DEB-TACE Combined With Hepatic Artery Infusion Chemotherapy Might Be an Affordable Treatment Option for Advanced Stage of HCC: Retrospective Study

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Abstract

Backgrounds

Alternative treatment modalities are required because of the low response rates and unsuitability of Molecular-targeted agents (MTA) and/or immune checkpoint inhibitors (iCIs) in HCC patients. Therefore, we analyzed whether Drug-eluting beads (DEB)-Transcatheter arterial chemoembolization (TACE) with Low-dose-FP (Ultra-FP) therapy could improve the efficacy and safety of treatment among the difficult-to-treat HCC patients, especially those with advanced stage HCC.

Methods

From November 2017 to April 2021, 118 consecutive patients with non-resectable difficult-to-treat HCC were included in this study. All patients were treated with Ultra-FP therapy. After the weak DEB-TACE procedure, we administered low-dose FP for 2 weeks followed by resting for 4 weeks.

Results

The numbers of HCC patients CR/PR/SD/PD induced by Ultra-FP therapy were 36/52/17/13 (Modified RECIST) patients, respectively. The objective response rate of Ultra-FP therapy was 74.6% (88/118 patients). Tumor marker reduction was observed in 81.4% (96/118 patients). The objective response rate (ORR) in the HCC patients with portal vein tumor thrombosis (PVTT) was 75% (18/24 patients). Median survival time (MST) of all included HCC patients was 738 days. The MST of HCC patients with PVTT (-)/PVTT (+) was 816 days/718 days. The proportion of patients based on ALBI grade system was not significantly different between pre and after 3 course Ultra-FP therapy.

Conclusions

Ultra-FP therapy might be an affordable treatment option for difficult-to-treat advanced HCC. ORR and overall survival after receiving Ultra-FP therapy were remarkable in comparison to various kinds of systemic therapy including MTA and iCIs.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant cancer and the second leading cause of cancer deaths worldwide[1]. The treatment efficacy of patients with early-stage HCC has been improved by the development of ablation therapy including radiofrequency ablation (RFA) and microwave ablation (MWA), surgery and selective transcatheter arterial chemoembolization (TACE)[2]. Moreover, the treatment efficacy for the patients with advanced-stage HCC has been improved by molecular-targeted agents (MTA), immune check point inhibitors (iCIs), and radiation therapy in addition to TACE and/or hepatic arterial infusion chemotherapy (HAIC)[3–7]. However, the treatment efficacy for patients with advanced-stage HCC treated by a single agent of has not been adequate[3–5]. iCIs and/or MTA including

sorafenib, lenvatinib, regorafenib and cabozantinib etc. are standard treatments according to current international guidelines[8]. However, alternative treatment modalities are required because of the low response rates and unsuitability of MTA and iCIs in the real world.

Combinations and/or sequential treatments with various agents have been carried out to improve the treatment efficacy for patients with advanced-stage HCC[9,10]. TACE was a major treatment option for patients with intermediate-stage HCC. However, it was reported that the treatment efficacy of TACE for patients with up-to-seven out in the intermediate and advanced stage HCC was not adequate[11]. It has been reported that TACE with drug-eluting beads (DEB-TACE) showed a higher complete response rate, objective response rate and overall survival time with fewer common adverse events than conventional TACE (cTACE) in some groups[12,13]. However, the other group reported that the DEB-TACE and the cTACE are equally effective and safe, with the advantage of DEB-TACE being less post-procedural abdominal pain[14]. Some institutions have adopted yttrium-90 radioembolization as the first-line therapy for intermediate-stage HCC[15]. Other groups developed a procedure for DEB-TACE using HepaSpheres and subsequent cisplatin-based lipiodol TACE in patients with HCC > 5cm[16].

The pharmacokinetics of HAIC were based on the theories of “first pass effect” and “increased local concentration”[17–19]. In HAIC, a highly concentrated chemotherapeutic drug is injected into the liver tumor and surrounding area via the hepatic artery. A high concentration of a chemotherapeutic drug in the tumor site could induce an efficient anti-tumor effect[20]. Moreover, fewer systemic side effects occurred due to the “first pass effect” of the liver[21]. Recently, many groups, especially in Asia, have reported the effectiveness of treatments with HAIC in patients with advanced stage HCC[22–26]. In comparison to sorafenib therapy, HAIC might have superior power for advanced stage HCC, especially, with a portal vein tumor thrombus (PVTT)[27]. Other groups reported that intrahepatic tumor reduction by HAIC significantly prolonged the survival of patients, irrespective of PVTT or initial distant metastasis[28].

In addition to the conventional methods of HAIC, novel methods of HAIC have been proposed by many groups[22,26,29–31]. Dr. Nagamatsu et al. reported that 5-fluorouracil (5-FU) HAIC with cisplatin suspension in lipiodol (New-FP) could be effective for HCC patients with PVTT[30]. Moreover, it has been reported that New-FP could prolong overall survival (OS) compared to sorafenib by using propensity score matching[29]. Dr.Guo et al. reported the efficacy and safety of TACE followed by HAIC for treating advanced HCC[7].

We modified the treatment regimens to improve the efficacy of DEB-TACE and HAIC for intermediate and advanced HCC as described above. In this study, we analyzed whether Ultra-FP therapy (combination weak embolization with DEB-TACE (CDDP) and HAIC (low dose FP: CDDP and 5-FU)) could improve the efficacy and safety of treatment in difficult-to-treat HCC patients, especially those with advanced stage HCC.

Methods

Study Design and Inclusion Criteria

This study was approved by the Ethics Committee of Sendai Kousei Hospital in accordance with the Declaration of Helsinki and written informed consent was obtained from all subjects. This study was a single center and retrospective observational study. The datasets used and analyzed during the current study available from the corresponding author on reasonable request. The protocol of chemotherapy was also approved by Ethics Committee of Sendai Kousei Hospital. From November 2017 to May 2021, 198 patients had been treated by HAIC. Eighty patients with metastatic liver cancer, performance status 3–4, BCLC D stage, low-dose-FP without DEB-TACE, and other liver cancers such as cholangiocarcinoma were excluded in this study (Fig. 1A). One hundred eighteen consecutive patients with non-resectable, difficult-to treat HCC (TACE-refractory HCC, Treatment response of MTAs were PD, Huge HCC with multiple intra/extra hepatic metastasis, multiple HCC beyond up-to seven criteria, HCC with macroscopic vascular invasion) were included in this study (Fig. 1A, Table 1). The following inclusion criteria were used: (1) HCC diagnosed by tumor biopsy or radiological evaluation using dynamic enhanced computed tomography (CT) and/or gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (EOB) enhanced-magnetic resonance imaging (MRI) combined with tumor markers: alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP); (2) age > 20 years, and (3) patients treated with Ultra-FP as a multidisciplinary treatment in progressed HCC.

Clinical data including age, sex, etiology of HCC, Child-Pugh score, ALBI Score, treatment history of HCC, treatment history of partial splenic embolization (PSE) and the presence of macroscopic vascular invasion (MVI) and extrahepatic spread (EHS). HCC was classified using General Rules for the Clinical and Pathological Study of Primary Liver Cancer staging, Union for International Cancer Control (UICC) staging, Barcelona Clinic Liver Cancer (BCLC) staging, BCLC staging with Kinki criteria[11,32].

Data evaluation

The following evaluation items were analyzed: (1) Overall Survival (OS) after receiving Ultra-FP treatment, (2) tumor response rate after receiving 3 course of Ultra-FP treatment using modified (Response Evaluation Criteria in Solid Tumors) RECIST criteria and RECIST version 1.1, and (3) Adverse events induced by Ultra-FP using Common Terminology Criteria for Adverse Events (CTCAE) Ver 5.0. If the patients had been treated with iCIs after Ultra-FP, they were censored to avoid the effects of iCIs.

Treatment protocol of Ultra-FP

All patients were treated by weak embolization (maximum 30% embolization of HCC) using Hepasphere with CDDP (Kondo 3 catheter and Michibiki, Hanaco Medical, Tokyo Japan). After weak DEB-TACE procedure, we carried out catheter implantation immediately. Some patients needed gastroduodenal artery coiling and/or right gastric artery coiling using metallic coils to avoid gastroduodenal ulcer or pancreatitis. Five-French catheter (Anthron P-U Catheter; Toray Medical Co. Ltd., Tokyo, Japan) was inserted in the proper hepatic artery or targeted for a more specific hepatic artery. On day 1 we carried out weak DEB-TACE with CDDP and low dose FP (injection of 250mg of 5FU and 2 to 8mg of CDDP using

injection pump). Low dose FP was carried out 10 times for two weeks followed by a rest for 4 weeks. This regimen is a course of Ultra-FP. This regimen was continued until the appearance of severe AE, tumor progression, or a remarkable effect of treatment and conversion to curative therapy (Liver resection or RFA/MWA ablation).

Statistical analysis

All statistical analyses were carried out using JMP statistical analysis software (JMP Pro version 15, SAS Institute Inc., Cary, NC, USA). The survival time was calculated using Kaplan-Meier method and the analysis of log-rank test.

Results

Baseline characteristics of patients treated with Ultra-FP therapy

One hundred eighteen patients were involved in this study (Fig. 1A and Table 1). The mean age was 72 years. Most of the HCC etiology was non-HBV and/or non-HCV-related HCC (71 patients/118 patients). A treatment history of HCC existed in 71 patients including resection, TACE, RFA/MWA ablation and MTA (Table 1). The numbers of patients based on the stage of the general rules for the clinical and pathological study of primary liver cancer, I/□/□/□A/□B, were 0/25/45/26/22 patients, respectively. All patients of stage □ were TACE refractory patients.

The numbers of patients based on the HCC BCLC staging A, B, C and D system were 15/47/56/0 patients, respectively. The presence of portal vein tumor thrombosis (PVTT) was detected in 24 out of 118 patients. The level of the liver reserve was evaluated by the Child-Pugh classification and ALBI grade system. The numbers of patients based on the Child-Pugh classification, A/B/C, were 93/25/0 patients, respectively. The numbers of patients based on ALBI grade system, 1/2a/2b/3 were 34/28/44/12 patients, respectively (Table 1).

Treatment effect of Ultra-FP therapy and adverse events

The treatment effect of Ultra-FP therapy was evaluated by modified RECIST and RECIST ver1.1 after 3 courses of therapy (Table 2 and Fig. 1B). The numbers of HCC patients, CR/PR/SD/PD (modified RECIST), induced by Ultra-FP therapy were 36/52/17/13 patients, respectively. The objective response rate (ORR) of Ultra-FP therapy was 74.6% (88/118 patients) and the disease control rate (DCR) was 89.0% (105/118 patients). Tumor marker reduction (AFP or DCP) was in observed 81.4% (96/118 patients). ORR in the patients with PVTT was 75% (18/24 patients). ORR in the patients with extrahepatic lesion was 64.7% (11/17 patients). Median survival time (MST) of all included HCC patients was 738 days (Fig. 1C).

Grade 1/2 adverse events after initial Ultra-FP therapy were analyzed by using CTCAE ver 5.0. Some patients experienced abdominal pain, fever, malaise, nausea and/or vomiting, anorexia, diarrhea, hypertension creatinine increased, anemia and platelet count decreased (Table 3). Grade 3/4 adverse events induced by tumor lysis (asparate aminotransferase increased, alanine aminotransferase

increased, blood bilirubin increased, GGT increased and hypoalbuminemia) were temporary observed in some patients (Table 3). However, there are no severe adverse events that might have resulted in death.

Subgroup analysis of MST due to the tumor conditions and liver functional reserve

At first, we analyzed the subgroup of HCC patients depending on the various kinds of tumor staging systems. The MST stage based on the general rules for the clinical and pathological study of primary liver cancer, I/□/□/□A/□B, was NA/1065/764/718/280 days, respectively (Fig. 2A). The MST of UICC staging, IB/□/□A/□B/□A/□B was Not reached/1065/384/738/NA/280 days, respectively (Fig. 2B). The MST of BCLC stage A/B/C/D was Not reached/816/585/NA days, respectively (Fig. 2C). The MST of the sub-classification of BCLC (Kinki criteria) stage A/B1/B2/B3/C/D was Not reached/1065/764/596/585/NA days, respectively (Fig. 2D).

Then, we analyzed the subgroup of HCC patients depending on the criteria of the liver functional reserve. The MST of the HCC patients in the Child-Pugh A/B/C were 1065/350/NA days, respectively (Fig. 2E). Moreover, the MST of the HCC patients with ALBI grade 1/2a/2b/3 were NA/1065/476/212 days, respectively (Fig. 2F).

Finally, we analyze the subgroup of HCC patients depending on the existence of PVTT. The treatment response of HCC patients with PVTT by Ultra-FP therapy, CR/PR/SD/PD (modified RECIST), were 2/16/5/1 patients, respectively (Fig. 3A). The response rate of HCC patients with PVTT was 75%. The survival curves of HCC patients with or without PVTT were almost the same (Fig. 3B). The MST of HCC patients with PVTT (-)/PVTT (+) was 816 days/718 days. The treatment response of HCC patients with Vp2, Vp3 and Vp4 by Ultra-FP therapy were shown in Fig. 3C. The treatment response of HCC patients with Vp4 PVTT by Ultra-FP therapy, CR/PR/SD/PD (modified RECIST), were 0/5/1/1 patients, respectively (Fig. 3C). The MST of HCC patients with Vp2/Vp3/Vp4 were 718/Not reached/458 days, respectively (Fig. 3D).

Analysis of liver functional reserve during Ultra-FP therapy

The comparison of ALBI score between before and after 3 course of Ultra-FP therapy was carried out (Fig. 4A). ALBI score was significantly increased during 3 course of Ultra-FP therapy (*p = 0.02*). However, the change of mean score was 0.1 (pre=-2.23: after=-2.13) (Fig. 4A). The numbers of patients based on ALBI grade system at the pre-treatment, 1/2a/2b/3 were 34/28/44/12 patients, respectively (Fig. 4B). The numbers of patients based on ALBI grade system after 3 course of Ultra-FP therapy, 1/2a/2b/3 were 38/20/42/18 patients, respectively. The proportion of patients based on ALBI grade system was not significantly different between pre and after 3 course Ultra-FP therapy (Fig. 4B).

Discussion

The treatment efficacy of the patients with advanced-stage HCC and difficult-to-treat intermediate stage HCC has been improved by MTA, iCIs, and radiation therapy in addition to TACE and/or HAIC. However,

the treatment efficacy by a single agent of has not been adequate. Some groups including ours developed modified methods of HAIC that contributed to a better treatment response, less liver damage and fewer adverse events. In this study, we developed Ultra-FP therapy that combined weak embolization by DEB-TACE with low-dose FP HAIC. The HCC patients involved in this study had remarkably severe tumors and liver reserve in comparison to the SHARP trial, REFLECT trial and IMbrave150 trial, since we included Child-Pugh B patients and patients with a treatment history of MTA and/or TACE/RFA/liver resection[3–5]. Therefore, we analyzed HCC patients with Child-Pugh A liver reserve, MST was 1065 days in the patients treated by Ultra-FP therapy. Moreover, the MST of Child-Pugh B patients was 350 days. These results showed that the MST of Child B HCC patients treated with Ultra-FP therapy had a similar MST to Child-Pugh A HCC patients treated with MTA[4,5]. Moreover, we analyzed the survival of HCC by using BCLC staging with the Kinki criteria, which might well differentiate the conditions among BCLC B[11,32]. In our data, the survival of HCC patients treated with Ultra-FP therapy differed among BCLC B1, B2 and B3. The survival of BCLC B3 HCC patients treated with Ultra-FP therapy showed a better prognosis compared to previous reports[11]. Therefore, Ultra-FP therapy was effective for treating advanced stage HCC in patients with poor liver reserve.

Previous reports indicated that HCC patients with PVTT treated with sorafenib had a poor prognosis[33]. However, the treatment response of HCC patients with PVTT by Ultra-FP therapy were remarkably high. The ability of Ultra-FP therapy to reduce the tumor volume might maintain the liver reserve since a reduction of PVTT could improve the blood supply of the background liver. Some groups indicated that radiation therapy with HAIC could improve the treatment response of HAIC with PVTT[34,35]. These results suggested that Ultra-FP therapy with radiation therapy might be a better option for HCC with PVTT than Ultra-FP therapy alone.

It has been reported that atezolizumab and bevacizumab combination therapy had a better treatment response and OS than sorafenib therapy. However, various kinds of irAEs and poor liver reserve might restrict the usage of atezolizumab and bevacizumab combination therapy. The iCIs including atezolizumab might maintain the function for the re-activation of tumor immunity for several months. Therefore, Ultra-FP therapy as the post-treatment after atezolizumab and bevacizumab combination therapy could be a candidate treatment to enhance the tumor immunity since the cytotoxic effect of Ultra-FP therapy is quite strong. Immunogenic cell death induced by ferroptosis, necroptosis, and pyroptosis could enhance the anti-tumor immunity in patients treated by iCIs[36,37]. In addition to the strong cytotoxic effect of Ultra-FP therapy, the Ultra-FP therapy could maintain the liver reserve in this study. Some studies have shown that combination of MTA and ICIs could be more effective than monotherapy[38]. However, the combination of MTA and iCIs therapy requires adequate liver reserve.

Technical training for Ultra-FP therapy is necessary for the doctors who lack experience in catheter therapy. The limitation of technical expertise in Ultra-FP therapy for liver cancer might be overcome in high volume treatment centers. This study was single center and retrospective observational study.

Therefore, we need to analyze whether Ultra-FP therapy could be superior to DEB-TACE or HAIC alone in multiple centers.

Some groups reported that various kinds of biomarkers could predict the prognosis for advanced HCC treated with HAIC[39–46]. Previously, we reported that the myeloid derived suppressor cells (MDSCs) might contribute to the immunopathogenesis of HCC and affect the recurrence of HCC[47]. Dr. Mizukoshi et al. reported that the frequency of MDSCs before treatment was a prognostic factor in HAIC against HCC[39]. Immunological analysis of biomarkers is important since multidisciplinary treatments including iCIs, MTAs, radiation and Ultra-FP therapy etc. might improve the prognosis of HCC patients. Biomarkers for the treatment response of Ultra-FP therapy should be analyzed in near future.

In conclusion, Ultra-FP therapy could be an affordable treatment option for difficult-to-treat advance HCC. ORR and OS after receiving Ultra-FP therapy were remarkable in comparison to various kinds of systemic therapy including MTA and iCIs. Maintaining the liver reserve might contribute to enabling various kinds of treatment. We need to determine the best combination therapy with Ultra-FP since many systemic therapies after or during Ultra-FP therapy might contribute to the stabilization of HCC.

Declarations

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There are no conflicts of interest.

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Tables

Tables 1 to 3 xlsx are available in the Supplemental Files section.

Figures

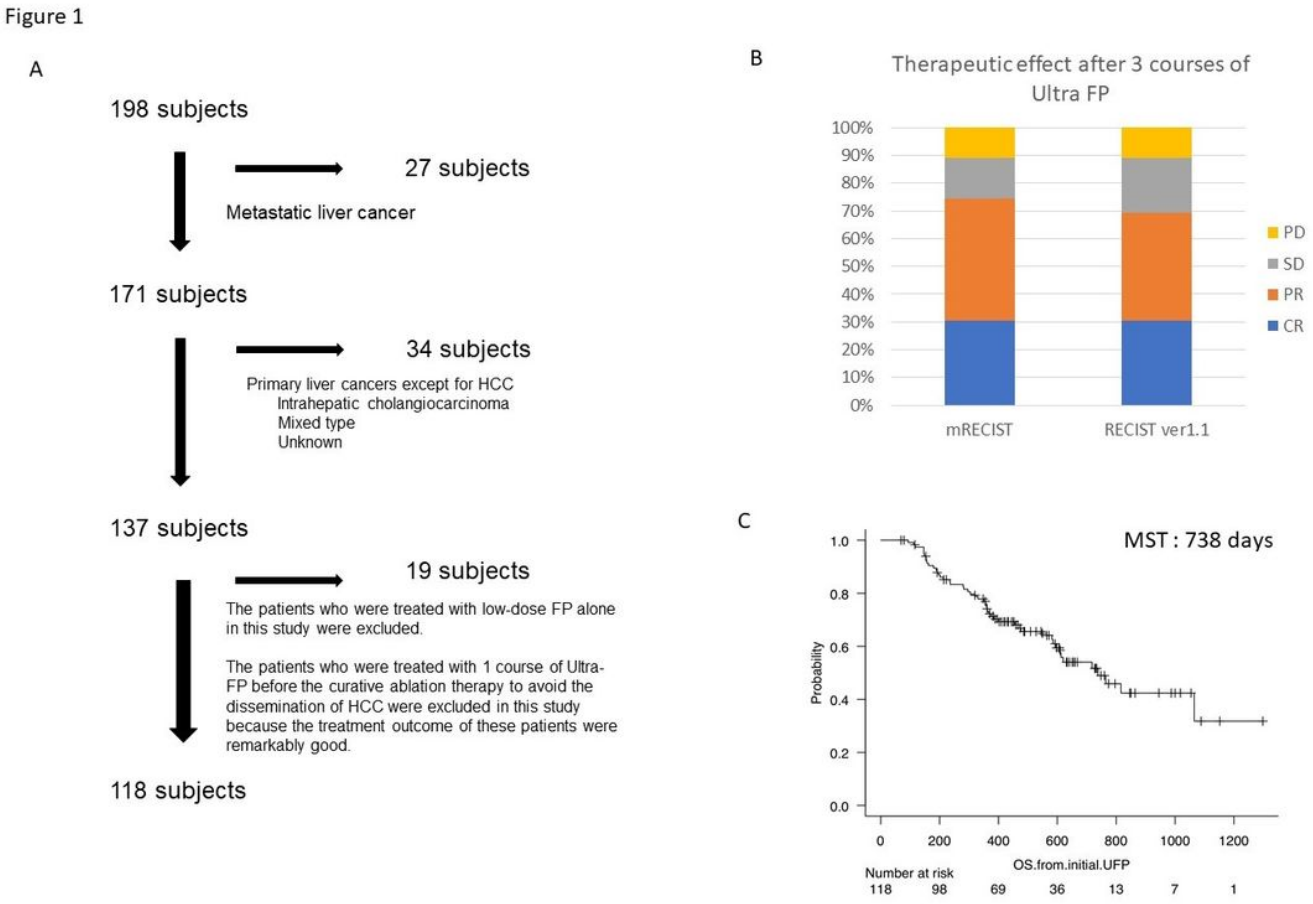

Figure 1

Flow chart of patients included in this study and survival and treatment response of Ultra FP therapy

Flow chart of patients included in this study is shown (A).

Treatment response of all included patients treated by Ultra-FP therapy (modified RECIST and RECIST ver1.1) is shown(B). The survival curve of included patients analyzed by Kaplan-Meier method is shown(C). Median survival time of all included patients (118 patients) is 738 days (24 Months) (C).

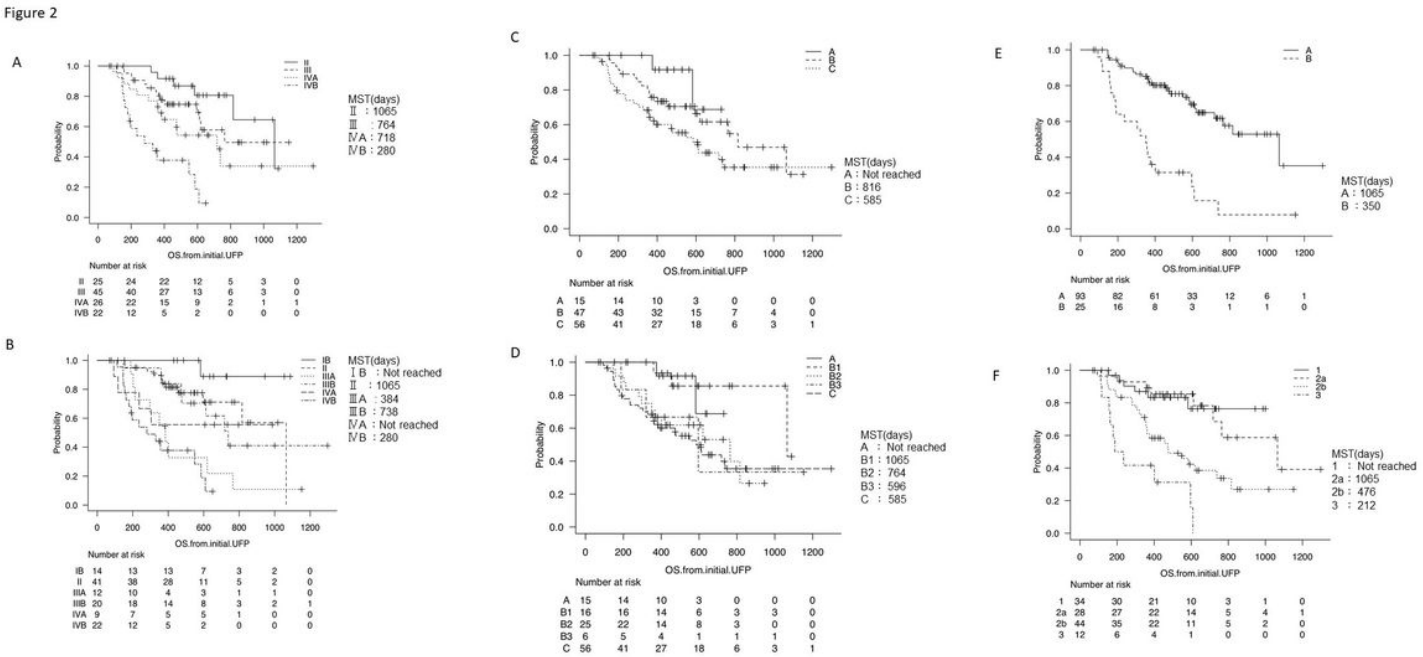

Figure 2

Survival time depending on the various kinds of tumor staging systems and the liver functional reserve.

The survival curves of tumor staging systems based on the general rules for the clinical and pathological study of primary liver cancer (A), UICC (B), BCLC (C) and BCLC with Kinki criteria (D) are shown. MST stage based on the general rules for the clinical and pathological study of primary liver cancer, I/□/□/□A/□B, was NA/1065/764/718/280 days, respectively (A). MST of UICC staging, IB/□/□A/□B/□A/□B, was Not reached/1065/384/738/Not reached/280 days, respectively (B). MST of BCLC stage, A/B/C, was Not reached/816/585 days, respectively(C). MST of a sub-classification of BCLC (Kinki criteria) stage, A/B1/B2/B3/C, was Not reached/1065/764/596/585 days, respectively (D).

The survival curves of liver functional reserve based on Child-Pugh (E) and ALBI grade (F) systems are shown. MST of HCC patients with Child-Pugh A/B/C were 1065/350 days, respectively (E). Moreover, the MST of HCC patients with ALBI grade 1/2a/2b/3 were Not reached/1065/476/212 days (F).

Figure 3

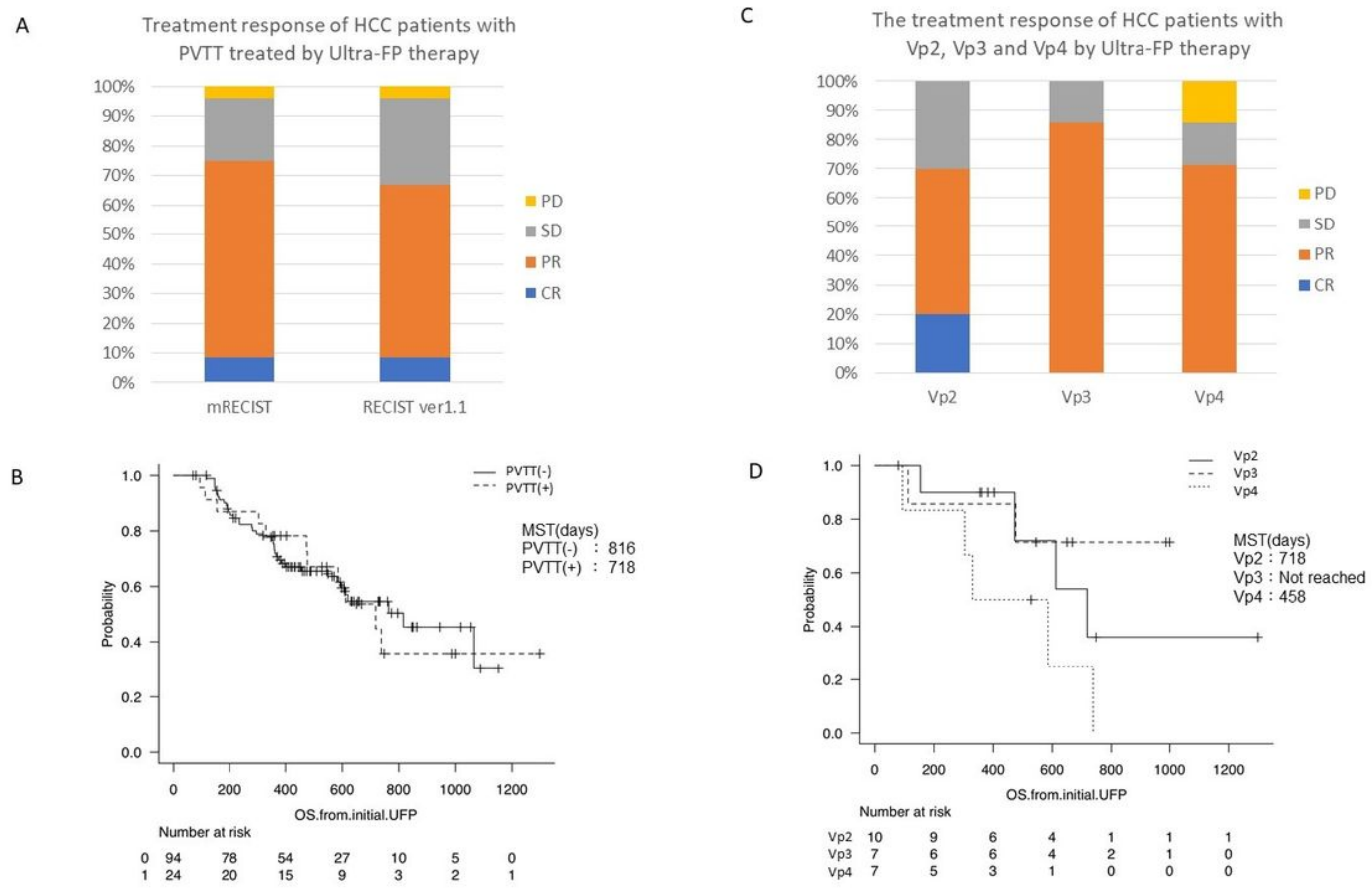

Figure 3

Treatment response and survival time depending on the existence of PVTT.

Treatment response of HCC patients with PVTT treated by Ultra-FP therapy (modified RECIST and RECIST ver 1.1) is shown (A). The survival curves of HCC patients with or without PVTT are shown (B). The treatment response of HCC patients with PVTT by Ultra-FP therapy CR/PR/SD/PD was 2/16/5/1 patients, respectively (A). The MST of HCC patients with PVTT (-)/PVTT (+) was 816 days/718 days, respectively (B). The treatment response of HCC patients with Vp2, Vp3 and Vp4 by Ultra-FP therapy were shown (C). The treatment response of HCC patients with Vp2 by Ultra-FP therapy CR/PR/SD/PD was 2/5/3/0 patients, respectively (C). The treatment response of HCC patients with Vp3 by Ultra-FP therapy CR/PR/SD/PD was 0/6/1/0 patients, respectively (C). The treatment response of HCC patients with Vp4 by Ultra-FP therapy CR/PR/SD/PD was 0/5/1/1 patients, respectively (C). The survival curves of HCC patients with Vp2/Vp3/Vp4 are shown (D). The MST of HCC patients with Vp2/Vp3/Vp4 were 718/Not reached/458 days, respectively (D).

Figure 4

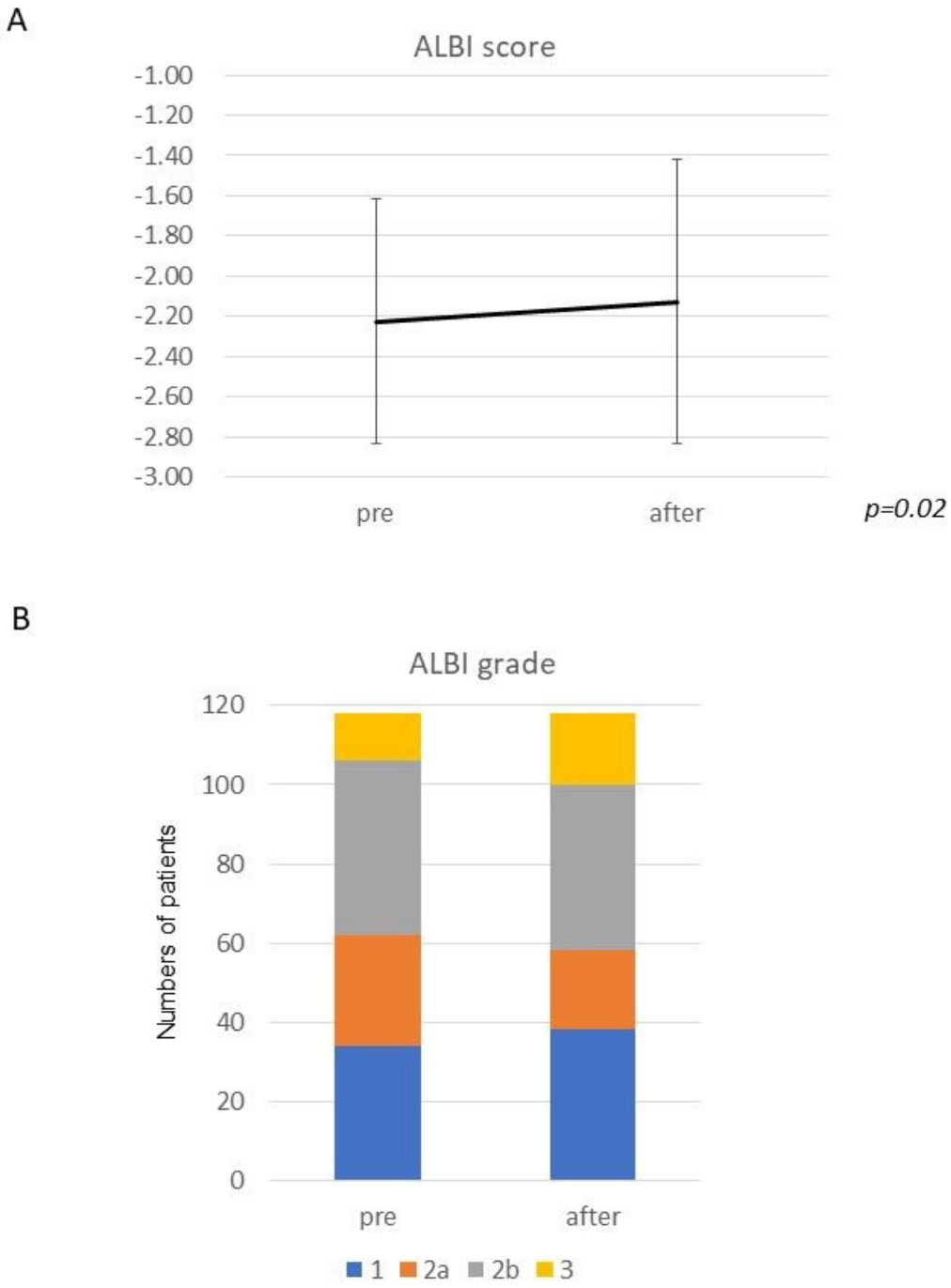

Figure 4

Analysis of liver functional reserve during Ultra-FP therapy

ALBI scores before and after 3 course of Ultra-FP therapy were shown (A). Y-axis indicates ALBI score. Error bars indicate standard deviation. The numbers of patients based on ALBI grade system at the pre-treatment and after 3 course of Ultra-FP therapy were shown (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx