The aims of this study were to confirm the efficacy of reduction surgery followed by TACE in the treatment of advanced T-staged HCC patients and to determine prognostic factors that could be used to identify those patients who would most benefit from reduction surgery. We focused particularly on the effect of the tumour volume ratio (volume of all tumours/volume of the whole liver × 100%) and the tumour reduction rate (volume of the resected tumours/volume of all tumours × 100%) on survival.

Patients and methods

Patient population

Three hundred and eighty-two patients with T3N0M0 HCC and 97 patients with T4N0M0 HCC were treated at the National Cancer Center Hospital East between November 1993 and November 2003. Among the T3N0M0 HCC patients, 173 had TACE, 122 had curative resection, 33 had ablation, 27 had hepatic arterial infusion (TAI), 15 had reduction hepatectomy followed by TACE, 8 had radiation, and 4 had systemic chemotherapy. Among the T4N0M0 HCC patients, 30 had TACE, 27 had TAI, 24 had reduction hepatectomy followed by TACE, 12 had curative resection, and 4 had radiation. The data of the 39 consecutive T3N0M0 HCC and T4N0M0 HCC patients who had reduction surgery followed by TACE were retrospectively examined. The patients consisted of 36 men and 3 women, ranging in age from 27 to 77 years (mean, 57 years). HCC staging was performed according to the staging criteria of the Japanese Liver Cancer Study Group.[18] The diagnosis of HCC was based on the pathological findings of the resected specimens.

The criteria for reduction hepatectomy were as follows: (1) the presence of multiple HCCs for which curative resection was not indicated and that appeared to be resistant to TACE due to tumour extent, tumour thrombus, or other factors; (2) no extrahepatic metastases; (3) sufficient liver function to tolerate the planned hepatectomy; and (4) written informed consent before treatment. All 39 patients had contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic angiography, abdominal ultrasonography, and chest X-Rays preoperatively to stage the HCCs and evaluate resectability. Liver function was assessed based on liver biochemistry tests, Child-Pugh grade,[19] and the indocyanine green retention rate at 15 min.[20] The patients' data were reviewed by hepatic surgeons, medical oncologists, and interventional radiologists during a conference to determine whether the patients met the aforementioned criteria.

Treatment procedure and follow up

First, large main tumours with satellite tumours that were obstacles for TACE were resected. Tumour thrombi in the portal or hepatic veins were also resected when they were recognized before or during the operation. Hepatic resection was performed by the forceps fracture method under inflow occlusion (Pringle's manoeuvre), and anatomic hepatectomy was performed whenever possible. All the resections were ultrasound-guided procedures.

Hepatectomy was followed by TACE as soon as liver function recovered during the postoperative period. TACE was repeated every 2–3 months until there was: complete remission of the remnant tumours; progressive disease despite treatment; or malfunction of the liver or other organs. The TACE procedure was performed by injecting a mixture of iodized oil (Lipiodol) 5 ml and farmorubicin 50 mg, followed by a gelatine sponge block (Gelfoam).

One month after treatment, the anti-tumour effects of TACE were assessed by CT. Subsequently, follow-up examinations, including CT, serum alpha-fetoprotein (AFP), and biochemistry assays, were conducted at least every 3 months. The median follow-up of the survivors was 23 months.

When disease progression was evident in the remnant liver, TACE was stopped and transcatheter arterial infusion chemotherapy with farmorubicin 50 mg was performed if possible. When disease progression was observed only outside the liver, TACE was continued if treatment to the hepatic tumour seemed to be beneficial.

Measurement of tumour volume ratio and tumour reduction rate

Tumour volumes were obtained from contrast-enhanced CT scans of the abdomen that were performed before hepatectomy using 5-mm collimation with administration of 120 cc of non-ionic intravenous contrast injected at 3 cc per second with 40-s, 60-s, and 3-min delays. Images were reconstructed at 5-mm intervals using a standard soft-tissue algorithm.

Tumours and the liver were outlined manually on each axial slice using a computer mouse. The tumour and whole liver volumes were calculated automatically by multiplying the sum of the areas from each slice by the reconstruction interval. Then, the tumour volume ratio (volume of all tumours/volume of the whole liver × 100%) and tumour reduction rate (volume of the resected tumours/volume of all tumours × 100%) were calculated. The resected part of the tumour was confirmed by both the surgical record and the findings of pre- and postoperative contrast-enhanced CT scans. All measurements were made by a radiologist.

Statistical analysis

Survival analyses were performed using the Kaplan–Meier method,[21] and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model.[22] A P value of less than 0.05 was considered significant.

Results

Patient characteristics and clinicopathological features of HCCs

Hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb) were positive in 10 and 18 patients, respectively. Twelve patients tested negative for both HBsAg and HCVAb. The mean results of the preoperative liver function tests were: ALT, 71.3 IU/L; serum albumin, 3.7 g/L; prothrombin time, 81.8%; and ICG R_{15} 16.2%. Based on the Child-Pugh grading system, 31 patients were stage A, and 8 were stage B. Twenty patients had liver cirrhosis. The median maximum tumour size was 11.5 cm (range, 4.5–21.5 cm); 20 patients had 10 or more tumours. The average tumour volume rate was 41%. The average preoperative AFP level was 802 ng/ml. Macroscopic portal vein invasion (thrombus) that involved a major branch was found in 12 patients. Four patients had tumour thrombus in the trunk of the portal vein. Based on the Japanese Liver Cancer Study Group classification of tumour growth extent, 31 cases had expansive tumour growth, and 8 had infiltrative growth.

Reduction hepatectomy

Four patients had tri-segmentectomies (Fig. 1), two had central bi-segmentectomies, 14 had lobectomies, 11 had segmentectomies, and 8 had partial resections; 7 patients had simultaneous direct removal of the portal tumour thrombus.

The average resected tumour volume was 1488 ml; the average tumour volume left in the remnant liver was 53 ml. The average tumour reduction was 94.7%.

One patient died on the 15th day after reduction hepatectomy due to liver failure. The morbidity rate was 41%: 8 cases had a biliary leak; 5 had ascites; 4 had a wound infection; 3 had an intra-abdominal abscess; 2 had bleeding; and 2 had liver failure.

Transcatheter arterial chemoembolization

All but one patient who underwent reduction hepatectomy received TACE; postoperative liver failure prevented the one patient from receiving TACE. The median interval from reduction hepatectomy to the first TACE treatment was 30 days, and the average number of TACE treatments was 3.6 (range, 1–15).

Survival

Survival time was calculated from the date of reduction hepatectomy. Actual overall 3-year survival was 32%, with a median survival of 11 months (Fig. 2). Six patients survived more than 3 years.

Among the 39 patients, 27 developed disease progression. The location of the initial progression included: remnant liver, 19 patients; lungs, 7; bone, 6; lymph nodes, 1; and brain, 1.

Correlation between clinicopathological factors and overall survival

To determine the prognostic factors related to survival after reduction hepatectomy in patients with advanced T-staged HCCs, the clinicopathological factors and overall survival of the 39 patients were analyzed (Table 1). Serum albumin level <3.5 g/L ($P = 0.03$), indocyanine green (ICG) $R_{15} \geq 15\%$ ($P < 0.01$), preoperative alpha-fetoprotein (AFP) ≥2000 ng/ml ($P = 0.04$), tumour reduction rate <98% ($P = 0.02$), macroscopic portal vein invasion ($P < 0.01$), and infiltrative growth ($P < 0.01$) were

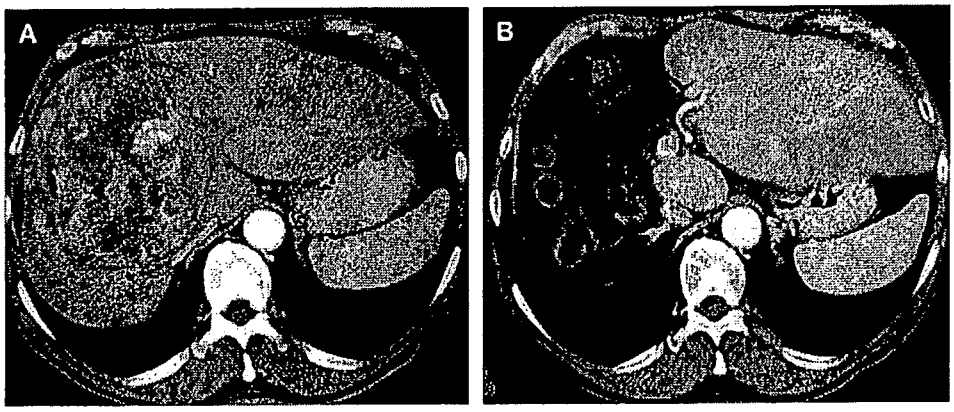

Figure 1. Contrast-enhanced computed tomography (CT) findings of a 66-year-old man with multiple hepatocellular carcinomas (HCCs). (A) CT before reduction hepatectomy demonstrates an HCC measuring 14 cm with many intrahepatic metastases throughout both lobes. The preoperative alpha-fetoprotein level was 6717 ng/ml, and no tumour thrombus was observed in the hepatic or portal veins. Liver function was preserved (ICG $R_{15} = 8.7\%$). The patient underwent reductive right tri-segmentectomy. (B) CT 4 years after reduction hepatectomy demonstrates small tumours well controlled by 10 successive transcatheter arterial chemoembolizations.

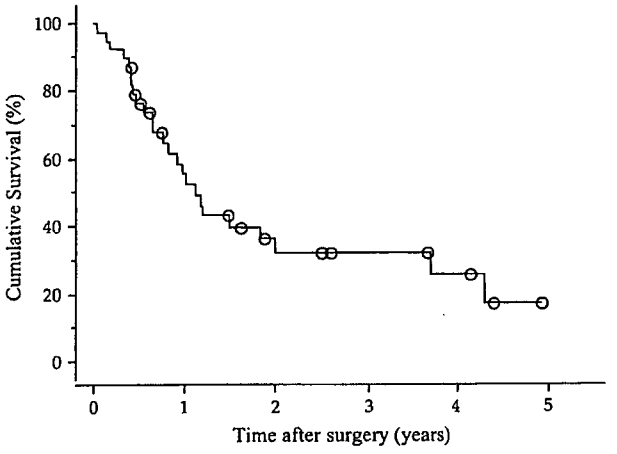

Figure 2. Cumulative survival curves after reduction hepatectomy followed by transcatheter arterial chemoembolization in patients with advanced T-staged HCCs.

significantly associated with poor overall survival. Neither the number nor size of tumours in the remnant liver was correlated with survival.

We examined the independent predictive value of the aforementioned factors for overall survival. The data were analyzed using a Cox regression model (Table 2). Serum albumin level <3.5 g/L was excluded from the analysis due to a possible correlation with ICG R_{15} ≥15%. ICG R_{15} ≥15% ($P < 0.01$; HR = 5.89; 95% CI, 1.98 to 17.5), preoperative AFP ≥2000 ng/ml ($P < 0.01$; HR = 5.85; 95% CI, 1.93 to 17.7), and tumour reduction rate <98% ($P < 0.01$; HR = 4.25; 95% CI, 1.55 to 11.7) were predictive for decreased overall survival.

When the three prognostic factors were used in a scoring system, with one point assigned for each factor, the total score was strongly correlated with survival after reduction hepatectomy ($P < 0.01$). The 3-year survival rates of patients with scores of 0 ($n = 7$), 1 ($n = 17$), 2 ($n = 13$), and 3 ($n = 2$) were 71%, 40%, 0%, and 0% respectively (Fig. 3). No patients with two or more criteria survived more than 15 months.

Table 1
Correlation between clinicopathologic factors and overall survival after reduction hepatectomy for multiple HCCs

	No. of patients	Median survival (mo)	P
HBsAg			
Negative	29	12.5	0.26
Positive	10	9.1	
HCVAb			
Negative	21	11.2	0.83
Positive	18	10.9	
ALT			
<70 IU/L	22	11.6	0.69
≥70 IU/L	17	9.3	
Albumin			
≥3.5 g/L	29	12.5	0.03
<3.5 g/L	10	5.0	
Prothrombin Time			
≥80%	22	11.0	0.65
<80%	17	11.2	
ICG R_{15}			
<15%	21	17.9	<0.01
≥15%	18	7.1	
Child-Pugh Stage			
A	31	11.9	0.61
B	8	7.3	
Tumor size			
<10 cm	19	7.9	0.17
≥10 cm	20	18.1	
Number of tumors			
<10	20	14.2	0.07
≥10	19	10.1	
AFP			
<2000 ng/ml	25	13.7	0.04
≥2000 ng/ml	14	6.1	
Tumor volume ratio[a]			
<50%	26	8.6	0.83
≥50%	13	12.5	
Tumor reduction rate[b]			
≥98%	21	17.9	0.02
<98%	18	7.1	
Macroscopical portal vein invasion			
Absent	27	13.7	<0.01
Present	12	5.8	
Growth type of tumor			
Expansive growth	31	13.7	<0.01
Infiltrative growth	8	6.9	

[a] Volume of all tumors/volume of whole liver × 100%.
[b] Volume of the resected tumors/volume of all tumors × 100%.

Discussion

The optimal treatment of patients with multiple HCCs who are not candidates for curative resection or TACE alone due to large tumours or tumour thrombi is unclear. Reduction surgery, which is also referred to as "debulking surgery", "tumour mass reduction surgery", and "tumour volume reduction surgery", is a potential treatment for patients with advanced T-staged HCCs.[11–17] Initially, large main tumours that are life-threatening and that can obstruct postoperative treatment are resected. Then, additional therapy, such as TACE or transcatheter arterial infusion chemotherapy, is given to treat the residual tumour in the remnant liver. Long-term survivors have been reported after reduction surgery for advanced HCCs. Several retrospective reports with small cohorts have shown that reduction surgery is superior to non-surgical treatment, such as TACE or transcatheter arterial infusion chemotherapy.[14,15] In a previous study, we reported the efficacy of reduction surgery followed by TACE in a small cohort of patients who had preserved liver function, tumour size greater than 10 cm, and residual tumour volume <10% of the remnant liver.[17] However, the indications for reduction hepatectomy followed by TACE are still unclear.

In the present study, all patients who underwent reduction hepatectomy were studied to confirm the efficacy of

Table 2
Multivariate analyses of factors affecting overall survival after reduction hepatectomy for multiple HCCs

	Hazard ratio	P
ICG R_{15} ≧15%	5.89 (1.98–17.5)	<0.01
AFP ≥2000 ng/ml	5.85 (1.93–17.7)	<0.01
Tumor reduction rate[a] <98%	4.25 (1.55–11.7)	<0.01
Macroscopical portal vein invasion	1.25 (0.38–4.07)	0.71
Infiltrative growth of tumor	2.19 (0.63–7.57)	0.22

Values in parentheses are 95 per cent confidence intervals.
[a] Volume of the resected tumors/volume of all tumors × 100%.

reduction surgery followed by TACE and to determine prognostic factors that might identify the patients who would most benefit from reduction hepatectomy. TACE was used as postoperative treatment since TACE is considered to be the first option for controlling unresectable multiple HCCs.

In this series, overall survival after reduction hepatectomy was 32% at 3 years and the results were not so much different from those of curative resection for stage IV HCC[23,24] while all our cases were classified as stage IVA according to the TNM classification system by UICC. Furthermore, patients who received the treatment were not a few because one quarter of patients with T4N0M0 HCC received the treatment.

Three factors associated with a poor prognosis were identified: ICG R_{15} ≥15%; preoperative AFP ≥2000 ng/ml; and tumour reduction rate <98%. These three factors capture the essence of the treatment strategy. First, the reduction hepatectomy tends to be a major hepatectomy due to the extent of tumour; however, postoperative liver failure or deterioration of liver function must be avoided, since this can delay the start of TACE. As well, sufficient liver function must be present preoperatively. Second, early

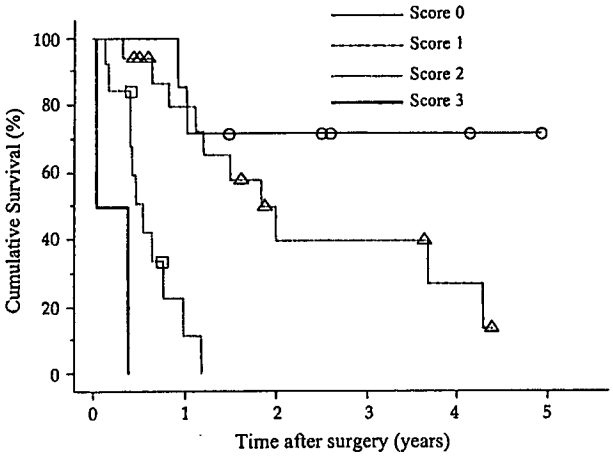

Figure 3. Cumulative survival curves after reduction hepatectomy followed by transcatheter arterial chemoembolization based on the scoring system. The scoring system was based on assigning one point for each of: ICG R_{15} ≥15%; preoperative alpha-fetoprotein ≥2000 ng/ml; and tumour reduction rate <98%.

progression is an issue with this treatment strategy; overall survival decreased to about 50% within a year in this series. A high preoperative AFP level has been reported to be a significant factor indicating a poor prognosis[2,25] and might be correlated with early death after reduction hepatectomy due to abrupt tumour progression inside or outside the liver. Third, control of the residual tumour in the remnant liver is necessary for long-term survival. A high tumour reduction rate indicates a low tumour burden in the remnant liver and may predict good control of the residual tumour with postoperative TACE.[9,10]

Extrahepatic disease,[12] residual tumour thrombus,[14] no effect of postoperative treatment,[14] and a remnant tumour index[13] have been reported as poor prognostic factors after reduction surgery for HCC. Yamamoto et al. proposed a remnant tumour index that is calculated based on the maximum diameter of the largest residual tumour (in cm) multiplied by the number of residual tumours; this index can be used to quantify the tumour burden in the remnant liver and select optimal candidates for reduction surgery.[13] The concept of a remnant tumour index is similar to that of the tumour reduction rate in the present study. However, the maximum diameter of the largest residual tumour, the number of residual tumours, and a remnant tumour index were not correlated with survival in the present study (data not shown). The tumour reduction rate may perhaps more accurately evaluate the efficacy of reduction surgery and the tumour burden in the remnant liver.

To select the best candidates for reduction hepatectomy, we would propose a scoring system that incorporates the aforementioned three factors for patients with multiple HCCs that are not treatable with curative resection. The score based on these factors was strongly correlated with survival after reduction hepatectomy; the 3-year survival rates of patients with scores of 0, 1, 2, and 3 were 71%, 40%, 0%, and 0% respectively. Patients with a score of 0 are good candidates for reduction hepatectomy followed by TACE. On the other hand, a score of 2 or 3 might be a contraindication for treatment, since there were no long-term survivors among patients who had scores of 2 or 3. Other non-surgical treatments, including experimental treatments, would be recommended for patients with a score of 2 or 3. Patients with a score of 1 sometimes survive a relatively long time; thus, patients with a score of 1 may be candidates for reduction hepatectomy, though other findings, such as cardiopulmonary function or performance status, should be considered in such patients.

Recently, intensive non-surgical treatments using transcatheter arterial infusion chemotherapy or systemic chemotherapy have improved the treatment of advanced T-staged HCCs.[26–31] A potential weakness of the present study is that our strategy using reduction hepatectomy followed by TACE did not take into account these new treatments. A clinical study comparing the efficacy of reduction hepatectomy followed by TACE with that of intensive non-surgical treatments in patients with advanced T-staged HCCs, especially

those with a score of 1, is needed. Moreover, the efficacy of reduction hepatectomy followed by one of these intensive non-surgical treatments should be investigated.

Since our study population was small, a prospective study is warranted to verify the validity of the scoring system.

In conclusion, reduction hepatectomy followed by TACE is effective in controlling advanced T-staged HCCs when the ICG R_{15} is <15%, the preoperative AFP is <2000 ng/ml, and the tumour reduction rate is ≥98%. Reduction hepatectomy followed by TACE is one of the options for controlling advanced T-staged HCCs in patients who are not candidates for curative resection or TACE alone.

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話題

進行肝細胞癌の化学療法—Sorafenib placebo-control randomized study (SHARP trial)を中心に*

古瀬純司**

Key Words：hepatocellular carcinoma, sorafenib, molecular-targeted therapy, systemic chemotherapy, placebo-control randomized study

はじめに

肝細胞癌は世界では5番目に多い癌であり，年間約626,000名の新規患者が診断されている[1]．地域別にみると，東アジア37,000名，日本40,000名，ヨーロッパ32,000名，米国19,000名の年間発症数が報告されている[2)~4)]．とくに米国，ヨーロッパではC型肝炎の増加に伴い，肝細胞癌の発症数が増加している．肝細胞癌の病因はB型，C型肝炎ウイルス感染，アルコール性肝硬変，アフラトキシン，非アルコール性脂肪性肝炎(non-alcoholic steatohepatitis：NASH)など多彩であり，東アジア諸国，アフリカ諸国ではB型肝炎，日本ではC型肝炎が主な病因であるなど地域による差が大きいのも特徴である[5)6)]．

肝細胞癌の治療は一般に癌進行度と肝障害度に応じて治療選択が行われ，肝切除などの局所療法や動脈塞栓療法から化学療法までその治療法は多岐にわたる．肝細胞癌に対する治療選択については日本では肝癌診療ガイドラインによる肝細胞癌治療アルゴリズムが公表されている[7)]．また，今回sorafenibによる大規模な第III相試験でも引用されたBarcelona groupによるBarcelona Clinic Liver Cancer(BCLC) staging classification[8)]がヨーロッパ中心に適応されている．これらの治療選択のガイドラインにおいて，肝切除やラジオ波(RFA)など局所壊死療法，肝移植，動脈塞栓化学療法(TACE)は適切な症例選択の下に標準治療として確立している．一方，化学療法はこれまで多くのレジメンが臨床試験として試みられてきたが，生存期間の改善が確認された標準治療もその位置づけも確立していない．

肝細胞癌に対する化学療法

肝細胞癌に対する化学療法は，肝動脈から注入する経動脈性化学療法(動注化学療法)と経静脈あるいは経口による全身化学療法に分けられる．肝細胞癌に対する化学療法は，肝切除，局所壊死療法，動脈塞栓(化学塞栓)療法の局所治療が無効あるいは適応困難な例(高度門脈腫瘍栓など)および遠隔転移例が適応となる．また肝細胞癌では肝硬変など慢性肝障害を背景にもつ例が多いことから，肝障害を助長するリスクも大きく，肝障害度C(Child-Pugh C)の肝機能不良例では化学療法は禁忌である．

わが国では肝動脈からの動注化学療法が盛んに行われている．動注化学療法剤としてepirubicin, mitomicin C, 5-FUが主に用いられてきたが，2004年7月，cisplatin(アイエーコール®)の保険適応が承認された．最近では5-FU＋cisplatinや5-FU＋interferon(IFN)で高い奏効率が報告されているが，いずれも前向きな臨床試験による検証は行われていない[9)10)]．

全身化学療法では，これまで肝細胞癌における無作為化比較試験としてdoxorubicin(DXR), tamoxifen, interferonなどいくつか行われてき

* Systemic chemotherapy of growth factor inhibitors for advanced hepatocellular carcinoma from the results of sorafenib placebo-control randomized study.

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表1　切除不能肝細胞癌におけるドキソルビシンと無治療との無作為化比較試験

	Doxorubicin	Best supportive care	
n	60	46	
Response	2 (3.3%)	−	
Median OS	10.6 weeks	7.5 weeks	P=0.036
Fetal complication	15 (25%)		
Cause of death			
Tumor progression with cachexia	60.0%	76.1%	
Sede effects of therapy	25.0%	0	
GI bleeding	6.6%	8.7%	
Ruputure of tumor	3.3%	6.5%	
Hypoglycemia	5.0%	4.3%	
Subarachnoid hemorrhage	0	2.3%	
Sicide	0	2.3%	

（文献[13]より引用）

表2　切除不能肝細胞癌におけるドキソルビシンとシスプラチン/インターフェロン/ドキソルビシン/フルオロウラシル併用療法(PIAF)との無作為化第III相試験

	Doxorubicin	PIAF	P-value
n	94	94	
Response	10.5%	20.9%	0.058
Median overall survival	6.83 months	8.67 months	0.83
Treatment-related mortality	3 %	9 %	0.194
Major toxicity*			
Neutropenia	63%	82%	0.003
Trhrombocytopenia	24%	57%	＜0.001
Vomiting	4 %	12%	0.058
Hypokalemia	0 %	7 %	0.007
Hyponatremia	1 %	6 %	0.054

* grade 3 or above

（文献[18]より引用）

た[11)~15)]．DXRでは無治療群に比べ有意に生存期間の延長が得られたが，25%の症例で致命的な合併症が認められている(表1)[11)]．TamoxifenやIFN-αでは生存期間の改善は認められておらず[12)~15)]，標準的治療法は確立していない．最近では多剤併用療法が試みられ，5-FU/mitoxantrone/cisplatin (FMP)，cisplatin/doxorubicin/5-FU/IFN-α (PIAF)などで25%を超える高い奏効率が報告されたが[16)17)]．しかし，DXRをcontrol armとしたPIAF regimenの第III相試験が行われたが，有意な生存期間の改善は示せず(表2)[18)]，既存の抗癌剤による化学療法は悲観的にとらえられている．

Sorafenibによる第III相試験 (SHARP trial)

SorafenibはRAFキナーゼ，VEGFR-1-3，PDGFR-βなどを標的とするマルチキナーゼ阻害薬である．肝細胞癌においてもRafキナーゼの高発現が認められ，RAF/MEK/ERKシグナル伝達経路が肝細胞癌発症に関与しているとの報告がある[19)]．またsorafenibの第I相試験では肝細胞癌例でpartial response(PR)が得られていた[20)]．以上の背景から，米国やヨーロッパなどで，sorafenib 400mg, 1日2回経口投与量により進行肝細胞癌に対する有効性と安全性を確認する第II相試験が行われた[21)]．その結果，奏効率は2%と低率であったが，十分な忍容性が確認され，無増悪期間中央値(median TTP)4.2か月，生存期間中央値(median OS)9.2か月と有効性も期待される結果であった(表3)．わが国では日本人肝細胞癌患者での薬物動態，安全性，推奨用量などを明らかにする目的で第I相試験が行われた[22)]．

表3 肝細胞癌に対するSorafenibの臨床第Ⅰ相，第Ⅱ相試験

Study	Phase II study	Phase I study
n	137	25
Dose	400 mg bid	200, 400 mg bid
Response	2 %	4 %
Stable disease	39%	76%
Disease control rate	42%	80%
Median time-to progression	4.2 mo	4.9 mo
Median overall survival	9.2 mo	15.6 mo
Author	Abou-Alfa (JCO 2006)[21]	Furuse (EORTC 2006)[22]

表4 進行肝細胞癌患者におけるsorafenibとplaceboの無作為化第III相試験(SHARP Trial)：試験デザイン

主要評価項目	Overall survival Time to symptomatic progression
副次評価項目	Time to progression
デザイン	国際多施設共同 二重盲検化プラセボ対照ランダム化第III相試験(Sorafenib群 vs. プラセボ群)
割付因子	門脈腫瘍栓 and/or 肝外転移 ECOG PS 地域
仮　説	Median survival timeを7か月から9.7か月(40%)に改善 検出力90%，α=0.02(片側)，予定症例数560例，死亡数424例

その結果，他癌種，米国・ヨーロッパと同様の薬物動態および忍容性が確認され，推奨用量も400mg，1日2回と決定された(表3)．同試験では症例数は少ないものの，有効性も同等であった．

以上，sorafenibの肝細胞癌に対する前臨床データおよび第I，II相試験の結果をもとに今回のプラセボコントロールによる無作為化比較試験SHARP(Sorafenib HCC Assessment Randomized Protocol) trialが実施された[23]．本試験の試験デザインを表4にまとめた．主な患者選択基準は，組織学的な肝細胞癌の確認，進行肝細胞癌，ECOG PS 0-2, Child-Pugh A Class, 全身化学療法歴なし，などである．

2005年3月から2006年4月までにSorafenib群299例，プラセボ群303例が登録された．治療はsorafenib 400mg/回，1日2回内服，あるいはplacebo 1日2回内服に割り振られ，両群の患者背景に有意な差はみられなかった(表5)．

表5 進行肝細胞癌患者におけるsorafenibとplaceboの無作為化第III相試験(SHARP Trial)：患者背景

	Sorafenib	Placebo
n	299	303
Median age	67歳	68歳
Male	87%	87%
Region Europe	88%	87%
Etiology HCV/HBV /Alcohol/other	29/19 /26/26%	27/18 /26/29%
ECOG PS 0	54%	54%
Child-Pugh A	95%	98%
BCLC stage C	82%	83%

BCLC stage：Barcelona Clinic Liver Cancer staging classification

主要評価項目である全生存期間はsorafenib群10.7か月，placebo群7.9か月であり，ハザード比0.69(95%CI：0.55-0.87；P=0.0006)と両者間に明らかな統計学的有意差を認めた(表6)．もう一つの主要評価項目である症状増悪までの期間(time to symptomatic progression)では差は認められなかった．副次評価項目である無増悪期間(time to progression)はsorafenib群5.5か月，placebo群2.8か月であり，ハザード比0.0.58(95%CI：0.45-0.74；P=0.000007)と全生存期間と同様両者間に明らかな統計学的有意差を認めた．有害事象については両群に差はなく，主なGrade 3/4の有害事象は下痢(sorafenib vs. placebo：11% vs. 2 %)，手足皮膚反応(8 % vs. 1 %)，疲労感(10 % vs. 15%)，出血(6 % vs. 9 %)であった．Sorafenibは十分な忍容性があり，進行肝細胞癌患者の生存期間を延長した初めての全身治療である．臨床的に大きな意義のある結果であり，sorafenibはこれらの患者に対する第一選択の治療法として確立すると報告された．

解　説

肝細胞癌は比較的遠隔転移が少なく，肝機能低下による肝不全が主な死因となることが多いことから，肝内病変への局所治療が主な治療法として行われる．しかし，再発がきわめて多く，局所治療が抵抗性になった病態や肝外転移を有する場合，有効な全身治療がないのが現状であっ

表6　進行肝細胞癌患者におけるsorafenibとplaceboの無作為化第III相試験(SHARP Trial)：結果

	Sorafenib	Placebo	HR (sorafenib/placebo)	*P*-value
n	299	303		
Median overall survival	10.7 mo	7.9 mo	0.69	0.0006
Time to progression	5.5 mo	2.8 mo	0.58	0.000007
Overall response				
Partial response(PR)	2.3%	0.7%		
Stable disease(SD)	71%	67%		
Progressive disease(PD)	18%	24%		
Progression-free rate at 4 month	62%	42%		
Serious adverse event (SAE)	52%	54%		
Drug-related treatment emergent SAE	13%	9 %		

た．これまでいくつかの無治療と全身治療の無作為化比較試験が行われてきたが，確立した標準治療は認められていない．そのような状況で，sorafenibによるplacebo-control無作為化比較試験が行われた．本試験では，placebo群のmedian OSを7か月に設定し，40%の改善を見込むとの仮説が立てられたことは臨床的に妥当であり，本試験により仮説通りの結果が得られたことは肝細胞癌治療にとって画期的なことと考えられる．

本試験の解釈において，患者背景でヨーロッパからの登録が90%近くと偏っていること，対象をChild-Pugh Aのみに限ったことが問題点としてあげられた．わが国にこの結果をそのまま導入してよいかという点について考察が必要である．肝細胞癌の病因については，日本では70%程度でC型肝炎感染が関連しているが，B型肝炎は15%程度である[6]．今回の試験ではC型肝炎関連は30%弱であり，病因による治療効果や有害事象の差はないかどうか検証する必要がある．しかし，欧米ではC型肝炎が非常に増えており，日本の状況と類似してきていることも確かである．Child-Pugh Aのみで試験が実施されたことについては，国際試験であり，肝障害による影響を可能な限り除外し，sorafenibの効果をより確実に評価したいという考えがあったかと推測される．わが国で行われた肝細胞癌患者でのsorafenibの第I相試験では，同数のChild-Pugh AとBで治療を行ったが，両者で有効性や安全性に大きな差は認めなかった．実地診療ではChild-Pugh Bも十分忍容性があり，適応可能と考えられる．

肝細胞癌の全身化学療法は，一定の抗腫瘍効果が得られても肝障害や静脈瘤出血などの有害事象により生存期間の改善につながらないことが多くみられる．今回の試験では重篤な有害事象はsorafenib群54%，placebo群52%と高頻度に認められたが，治療関連と考えられる有害事象はそれぞれ13%と9%と低く，差も認められていない．肝細胞癌患者では全身化学療法実施時の有害事象は原病や肝硬変など背景障害肝から生じる合併症の関与がきわめて大きいものと考えられる．つまり，sorafenibは高い忍容性が確認されているが，肝細胞癌での適応においては，薬物有害反応以外のさまざまな症状・合併症に注意を払う必要がある．

まとめ

今後，欧米を初め多くの国々，地域でsorafenibの肝細胞癌に対する適応承認が認められることが予想される．わが国でも他に有効な全身治療薬がない状況であり，すみやかな実地医療での適応承認が期待される．さらにより有効な治療法の確立に向けて，sorafenibを参照治療とした比較試験やsorafenibへの上乗せ効果を期待する治療法の開発が考えられる．現在，日本では肝細胞癌の動脈塞栓化学療法後の無増悪期間の改善を目的とした補助療法としてのplacebo-control無作為化比較試験が行われている．今回のSHARP trialとはまったく異なった患者群とコンセプトであり，世界的にも大きく注目されていることから，早期に完遂されることが期待される．

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