the abdominal cavity. The liver surface showed a macronodular appearance due to cirrhosis. Intraoperative US revealed the existence of both intrahepatic multiple metastases and TT in the PV as had been predicted preoperatively. According to the general rules for the clinical and pathological study of primary liver cancer<sup>14)</sup>, the macroscopic tumor staging corresponded to Stage IV-A. Although, from these findings, it was impossible to perform a curative operation, a palliative left lateral segmentectomy was carried out with, as far as possible, tumor thrombectomy from the incised left first branch of the PV. Nevertheless, it was impossible to remove macroscopically all of the TT which, were packed especially into the second and/or third branches of the right PV. Therefore, for the purpose of performing postoperative additional treatment, two heparin-coated catheters were inserted at operation time through the right gastroepiploic artery and the jejunal vein, respectively, tips placed at the junction of the common hepatic and gastroduodenal arteries, and in the trunk of the PV, respectively, and their other ends connected to reservoirs (Infuse-A-Port, Infusaid Inc., MA) embedded in the subcutaneous layers of the right and left anterior chest walls, respectively. Moreover, intraoperative ethanol injections for residual tumors in the remnant liver were added simultaneously.

The resected lateral segment weighed 170 g. The primary tumor was 4 cm in diameter with a fibrous capsule and several satellite nodules around it (Fig. 5). The removed TT in the trunk and right branch of the PV had a soft consistency and were fragmented.



**Fig. 5.** The resected specimen showed a well-capsulated primary tumor with satellite nodules around it.



**Fig. 6.** Microscopic examination of the resected primary tumor revealed that the tumor cells showed a solid growth pattern with an indistinct trabecular pattern and exhibited abundant cytoplasm with large and round nuclei. A variable degree of lymphoid cell infiltration can be recognized in the parenchyma of the cancer cells. This carcinoma corresponded to grade III of Edmondson's classification or to the poorly differentiated type according to the classification of the Liver Cancer Study Group of Japan.

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The postoperative course was uneventful. The patient twice underwent L-TAI, including 30 mg of 4-epidoxorubicin (Epirubicin; Pharmacia, Milan,

Italy) and 30 mg of Cisplatin with 3 ml of Lipiodol, respectively, into the hepatic artery via the reservoir, and continuous infusion of 5-FU, with a total dose of 2,000 mg, into the PV via another reservoir. Moreover, percutaneous ethanol injection therapy (PEIT) was performed several times for the intrahepatic residual tumors. The patient died of hepatic failure with cancer 6 years and 8 months after the operation.

## DISCUSSION

HCCs are often unresectable at the time of diagnosis because of a poor hepatic functional reserve due to accompanying cirrhosis, a tendency for multicentric development, and early portal vein involvement<sup>15,16</sup>. An extensive analysis by the Liver Cancer Study Group of Japan revealed that the most valuable prognostic factor for hepatectomized HCC patients is portal vein involvement<sup>17</sup>. Especially, HCC patients with TT in the trunk of the PV have had an extremely poor prognosis. Lee et al<sup>7</sup> reported that the median survival time in untreated HCC patients with TT in the trunk of the PV was only 90 days.

With respect to transcatheter arterial infusion (TAI) of anti-cancer drug with or without Lipiodol for HCC patients with TT in the trunk of the PV, there were few reports that showed any effectiveness. Takada et al<sup>18</sup> demonstrated that none of 104 HCC patients with TT in the trunk of the PV survived for more than 1 year after TAI, of which the response rate was only 9.6%, although the frequency of death within 30 days after that was only 2.3%. Urata et al<sup>18</sup> demonstrated that the 2-year survival rate of patients with TT in the trunk or the first branch of the PV, who were treated by L-TAI, was only 4.5% and the median survival time of these patients was 174 days. Hamazaki et al<sup>5</sup> reported a case of HCC in a primary tumor, intrahepatic metastases and TT in the trunk of the PV were completely necrotized by L-TAI. However, the prognosis of the patient was not described at all. Ando et al<sup>1</sup> recently reported a novel chemotherapy for HCC patients with TT in the trunk of the PV. One course of their regimen consisted of the daily administration of Cisplatin (10 mg for 1 hour on Days 1–5) and the subsequent infusion of 5-fluorouracil (250 mg for 5 hours on Days 1–5) using subcutaneously implanted reservoirs. Two of 9 patients had complete remission and were doing well at the end of the observation, showing normalization of the tumor markers with survivals of 38.3 and 48.9 months, respectively.

Transcatheter arterial embolization (TAE) or transcatheter arterial chemoembolization (TACE) have been contraindicated for the treatment of patients with HCC with TT in the trunk of the PV because of the potential risk of liver failure resulting from ischemia after those procedures<sup>2,18,19</sup>. However, recently, Lee et al<sup>7</sup> reported the safety

and the efficacy of TACE for HCC patients with TT in the trunk of the PV. Although none of the 31 patients who were treated by TACE survived for more than 5 years, the 1-year cumulative survival rate of patients with nodular-type HCC was 57%. Therefore, they recommended TACE for treating nodular-type HCC because of the potential benefit of prolonged survival. On the other hand, to prevent hepatic failure caused immediately by TAE or TACE in HCC patients with TT in the trunk of the PV, Okazaki et al<sup>9</sup> proposed that the contraindications for TACE were for patients with: 1) persistent hyperbilirubinemia above 2.0 mg/dl, 2) TT in the main portal trunk without cavernous transformation, 3) uncontrollable ascites and pleural effusion, or 4) uncontrollable esophagocardiac varices. Moreover, they reported that 3 of 82 HCC patients with TT in the trunk of the PV, who were treated by TACE according to their patient selection criteria, survived for more than 5 years. Consequently, in their study, the 5-year survival rate was 6.1%.

Alternatively, surgical treatment for HCCs with TT in the trunk of the PV has been contraindicated<sup>20</sup>. However, Tanaka et al<sup>12</sup> reported that 55 HCC patients with TT in the first branch or the trunk of the PV had undergone hepatic resections with tumor thrombectomy. They demonstrated that although the operative mortality rate within 30 days after operation was high (20.3%), the mean survival time, except for cases of operative death, was 796 days, including one patient who survived for more than 8 years after the operation. Furthermore, from their study, they concluded that the indications for surgical treatment for HCC with TT in the PV were: (1) absence of extrahepatic metastasis and intrahepatic metastasis in the remnant liver after hepatectomy, (2) the location of the TT neither exceeded the first branch of the contralateral PV nor was confluent with the superior mesenteric vein and splenic vein, (3) normal liver or liver fibrosis, and (4) a relatively small main tumor. Moreover, they considered advanced HCC patients with liver cirrhosis or multiple intrahepatic metastases to be subjects unsuitable for surgical treatment. However, according to their criteria, the case presented herein would not be suitable for surgical treatment.

In a previous study (unpublished) with respect to hepatic resection with tumor thrombectomy for HCC with TT in the first branch and/or the trunk of the PV, we found that the median and mean survival times in such advanced HCC patients were 7.8 and 18.5 months, respectively, and the 1- and 5-year survival rates were 36.4%, 18.2%, respectively. From that study, we concluded that patients with relatively small primary tumors, around 5 cm in diameter, good hepatic functional reserves and without distant metastasis would

have good prognoses, if hepatic resections with tumor thrombectomies could be performed. However, because, in such advanced patients, it would be impossible to perform a curative operation, it would be most important to have a good hepatic functional reserve to tolerate postoperative multimodality treatments such as L-TAI, TACE and PEIT, irrespective of the existence of intrahepatic dissemination. The case presented herein had a primary tumor of 4 cm in diameter without distant metastasis. Although she had Child-Pugh grade B hepatic functional reserve, she could tolerate the postoperative multimodality treatments such as L-TAI and chemotherapy via the PV and PEIT. We recommend that for the purpose of life prolongation and improvement of the quality of life, we should determinedly try hepatic resection with tumor thrombectomy for suitable patients even if the operation is non-curative.

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