v) RFA10年間のまとめと長期成績

表3，表4にRFA導入以降10年間の施行症例の概括を示した．ほとんどは肝細胞癌であるが，近年転移性肝癌の例も増えてきている．腫瘍径2cm以下であれば多くは1セッションで終了しているが，サイズが大きくなるとともにセッション数は多くなっている．表5に合併症とその転帰を示した．対処を必要としたものを重篤なものとすればセッションあたり1%であり，幸い死亡例はなくその後も現在まで4000セッションを超えているが死亡例は経験していない．RFAの長期成績は，第18回全国原発性肝癌追跡調査1)（日本肝癌研究会，2009年）によれば最大腫瘍径2-3cmの肝癌に対するRFA2948例の5年累積生存率は54.5%である．同調査での2-5cmの切除12801例の5生率56.8%と差はなく，海外で施行された切除とRFAの無作為比較試験（RCT）においても差は認められていない[13]．図11に当施設における3cm以下，3cm以下の肝癌の初回治療法別の累積生存率を示した．RFAの5年，10年累積生存率はそれぞれ63.8%，30.6%であり，手術のそれぞれ62.1%，32.1%と差はなかった．初期にはRFAがやや良好であるが，7年目以降では手術がやや良好となる傾向を認めた．現在我が国においても3cm以下，3個以下の肝癌を対象として切除とRFAのRCT（SURF試験）が進行しておりその結果が待たれる．

表3．RFA施行症例（1999年6月−2009年5月）

肝悪性腫瘍1307例，3457結節，3289セッション

診断	N	結節径 mean ± SD (最小-最大)
HCC	3302	2.0 ± 0.8 (0.5-6.4)
META	146	2.2 ± 1.1 (0.6-6.1)
CCC	4	3.1 ± 2.0 (1.2-5.9)
その他	5	2.8
計	3457	2.0 ± 0.8 (0.5-6.4)

HCC; hepatocellular carcinoma, META; metastatic liver cancer, CCC; cholangiocellular carcinoma

表4．セッション数と腫瘍径

3455結節　1.17±0.43 (1-4) セッション

セッション数	n	腫瘍径(mean ± SD) cm
1	2924 (85%)	1.9 ± 0.7*
2	478 (14%)	2.2 ± 0.9*
3	48 (1%)	3.0 ± 1.2*
4	7 (<1%)	3.9 ± 1.4*
total	3457	2.0 ± 0.8

表5．合併症と転帰

[illegible]

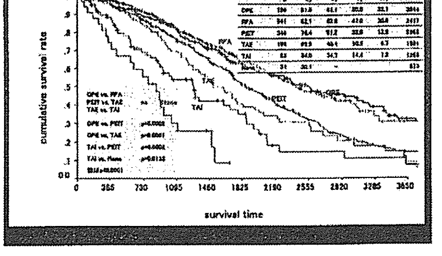

図11．3cm以下，3結節以内，全症例（n=1356）

2. 分子標的薬の導入とガイドラインにおける化学療法の位置

前述のように肝癌の3大治療法は手術，TAE，穿刺局所療法であり

メモ欄

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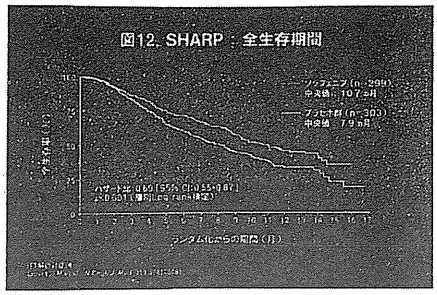

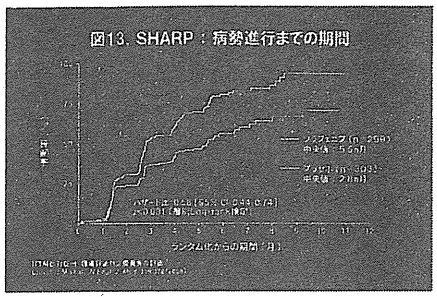

（表2），この３つが全治療例の94％を占めている（図5）．化学療法は5.5%であったが，その多くは経肝動脈性であり全身化学療法は全体の0.7%にすぎない．他方近年分子標的薬の開発の動きは著しく，肝癌の分野においても急速に進展している．2008年New England Journal of Medicineにソラフェニブの大規模臨床試験（Sharp study）の結果が報告された[14]．ソラフェニブはセリンスレオニンキナーゼであるRAFとVEGF-R，PDGF-Rなどのチロシンキナーゼを阻害するマルチキナーゼインヒビターである．その全生存期間中央値（MST），無増悪期間（TTP）はそれぞれ10.7ヶ月，5.5ヶ月でありPlaceboのそれぞれ7.9ヶ月，2.8ヶ月に比して有意に良好であった（P<0.001，図12，13）．生存期間，無増悪期間を改善することを示したはじめての薬剤であり，欧米に次いで本邦においても2009年に適応が追加承認された．本邦での適応は肝機能がChild-Pugh A，切除不能で，TAEやRFAなどの局所療法の対象とならない肝癌となっている．そのためChild-Pugh分類Aで遠隔転移を伴うもの，TAE不能あるいは不応例に推奨されている．従来これらの集団に対しては肝動注化学療法が選択されることが多く，両者の併用療法も含めて治療法選択の基準が論議されている．

本邦での市販後調査（2373例）によると重篤な副作用は17.6%でありSharp studyに比してむしろ低値ではあったが，重篤な肝胆道系の副作用は5.7%と高値であり，また薬剤との関連の疑われる死亡例も1.6%あった．副作用の多くは1ヶ月以内に発現しており，アドバイザリーコミッティーから使用に関する注意喚起が行われ投与1ヶ月以内は1週間毎に観察検査することが推奨されている．またTAEや動注との併用，切除後のアジュバント療法等に関してはグローバルの開発試験や国内の医師主導型臨床試験，厚労省の研究班などで検討されている．

ソラフェニブだけではなく現在多数の分子標的薬の開発試験が行われている．スニチニブはその強い毒性のため開発が中止されたが，最も開発の進んでいるのはブリバニブである．VEGF-RとFGF-Rに対するdual selective inhibitorであり，ソラフェニブとのhead-to head試験，ソラフェニブ不応・不耐例に対するセカンドライン試験，TACE併用試験が進行している．他にもエベロリムス，ラムシルマブ，ABT-869等さらにTSU-68，E7080等国内メーカーのものも含めて多数の開発試験が進行中である．これらの結果如何によって肝癌治療体系の中に分

子標的薬による化学療法の位置が確定してくる．分子標的薬による化学療法が肝癌治療の第4の柱としてなり得るのかどうかは2010年代の最大の課題といえる．

メモ欄

メモ欄

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セルフチェック問題（肝細胞癌（治療））

メモ欄

問題１．肝癌患者の推移とラジオ波凝固療法の特徴に関して誤っているものを選べ．

1．診断時年齢は高齢化し、女性患者が増えている．
2．背景肝病変はC型が最も多く，次いでB型，非B非C型である．
3．RFAによる熱凝固は，炭化をおこすことなく広い範囲の凝固が可能である．
4．RFAでは血流によるクーリング効果があり胆管障害のリスクが低く安全性が高い．
5．RFAの凝固域内にはしばしば血管の残存を認めるが，血管壁に浸潤した腫瘍細胞は残存する可能性がある．

問題２．分子標的薬sorafenibについて誤っているものを選べ．

1．セリンスレオニンキナーゼであるRAFとVEGF-R，PDGF-Rなどのチロシンキナーゼを阻害するマルチキナーゼインヒビターである．
2．頻度の高い副作用は手足皮膚症候群，高血圧，下痢，食欲減退，肝機能障害である．
3．海外での大規模な開発試験での完全著効例は約5%であった。
4．海外の大規模臨床試験の結果に比して，本邦では肝性脳症を含めた肝胆道系の重篤な副作用の頻度が高い．
5．投与後１ヶ月間は週1回の頻度での観察・検査が推奨されている．

Effect of Vitamin K2 on the Recurrence of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is characterized by frequent recurrence, even after curative treatment. Vitamin K2, which has been reported to reduce HCC development, may be effective in preventing HCC recurrence. Patients who underwent curative ablation or resection of HCC were randomly assigned to receive placebo, 45 mg/day, or 90 mg/day vitamin K2 in double-blind fashion. HCC recurrence was surveyed every 12 weeks with dynamic computed tomography/magnetic resonance imaging, with HCC-specific tumor markers monitored every 4 weeks. The primary aim was to confirm the superiority of active drug to placebo concerning disease-free survival (DFS), and the secondary aim was to evaluate dose-response relationship. Disease occurrence and death from any cause were treated as events. Hazard ratios (HRs) for disease occurrence and death were calculated using a Cox proportional hazards model. Enrollment was commenced in March 2004. DFS was assessed in 548 patients, including 181 in the placebo group, 182 in the 45-mg/day group, and 185 in the 90-mg/day group. Disease occurrence or death was diagnosed in 58, 52, and 76 patients in the respective groups. The second interim analysis indicated that vitamin K2 did not prevent disease occurrence or death, with an HR of 1.150 (95% confidence interval: 0.843-1.570, one-sided; $P = 0.811$) between the placebo and combined active-drug groups, and the study was discontinued in March 2007. Conclusion: Efficacy of vitamin K2 in suppressing HCC recurrence was not confirmed in this double-blind, randomized, placebo-controlled study. (HEPATOLOGY 2011;54:532-540)

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer death worldwide, claiming 600,000 victims each year. Because of advances in diagnostics and therapeutics, HCC can now be curatively treated, if detected at an early stage. Nevertheless, the long-term prognosis of HCC is not satisfactory, mainly because of its very frequent recurrence, which may occur after a long interval from initial "curative" treatment. Most cases of HCC develop in the liver with cirrhosis or advanced fibrosis.[1-4] Even if HCC nodules have been completely resected or ablated, the remaining liver retains the potential for *de novo* carcinogenesis.[5-7] In addition, precancerous lesions and microscopic metastasis may already exist in the remaining liver.

Adjuvant chemotherapy would be considered for other solid malignancies with high risk of recurrence. However, this is difficult in the case of HCC because few conventional chemotherapeutic agents are effective and hepatotoxicity can be of critical significance, as liver function is often already impaired. A randomized trial was performed with uracil-tegafur as postoperative

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein lens culinaris agglutinin fraction-3; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer Staging System; CI, confidence interval; CT, computed tomography; DCP, des-gamma-prothrombin; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRs, hazard ratios; IDMC, independent data monitoring committee; MRI, magnetic resonance imaging; RR, risk ratio.

adjuvant therapy, but did not improve recurrence-free survival, and overall survival appeared to be worsened.[8] Safety is clearly a prerequisite to the use of adjuvant therapy agents for HCC. Recently, a randomized trial with peretinoin, a retinoid, in patients with previously treated HCC was conducted. Although recurrence-free survival was higher with high-dose peretinoin than with placebo, there was no statistically significant difference in the predefined primary analysis.

In 2004, Habu et al.[9] reported that the incidence of development of HCC was reduced among cirrhotic women assigned to receive oral vitamin K2 (45 mg/day), originally for the prevention of osteoporosis, compared to controls (risk ratio [RR]: 0.13; 95% confidence interval [CI]: 0.02-0.99) with a limited number of subjects. Des-gamma-carboxy prothrombin (DCP), an abnormal prothrombin produced in vitamin K deficiency, is not only an HCC-specific tumor marker, but also a predictor of portal venous tumor invasion.[10] A number of findings *in vitro* have indicated that vitamin K may play a role in controlling cell growth, including inhibition of growth of HCC cells.[11-15] Vitamin K2 (menatetrenone) reportedly induced differentiation of human myeloid leukemia cells, as well as apoptosis in immature blast cells.[16-18] Vitamin K2 has been widely used for osteoporosis, and its long-term safety has been confirmed.[19-22] Thus, vitamin K2 would be an ideal adjuvant agent, if it could reduce HCC recurrence by preventing *de novo* carcinogenesis or suppressing tumor growth.

In fact, a few small-sized, controlled trials enrolling 45-61 patients have been performed to assess the effects of vitamin K2 on HCC recurrence. Mizuta et al.[23] reported that vitamin K2 reduced HCC recurrence with a multivariate-adjusted RR of 0.27 (95% CI: 0.12-0.60) and, possibly, improved survival. A preventive effect on HCC recurrence was also suggested by Kakizaki et al.,[24] who found an adjusted RR of 0.45 (95% CI: 0.10-2.05) for recurrence, although they failed to observe survival benefits. Another study failed to detect a reduction of HCC recurrence.[25] Although these previous results were inconsistent, considering the urgent need for prevention of HCC recurrence, we judged that the effect of vitamin K2 on HCC recurrence deserved evaluation in a larger scale, randomized, controlled trial. The present study was, therefore, performed as a multicenter, placebo-controlled, double-blind trial enrolling 548 patients at 31 study sites in Japan.

Patients and Methods

Patients. Candidate participants were those who had received curative treatment, in the form of local ablation or surgery, for primary HCC or first intrahepatic recurrence. Diagnosis of HCC was based on

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histopathologic examination or typical findings on dynamic computed tomography/magnetic resonance imaging (CT/MRI) (i.e., hyperattenuation in the arterial phase with washout in a later phase[26]). Inclusion criteria were the following: 20 years of age or older; performance status (Eastern Cooperative Oncology Group; ECOG) 0-2; and compensated liver function (albumin, ≥2.8 g/dL; total bilirubin, <2.0 mg/dL; prothrombin time activity, ≥40%). Exclusion criteria included the following: previous systemic or hepatic arterial chemotherapy; extrahepatic metastasis; portal vein invasion; interferon treatment within the previous 2 years or a sustained virologic response; uncontrollable encephalopathy, ascites, or plural effusion; a history of gastrectomy or extensive resection of the digestive tract; malabsorption of lipophilic agents, including a history of cholecystectomy; comorbidity with severe cardiovascular, hematological, or renal disease; a history of cancer other than HCC within 5 years; administration of warfarin; administration of vitamin K preparations within the previous 6 months; pregnant or breast-feeding women, or women with childbearing potential or intention; and ongoing participation in other clinical studies.

Assignment. The study was conducted as a multicenter, three-armed, randomized, placebo-controlled, double-blind, comparative, clinical study. Patients who met all criteria were enrolled and randomly assigned in double-blind fashion to receive 45 or 90 mg/day of oral vitamin K2 or a placebo with dynamic allocation, based on the modified minimization method by the registration center, which randomly allocated each patient a randomized study-drug number in the order of registration with a preset computer algorithm, adjusting for balance within each study site and across total registration, considering factors that may affect HCC recurrence (i.e., primary or recurrent HCC, medical ablation or surgical resection, hepatitis C virus (HCV)-related or -unrelated disease, and concomitant administration of glycyrrhizic acid).[27] The investigators, study sponsor, and patients remained blinded to the allocated drug during the study. The protocol was approved by the ethics committee of each participating institution. Patients were well informed of the details of the study and agreed to participate with written informed consent. This trial was conducted in conformity with CONSORT statements and in accord with the Declaration of Helsinki and good clinical practice and is registered as NCT00165633 at Clinicaltrial.gov.

Vitamin K2/Placebo Administration. Each patient took one of the identical capsules (Eisai Co., Ltd., Tokyo, Japan), containing 15 or 30 mg of menatetrenone, vitamin K2 with four isoprenoids, or a placebo, according to group assignment, three times a day after each meal. Medications for chronic hepatitis, such as glycyrrhizic acid and ursodeoxycholic acid, were continued but could not be newly commenced. Antiviral therapies (i.e., interferon, ribavirin, and nucleos(t)ide analogues, such as lamivudine) could not be administered during the study. Vitamin K2/placebo administration was discontinued when recurrent HCC was detected.

Sample Size. The sample size was determined based on previous reports on HCC recurrence among patients who received vitamin K2 and those who did not. Although a previous study reported an adjusted HR of 0.27 (95% CI: 0.12-0.60),[23] the study was conducted in a small number of subjects and the 95% CI ranged widely. We considered 30% risk reduction clinically significant, and the 30% risk reduction was conservatively adopted. Median disease-free survival (DFS) was considered to be 2 years in the placebo group, and the HR in the combined active drug groups was assumed to be 0.67-0.70. Assuming that DFS function followed an exponential distribution, a total of 240-360 events were required to detect the effect of vitamin K2 on DFS, with a one-sided significance level of 2.5%, power of 90%, and an allocation ratio of 1:2 (placebo group:combined active drug groups). To observe the number of events during the follow-up of 3-3.5 years, 180 patients were required in each group (540 in total), assuming loss of information in 5% patients.

DFS. The primary endpoint was DFS, defined as the interval between randomization and either diagnosis of HCC recurrence (i.e., intrahepatic lesions adjacent to or distant from previously treated nodules, and extrahepatic metastasis), cancer other than HCC, or death from any cause. Patients who survived without HCC recurrence or cancer other than HCC at the end of the study were censored on the day of last CT/MRI examination showing no recurrence.

Assessment of Recurrence. HCC recurrence was surveyed every 12 weeks with dynamic CT/MRI, together with ultrasonography. HCC-specific tumor markers, including alpha-fetoprotein (AFP), AFP lens culinaris agglutinin fraction-3 (AFP-L3), and DCP, were monitored every 4 weeks, and dynamic CT/MRI was additionally performed when recurrence was suspected by an increase in tumor marker levels. HCC recurrence was diagnosed by hyperattenuation in the arterial phase and hypoattenuation in the portal venous or equilibrium phase of dynamic CT/MRI. Tumor biopsy was performed when findings on CT/

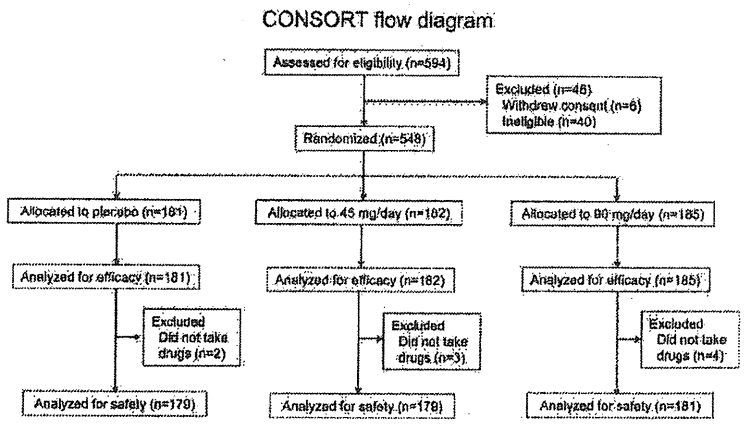

Fig. 1. CONSORT flow diagram.

MRI were equivocal. The presence of recurrence was finally judged by an independent review committee, which thoroughly reviewed the diagnostic imagings in blind fashion. The day of recurrence was defined at the time of first detection of recurrence.

Assessment of Safety. Safety was assessed at 4-week intervals by interview, physical examination, and laboratory tests. Adverse events were defined as any untoward or unintended events that occurred in a subject receiving a study drug. Serious adverse events were defined as those that resulted in death or required hospitalization. Adverse drug reactions were defined as adverse events possibly related to the study drug.

Statistical Analysis. The primary aim of this study was to confirm the superiority of active drug to placebo concerning DFS, and the secondary aim was to evaluate the dose-response relationship between the two active drug groups. DFS rate and median DFS were calculated using the Kaplan-Meier method. Superiority and dose-response relationship were evaluated by the log-rank test, using score statistics with contrast coefficients (−2, 1, and 1) and (0, −1, and 1), respectively, for placebo, 45-mg/day, and 90-mg/day groups. HRs were calculated using Cox's proportional hazards regression model. Adverse events and adverse drug reactions were tabulated based on groups and compared with placebo by Fisher's exact test.

Two interim analyses by the independent data monitoring committee (IDMC) were scheduled. The first was planned 1 year after the commencement of registration to assess safety. The second was planned when 160 events were recorded to assess significance of effect by the finding of $P < 0.005$ (one-sided) or futility. Alpha spending was, for this interim analysis, defined as 0.5% (one-sided), and the overall significance level of statistical tests for the primary aim was maintained at one-sided 2.5%, adjusted for multiplicity associated with interim analyses by the method of Lan and DeMets.[28] The rule for stopping for reasons of futility was defined as follows: The Bayesian predictive probability[29] of detecting a significant effect on observation of 360 events was less than 5%, or the number of events required to assure 50% conditional power exceeded 360. If the IDMC decided to continue the trial, the final required number of events (maximum, 360 events) was to be recalculated to assure 80% conditional power, with the overall significance level maintained for recalculation of the required number of events by Cui's method.[30]

Significance levels for homogeneity among the groups were two-sided 15%, and others were two-sided 5%.

Results

A total of 548 patients were enrolled at 31 study sites in Japan and randomly assigned between March 2004 and September 2005 (Fig. 1). Tumor biopsy was performed in 14 patients, whereas diagnosis was obtained radiologically in remaining patients.[26] Efficacy (i.e., DFS) was assessed among 548 patients (placebo group: 181; 45-mg/day group: 182; 90-mg/day group: 185). Safety was assessed among 539 patients, excluding nine patients who never took drugs. Two patients took drugs at a dose different from that allocated. They were included in the group of allocated dose in the efficacy analysis, but in the group of actually received dose in the safety analysis.

Table 1. Demographic Data

Parameter Category/mean ± SD	Placebo (n = 181)	45 mg/day (n = 182)	90 mg/day (n = 185)	Total (n = 548)	P Value
Gender (male/female)	108/73	117/65	117/68	342/206	0.635†
Age (y)	68.9 ± 8.1	68.2 ± 7.8	68.6 ± 7.7	68.6 ± 7.9	0.716‡
Primary or recurrence (primary/first recurrence)	144/37	144/38	144/41	432/116	0.915†
Medications given immediately before registration (local therapy/surgery)	174/7	173/9	180/5	527/21	0.534†
History of drinking (no/yes)	79/102	67/115	73/112	219/329	0.407†
Hepatitis (no/yes)	3/178	1/181	3/182	7/541	0.563†
Etiology§ (HBV/HCV/alcoholic/UK)	20/150/6/5	22/152/10/3	16/153/11/5	58/455/27/13	–
Concomitant administration of glycyrrhizic acid (no/yes)	101/80	99/83	101/84	301/247	0.958†
Liver cirrhosis (no/yes)	32/149	37/143	45/137	114/429	0.253†
Number of tumors	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7	0.953‡
(1/2/3 ≤)	127/39/15	129/40/13	131/37/17	387/116/45	–
Diameter of tumor (mm)	20.3 ± 7.6	20.4 ± 7.9	19.3 ± 7.2	20.0 ± 7.6	0.340‡
Stage¶ (I/II/III)	81/75/25	87/74/21	93/74/18	261/223/64	0.439‖
PS (ECOG) (0/1/2)	165/14/2	171/19/1	176/7/2	512/31/5	0.295‖
Child-Pugh class** (A/B)	154/27	163/19	160/25	477/71	0.430‖
BCLC staging system (0/A/B/C)	53/115/11/2	54/117/10/1	61/109/13/2	168/341/34/5	0.862‖
Albumin (g/dL)	3.81 ± 0.50	3.83 ± 0.40	3.85 ± 0.46	3.83 ± 0.46	0.631‡
Total bilirubin (mg/dL)	0.93 ± 0.36	0.91 ± 0.35	0.86 ± 0.35	0.90 ± 0.35	0.139‡,*
Active prothrombin (%)	79.4 ± 13.9	80.0 ± 13.7	81.1 ± 15.1	80.2 ± 14.3	0.512‡
Platelet count ($\times 10^4/\mu L$)	10.66 ± 4.38	10.72 ± 5.10	11.32 ± 5.69	10.90 ± 5.08	0.389‡
AST (IU/L)	61.7 ± 28.7	71.1 ± 50.0	59.6 ± 29.8	64.1 ± 37.7	0.008‡,*
ALT (IU/L)	55.9 ± 33.4	60.8 ± 46.3	53.6 ± 38.2	56.7 ± 39.7	0.211‡
DCP (mAU/mL)††	33.7 ± 71.5	184.1 ± 1,869.5	27.4 ± 26.0	81.9 ± 1082.7	0.295‡
(<40/40 ≤/UK)	155/25/1	165/17/0	163/19/3	483/61/4	–
AFP (ng/mL)††	38.79 ± 74.42	355.50 ± 4,212.33	30.71 ± 50.25	140.86 ± 2,423.86	0.346‡
(< 100/100 ≤/UK)	164/17/0	166/15/1	178/7/0	508/39/1	–
AFP-L3 (%)††,‡‡	4.09 ± 8.96	3.46 ± 6.99	4.75 ± 10.76	4.10 ± 9.06	0.399‡
(<15.0/15.0 ≤/UK)	174/6/1	173/5/4	171/13/1	518/24/6	–

*$P < 0.15$.
†χ^2 test.
‡One-way analysis of variance.
§Multiple complication.
¶The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, November 2000 (4th ed.).
‖Kruskal-Wallis test.
**Classified in accord with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.
††Calculated, excluding unknown cases.
‡‡Calculated, assuming that values less than the lower limit of detection were 0.
AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein lens culinaris agglutinin fraction-3; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer Staging System; DCP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status.

The first interim analysis was performed in June 2005, and no problem was found concerning safety. The second interim analysis, performed in November 2006, indicated that vitamin K2 did not prevent recurrence. The IDMC thus recommended discontinuation of the study. Data on efficacy shown in the current report were those presented at the second interim analysis, and data on safety were those obtained at termination of the study (March 2007).

Patients. Baseline characteristics of the 548 patients are summarized in Table 1. The study population was composed of 342 males (62.4%) and 206 females (37.6%), with a mean age of 68.6 years (range, 39-88). The majority (432 patients; 78.8%) were enrolled after treatment of primary HCC. Medical ablation was the dominant therapeutic modality for HCC (527 patients; 96.2%). The tumor nodule was solitary in the majority of patients (387 patients; 70.6%), and median diameter was 19 mm (range, 6-60). HCV infection (455 patients; 83.0%) and the presence of cirrhosis (429 patients; 79.0%) were both common. The majority of patients had liver function reserve in Child-Pugh class A (477 patients; 87.0%) and ECOG performance status of 0 (512 patients; 93.4%). Homogeneity was shown among the three groups for all baseline characteristics, including all stratification parameters, except total bilirubin and aspartate aminotransferase levels.

Events. During the study, HCC recurrence (i.e., intrahepatic lesions adjacent to or distant from previously treated nodules, and extrahepatic metastasis), cancer other than HCC, or death from any cause were detected in 58, 52, and 76 patients in the placebo,

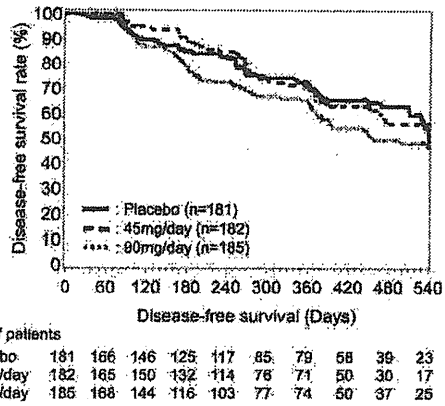

Fig. 2. Disease-free survival of placebo, 45-mg/day, and 90-mg/day groups.

45-mg/day, and 90-mg/day groups, respectively. Three patients developed cancer other than HCC. One patient in the placebo group developed malignant lymphoma, one patient in the 90-mg/day group developed colon cancer, and another developed lung cancer. In addition, four patients in the placebo group and one patient each in the 45-mg/day and 90-mg/day groups died without HCC recurrence. Causes of death were liver failure in four patients and acute myocardial infarction and pneumonia in one patient each. Death without HCC recurrence was treated as an event, along with HCC recurrence and development of cancer other than HCC, in DFS analysis.

Local recurrence, as defined by adjacency to a previously treated HCC nodule, is mainly the result of incomplete ablation and may have compromised the efficacy of the active drug. Whether or not recurrence was local was rigorously reviewed by the independent review committee, and HCC recurrence in 8, 6, and 11 patients in the placebo, 45-mg/day, and 90-mg/day groups, respectively, was judged to be local. Incidence of local recurrence did not differ among groups.

Intrahepatic recurrence not adjacent to previously treated nodules may have actually been the result of a small HCC not detected at the time of initial treatment. Although such a residual tumor cannot easily be distinguished from *de novo* carcinogenesis, recurrence resulting from residual tumor is thought to occur early after treatment. Incidences of recurrence within 180 days of HCC treatment were 25, 16, and 34 in the placebo, 45-mg/day, and 90-mg/day groups, respectively ($P = 0.029$ among the groups by log-rank test).

Extrahepatic metastasis also indicates the presence of surviving cancer cells. However, extrahepatic recurrence as the first manifestation of recurrence was rare in the present study and was found in only one patient each in the placebo and 90-mg/day groups.

DFS, Time to Disease Occurrence, and Overall Survival. Median DFS values were 540 and 541 days for the placebo and combined active-drug groups, respectively, as estimated by the Kaplan-Meier method. DFS rates were 69.8% (95% CI: 61.4%-76.7%) and 64.9% (58.8%-70.4%) at 1 year for placebo and combined active-drug groups, respectively. The difference in DFS was not statistically significant (HR: 1.150 [0.843-1.570]; one-sided; $P = 0.811$ by log-rank test).

The dose-response relationship was assessed between the 45-mg/day and 90-mg/day groups. Median DFS values were 560 days in the 45-mg/day group and 455 days in the 90-mg/day group (Fig. 2). DFS rates at 1 year were 68.3% (95% CI: 59.2%-75.8%) in the 45-mg/day group and 61.6% (53.0%-69.1%) in the 90-mg/day group. There was no trend toward dose-dependent increase in DFS (HR: 1.451 [1.018-2.067]; one-sided; $P = 0.982$ by log-rank test).

Analysis of DFS for per protocol population was performed among 510 patients, excluding 38 from 548 randomized patients because of major protocol violations. Similar results were obtained in the per protocol population in DFS analysis.

Median time to disease occurrence was 547, 560, and 496 days in the placebo, 45-mg/day, and 90-mg/day groups, respectively (Fig. 3). Cumulative disease occurrence rates at 1 year were 28.2% (95% CI:

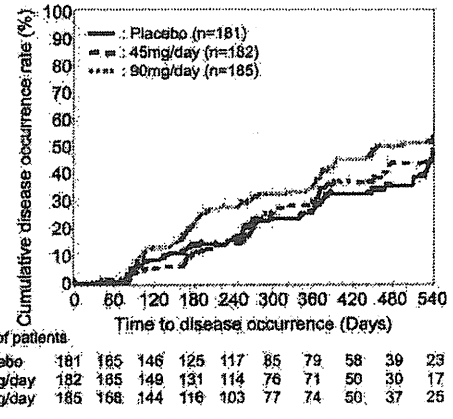

Fig. 3. Cumulative disease occurrence rate of placebo, 45-mg/day, and 90-mg/day groups.

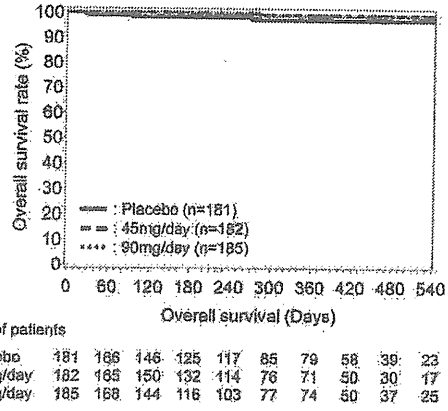

Fig. 4. Overall survival rate of placebo, 45-mg/day, and 90-mg/day groups.

21.4%-36.6%), 31.2% (23.7%-40.4%), and 37.7% (30.2%-46.3%), respectively.

Overall survival rates at 1 year were 97.2% (95% CI: 92.4%-99.0%), 99.2% (94.7%-99.9%), and 98.7% (91.4%-99.8%) in the placebo, 45-mg/day, and 90-mg/day groups, respectively (Fig. 4).

Subgroup Analyses. Enrollment was stratified by whether patients had been treated for primary HCC, medical ablation or surgical resection, HCV-related or -unrelated disease, and concomitant administration of glycyrrhizic acid. There was no significant difference in DFS between the placebo and combined active-drug groups in any stratification parameters (Table 2).

Safety. Safety was assessed among 539 patients. Incidences of adverse events were 88.3%, 88.3%, and 89.0% in the placebo, 45-mg/day, and 90-mg/day groups, respectively, and those of adverse drug reactions were 11.2%, 18.0%, and 15.5%, respectively (Table 3). There was no significant difference in the incidence of any adverse event or adverse drug reaction between the placebo and active-drug groups.

Discussion

In this study, we found no effect of vitamin K2 on the recurrence of HCC. Even the dose of 90 mg/day of vitamin K2, twice the recommended dose for osteoporosis, was not effective. In fact, recurrence was more frequent in the 90-mg/day than in the 45-mg/day group, though not to a statistically significant extent. There was a trend toward high AFP-L3 positivity at entry in the 90-mg/day group, including 13 patients positive for AFP-L3, compared to six and five patients in the placebo and 45-mg/day groups, respectively. AFP-L3 positivity may have indicated residual cancer cells, which may have been related to the increased incidence of recurrence. However, the results of analysis of recurrence remained similar when patients positive for AFP-L3 were excluded.

In this study, status after treatment of recurrent lesions versus naive was associated with an increased risk of recurrence (data not shown). Because this was characteristic of the original neoplasm, this was probably related not with *de novo* or secondary primary

Table 2. Subgroup Analyses of DFS by Stratification Parameter

Parameter Level	Treatment Group	N	HR	(95%CI)
Primary or recurrence HCC				
Primary	Placebo	144	1.000	
	Combined active drug	288	1.061	(0.742-1.519)
Recurrence	Placebo	37	1.000	
	Combined active drug	79	1.414	(0.751-2.664)
Medical ablation or surgical resection				
Medical ablation	Placebo	174	1.000	
	Combined active drug	353	1.152	(0.840-1.579)
Surgical resection	Placebo	7	1.000	
	Combined active drug	14	0.807	(0.113-5.745)
HCV-related disease				
Yes	Placebo	150	1.000	
	Combined active drug	305	1.214	(0.862-1.710)
No	Placebo	31	1.000	
	Combined active drug	62	0.837	(0.397-1.767)
Concomitant administration of glycyrrhizic acid				
Yes	Placebo	80	1.000	
	Combined active drug	167	1.360	(0.869-2.129)
No	Placebo	101	1.000	
	Combined active drug	200	0.958	(0.620-1.479)

DFS, disease-free survival; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio.

Table 3. Summary of Adverse Events (Safety Analysis Set)

	Treatment Group	N	Incidence			P Value*
			Case	%	(95% CI)	
Adverse event	Placebo	179	158	88.3	(82.6-92.6)	–
	45 mg/day	179	158	88.3	(82.6-92.6)	1.000
	90 mg/day	181	161	89.0	(83.5-93.1)	0.869
Adverse drug reaction†	Placebo	179	20	11.2	(7.0-16.7)	–
	45 mg/day	179	32	18.0	(12.6-24.3)	0.098
	90 mg/day	181	28	15.5	(10.5-21.6)	0.278
Serious adverse event	Placebo	179	52	29.1	(22.5-36.3)	–
	45 mg/day	179	40	22.4	(16.5-29.2)	0.183
	90 mg/day	181	48	26.5	(20.2-33.6)	0.638
Serious adverse drug reaction†	Placebo	179	1	0.6	(0.0-3.1)	–
	45 mg/day	179	3	1.7	(0.3-4.8)	0.622
	90 mg/day	181	2	1.1	(0.1-3.9)	1.000

*Comparison with placebo group by Fisher's exact test.
†Among adverse events, causal relationship of something other than "not related" to the study drug.

HCC, but with recurrence resulting from microscopic residual cancer or intrahepatic metastasis. On the other hand, other factors, such as alcohol consumption, low albumin concentration, and high total bilirubin concentration, were also associated with risk of recurrence (data not shown). These are also risk factors of primary HCC development among chronic hepatitis patients, and we consider them to indicate the risk of *de novo* carcinogenesis. In other words, we observed two types of HCC "recurrence," intrahepatic metastasis and *de novo* HCC, although it may be difficult to distinguish them in each case. Previous reports suggested the possibility that vitamin K may be effective against both types of HCC recurrence.[23] However, it is also possible that the effect of vitamin K on HCC recurrence is limited to either inhibition of tumor cell growth or reduction of *de novo* carcinogenesis. We performed subgroup analyses by stratifying patients, based on several tumor-related factors, and evaluated the effect of vitamin K on HCC recurrence in each stratum, but recurrence was decreased in none (data not shown).

Prevention of *de novo* hepatocarcinogenesis by vitamin K was first reported by Habu et al.[9] among cirrhotic women who took vitamin K2 to prevent osteoporosis. In the present study, HCC recurrence resulting from metachronous *de novo* carcinogenesis should have been reduced by vitamin K2. However, such an effect may have been obscured in the overall analysis because of the presence of recurrence resulting from intrahepatic metastases. In the subgroup analysis among patients with decreased platelet count, HCC recurrence was marginally reduced in the 45-mg/day group, compared to the placebo group (data not shown). However, no effect was observed with the dose of 90 mg/day. High-dose vitamin K is unlikely to induce hepatocarcinogenesis, because no carcinogenicity has been reported for this vitamin. However, the growth of HCC cells may be dependent on vitamin K. Vitamin K deficiency has been reported in HCC tissues,[31] but it is not known whether replacement of vitamin K facilitates or suppresses tumor growth *in vivo*. Caution is needed in the administration of high-dose vitamin K to HCC patients at high risk of intrahepatic metastasis. The estimated 30% risk reduction of recurrence was not confirmed, and the effect of vitamin K on recurrence, if any, might be observed only in carefully selected patients in a very large-scale trial. If effects of vitamin K2 on HCC prevention are to be further investigated, a preferable endpoint would be the suppression of primary HCC in patients with cirrhosis or advanced fibrosis using the dose of 45 mg/day.

Poon et al.[5] reported that intrahepatic recurrence were classified into early (<1 year) and late (>1 year) recurrences, which seemed to correspond to intrahepatic metastasis and be multicentric in origin, respectively. The present study was terminated approximately 1.5 years after the start of enrollment, according to the recommendation of IDMC. If we are to assume that vitamin K2 at 45 mg/day reduced *de novo* carcinogenesis, it may have been necessary to observe for recurrence for more than 2 years.

Conclusion

In conclusion, the efficacy of vitamin K2 in suppressing HCC recurrence was not confirmed in this double-blind, randomized, controlled study.

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第46回 日本肝癌研究会

記録集

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会場:大阪国際会議場

会長:林 紀夫

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SY1-2　当院における肝細胞癌に対するRFA 10年間の治療成績

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【背景】

Radiofrequency ablation（以下，RFA）は，小型肝腫瘍に対して，低侵襲で比較的高い局所制御能を有するため，本邦では局所療法の標準的治療法として広く普及している．しかし，長期予後は，十分明らかにされているとは言えない．今回我々は，当院にてRFAを導入してから10年間の施行内容と，肝細胞癌患者における長期予後を検討したので報告する．

【対象および方法】

1．対象

対象は1999年6月より，2009年5月末までの10年間に，当院にて施行された肝腫瘍に対するRFAの全1306例，3455結節，3295セッションある．対象症例の内訳は肝細胞癌（以下，HCC）1228例，3297結節，平均年齢68.2（34-88）才，転移性肝腫瘍（以下，META）73例152結節，平均年齢65.6（36-83）才，胆管細胞癌（以下，CCC）5例，6結節，68.4（56-73）才である．また初回治療法として当院にてRFAが施行されたHCC 705例（平均年齢70才，平均腫瘍径2.2cm）において長期予後を検討した．観察期間の中央値は2年11ヶ月（1-127ヶ月）である．

2．当院におけるRFAの手技について

当院におけるRFAの適応は，腫瘍長径3cm以下，3結節以内，血小板3万以上，PT 40%以上，コントロール不能の腹水がない，経皮的に穿刺可能であることを原則としている．しかし，これらの条件を逸脱する症例も存在した．

RFAは，全例，超音波誘導下に経皮的に行った．用いたRFA装置は，Cooltip RF System，LeVeen（旧RTC），RITAシステム，Celon RFAシステムの4機種である．

以下，当院におけるRFA手技と標準化を目指した取り組みについて概説する．

1）治療効果判定法の提唱

肝細胞癌患者では，原則として全例，RFA施行前に血管造影検査を行い，多血性病変に対しては抗癌剤とLipidolのemulsionを動注した．治療効果判定は，RFA後のdynamic CTで行い，Lipiodolが集積した腫瘍とablative areaとの関係から，治療効果をR0～R3の4群に分類し，全周性にablative marginが確保されているR2以上を治療目標とした．

2）治療困難例に対する対応

横隔膜直下病変に対し人工胸水法（2001年～）を導入し，98セッションに併用した．消化管隣接病変に対しては，人工腹水法（2002年～）を導入し33セッションに併用した．

3）RFA 支援超音波画像の導入

通常の B-mode 超音波にて描出困難な症例，追加治療や局所再発例に対しては，標的結節または標的部位をより明確に同定するために，Realtime virtual sonography (RVS; 日立メディコ社，2003 年～）やソナゾイド造影エコー法（2007 年～）を導入した．

【成績】

1．RFA セッションの検討

結節別の疾患と腫瘍径の検討では，HCC 群，2.0±0.8 (0.5-8.4) cm，META 群，2.3±1.1 (0.6-6.1) cm，CCC 群，3.3±1.7（1.2-5.9）cm で，CCC 群，META 群，HCC 群の順で有意の大きかった（$p<0.01$）．使用した装置の割合は，Cooltip-RFA system（77.5%），LeVeen（7.4%），RITA（14.3%），Celon（0.8%）であった．使用した装置と腫瘍径の検討では，展開型の LeVeen および RITA が Cool-tip RF system に比べて有意に大きな結節に選択されていた（$p<0.001$）．1 結節当たりに施行された RFA のセッション数は平均 1.18±0.44（1-4）セッションで，結節径の大きな腫瘍には複数セッションの RFA が施行されていた．

2．HCC に対する RFA の長期予後の検討

全症例（n=705）の累積生存率は，3 年 79，5 年 59.8，7 年 44.1% であった．JIS score 別の 3 年，5 年，7 年生存率は，JIS 0（141 例）で，それぞれ 91.9, 74.5, 49.8%，JIS 1（257 例），81.3，64.3，48.9%，JIS 2（169 例），72.4，45.3，32.2% であった．

3．合併症について

観血的処置を必要としたり，生命を脅かす重篤な合併症を 33/3295 セッション（1.0%），33/1306 症例（2.5 %）に認めた．在院死亡例は認めなかった．

【考案】

Livraghi らは，2cm 以下，単結節の HCC では RFA を 1st choice として良いと報告している．外科的成績と比較しやすい JIS 0 に着目してみると，我々の 74.5% というデータは，本邦の肝切除のデータと比較しても遜色ない数字である．当院の RFA の成績は，手技の標準化に取り組んだ上での成績であり，再現性の高い数字と考えている．

【結語】

より合併症を回避する努力は必要だが，RFA は小型肝細胞癌に対して，第一選択の治療法として良いと考えられる．

(文献)

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SY2-3　B型慢性肝疾患関連肝癌の初回根治治療後における核酸アナログ投与の意義 —無再発生存・全生存期間の検討

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【背景】

HBVキャリアは全世界中で約3億5千万人おり，本邦では約130万人程度の患者が推定されている。特にB型慢性肝炎は病期が進むにつれ，非代償性肝硬変への移行や肝発癌が起こり，合併症などで死に至る。現在本邦では，B型肝炎ウイルス(HBV)の治療としてインターフェロン，核酸アナログ製剤(NA)が認可されているが，NA治療の長期成績などについては不明な点も多い。

近年，NA治療により血中ウイルス量を抑えることで，肝病変の進展を抑制し肝発癌を抑制する可能性があることが示されつつある。[1,2]

だが，実際に肝発癌した症例におけるNA治療の意義について言及している論文は少なく，NA治療の発癌抑制効果についてはっきりとした見解がない。[3,4]

本邦ではNA治療は既に保険認可されており，現時点で前向きランダム化比較試験は非現実的である。今回我々は初発肝癌患者における根治後のNA治療の効果について後ろ向きに検討した。

【方法】

1992年よりこれまでに当院で経験したHBsAg陽性かつHCVAb陰性の症例で，3cm以下3個以下もしくは5cm以下単発の肝癌に対し手術もしくはラジオ波熱凝固療法を選択し，根治治療を得たと考えられる98例のうち，ウイルス量を検討できた81例を選び，さらに半年以内に他部位再発を認めた9例を除いた72例（男/女:57/15，年齢中央値58歳，観察期間57.6±34.8カ月）を対象に，①全生存期間と②他部位再発率およびそれに寄与する因子を検討した。初回治療直後(もしくは，それ以前)からのNA治療の有無により，NA治療群(n=37)，コントロール(無治療)群(n=35)の2群に分けた。生存率の検討では，再発後よりNAを投与した6例をコントロール群より除外した66例について検討した。

主要19因子(年齢・性別・Genotype・HBe抗原・初回治療時のHBV DNA量・ALT・T-bil・ALB・Child Pugh分類・Plt・肝硬変有無・腫瘍個数・腫瘍サイズ・AFP・PIVKA-2・NA治療の有無・肉眼型・局所再発有無・肝癌治療法)を単変量解析・多変量解析を用い，生存率や肝癌累積再発率に寄与する因子を検討した。なお，生存関数・累積再発関数の検定にはKaplan-Meier法およびLog-rank検定を用いた。また，多変量解析にはCox比例ハザード分析を用いた。

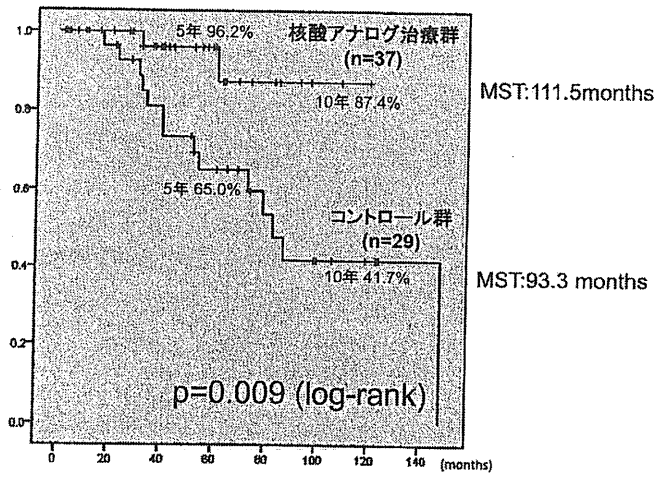
【結果①】

全生存期間の検討では，単変量解析でHBe抗原(p=0.001)，血清ALB値(p=0.004)，Child Pugh分類(A vs B,C)(p=0.04)，NA治療(p=0.009)が生存に寄与する有意な因子であった。特

に平均生存期間 (MST) は NA 治療群で 111.5 カ月であり，コントロール群で 93.3 カ月で，両群間に 18.2 カ月の差が認められた。

また，多変量解析では HBe 抗原陽性 (HR 5.02[95%CI:1.15-21.8]) と NA 治療 (HR 0.164 [95%CI:0.03-0.84]) の 2 項目が生存に寄与する因子であった。

Overall Survival : NA treatment +/-

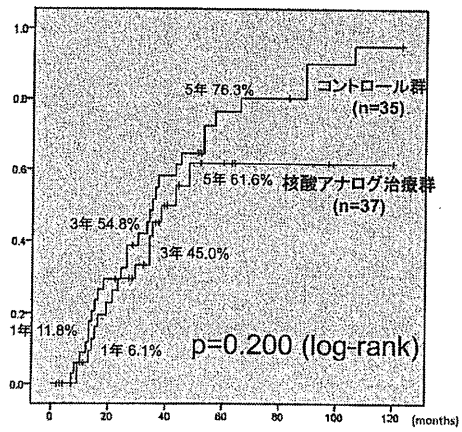


【結果 ②】

累積再発率の検討では，単変量解析で HBe 抗原 (p=0.004)，血清 ALB 値 (p=0.020)，Child Pugh 分類 (p=0.001)，腫瘍個数 (1 vs 2,3) (p=0.003) が根治後再発に寄与する因子であり，NA 治療 (p=0.200) はコントロール群に再発が多い傾向はあるものの，有意差は得られなかった。

また，多変量解析では腫瘍個数 (HR 4.02[95%CI:1.28-12.6]) のみが根治後再発に寄与する因子であった。

Cumulative Recurrence Rate : NA treatment +/-



【考察・結語】

今回の解析でNA治療が生命予後改善に関わる重要な因子であることが示された。ただ，肝癌根治後の再発抑制への関与は示せず，主にウイルス抑制効果による肝機能向上や，それに伴い再発肝癌への追加治療が可能となることが最終的な生存率の改善につながるものと推測される。

ただ，コントロール群における再発率は初めの3年以前とそれ以降で大きく異なることからも，根治後から早期に起こる肝癌再発は肝内転移や微小癌の顕在化による遺残再発である可能性が高い。そのためNA治療による発癌抑制効果は，多中心性発癌が主として現れる時期(3年以降)に現れる可能性がある。NA治療が始まってまだ10年程であり，長期的治療による発癌抑制効果については今後の検討の結果を待つ必要がある。

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