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J Gastroenterol 2005; 40:171–178
DOI 10.1007/s00535-004-1516-5

Journal of Gastroenterology



# Percutaneous radiofrequency ablation with cooled electrodes combined with hepatic arterial balloon occlusion in hepatocellular carcinoma

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***Background.*** We have reported that percutaneous radiofrequency ablation (RFA) with balloon occlusion of the hepatic artery (balloon-occluded RFA), using an expandable electrode, increases the coagulation area. In this study, we investigated the efficacy of balloon-occluded RFA and balloon-microcatheter-occluded RFA, using a cool RF single electrode. ***Methods.*** We studies 41 patients with 47 hepatocellular carcinoma (HCC) lesions. We treated 28 patients (32 nodules) with balloon-occluded RFA, 5 patients (6 nodules) with balloon-microcatheter-occluded RFA, and 8 patients (9 nodules) with standard RFA. Initial therapeutic efficacy was evaluated with dynamic computed tomography performed 1 week after one session of treatment. ***Results.*** One session of treatment was done for 20 nodules (62.5%) in the balloon-occluded RFA group and for 4 nodules (66.7%) in the balloon-microcatheter-occluded RFA group. We compared the coagulation diameter for balloon-occluded RFA (7 nodules), balloon-microcatheter-occluded RFA (6 nodules), and standard RFA (9 nodules) after one application cycle (12 min). The greatest dimension of the area coagulated by balloon-occluded RFA was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension). However, there was significant difference only in the greatest short-axis dimension of the area coagulated comparing balloon-microcatheter-occluded RFA and standard RFA. ***Conclusions.*** We consider balloon-occluded RFA using a cool RF electrode to be superior to standard RFA for the treatment of HCC, especially when larger coagulation volumes are required.

Received: March 22, 2004 / Accepted: August 24, 2004
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**Key words:** hepatocellular carcinoma, radiofrequency ablation, balloon occlusion, percutaneous local treatment

## Introduction

Radiofrequency ablation (RFA), a new technique for the destruction of hepatic tumors, has been reported previously.[1–8] Recently, RFA has been performed as a percutaneous local treatment for hepatocellular carcinoma (HCC) in Japan.[9–11] There are three types of RFA systems used in Japan: the RITA 500PA (RITA Medical Systems, Mountain Views CA, USA) Cool-tip RF (Radionics, Burlington, MA, USA), and RF 2000 (RadioTherapeutic, Sunnyvale, CA, USA) Previous studies have documented necrotic areas of up to 26.7 mm, using the RITA 500PA and an expandable electrode from the some manufacturer (Model 30).[12] A necrotic area of up to 30 cm in diameter produced with a cool RF single electrode has been observed in tumors,[6] and cluster electrodes achieve a much larger necrotic area.[5,8,13] However, the limited volume of coagulation necrosis obtained with each activation of the RF system, and the sometimes irregular burn shape, due to the proximity of large vessels that have a cooling effect, have thus far limited the therapeutic efficacy of RFA for the treatment of HCC.[14] Therefore, we designed an RFA procedure with balloon occlusion of the hepatic artery (balloon-occluded RFA), and we have also reported that balloon-occluded RFA using an expandable electrode increases the area of coagulation necrosis.[9,12] However, our procedure can be performed equally well using other RF systems.

In this study, we investigated the efficacy of balloon-occluded RFA using a cool RF single electrode. In addition, as we do not always succeed with this technique because of variant vascular anatomy or irregular shape

of the hepatic artery, we designed an RFA procedure with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA) and decided to undertake a study to evaluate the efficacy of this new technique.

## Patients, materials, and methods

### *Patients*

We retrospectively studies 41 patients with 47 HCC lesions. They were admitted to the Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, between July 2001 and December 2002. Clinical characteristics of the patients are shown in Table 1.

Of these patients, 28 (32 nodules) were treated with balloon-occluded RFA, 5 (6 nodules) were treated with balloon-microcatheter-occluded RFA, and 8 (9 nodules) were treated with standard RFA. We die not perform RFA with artificial pleural effusion,[15] because HCC lesions located in the hepatic dome were well-visualized by ultrasonography. The diagnosis of HCC was made by imaging studies and/or histological findings, and was based on elevated serum levels of α-fetoprotein (AFP) and/or des-γ-carboxy-prothrombin (DCP).

In the balloon-occluded RFA group, 10 patients (10 nodules) had not received previous treatment for HCC and 18 patients (22 nodules) had previously undergone treatment for HCC. In the 18 patients who had previously undergone treatment for HCC, 21 of the 22 nodules were recurrent intrahepatic nodules, and 1 nodule was at the margin of the treatment area and recurred 6 months after RFA. Nine nodules (9 patients) measured more than 3 cm in diameter. The average tumor size was 25.8 mm and the largest size was 53 mm.

In the balloon-microcatheter-occluded RFA group, three patients (four nodules) had not received previous treatment for HCC, and two patients (two nodules) had previously undergone treatment for HCC. Of the two patients who had previously undergone treatment for HCC, one had a recurrent intrahepatic nodule, and the other had a recurrent nodule at the margin of the treatment area 9 months after RFA. All nodules in this group measured less than 3 cm in diameter. The average tumor size was 19.2 mm and the largest size was 28 mm.

In the standard RFA group, seven patients (eight nodules) had not received previous treatment for HCC. The eighth patient (one nodule) had previously undergone treatment for HCC, and had a recurrent intrahepatic nodule. All nodules measured less than 3 cm in diameter. The average tumor size was 12.8 mm and the larges size was 16 mm.

The underlying liver disease was classified as Child-Pugh class[16] A, B, or C. Patients were asked to give their written informed consent to enter the study, which was approved by the Institutional Review Board of Yamaguchi University Hospital.

### *Techniques*

#### *RF system*

The Cool-tip RF system produced radiofrequency waves with a frequency of 480 kHz and a maximum output power of 200 W. Circuitry in the generator allowed continuous monitoring of impedance between the active part of the cooled electrode and the grounding pads placed on the patient's thigh. A 20-cm-long, 17-gauge, cool-tip RF electrode, with a 3-cm-long (CT-2030) or a 2-cm-long (CT-2020) exposed metallic tip was used to deliver RF energy. Two patients who received balloon-occluded RFA were treated using the CT-2020, and the other patients were treated using the CT-2030. During lesion ablation, a thermocouple embedded in the electrode tip continuously measured the local temperature, and the maximum radiofrequency

**Table 1.** Clinical characteristics of patients with hepatocellular carcinoma (HCC) treated by balloon-o cluded radiofrequency ablation (RFA), balloon-microcatheter-occluded RFA, or standard RFA

| Clinical characteristics | Balloon-occluded RFA ($n$ = 28; 32 nodules) | Balloon-microcatheter-occluded RFA ($n$ = 5; 6 nodules) | Standard RFA ($n$ = 8; 9 nodules) |
|---|---|---|---|
| Sex (male/female) | 22/6 | 3/2 | 3/5 |
| Age (years)[a] | 66.7 ± 9.2 | 70.6 ± 6.0 | 67.8 ± 7.0 |
| Child-Pugh (A/B/C) | 22/6/0 | 3/2/0 | 8/0/0 |
| HCV/HBV/unknown | 22/3/3 | 5/0/0 | 7/1/0 |
| Tumor size (mm)[a] | 25.8 ± 10.8 | 19.2 ± 5.4 | 12.8 ± 2.4 |
| Initial/previous treatment | 10/18 | 3/2 | 7/1 |

HCV, hepatitis C virus; HBV, hepatitis B virus
[a] Data values are expressed as means ± SD

power prevented impedance from rising more than 30 Ω above the baseline value. A peristaltic pump ensured cooling of the electrode with 0°C water at a flow rate sufficient to maintain the temperature of the electrode below 25°C. In principle, RF energy was applied for 12 min (one application cycle). For two nodules treated with balloon-occluded RFA, the application time was only 6 min, because one tumor was located close to the gallbladder and another was located to the liver surface. When necessary, after the first ablation, the electrode was pulled out 1.5 cm, and a second application was started. The application time after the first ablation was 6 min.

In the balloon-occluded RFA group, the tumors were treated with one to three insertions of the electrode per procedure, because the tumor size was larger than that in the other groups. In principle, for each tumor larger than 3 cm in diameter, two to three insertions were planned. One to nine application cycles (range, 6–60 min; mean ± SD, 21 ± 12.9 min) were performed. In the balloon-microcatheter-occluded RFA group and standard RFA group, the tumors were treated with one insertion of the electrode per procedure and one application cycle (12 min).

*Balloon-occluded RFA*

Catheter placement was done using the Seldinger approach through the femoral artery, with a 5.0-Fr catheter (Clinical Supply, Gifu, Japan). The angiography combined with computed tomography (angio-CT)[17] system used was a Somatom plus 4F (Siemens, Erlagen, Germany). Before treatment, CT during arterial portography (CTAP) and CT arteriography (CTA) were performed. A catheter was placed in the superior mesenteric artery for CTAP and in the common or proper hepatic artery for CTA. CT scanning for CTAP started 30 s after 50 ml of contrast medium (Iomeron 300; Eisai, Tokyo, Japan) diluted with saline (1:1 ratio), was injected at a rate of 2 ml per s. CT scanning for CTA started 5 s after the injection of 15–20 ml of diluted contrast medium, at a rate of 1.5–2 ml per s.

The procedure was performed under real-time Ultrasound (US) guidance (SSD-5500; ALOKA, Tokyo, Japan) with a 3.5-MHz convex probe. First, CTAP and CTA were performed before treatment. Local anesthesia was induced with 5 ml of 0.5% lidocaine. Before treatment, 15 mg pentazocine hydrochloride and 25 mg hydroxyzine hydrochloride were administered intramuscularly, and then 15 mg pentazocine hydrochloride was administered intravenously. In addition, 10–20 mg ketamine hydrochloride, diluted with 100 ml of saline, was administered intravenously for reduction of severe pain. We then performed RFA with balloon occlusion of the proper hepatic artery (balloon-occluded RFA), using a balloon with a 9-mm outer diameter attached to a 5-Fr catheter (Clinical Supply). During interruption of the hepatic arterial flow, the RF generator was activated; 2–3 ml of heparin sodium (10 U/ml) was sometimes administered to prevent thrombosis of the hepatic artery during the occlusion. After treatment, CTA was performed again to evaluate the effect of the procedure (RFA with angio-CT assistance[9]). Patients were instructed to lie quietly in bed for 12 h after treatment.

*Balloon-microcatheter-occluded RFA*

This technique was performed when we did not succeed with the balloon-occluded RFA because of variant vascular anatomy or irregular shape of the hepatic artery. The procedures for the catheter placement and the angio-CT assistance[9] were same as those described above.

To insert the balloon microcatheter, we exchanged the 5.0-Fr catheter for a 5.1-Fr guiding catheter (Elway; inner diameter, 1.32 mm; Clinical Supply.) We then performed RFA with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA). A 10-mm-length balloon, with a 4-mm outer diameter, attached to a Commodore temporary occlusion balloon catheter (Cordis; Johnson and Johnson, USA) and Agility guidewire (Cordis; Johnson and Johnson) were used for occlusion of the right or left hepatic artery (Fig. 1); 0.11 ml of contrast medium diluted with saline (1:3 ratio) was injected into the balloon. During interruption of the hepatic arterial flow, the RF generator was activated.

*Assessment of therapeutic efficacy*

To examine the initial therapeutic effect, dynamic CT scans were obtained 1 week after treatment. We measured the size of the nonenhanced portion of the liver. Tumor necrosis was considered complete when no areas of enhancement were seen in the tumor or at the periphery on CT scans. If the size of the necrotic area was almost the same as that of the tumor, and CT scans showed partial enhancement of a portion of the tumor, we performed an additional session of standard RFA. A second RF procedure was planned as soon as possible for patients who did not show a complete response after the first procedure. Repeated dynamic CT scans were performed every 3–4 months thereafter.

Overall follow up ranged from 2.8 to 24.8 months (mean ± SD, 15.6 ± 5.5 months). Follow up in the balloon-occluded RFA group was from 2.8 to 24.8 months (mean ± SD, 14.8 ± 5.5 months), that in the balloon-microcatheter-occluded RFA group was from 12.8 to 24.1 months (mean ± SD, 20.1 ± 5.2 months), and that in the standard group was from 9.9 to 22.3 months (mean ± SD, 15.8 ± 4.6 months). α-Fetoprotein

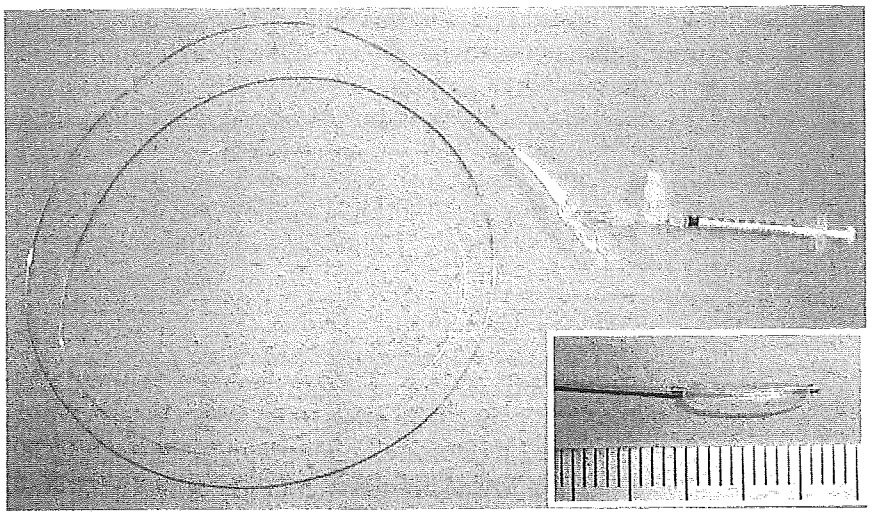

**Fig. 1.** Balloon microcatheter: Commodore (Cordis; Johnson and Johnson) temporary occlusion balloon catheter; a 10-mm-length balloon, with a 4-mm outer diameter, was attached to a microcatheter

(AFP) and DCP levels were examined before treatment, and 1 month after treatment, and subsequently every 1–2 months.

*Balloon-occluded RFA versus standard RFA*

We compared the coagulation diameters for balloon-occluded RFA and standard RFA on CT scans 1 week after one application cycle (12 min) in seven patients (seven nodules) treated with balloon-occluded RFA, and eight patients (nine nodules) treated with standard RFA. The CT-2030 was used for all of these patients.

*Balloon-microcatheter-occluded RFA versus standard RFA*

We compared the coagulation diameters for balloon-microcatheter-occluded RFA and standard RFA on CT scans 1 week after one application cycle (12 min) in the five patients (six nodules) treated with balloon-microcatheter-occluded RFA and the eight patients (nine nodules) treated with standard RFA. The CT-2030 was used for all of these patients.

*Statistical analysis*

Data values were expressed as means ± SD. Statistical analyses were performed using the unpaired *t*-test. A *P* value of less than 0.05 was considered statistically significant.

## Results

*Treatment efficacy*

In the balloon-occluded RFA group (see Fig. 2 for representative images), the average number of needle insertions was 1.5 ± 0.8. One session of balloon-occluded RFA treatment was done for 20 nodules (62.5%) in 17 patients. Additional sessions of standard RFA were performed for 12 nodules (37.5%) in 11 patients. Thus, the average number of treatment sessions was 1.7 ± 1.1. Nine nodules (9 patients) measured more than 3 cm in diameter. Although the average number of needle insertions in these 9 nodules was 2.1 ± 0.8, combined balloon-occluded RFA and angio-CT assistance[9] techniques could achieve one-session treatment for 4 patients (4 nodules) with large HCC nodules (>3 cm in diameter). During follow up, detection of residual foci of unablated tumors occurred in 2 patients (2 nodules [6%]), at 5 and 8 months after treatment. One patient was treated with balloon-occluded RFA and the other was treated with transcatheter arterial chemoembolization (TACE).

In the balloon-microcatheter-occluded RFA group (Fig. 3), the number of needle insertions was 1. One session of treatment with balloon-microcatheter-occluded RFA was done for four nodules (66.7%) in three patients. Additional sessions of standard RFA were performed for two nodules (33.3%) in two patients. Thus, the average number of treatment sessions was 1.3 ± 0.5. During follow up, there was no detection of residual foci of unablated tumors.

In the standard RFA group, the number of needle insertions was 1. One treatment session of standard RFA was done for eight nodules (88.9%) in seven

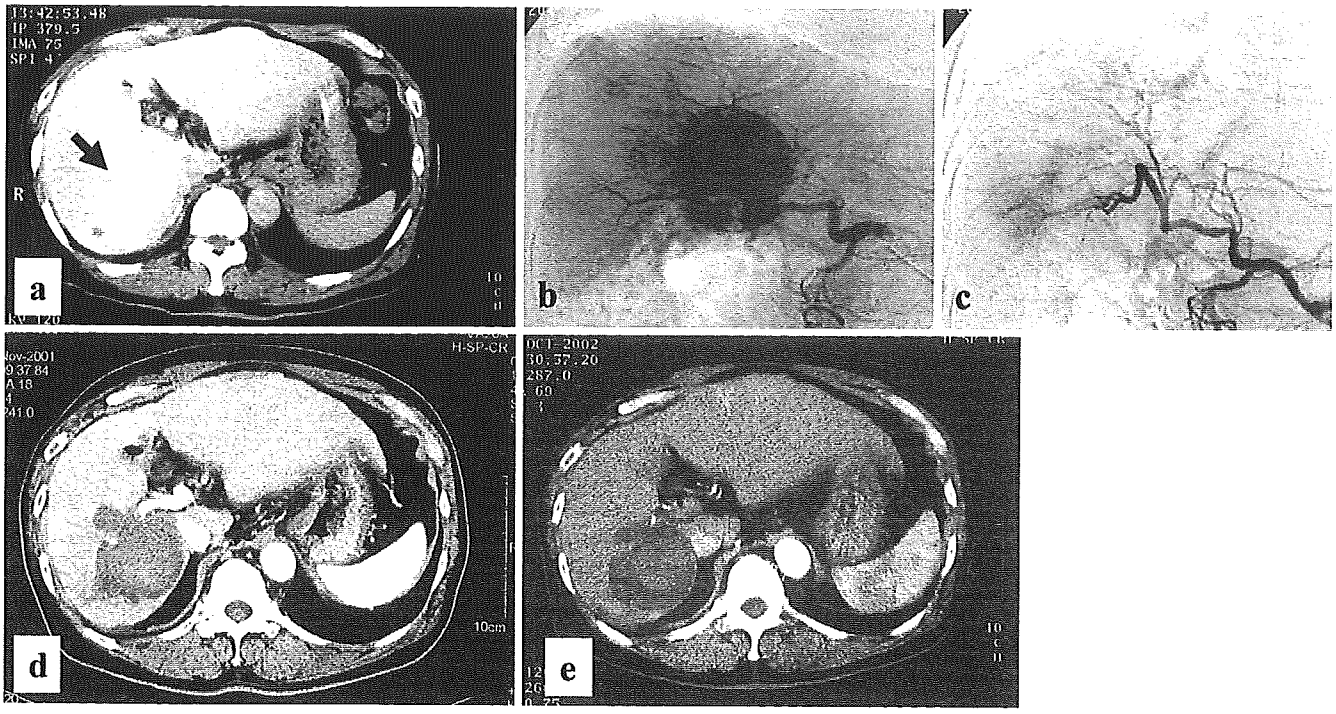


**Fig. 2a–e.** Balloon-occluded radiofrequency ablation (RFA), using a cool RF single electrode, in a 68-year-old man with a 53-mm-diameter hepatocellular carcinoma in segment 7. **a** Computed tomography arteriography (CTA) before treatment shows a tumor (*arrow*). **b** Digital subtraction angiography (DSA) before treatment shows a tumor stain. **c** We performed balloon-occluded RFA, using a cool RF single electrode (number of needle insertions, 3; total treatment time, 60 min). After treatment, the tumor stain disappearred on DSA. **d** Dynamic CT scan taken 1 week after treatment shows no enhancement in the treated area (85 × 70 mm). **e** Dynamic CT scan taken 1 year after treatment shows no enhancement in the treated area

patients. Additional sessions of standard RFA were performed for one nodule (11.1%) in one patient. Thus, the average number of treatment sessions was 1.1 ± 0.3. During follow up, there was no detection of residual foci of unablated tumors.

During follow up, four patients in the balloon-occluded RFA group died. The cause of death was liver failure in two patients (8.5 months, 18 months) and other causes (encephalitis, aspiration pneumonia) in the other two patients (9.5 months, 2.8 months).

*Complications*

In the balloon-occluded RFA group, biloma occurred in one patient, hepatic infarction in one patient, and liver abscess in one patient. Biloma and hepatic infarction did not require treatment. Liver abscess was successfully treated with antibiotics. In the balloon-microcatheter-occluded RFA group and the standard RFA group, no severe complications occurred.

Transient increases in the serum aspartate aminotransferase (AST) concentration were observed in all patients. However, 1 week after treatment, the concentration had decreased almost to the pretreatment level.

*Balloon-occluded RFA versus standard RFA*

The greatest dimension of the area coagulated by balloon-occluded RFA was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm; $n = 7$ nodules) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $n = 9$ nodules; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension; Table 2).

*Balloon-microcatheter-occluded RFA versus standard RFA*

The greatest short-axis dimension of the area coagulated by balloon-microcatheter-occluded RFA was significantly larger (greatest short-axis dimension, 31.5 ± 4.6 mm; $n = 6$ nodules) than that coagulated by standard RFA (greatest short-axis dimension, 25.9 ± 3.7 mm; $n = 9$ nodules; $P = 0.022$; Table 2). However, there was no significant difference between these groups in the greatest long-axis dimension (balloon-microcatheter-occluded RFA, 38.3 ± 5.7 mm; standard RFA, 35.5 ± 4.7 mm; $P = 0.285$; Table 2).

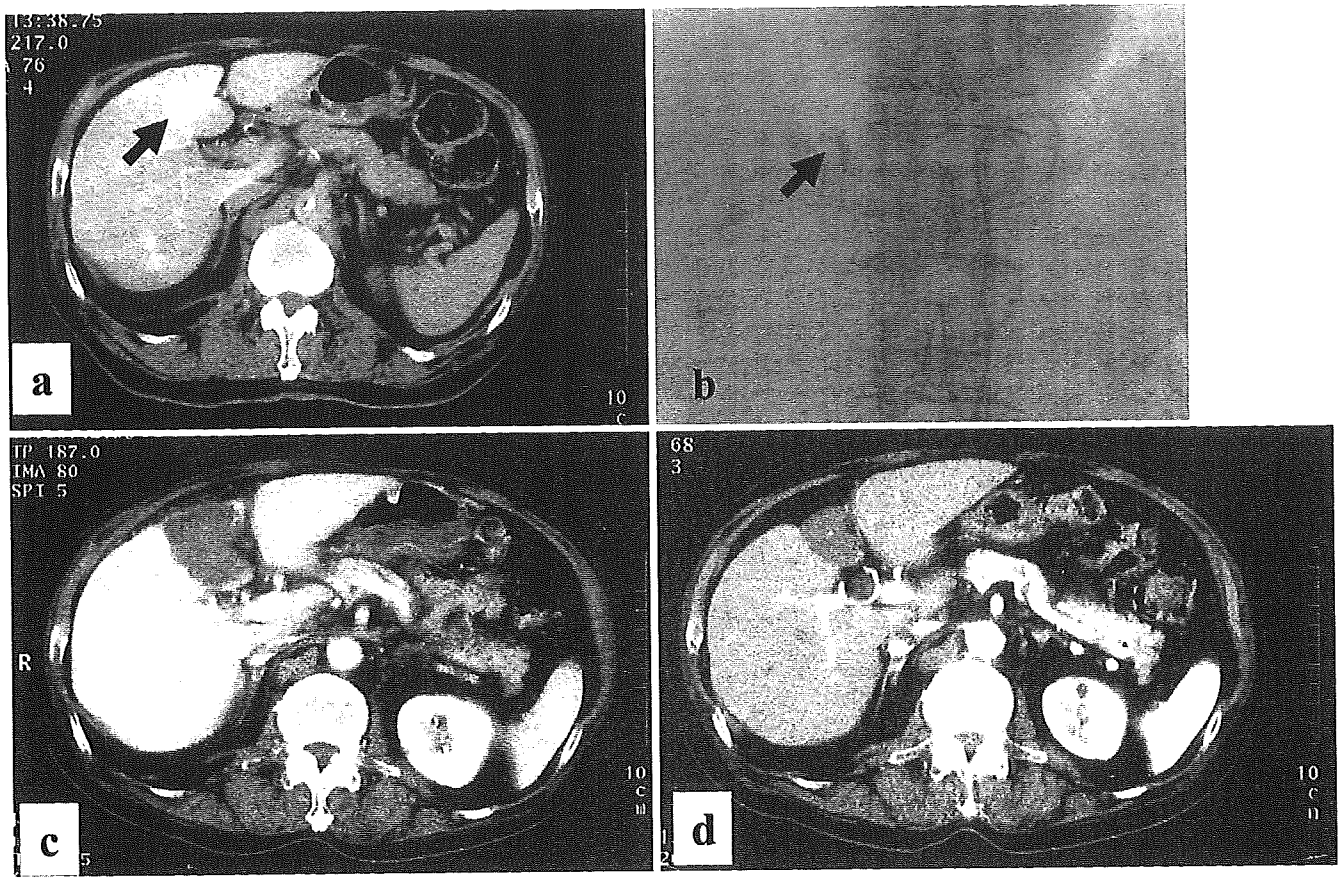


**Fig. 3a–d.** Balloon-microcatheter-occluded RFA, using a cool RF single electrode, in a 68-year-old man with a 28-mm-diameter hepatocellular carcinoma in segment 4. **a** CTA before treatment shows a tumor (*arrow*). **b** The balloon microcatheter (*arrow*) is placed in the left hepatic artery. We performed balloon-microcatheter-occluded RFA, using a cool RF single electrode (number of needle insertions, 1; treatment time, 12 min). **c** Dynamic CT scan taken 1 week after treatment shows no enhancement in the treated area (43 × 40 mm). **d** Dynamic CT scan taken 1 year after treatment shows no enhancement in the treated area

**Table 2.** Comparison of balloon-occluded RFA, balloon-microcatheter-occluded RFA, and standard RFA

| | Balloon-occluded RFA ($n$ = 7; 7 nodules) | Balloon-microcatheter-occluded RFA ($n$ = 5; 6 nodules) | Standard RFA ($n$ = 8; 9 nodules) |
|---|---|---|---|
| Tumor size | 19.6 ± 6.1 | 19.2 ± 5.4 | 12.8 ± 2.4 |
| Coagulation area | | | |
| Long-axis diameter (mm) | 47.6 ± 7.8[1*] | 38.3 ± 5.7[3*] | 35.3 ± 4.7 |
| Short-axis diameter (mm) | 33.4 ± 7.5[2*] | 31.5 ± 4.6[4*] | 25.9 ± 3.7 |

[1*] $P$ = 0.002 (vs standard RFA); [2*] $P$ = 0.041 (vs standard RFA); [3*] $P$ = 0.285 (vs standard RFA); [4*] $P$ = 0.022 (vs standard RFA)
Data values are expressed as means ± SD. Student's $t$-test was used for unpaired data

## Discussion

Although radiofrequency ablation (RFA), a new technique for the destruction of hepatic tumors, has been reported previously,[1–8] the limited volume of coagulation necrosis obtained with each activation of the RF system, and the sometimes irregular burn shape due to the proximity of large vessels that have a cooling effect, have thus far limited the therapeutic efficacy of RFA for the treatment of HCC.[14] On the other hand, both animal and clinical studies have suggested that reduction of blood flow can improve tumor ablation efficacy when thermal ablation is used.[14,18–23] To improve the efficacy of PFA, we designed RFA with balloon occlusion of the hepatic artery (balloon-occluded RFA). We have also reported that balloon-occluded RFA increases the area

of coagulation necrosis compared with standard RFA.[9,12] In a previous study, we used an RITA 500PA (RITA Medical Systems) and an expandable electrode (model 30). However, our procedure can be performed equally well using other RF systems.

In this study, we investigated the efficacy of balloon-occluded RFA, using a cool RF single electrode. The Cool-tip RF system is a powerful generator compared with the RITA 500PA. In fact, a necrotic area of up to 3 cm in diameter produced with a cool RF single electrode has been observed in tumors.[6] Therefore, we expected a much larger necrotic area than we achieved before to be achieved with balloon-occluded RFA using the RITA500PA and an expandable electrode (model 30). In our previous study, the greatest long-axis and short-axis dimensions of the coagulation area in balloon-occluded RFA using the RITA 500PA and an expandable electrode (model 30) were 36.6 ± 3.8 mm and 30.1 ± 6.0 mm, respectively.[12] In our current study, the greatest dimension of the area coagulated by balloon-occluded RFA using a cool RF electrode (CT-2030) was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension), with the same thermal ablation times. We also demonstrated that balloon-occluded RFA using another RF electrode increased the area of coagulation necrosis compared with standard RFA. We could achieve a much larger necrotic area compared with that in balloon-occluded RFA using an expandable electrode. It is also possible to perform balloon-occluded RFA using a cool RF electrode for large HCC nodules (>3 cm in diameter). In this study, nine HCC nodules (nine patients) measured more than 3 cm in diameter. The largest diameter was 53 mm. Although we required a few needle insertions (mean, 2.1), combined balloon-occluded RFA using a cool RF single electrode and angio-CT assistance[9] techniques could achieve one-session treatment for four large HCC nodules in four patients.

Balloon-occluded RFA is a simple and easy technique. However, we do not always succeed with this technique because of variant vascular anatomy or irregular shape of the hepatic artery. Therefore, we also designed RFA with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA). Using the same thermal ablation times for balloon-microcatheter-occluded RFA and standard RFA, there was a significant difference in the greatest short-axis dimension (balloon-microcatheter-occluded RFA, 31.5 ± 4.6 mm; standard RFA, 25.9 ± 3.7 mm; $P = 0.022$), but not in the greatest long-axis dimension (balloon-microcatheter-occluded RFA, 38.3 ± 5.7 mm; standard RFA, 35.3 ± 4.7 mm; $P = 0.285$). We think that the coagulation necrosis obtained with balloon-microcatheter-occluded RFA is insufficient. The first reason is the small balloon size of the microcatheter. The balloon size is 4 mm in outer diameter. On the other hand, the balloon size of the 5-Fr catheter used in the balloon-occluded RFA procedure is 9 mm in outer diameter. Thus, balloon-microcatheter-occluded RFA may not prevent the cooling effect exerted by the arterial flow, compared with balloon-occluded RFA. The second reason is variant vascular anatomy. In two of the five such patients, the right hepatic artery was supplied from the superior mesenteric artery. Therefore, when the right hepatic artery was occluded by means of the balloon microcatheter, the arterial flow in the right lobe was supplied through an anastomosis. Thus, we think that a sufficient effect could not be obtained because a cooling effect remained in the tumor. Balloon-occluded RFA (or balloon-microcatheter-occluded RFA) may not be indicated for patients with separate flow in the liver. In addition, there are some disadvantages of balloon-microcatheter-occluded RFA. First, this technique is troublesome. In fact, we need to exchange the 5.0-Fr catheter for a 5.1-Fr catheter to insert the balloon microcatheter and to exchange the balloon microcatheter for an ordinary microcatheter to perform angio-CT assistance.[9] Second, we cannot inject contrast medium because of the small inner luminal diameter (0.38 mm) of the balloon microcatheter. Therefore, further development of the balloon microcatheter will be required. This is a preliminary report and we need further study with a greater number of patients.

Complications after RFA for hepatic tumors have been reported. The rate of major complications for the treatment of hepatic tumors ranged from 0% to 12.7%.[24] The rate of major complications in our treatments (balloon-occluded RFA and balloon-microcatheter-occluded RFA) was 9.1%. Because the rate of major complications was relatively high, we should limit the indications of RFA with balloon occlusion of the hepatic artery. At this time, we think that patients who have HCC in peripheral sites of the liver, with favorable liver reserve capacity, are suitable candidates for these procedures, because of the larger areas of coagulation. However, we cannot refer to adequate indications for these procedures because of the small patient population and the short follow-up periods. Further studies with more patients and longer follow-up periods are needed to investigate adequate indications.

In conclusion, balloon-occluded RFA using a cool RF single electrode is superior to standard RFA. In addition, the coagulation area obtained with balloon-occluded RFA using a cool RF single electrode is larger

than that obtained with balloon-occluded RFA using the RITA 500PA and an expandable electrode (model 30). Balloon-occluded RFA using a cool RF single electrode may be indicated for patients with large HCC nodules. Furthermore, we also reported balloon-occluded RFA using a balloon microcatheter (balloon-microcatheter-occluded RFA) for the treatment of HCC. Although further development of the balloon microcatheter is required, this technique may have the potential to become widespread.

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# The effect of a late evening snack in patients with liver cirrhosis

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Received 2 August 2004; received in revised form 15 November 2004; accepted 22 November 2004
Available online 6 January 2005

**Abstract**

*Objectives:* As an intervention for energy malnutrition, frequent meals or a late evening snack (LES) has been recently recommended. On the other hand, it has been reported that glucose intolerance is found in approximately 70% of patients with liver cirrhosis. Thus, we investigated which would be better for the improvement of energy malnutrition and glucose intolerance, treatment with LES alone or LES plus divided meals.

*Methods:* One group of oral supplementation with one pack of a branched-chain amino acid (BCAA)-enriched nutrient, Aminoleban EN (210 kcal), at 10 p.m. LES and the other group with two packs of Aminoleban EN (one pack at 10 p.m. as LES and another pack during the day, i.e. at sometime from 10 a.m. to 3 p.m.) were examined to determine the influence of LES on the blood glucose level, biochemical parameters, and energy metabolism. Twenty-six patients participated in this study. The administration period was 7 days. Metabolic measurements were performed using an indirect calorimeter.

*Results:* The fat oxidation rate was significantly decreased and the carbohydrate oxidation rate significantly increased in both groups. As a result, respiratory quotient (RQ) was significantly improved. In many cases, the increase of the glucose level after meals seemed to be reduced after LES administration for 1 week. LES could improve energy malnutrition, and correct amino acid imbalance. There was also a significant correlation between non-protein respiratory quotient (npRQ) and the creatinine height index.

*Conclusion:* LES alone improved the energy malnutrition state and glucose intolerance equivalent to LES plus divided meals. Thus, LES may improve glucose intolerance in patients with liver cirrhosis.


*Keywords:* Liver cirrhosis; Late evening snack (LES); Nutrition

## 1. Introduction

The liver has an important role in nutritional homeostasis, and liver diseases lead to abnormalities in the nutrient metabolism and subsequent malnutrition [1].

Protein-energy malnutrition (PEM) is a common finding in cirrhotic patients [2–5]. PEM may be present in 20% of patients with well-compensated disease, and in more than 60% of patients with severe liver insufficiency [1]. Owen et al. reported that, after an overnight fast, the nature of fuels oxidized in cirrhotic patients was similar to that in healthy controls after 2–3 days of total starvation; that is, there was a relatively high contribution of fat to energy metabolism [6]. Several studies have reported that the protein nutrition state and malnutrition determine the survival rate of cirrhotic patients [7]. Nutritional support for protein malnutrition partly improves the survival rate and surgical outcome of these patients [3,4,8–11], although there have been some criticisms of the hypothesis of the nutrition state as a survival factor or therapeutic strategy [12,13].

Therefore, special attention is required in the management of these patients. Proper nutritional assessment and support for cirrhotic patients is very important. As an intervention for energy malnutrition, frequent meals or a late evening snack (LES) has been recently recommended [14–21].

Krahenbuhl et al. showed that the glucose uptake and hepatic glycogen stores were decreased rapidly in response to

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doi:10.1016/j.hepres.2004.11.009

starvation in cirrhotic rats. In liver cirrhosis, the supply of glucose from the liver is disturbed, and thus energy utilization from lipids and proteins is accelerated [22]. At the same time, after meals, excess elevation of blood glucose occurs in liver cirrhosis. This results in glucose intolerance, and finally in diabetes. It has been reported that glucose intolerance is found in approximately 70% of patients with liver cirrhosis, and in about 40% of those with diabetes [23,24]. Bianchi et al. reported that diabetes affects the survival rate in cirrhosis [25].

However, there has been no report about the comparison of LES alone or LES plus divided meals for the improvement of energy malnutrition and glucose intolerance.

In this study, we examined the effects of LES alone and LES plus divided meals on the metabolism, using indirect calorimetry and the changes of the blood glucose level after meals.

## 2. Subjects and methods

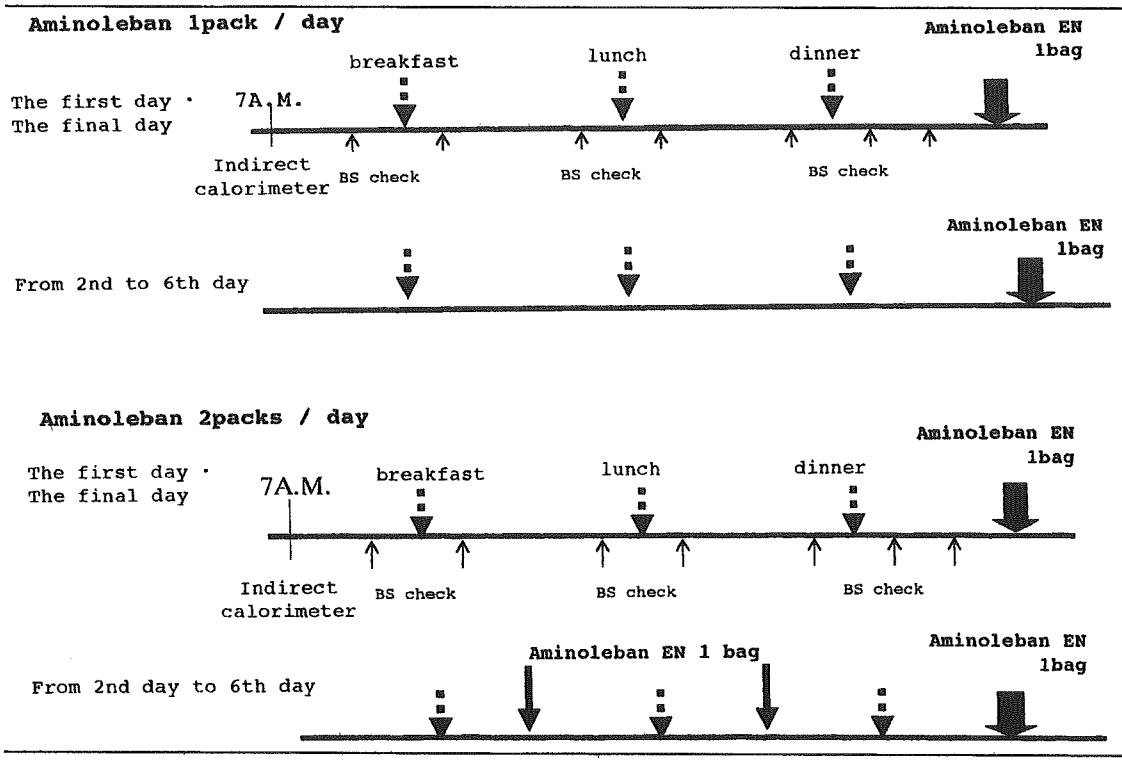
This study was performed on 26 patients with liver cirrhosis hospitalized in our hospital. The patients, aged from 47 to 80 years, consisted of 17 males and 9 females. Liver cirrhosis was caused by HBV in 3 cases and HCV in 22 cases. One case was caused by autoimmune hepatitis (AIH). Twenty patients had hepatocellular carcinoma (HCC) as a complication. Among the patients with HCC complication, all had one to three lesions with a size of 3 cm or less. Child-Pugh scores, used for severity of liver damage, were A in 12 cases, B in 10 cases and C in 4 cases (Table 1). Two patients also had diabetes and one patient was receiving insulin treatment. The patients were randomly divided into two groups. There was no statistically significant difference of background between two groups, e.g. serum albumin or bilirubin level as shown in Table 1.

Examinations were performed when the patients were in stable condition at least 1 week after admission. We investigated the effect of nutrition for two groups, one group with oral supplementation of one pack of Aminoleban EN at 10 p.m. as an LES, the other group with two packs of Aminoleban EN, one taken at 10 p.m. as LES and the other in the daytime (during the period from 10 a.m. to 3 p.m.) (Table 2). The oral supplement (Aminoleban EN) with enriched branched-chain amino acids (Fisher ratio; 38) used in this study was comprised mainly of carbohydrate (59%), protein (26%) and fat (15%), which allowed high protein intake. Energy metabolism at baseline was analyzed with indirect calorimetry. Indirect calorimetry was performed for 30 min after overnight bedrest and fasting. The indirect calorimeter

Table 1
Characteristics of patients

| | Case | Age | Gender | Height (cm) | Weight (kg) | Body mass index (kg/m$^2$) | Child-Pugh classification [score] | Bilirubin (mg/dl) | Albumin (g/dl) | PT (%) | Ammonia (μmol/dl) | HbAlc (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| One pack | 1 | 59 | M | 165 | 71 | 26 | B [9] | 2.0 | 2.4 | 48 | 85 | 5.4 |
| | 2 | 70 | M | 162 | 61 | 23.2 | A [6] | 0.5 | 3.3 | 83 | 72 | 4.9 |
| | 3 | 67 | F | 155 | 45 | 18.7 | B [7] | 0.9 | 3.4 | 70 | 39 | 3.8 |
| | 4 | 71 | F | 147 | 53 | 25.5 | C [10] | 2.0 | 2.1 | 69 | 27 | 4.0 |
| | 5 | 60 | M | 162 | 67 | 26 | C [10] | 2.3 | 2.6 | 65 | 46 | 5.0 |
| | 6 | 68 | F | 154 | 59 | 24.9 | A [6] | 1.4 | 3.1 | 71 | 96 | 5.7 |
| | 7 | 71 | F | 158 | 54 | 21.6 | A [6] | 0.4 | 3.4 | 88 | 41 | 6.0 |
| | 8 | 76 | F | 151 | 44 | 19.3 | B [7] | 0.9 | 2.6 | 77 | 52 | 4.6 |
| | 9 | 63 | F | 151 | 55 | 24 | A [6] | 1.2 | 3.3 | 87 | 51 | 3.6 |
| | 10 | 70 | F | 151 | 58 | 25.4 | B [9] | 2.0 | 2.3 | 59 | 80 | 3.9 |
| | 11 | 76 | M | 161 | 51 | 19.7 | B [8] | 1.0 | 2.6 | 63 | 100 | 4.7 |
| | 12 | 67 | M | 167 | 66 | 23.7 | A [6] | 1.0 | 3.2 | 88 | 56 | 5.3 |
| | 13 | 73 | M | 170 | 65 | 22.5 | A [6] | 1.1 | 3.5 | 91 | 43 | 5.3 |
| | | | | | | | | 1.1 (0.4–2.3) | 3.1 (2.1–3.5) | 71 (48–91) | 52 (27–100) | 4.9 (3.6–6.0) |
| Two packs | 1 | 75 | M | 158 | 50.6 | 20.3 | A [5] | 0.3 | 3.1 | 80 | 43 | 5.8 |
| | 2 | 75 | M | 158.5 | 64.5 | 25.7 | A [6] | 1 | 2.5 | 74 | 41 | 4.6 |
| | 3 | 77 | F | 138 | 42.5 | 22.3 | C [10] | 1.2 | 2.3 | 55 | 36 | 7.1 |
| | 4 | 68 | M | 162 | 54 | 20.6 | B [9] | 2.3 | 2.7 | 85 | 82 | 4.5 |
| | 5 | 70 | M | 158 | 57 | 22.7 | B [7] | 2.4 | 3.3 | 68 | 81 | 4.1 |
| | 6 | 80 | F | 140.7 | 42.5 | 21.2 | A [5] | 0.4 | 3.2 | 77 | 40 | 5.2 |
| | 7 | 66 | M | 172 | 74 | 25 | A [5] | 1.2 | 3.7 | 87 | 51 | 4.6 |
| | 8 | 73 | M | 168 | 80 | 28.3 | B [8] | 1.1 | 2.6 | 65 | 97 | 5 |
| | 9 | 73 | M | 159 | 49 | 19.4 | B [7] | 1.3 | 2.6 | 72 | 46 | 5.2 |
| | 10 | 47 | M | 175 | 75 | 24.5 | A [5] | 1 | 3.9 | 76 | 44 | 3.6 |
| | 11 | 60 | M | 169 | 68.5 | 24 | A [6] | 1.9 | 3.4 | 77 | 108 | 4.8 |
| | 12 | 64 | M | 166 | 68 | 24.7 | B [7] | 2.4 | 3.2 | 70 | 25 | 4.4 |
| | 13 | 79 | M | 164 | 57 | 21.2 | C [10] | 2.2 | 2.3 | 60 | 51 | 4.6 |
| | | | | | | | | 1.2 (0.4–2.4) | 3.1 (2.3–3.9) | 74 (55–87) | 46 (25–108) | 4.6 (4.1–7.1) |

Table 2
Protocol




used was a CALORIE SCALE (Chest MI). We measured oxygen consumption per minute ($VO_2$), carbon dioxide production per minute ($VCO_2$), total urine nitrogen (TUN) on the day prior to the examination, fat oxidation, and the non-protein respiratory quotient (npRQ) were calculated. Calculation of the diet for each patient was based on the following conditions: 30–35 kcal/kg per day as total calories for ideal body weight (BMI, 22), 1–1.5 g protein/kg per day, fat content equivalent to 25% of the total calories. During LES administration, reduced-calorie diets were used, i.e.

Table 3
Diet

**Calorie of supplementation**

| | |
|---|---|
| **total energy** | 30 ~ 35 (kcal/kg) as BMI 22 |
| **protein** | 0.8 ~ 1.3 (g/kg) |
| **fat** | 25% of total calories |

**"" During LES administration, reduced the equivalent calorie of…. ""**

The Group of 1 pack Aminoleban EN
210 kcal (Protein 13.5 g, Fat 3.5 g)

The Group of 2 packs Aminoleban EN
420 kcal (Protein 27 g, Fat 7 g)

the calories equivalent to two or one packs of Aminoleban EN (210 kcal/pack, protein 13.5 g/pack, fat 3.5 g/pack) were subtracted (Table 3). The administration period was 7 days and the calorie consumption of all patients was checked by a nutrition technician and all patients took all prescribed-calorie. On days 1 and 7, nutritional evaluation by the indirect calorimeter of the blood glucose level, and biochemical examinations were performed. The change in the blood glucose level was measured at seven time points: 30 min before and 2 h after each meal and at 10 p.m. The levels before meals and those after meals on days 1 and 7 were compared. The branched-chain amino acid/tyrosine ratio (BTR) [23,26] was also examined on days 1 and 7. BTR is the molar ratio of (valine + leucine + isoleucine)/tyrosine, determined by measuring only tyrosine as an aromatic amino acid (AAA), different from the Fischer ratio. Besides indirect calorimetry, nutrition evaluation was based on the biochemical parameters, serum albumin and anthropometric parameters, BMI and creatinine-height index (CHI).

The study design was explained and written informed consent was obtained from all patients. All procedures in this study were conducted in accordance with the Helsinki Declaration of 1975 (1983 version).

## 3. Statistical analysis

Data were expressed as the mean ± S.E. Two-tailed *t*-test was used to compare means for continuous variables. Non-parametric methods were also used for non-normally distributed values and differences were tested by the Wilcoxon signed rank test. To calculate correlation coefficients between selected variables, the Spearman rank correlation coefficient was used. For all tests, *P*-values of less than 0.05 were considered significant.

## 4. Results

### 4.1. Indirect calorimetry

The value of npRQ in both groups increased significantly after 1-week treatment (one-pack group; 0.84 ± 0.06 versus 0.89 ± 0.06, $P < 0.05$, two-pack group; 0.78 ± 0.05 versus 0.83 ± 0.06, $P < 0.05$) (Fig. 1). The fat oxidation rate as an energy substrate decreased significantly (one-pack group; 44.3 ± 20.3 versus 30.3 ± 19.7, $P < 0.05$, two-pack group; 68.1 ± 14.4 versus 53.8 ± 21.7, $P < 0.05$) (Fig. 2) with

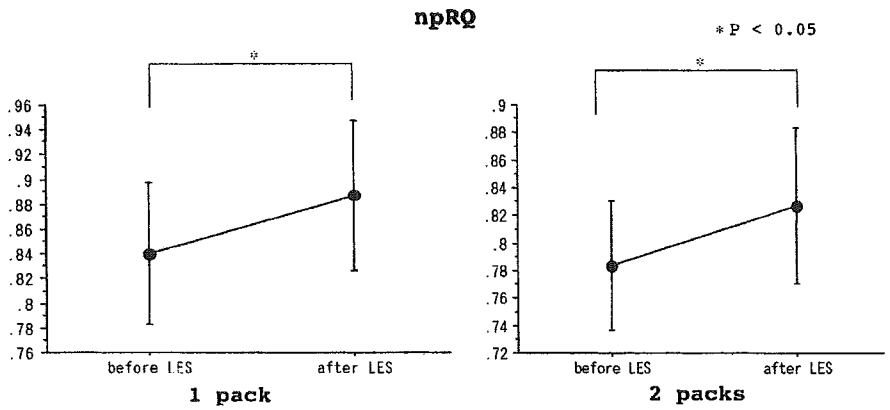



Fig. 1. NpRQ was measured before and after treatment with LES (one pack) and LES plus divided meals (two packs).

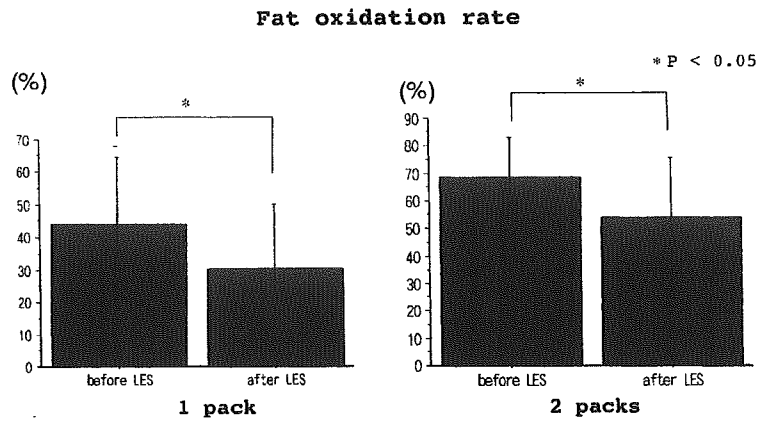



Fig. 2. Fat oxidation rate was measured before and after treatment with LES (one pack) and LES plus divided meals (two packs).

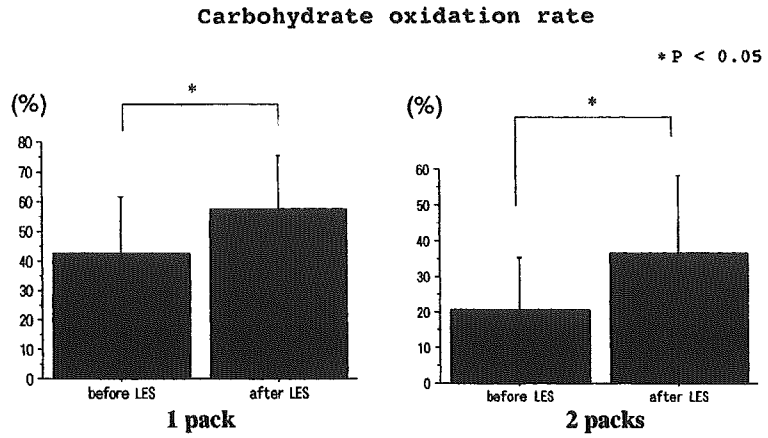



Fig. 3. Carbohydrate oxidation rate was measured before and after treatment with LES (one pack) and LES plus divided meals (two packs).

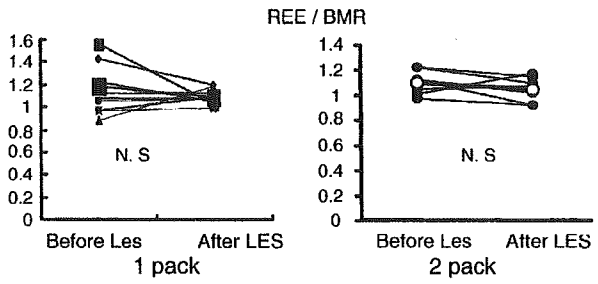



Fig. 4. REE/BMR was measured before and after treatment with LES (one pack) and LES plus divided meals (two packs).

the increase of the glucose oxidation rate (one-pack group; $42.6 \pm 19.2$ versus $57.7 \pm 17.6$, $P < 0.05$, two-pack group; $20.7 \pm 14.7$ versus $36.7 \pm 21.4$, $P < 0.05$) (Fig. 3).

The ratio of resting energy expenditure to the basal metabolic rate (one-pack group; $1.23 \pm 0.03$, two-pack group; $1.11 \pm 0.03$) indicated a hypermetabolic state before treatment. After nutritional treatment, this ratio in both groups changed to the normal range (one-pack group; $1.09 \pm 0.04$, two-pack group; $1.05 \pm 0.03$) although without statistical significance (Fig. 4).

### 4.2. BTR measurement

A significant increase in BTR was also observed after treatment (one-pack group; $3.13 \pm 1.05$ versus $4.55 \pm 1.17$, $P < 0.05$, two-pack group; $3.62 \pm 1.61$ versus $5.38 \pm 2.25$, $P < 0.05$) (Fig. 5). However, no significant difference was observed in the blood ammonia level (data not shown).

### 4.3. The change of the blood glucose level

In this study, there was no case with an abnormal increase of the blood glucose level before breakfast. Two

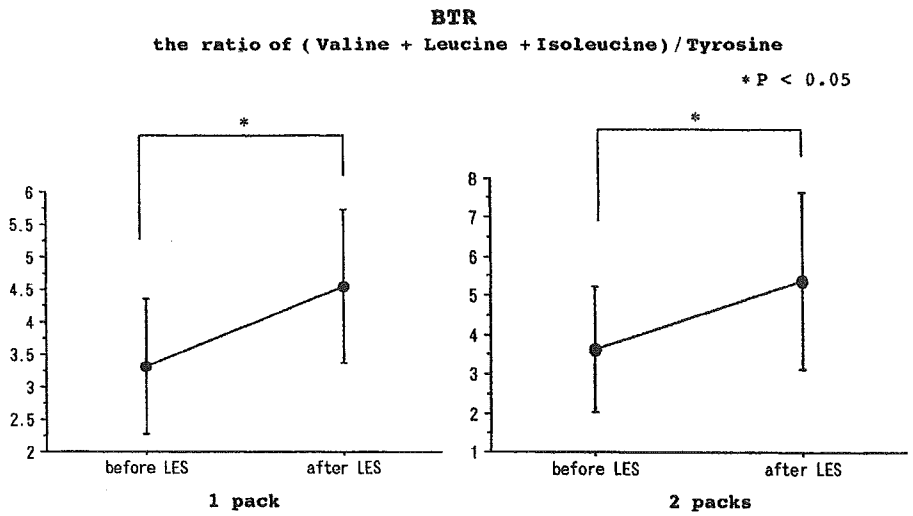



Fig. 5. BTR was measured before and after treatment with LES (one pack) and LES plus divided meals (two packs).

patients had abnormally high levels of HbAlc with diabetes therapy. When we checked the changes of the blood glucose level before the LES administration, there were seven cases with an excess increase of the blood glucose level after meals, especially after breakfast. In this study, seven patients had glucose intolerance, four in the LES-alone group and three in the LES-plus-divided-meal group, with an increased blood glucose level of more than 200 mg/dl 2 h after breakfast, lunch or dinner, before nutritional intervention. However, nutritional support for only 1 week reduced this excess increase of the glucose level after the meals, reducing it to less than 200 mg/dl (data not shown).

We investigated the change of area under the curve (AUC) for the blood glucose level after the meals, before and after the nutritional support. The AUC of the one-pack group decreased significantly ($81.8 \pm 15.4\%$, $P<0.05$) (Fig. 6) as compared to that before the treatment (100%). Although the AUC of the two-pack group tended to decrease compared to that before the treatment, there was no significant difference ($92.2 \pm 22.5\%$) (Fig. 6). There was no significant elevation of the blood glucose level before breakfast after 1-week treatment in either group.

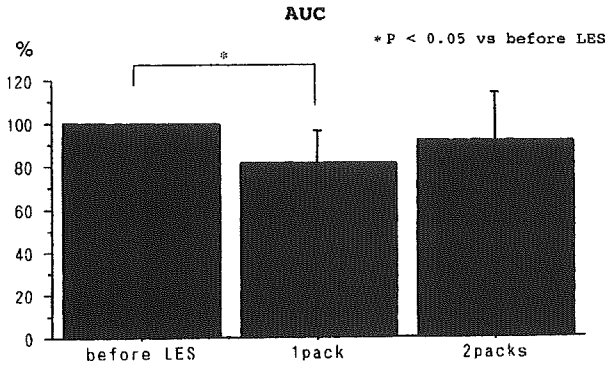



Fig. 6. Area under the curve (AUC) was compared with that of before and after the nutritional treatment with LES (one pack) and LES plus divided meals (two packs).

### 4.4. Changes of npRQ according to Child-Pugh classification

The effect of nutritional intervention on the change of npRQ was examined in the two groups according to the Child-Pugh classification. Patients in Child-Pugh groups A and B showed improved npRQ after the treatment either with LES alone or LES plus divided meals ($P<0.05$, Child-Pugh A;

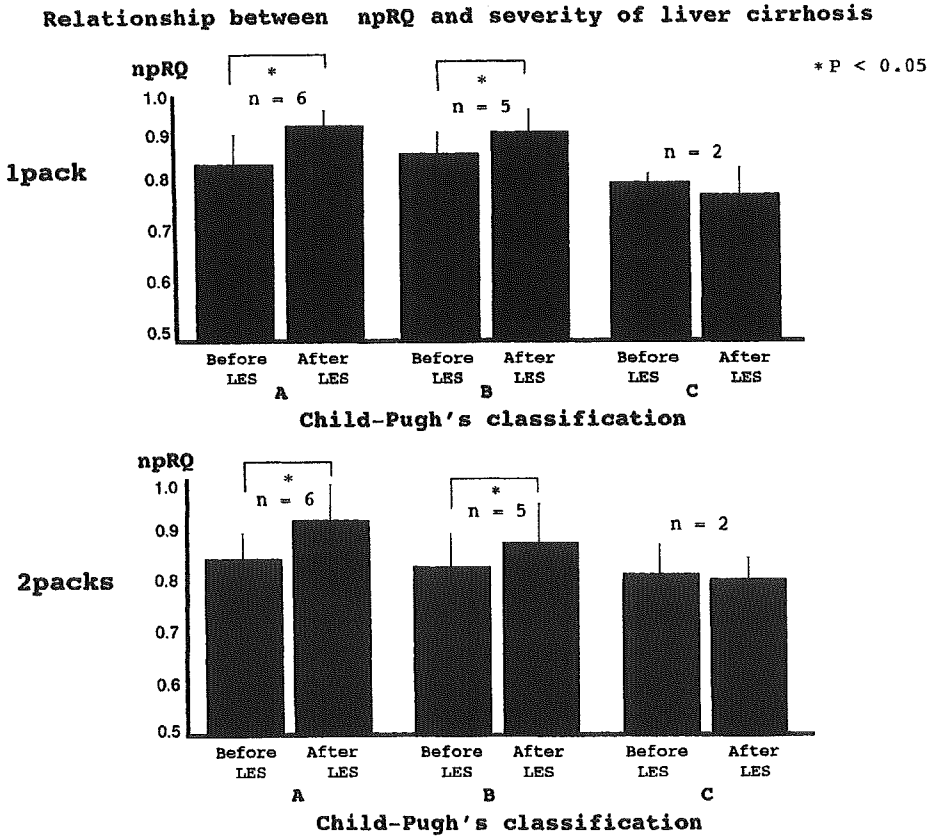



Fig. 7. The change of npRO was compared with that of before. and after the nutritional treatment with LES (one pack) and LES plus divided meals (two packs) among the groups classified by the Child-Pugh score.

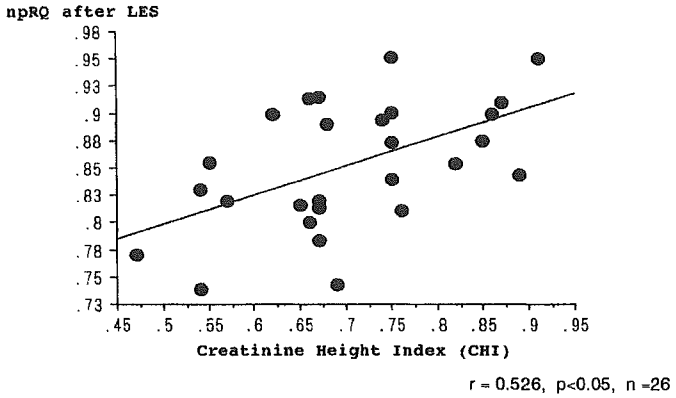



Fig. 8. Correlation between the creatinine height index and npRQ was examined for all patients.

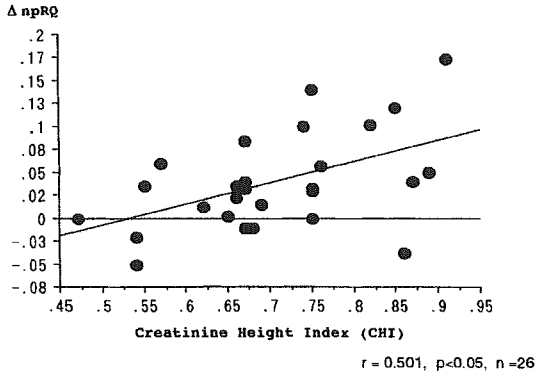



Fig. 9. Correlation between the creatinine height index and the change of npRO before and after the nutritional treatment for 1 week was examined for all patients.

$n = 6$/each group, Child-Pugh B; $n = 5$/each group) (Fig. 7). However, for the patients who had severe decompensated cirrhosis (Child-Pugh C), nutritional treatment did not improve npRQ ($n = 2$/each group) (Fig. 7).

### *4.5. The correlation between npRQ and the biochemical and nutritional parameters*

We examined the correlation between npRQ and various parameters. There was a significant correlation between the value of npRQ after nutritional treatment and the creatinine height index ($P < 0.05$) (Fig. 8), as well as for the change of npRQ after treatment (npRQ after treatment minus npRQ before treatment) and the creatinine height index ($P < 0.05$) (Fig. 9), although there were no significance correlations between npRQ and BMI, albumin, total bilirubin, ammonia, etc.

## 5. Discussion

Owen et al. reported that, after an overnight fast, the nature of fuels oxidized in cirrhotics was similar to that in healthy controls after 2–3 days of total starvation; that is, there was a relatively high contribution of fat to the energy metabolism [27]. However, at the same time, Yamashita et al. reported that glucose oxidation in peripheral tissue after eating was intact or increased [28]. Therefore, special attention is required in the management of these patients. In this study, we showed that LES (as in the one-pack group) and LES plus divided meals (as in the two-pack group) were very effective for morning starvation. The presence of a severe catabolic state in cirrhotic patients results in the loss of muscle, and malnutrition, resulting in a poor prognosis [4,7]. In the one-pack and two-pack groups, the npRQ improved significantly, with increased carbohydrate oxidation. The two-pack group tended to have more increased BTR than the one-pack group, but in both of groups the value of BTR after treatment was elevated to more than 4.0. One-pack LES treatment significantly decreased the AUC but unexpectedly, the reductive effect of AUC with LES plus divided meals was less than that of the LES-alone group. Other researchers have reported that the problem of glucose intolerance and diabetes in cirrhotic patients is the excess elevation of blood glucose after meals [23,24]. In our study, before nutritional treatment, no patient had an abnormally high glucose level before breakfast, but some had an excess increase of blood glucose level after meals, especially after breakfast. Nutritional treatment reduced such elevation of the glucose level after 1 week in both groups. These results suggest that LES-alone treatment with one pack of BCAA-enriched supplement will have an equal effect on energy metabolism and the blood glucose level equivalent to the treatment using LES and divided meals.

Our study indicated that patients in the compensated stage i.e. Child-Pugh A or B, will respond to the nutritional intervention easily. However, a long-term study is necessary to determine whether patients in the decompensated stage (e.g. Child-Pugh C) will respond to nutritional intervention such as LES. In our study, we showed that there was a significant correlation between npRQ and the creatinine height index (CHI). CHI is useful for the reflection of skeletal muscle volume [29]. Although the liver is considered the major site of

amino acid degradation [30], skeletal muscles are also another important site for amino acid metabolism [31]. As described previously, many cirrhotic patients had PEM [2–5], which caused decreased muscle mass and affected the patients' prognosis [18]. Our results also suggest that muscle is very important for the uptake and utilization of the LES nutritional supplement. That is, it is important to maintain proper muscles and, in order to do that, it is necessary to ingest suitable protein and perform appropriate exercise. Recent studies have suggested that leucine may play an especially important role in skeletal muscles for the regulation of protein synthesis and for glucose metabolism [32–34]. This suggests that muscles may play an important role not only for amino acids and ammonia metabolism but also for improvement of glucose intolerance. Thus, our results show that muscle volume will affect the improvement of energy metabolism, e.g. increase of npRQ, which coincides with those reports [32–34].

There are different opinions as to what is the best substrate and the method of administration [35]. In cirrhotic patients, impaired glucose tolerance and insulin resistance are often observed. Nakaya et al. reported that among a BCAA mixture, carbohydrate-rich snack (rice ball) and oral glucose with equal caloric value, oral glucose resulted in the greatest increase in the blood glucose level [36]. On the other hand, in cirrhotic patients, protein malnutrition occurs more frequently [2–5], and prevention of PEM is critical for patients. Certainly, long-term oral administration of BCAA increased serum albumin in cirrhosis, leading to better QOL and prognosis [37]. Moreover, for the synthesis and breakdown of protein molecules, a substantial amount of energy is simultaneously required in the cell [32]. For these reasons, we selected Aminoleban EN, a BCAA and glucose mixture also containing vitamins and trace elements, usually lacking in patients with liver cirrhosis. Actually, after 1 week of LES administration, the value of BTR rapidly increased. Also, patients showed excellent compliance to the LES used in this study. Since they could all eat every meal, including the Aminoleban EN, none dropped out. However, further study is necessary to determine whether Aminoleban EN is better than a light glucose-rich snack as LES.

Certainly, LES could improve energy malnutrition, correct amino acid imbalance, and improve glucose intolerance in patients with liver cirrhosis. Since alimentary therapy may have an effect on prognosis, etc., effects of longer administration of LES on prognosis and QOL must be investigated in the future, including detailed examinations for glucose tolerance.

## Acknowledgements

This work was supported in part by Grants-in-Aid Nos. 11670507, 12670490 and 10470136 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and a Grant-in-Aid for translational research from the Ministry of Health, Labor and Welfare of Japan.

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研究速報 PP2-15

# 肝細胞癌における合併症と治療を考慮した医療費推定の試み

石田　博[*1]　井上裕二[*1]　黒川典枝[*2]　日野啓輔[*3]　沖田　極[*2]

合併症を起こしやすい肝硬変症を基礎疾患とする肝細胞癌患者を対象として医療費変動の主要な説明要因および医療費推定の検討を行った．

肝細胞癌で入院した患者を対象に，レセプト請求データから入院期間，実施された診療行為および診療報酬請求額を抽出した．肝硬変症の非代償性合併症および肝細胞癌への治療の種別とその実施の有無を関連する診療行為から判定し，診療報酬請求額を目的変数とした単変量解析および多変量解析を行った．

単変量解析から合併症や治療の有無により入院日数および診療報酬請求額に有意な差が見られ，さらに，それぞれの要因で分けた診療報酬請求額と入院日数の間に有意な相関が見られた．そのため，得られた医療費の重回帰モデルでは入院期間が最も有意な変数で，以下，肝細胞癌治療，非代償性合併症の順で有意であった．検証用データにおいてもモデルによる予測額と実際額との相関係数(Spearman)は0.89と良好であった．

今回のような診療報酬請求データをもとにした統計モデルによって合併症などの病態や治療による医療費の主たる変動要因を明らかにし，それらの組み合わせの医療費を推定することが可能と考えられた．

■キー・ワード：医療費，肝細胞癌，合併症

**Estimation of Inpatient Cost for Hepatocellular Carcinoma with its Complications and the Specific Treatments**：Ishida H[*1], Inoue Y[*1], Kurokawa F[*2], Hino K[*3], Okita K[*2]

Appropriate estimation of inpatient cost is difficult especially among the complicated cases with several complications or combination of specific treatments. We made a regression model to estimate inpatient cost per admission for hepatocellular carcinoma(HCC) with or without decompensated complications. 260 patients hospitalized due to HCC in our hospital were tracked retrospectively. For each case, the period of hospitalization and records of underwent specific medical interventions during it were extracted from the insurance claim data.

Relationship between the total costs(insurance reimbursement) included basic hospital charge and each 0-1 variable corresponding to execution of the specific medical interventions for each complication or HCC therapy(resection, percutaneous ethanol injection, Chemo-lipiodol therapy or parental anticancer agent injection, etc.) was investigated using univariate and multivariate analysis.

As a result of multivariate analysis, a model consisted of several variables of medical interven-

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tion : resection, Chemo-lipiodol therapy and parental anticancer agent injection, and complication : ascites and edema, and variceal bleeding in addition to the period of hospitalization was obtained. It predicted total inpatient cost with the high correlation coefficient(0.89) among HCC cases of separated data set for validation.

This study suggested that the model consisted of several specific medical interventions corresponding to each complication or treatment obtained from insurance claim data can reveal significant factors causing considerable variance of costs and predict more precisely cost of the complicated disease status.

**Key words** : Cost of illness, Hepatocellular carcinoma, Complication

## 1. 緒　論

医療経済において医療費の適切な推定は中心となる課題であり，費用効果分析などの関連する研究においてもその精度の高さは重要である．しかし，医療費推定の方法論についての研究は多くはない[1,2]．

疾患別に医療費の推定を行う場合には，該当する患者の総医療費をもとに平均値あるいは中央値により求める方法が一般的であるが，相当数の症例がないとばらつきの少ない信頼性の高い費用を求めることは容易ではない．さらに合併症などにより複合化した病態を有する場合には，その合併症の治療により医療費の変動が大きくなるため，多数の症例を集積し，それぞれの病態に合併症の組み合わせを加えて層別化した後に医療費を推定することが必要となる．例えば，2003年から導入された包括支払い制度のDPC(Diagnosis procedure combination)ごとの診療点数は，個別の疾患群やその特異的な治療が行われた実際の症例をもとにした医療費，厳密には診療報酬点数の積み上げによる保険償還額であり，調査医療機関から提出された多数の類似症例の層別化による平均入院日数およびその費用から求められ，行政が保有する大規模データベースとして期待が寄せられている．しかし，このような大規模データベースといえども層別化後にも十分と言える多症例のデータを得る保証はないため，複合病態において比較的少ない症例数であってもばらつきの少ない医療費を推定する方法を開発することは重要な課題と考えられる．

一方，医療費の推定ならびにその変動要因を明らかにするために多変量解析が用いられることが増えている[3,4]．この推定モデルによって，合併症および種々の治療に伴う診療行為に要する医療費を，総医療費における独立したコンポーネントとして切り分けることが可能であれば，その組み合わせにより医療費の推定が可能になると考えられる(**図1**)．

今回，複合した病態を有する患者の入院医療費の推定を課題として，様々な合併症およびその状態に応じた治療選択がなされる肝細胞癌患者の入院医療費の推定を診療報酬請求データをもとに多変量解析を用いて行った．

## 2. 目　的

診療報酬請求データから抽出された種々の合併症に対する治療および肝細胞癌に対する治療の実施の有無を変数とし，総医療費に対する変数毎の有意性の検証を行うとともに，重回帰モデルを作成し，それぞれの変数の総医療費に関わる寄与度について検討する．そして得られた医療費推定モデルにおいて有意となった変数を独立したコンポーネントとして捉える医療費の構成モデル(**図1**)の妥当性を考察する．

## 3. 対象と方法

対象症例はモデル作成群と検証群の2群とした．モデル作成群は，当大学附属病院に肝細胞癌の診断・治療目的で入院し2003年7月1日から2004年3月31日までに退院となったのべ260症例(実患者187人，うち男性141人，年齢は50～85歳で平均およびその標準偏差は68.3±7.7歳)であり，この中で入院期間が5日未満のもの，情報に欠損