cancer recurrence. To our knowledge, there has been no detailed analysis of a large series of HCC patients with more than 10 years disease-free survival after curative hepatic resection. In the current series, 74 patients (8 %) survived for 10 years without disease recurrence after the initial hepatectomy. Fourteen of these patients (19 %) had later disease recurrence and received treatment with one or more treatment modalities. Generally, surgeons think that if there is no recurrence of cancer for 10 years after the initial operation, it should be thought that there will be little likelihood of recurrence of cancer long afterward. Should clinical follow-up then be terminated? From the results of this study, we believe that clinical follow-up after resection of HCC is very important and should continue for the remainder of the patient's life. Intrahepatic recurrence has been suggested to arise from three causes [28]: (1) the continued growth of residual tumor after incomplete excision may cause recurrence near the cut margin and may be responsible for early recurrence; (2) a metachronous and unrecognized synchronous multifocal primary tumor may cause recurrence far from the original site of the lesion and may be responsible for a late recurrence; and (3) a new primary tumor may develop. Because the median disease-free interval between the first operation and recurrence was 11.0 years in this series, and based on the higher incidence of dysplasia in patients with cirrhosis, it might be possible that there was new development of the cancer in these patients.

In multivariate analysis, the preoperative and 10-year platelet counts were identified as favorable independent factors for survival after 10 years of recurrence-free survival after curative hepatic resection of HCC. The platelet count is a simple test, and results can be determined easily by a routine laboratory procedure. In the present study, there was a significantly higher incidence of esophageal and/or gastric varices and serum type IV collagen 7S at 10 years after surgery in the recurrence group. In four patients with repeat hepatectomy for recurrent HCC, histological fibrosis of the underlying liver at the second operation was more advanced than at the first operation. Type IV collagen 7S is known to be useful for quantitative evaluation of liver fibrosis, and is employed for indirect testing of serum samples [17]. A low platelet count at 10 years after surgery, with a higher incidence of varices, higher levels of type IV collagen 7S, and more advanced fibrosis in patients with repeat hepatectomy, reflects the severity of portal hypertension, and indicates development of liver fibrosis in the recurrence group. Moriyama et al. [29] reported that monitoring of platelet counts is useful for determining the development of liver fibrosis in HCV-associated chronic liver diseases and for the determination of a highly carcinogenic state in the liver after interferon therapy. The importance of fibrosis in hepatocarcinogenesis has been described in patients with chronic viral hepatitis [30–32]. The annual incidence of development of HCC increased with the progression of liver fibrosis during long-term follow-up in patients with hepatitis B and C [31, 32]. Fibrosis of the liver develops through repeated necroinflammation and regeneration in the liver of patients with chronic hepatitis, and eventually progresses to liver cirrhosis [33]. Because this process requires vigorous mitosis of the hepatocytes in response to cell destruction, increased fibrosis is associated with a large amount of mitotic activity, which may allow accumulation of genetic transformations [34, 35].

The mechanisms involved in thrombocytopenia, which is observed in patients with chronic hepatitis, have not been fully elucidated. Increased sequestration and destruction of platelets in the enlarged spleen, which is an important mechanism involved in liver cirrhosis and portal hypertension, may not contribute to thrombocytopenia in chronic hepatitis C [36]. Possible mechanisms for thrombocytopenia have been proposed in chronic hepatitis, including decreased production of liver-derived thrombopoietin [37, 38], and increased destruction of platelets by antiplatelet antibodies [39]. Recent accumulated evidence indicates that the thrombocytopenia is caused by an autoimmune mechanism as a result of HCV infection. Nagamine et al. [40] found HCV-RNA in the platelets obtained from HCV-positive patients, indicating the possibility that an association of HCV/anti-HCV antibody immune complexes with the platelet surface can result in platelet antibody immunoglobulin) G (IgG) expression. They also demonstrated that platelet-associated IgG levels increased with the degree of histological progression in patients with chronic hepatitis C. In any case, thrombocytopenia is related to hepatocarcinogenesis through the development of liver fibrosis in patients with chronic hepatitis. It seems likely that a low platelet count is a risk factor for carcinogenesis from chronic hepatitis and for recurrence and survival of HCC after treatment, including liver resection [41–44]. The platelet count may be useful as a marker of late recurrence in HCC patients who survived in the long term.

Our first choice of treatment for recurrence of HCC is principally repeat hepatectomy because this procedure has been accepted as the most effective treatment [45]. However, repeat hepatectomy is limited to patients with resectable intrahepatic recurrence and well-preserved liver function. Our study indicated that nonsurgical treatments, such as RFA or TACE, could contribute to prolongation of survival when repeat hepatectomy is not indicated. Therefore, it is important to select appropriate treatment according to the pattern of recurrence, location of the tumor, and preserved liver function.

In conclusion, our data demonstrated that for patients with higher preoperative and 10-year platelet counts who

underwent curative resection of HCC, long-term survival after resection could be expected. However, because tumor recurrence is common even after 10 years, postoperative follow-up is important and should continue for the remainder of the patient's life. The platelet count is a useful, inexpensive, and convenient marker of late recurrence (later than 10 years following curative resection) of HCC. Finally, aggressive therapy for recurrence, including a second resection when necessary, is recommended.

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Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy

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KEYWORDS:
Liver cancer;
Cirrhosis;
Hepatectomy;
Exercise;
Insulin resistance

Abstract

BACKGROUND: The aim of this study was to examine the outcomes of exercise therapy in patients with hepatocellular carcinoma who underwent hepatectomy.

METHODS: Fifty-one patients with hepatocellular carcinoma were randomized to diet therapy alone (n = 25) or to exercise in addition to diet therapy (n = 26). Exercise at the anaerobic threshold of each patient was started 1 month preoperatively, resumed from 1 week postoperatively, and continued for 6 months.

RESULTS: Whole body mass and fat mass in the exercise group compared with the diet group were significantly decreased at 6 months postoperatively. Fasting serum insulin and the homeostasis model assessment score were also significantly decreased. At 6 months, anaerobic threshold and peak oxygen consumption were significantly increased, while serum insulin and insulin resistance were significantly improved in a high-frequency exercise subgroup compared with a low-frequency group.

CONCLUSIONS: Perioperative exercise therapy for patients with hepatocellular carcinoma with liver dysfunction may improve insulin resistance associated with hepatic impairment and suggests a benefit to the early resumption of daily exercise after hepatectomy.

Interest in the role of physical activity in the primary prevention of cancer is increasing as evidence of a protective effect accumulates. Recent reviews of physical activity in relation to cancers such as colon cancer,[1] breast cancer,[2–4] prostate cancer,[5] and all cancers[6–12] have provided a detailed assessment of the level of epidemiologic evidence for the putative association. In Japan, a westernized lifestyle has become common in recent years, and the rates of obesity, diabetes, dyslipidemia, and hypertension have gradually increased. Metabolic syndrome is characterized by insulin resistance and is associated with atherosclerosis and hypertension, as is also recognized as an inflammatory condition.[13,14] Accumulating evidence suggests that insulin resistance plays a key role in both hepatocellular damage and hepatocarcinogenesis by inducing oxidative stress in patients with various liver diseases, including viral infection and fatty liver.[15–17] Because the liver is a major target organ for insulin when regulating the blood glucose level, >70% of patients with liver cirrhosis also exhibit insulin resistance regardless of the etiology.[18]

Management of insulin resistance is a critical issue for patients with chronic liver disease in terms of both

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maintaining liver function and preventing hepatocarcinogenesis. Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide.[19] It is important to maintain good perioperative nutrition and metabolism to improve the prognosis of patients with HCC undergoing hepatectomy.[20,21] So far, little attention has been paid to the role of exercise in the management of hepatectomy patients. In the present study, we aimed to clarify whether a perioperative and postoperative exercise program had any metabolic or physical advantages for cirrhosis patients with HCC who underwent hepatectomy.

Methods

Patients

Patients with HCC who had chronic hepatitis or cirrhosis and were scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between December 2008 and February 2010 were screened for this study. The eligibility criteria for inclusion were as follows: (1) elective hepatectomy, but no bilioenterostomy; (2) age 20 to 80 years; (3) a preoperative diagnosis of HCC with no previous treatment; (4) no other malignancies; (5) Child-Pugh score A or B; (6) adequate cardiopulmonary function (results of electrocardiography, echocardiography, and spirometry within the normal range); (7) leukocyte count $\geq$3,000/mm^3; (8) hemoglobin level $\geq$9.5 g/dl; (9) platelet count $\geq$50,000/mm^3; (10) serum creatinine <1.2 mg/dL; (11) total bilirubin <2.0 mg/dL; (12) local nodular disease without extrahepatic metastasis; and (13) Eastern Cooperative Oncology Group performance status 0 or 1.[22] Exclusion criteria were inability to perform exercise, ischemic cardiomyopathy, 3rd-degree atrioventricular block, severe obstructive pulmonary disease, and severe hypertension (blood pressure >180/110 mm Hg). All patients gave written informed consent for participation in this study, and the protocol was approved by the institutional ethics committee.

The study protocol was explained to all patients, and they understood that they would be randomly assigned to either conventional perioperative management with diet alone (diet group, n = 26) or would receive exercise combined with diet (exercise group, n = 25). The protocol for this study was approved by the institutional ethics committee.

In a preliminary study, we examined the changes in portal blood flow (PBF) with exercise. The pre-exercise and postexercise PBF rate and volume were measured using Doppler ultrasound in healthy age-matched volunteers and patients with HCC with chronic hepatitis or cirrhosis (at 1 month after surgery) using the Ascendus Ultrasound System (Hitachi Aloka Medical, Ltd, Tokyo, Japan), equipped with a multifrequency (2 to 5 MHz) convex transducer. Exercise was performed at the anaerobic threshold (AT) for 20 minutes on a bicycle ergometer, and measurements were obtained before exercise, immediately afterward, and 1 hour after the completion of exercise. In the healthy volunteers, data were also measured at one-third the respiratory compensation point.

Exercise program

Before starting exercise therapy, patients underwent cardiopulmonary exercise testing on a bicycle ergometer using an incremental protocol (5.0, 7.5, and 10 W/min). The 12-lead electrocardiogram was continuously monitored for ST-segment deviation, arrhythmias, and heart rate at rest and during the exercise and recovery periods. Blood pressure was recorded at rest and every 2 minutes during the exercise and recovery periods. Peak oxygen consumption per unit time (Vo_2) was obtained from breath-by-breath analysis of expired air. Peak Vo_2 was defined as the highest mean value during exercise when the subject could no longer continue pedaling at 60 rpm. The AT, the onset of metabolic acidosis, was defined as the break point between carbon dioxide production and Vo_2[23] or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again.[24] Thus, AT was set at the time of maximum fat combustion[25] (Fig. 1). The respiratory compensation point was set at the point at which the ventilatory equivalent for carbon dioxide was lowest before a systemic increase and when the end-tidal carbon dioxide partial pressure reached a maximum and began to decrease.[26] Exercise was stopped when the patient requested it because of fatigue, pain, or headache or if there was a failure to maintain a speed >40 rpm for >30 seconds despite encouragement.

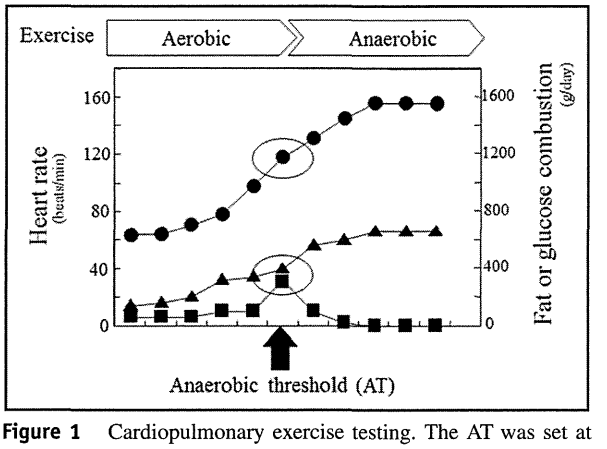

Figure 1 Cardiopulmonary exercise testing. The AT was set at the break point between carbon dioxide production and Vo_2, or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again. Thus, the AT was set at a maximum point of fat combustion. Circles indicate heart rate, triangles indicate glucose combustion, and squares indicate fat combustion.

An exercise program was tailored for each patient. Exercise was started as soon as possible after diagnosis, up to 1 month preoperatively, and was resumed from 1 week postoperatively and continued for 6 months (Fig. 2). The program consisted of 3 60-minute exercise sessions per week. Each session included 5 minutes of stretching exercises, 30 minutes of walking at an intensity based on the AT of each patient, 20 minutes of targeted stretching exercises, and 5 minutes of cooling down with stretching. Once or twice a month postoperatively, a medical doctor and exercise trainer confirmed the frequency and quantity of exercise each patient undertook. Patients in the exercise group showed 2 patterns at 6 months postoperatively, a highly active group and a less active group. We stratified the patients according to the frequency of exercise as standard (3 times a week) or high (5 or 6 times a week).

Diet

Both groups of patients were required to conform to specific diets. The dietitian provided instruction on the specific diet to both groups of patients and checked patient adherence preoperatively and at 1, 3, and 6 months postoperatively. For patients with chronic hepatitis or liver cirrhosis, the daily energy intake was set at 25 to 30 kcal/kg body weight, with a daily protein intake of 1.0 to 1.2 g/kg body weight and a daily sodium chloride intake of 5 to 7 g/kg body weight during the 1-month preoperative and 6-month postoperative periods. For patients with diabetes or fatty livers, daily energy intake was set at 20 to 25 kcal/kg body weight, while the daily sodium chloride intake was set at 6 g/kg body weight for patients with hypertensive.

Laboratory tests and surgery

Before surgery, each patient underwent conventional liver function tests, with measurement of the indocyanine green retention rate at 15 minutes, and ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin liver scintigraphy.[27] Hepatitis screening was performed by measurement of hepatitis B surface antigen and hepatitis C antibody. Levels of α-fetoprotein and protein induced by vitamin K absence/antagonism-II were also measured in all patients. Insulin resistance was calculated from the homeostasis model of assessment of insulin resistance (HOMA-IR) using the following formula: HOMA-IR = fasting plasma insulin (μU/mL) × fasting plasma glucose (mg/dL)/405, which primarily reflects hepatic insulin resistance.[28] Total body mass, mineral-free lean mass (nonbone fat-free mass), fat mass, and truncal fat were measured using whole-body dual-energy x-ray absorptiometry.[29]

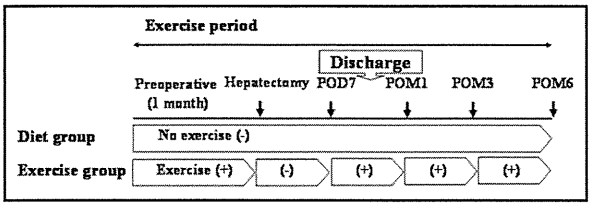

Figure 2 Experimental protocol. An exercise program was tailored for each patient. Exercise was started 1 month preoperatively, resumed from 1 week postoperatively, and continued for 6 months. Patients in both groups were given dietary advice. POD = postoperative day; POM = postoperative month.

Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al.[30] Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic artery and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of ≥1 additional contiguous segment), sectionectomy (resection of 2 Couinaud subsegments[31]), or segmentectomy (resection of 1 Couinaud subsegment). All of the nonanatomic procedures were classified as limited resection. One senior pathologist reviewed each specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the line of resection. Perioperative and postoperative complications and deaths were recorded.

Statistical analysis

Continuous variables are presented as mean ± SD. Differences between 2 groups were assessed using χ^2 tests or Mann-Whitney U tests, as appropriate. The level of significance was set at $P < .05$. All statistical analyses were performed using SPSS for Windows version 11.0J (SPSS, Inc, Chicago, IL).

Results

The study included 51 patients (36 men, 15 women; mean age, 69.7 years). In a preliminary study, we examined the changes in PBF with exercise. PBF during exercise at the AT showed no significant changes from before (PBF rate, 24.3 ± 6.6 cm/s; PBF volume, 606 ± 168 mL/min) to immediately after exercise (PBF rate, 21.5 ± 4.1 cm/s; PBF volume, 579 ± 126 mL/min) or 1 hour after exercise (PBF rate, 23.6 ± 4.3 cm/s; PBF volume, 667 ± 80 mL/min) in healthy volunteers. However, PBF was significantly decreased on completion of exercise at one-third of the respiratory compensation point (PBF rates before, immediately after, and 1 hour after exercise, 24.0 ± 6.2, 14.9 ± 3.8, and 23.1 ± 3.4 cm/s, respectively; before vs immediately after, $P = .0472$, immediately after vs 1 hour after, $P = .0451$; PBF volumes before, immediately, and 1 hour after exercise, 588 ± 210, 386 ± 155, and 702 ± 230 mL/min, respectively; before vs immediately after, $P = .0105$, immediately after vs 1 hour after, $P = .0443$).

In patients with HCC with hepatic impairment exercising at the AT, portal flow showed no significant changes

(PBF rates before, immediately after, and 1 hour after exercise, 18.0 ± 4.7, 17.2 ± 3.6, and 18.3 ± 3.4 cm/s, respectively; PBF volumes before, immediately after, and 1 hour after exercise; 495 ± 290, 437 ± 139, and 504 ± 156 mL/min, respectively). Therefore, we concluded that exercise at the AT was safe for patients with HCC with hepatic impairment.

Preoperative characteristics

Table 1 summarizes the preoperative characteristics of the 2 groups of patients. There were no differences between the 2 groups with respect to age, gender, hepatitis virus status, Child-Pugh class, preoperative liver function (serum albumin, total bilirubin, cholinesterase, prothrombin time, platelet count, alanine aminotransferase, indocyanine green retention rate at 15 minutes, and ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin Rmax), α-fetoprotein, protein induced by vitamin K absence/antagonism-II, and esophageal and/or gastric varices.

Perioperative parameters and pathologic findings

As shown in Table 2, the operating time, blood loss, blood transfusion, surgical procedures, postoperative complications, and hospital death rate did not differ significantly between the 2 groups. The postoperative hospital stay of the exercise group was shorter than that of the diet group, but not significantly. The pathologic findings of the 2 groups are also listed in Table 2. There were no differences between them with respect to tumor size, number of tumors, histology, microscopic capsule formation, microscopic vascular invasion, microscopic surgical margin <5 mm from the tumor border, associated liver diseases, and tumor-node-metastasis stage.

Physical and biochemical parameters

Whole body mass and body and fat mass at the waist were significantly decreased in the exercise group compared with the diet group after 6 months (Table 3). No differences were detected between the 2 groups with respect to the serum levels of protein (albumin and rapid turnover proteins) and lipids (triglycerides, total cholesterol, and low-density lipoprotein cholesterol) at 6 months postoperatively (data not shown). As an indicator of insulin resistance, fasting insulin, glucose, and HOMA-IR levels were measured before and after treatment (Fig. 3). In the exercise group, fasting serum insulin and HOMA-IR both showed significant decreases at 3 and 6 months postoperatively compared with the diet group. There were no differences between limited and anatomic resection on glucose, insulin, and HOMA-IR outcomes.

Comparison between standard and high-frequency exercise subgroups

Some patients failed to continue to exercise in the long term for various reasons (tumor recurrence, financial reasons, exacerbation of other diseases, etc). The changes in AT Vo_2 and peak Vo_2 after 6 months were significantly greater in the high-frequency exercise group than in the standard group (Table 4). The decreases in whole body mass and whole body fat mass were significantly greater in the high-frequency group. There were no significant

Table 1 Preoperative characteristics of the 2 groups of patients with HCC

Variable	Diet group (n = 26)	Exercise group (n = 25)	*P*
Age (y)	71.3 ± 8.8	68.0 ± 9.1	.1952
Men/women	19/7	17/8	.6908
HBV/HCV/NBC	4/18/4	6/11/8	.1823
Child-Pugh class (A/B)	25/1	24/1	.9774
Diabetes mellitus (yes/no)	3/23	3/22	.9592
ICGR15 (%)	16.8 ± 7.5	15.3 ± 8.0	.5098
Albumin (g/dL)	3.85 ± .32	3.93 ± .43	.4779
Total bilirubin (mg/dL)	.83 ± .23	.80 ± .20	.4172
Cholinesterase (U/L)	230 ± 65	237 ± 69	.4533
Prothrombin time (%)	90 ± 13	91 ± 10	.4080
Platelet count ($\times 10^4/\mu L$)	15.4 ± 8.9	16.0 ± 6.0	.6196
ALT (U/L)	46 ± 21	55 ± 33	.2325
GSA-Rmax (mg/min)	.460 ± .208	.469 ± .154	.2394
AFP (ng/mL)	694 ± 2,242	2,804 ± 10,176	.3166
PIVKA-II (mAU/mL)	711 ± 1,761	2,124 ± 5,620	.2461
Esophageal and/or gastric varices (yes/no)	7/19	8/17	.6908

Data are expressed as mean ± SD or as numbers of patients.

AFP = α-fetoprotein; ALT = alanine aminotransferase; GSA-Rmax = regional maximum removal rate of ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin; HBV = hepatitis B virus; HCV = hepatitis C virus; ICGR15 = indocyanine green retention rate at 15 minutes; NBC = no hepatitis B or C virus; PIVKA-II = protein induced by vitamin K absence/antagonism-II.

Table 2 Operative and postoperative characteristics of the 2 groups of patients with HCC

Variable	Diet group (n = 26)	Exercise group (n = 25)	*P*
Surgical procedure (limited/anatomic)	16/10	14/11	.6879
Operating time (min)	326 ± 115	338 ± 152	.7404
Operative blood loss (mL)	986 ± 1,129	1,219 ± 1,767	.5811
Blood transfusion (yes/no)	3/23	4/21	.6435
Tumor size (cm)	4.10 ± 2.29	5.53 ± 5.33	.2230
Number of tumors	1.42 ± .70	1.40 ± .65	.9034
Histology (good/moderate/poor)	6/18/2	5/20/0	.3367
Microscopic capsule formation (yes/no)	21/5	22/3	.5466
Microscopic vascular invasion (yes/no)	14/12	12/13	.6763
Microscopic surgical margin (yes/no)	2/24	2/23	.9674
Associated liver disease (normal/fibrosis or hepatitis/cirrhosis)	3/14/9	5/11/9	.6568
Tumor stage (I or II/III or IV)	21/5	19/6	.6789
Morbidity (yes/no)	3/23	2/23	.6710
Mortality (yes/no)	0/26	0/25	
Postoperative hospital stay (d)	17.5 ± 11.3	13.7 ± 4.0	.1200

Data are expressed as mean ± SD or as numbers of patients.

changes in whole body fat-free mass ("muscle mass") in either group. Laboratory tests revealed that the platelet count at 6 months was significantly higher in the high-frequency group than in the standard group. Both fasting serum insulin and HOMA-IR showed significant decreases in the high-frequency group compared with the standard group. The branched-chain amino acid/tyrosine ratio was also significantly increased in the high-frequency group.

Comments

Rest has traditionally been considered essential for patients with chronic liver disease, because hard exercise causes a decrease in hepatic blood flow. However, attention has recently been paid to the negative effect of reduced muscle mass due to lack of exercise in patients with chronic liver disease.[32] In fact, when patients with liver disease performed exercise, there was no clinically important deterioration in hepatic function, and a slight improvement was actually observed.[33,34] It is known that physical activity reduces the risk for breast cancer and colon cancer and may also reduce the risk for several other types of cancer.[35–39] Regular exercise plays an important role in helping maintain a healthy body weight, while excess weight increases the circulating levels of estrogens, androgens, and insulin, all of which are associated with cell proliferation and tumor growth.[40] Physical activity may reduce the risk for cancer by decreasing circulating levels of insulin and insulin-like growth factors and by improving energy metabolism. Physical activity also helps prevent the occurrence of type 2 diabetes, which is associated with an increased risk for cancer of the colon, pancreatic cancer, and possibly other tumors.[41–44]

Table 3 Physiologic parameters of the 2 groups of patients with HCC

Variable	Whole body	Trunk	Waist	Hip
Body mass at 6 mo (% of baseline)				
Diet group	100 ± 4	99 ± 7	102 ± 8	99 ± 8
Exercise group	95 ± 5	95 ± 5	93 ± 7	96 ± 3
P	.0375*	.1119	.0028*	.0894
Fat mass at 6 mo (% of baseline)				
Diet group	97 ± 18	96 ± 18	99 ± 18	96 ± 17
Exercise group	86 ± 14	84 ± 15	82 ± 22	89 ± 14
P	.0685	.0595	.0365*	.2268
Fat-free mass at 6 mo (% of baseline)				
Diet group	100 ± 6	101 ± 7	105 ± 9	101 ± 9
Exercise group	101 ± 6	102 ± 9	102 ± 15	101 ± 7
P	.6492	.7422	.4822	.9479
Bone mineral density at 6 mo (% of baseline)				
Diet group	98 ± 3	95 ± 8	103 ± 12	92 ± 26
Exercise group	98 ± 3	97 ± 9	100 ± 17	98 ± 5
P	.9923	.6309	.6009	.4119

*Statistically significant ($P < .05$).

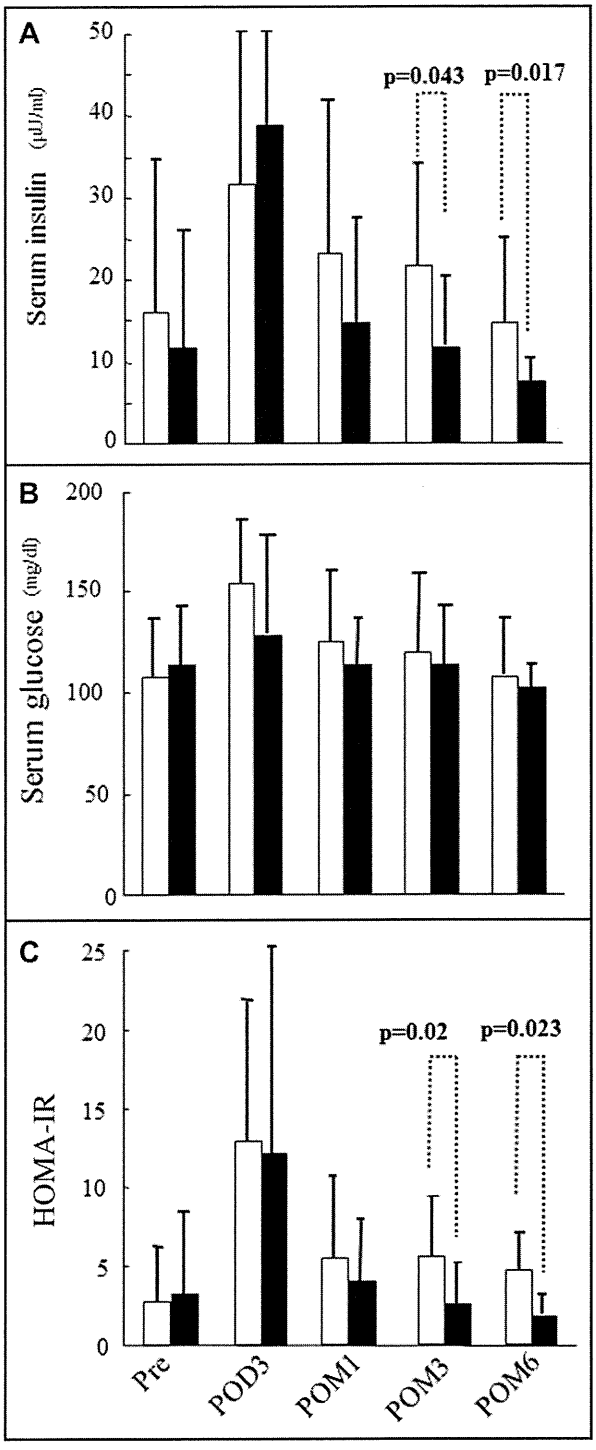

Figure 3 Effect of exercise on insulin resistance in patients with HCC with hepatic impairment. (A) Serum free insulin, (B) serum glucose, and (C) HOMA-IR in the diet group (white bars) and the exercise group (black bars). POD = postoperative day; POM = postoperative month.

However, there have been few reports about the effects of long-term exercise, and there have been no studies of perioperative exercise in patients with chronic hepatitis or cirrhosis undergoing hepatectomy for HCC. In the present study, exercise was started at approximately 1 month preoperatively, resumed approximately 1 week after surgery, and continued for 6 months at an intensity based on the AT of each patient. Each patient performed >3 60-minute exercise sessions weekly (mainly on a bicycle ergometer during hospitalization and by walking after discharge), and also received dietary guidance at 1, 3, and 6 months. Exercises mainly targeted the lower body, while upper-body muscle training was started from 2 months postoperatively to avoid wound pain. We hypothesized that exercise at the AT would reduce visceral fat and prevent loss of muscle mass. We found that the whole body mass and the fat mass at the waist both decreased significantly in the exercise group, while the skeletal muscle mass showed little change in either group (Table 3). No significant differences were detected between the 2 groups with respect to laboratory data such as lipids or rapid turnover proteins. None of the patients showed an increase of transaminases with exercise, and there were no clinical problems in the patients who performed exercise >3 times a week. At 3 and 6 months postoperatively, both serum insulin and the insulin resistance index showed significant improvement in the exercise group (Fig. 3).

It was recently reported that hepatic impairment, particularly cirrhosis, leads to secondary insulin resistance and hyperinsulinemia, which can then promote carcinogenesis. Management of insulin resistance is thus a critical issue for patients with chronic liver disease both to protect liver function and to prevent hepatocarcinogenesis. Alterations in glucose metabolism also affect fat metabolism, which may result in the excess production of lipid peroxide and reactive oxygen species,[45,46] which in turn damages hepatocytes,[17] leading to possible development of HCC.[46] However, it is difficult to manage insulin resistance associated with chronic liver disease because restriction of calorie intake conflicts with the need to overcome malnutrition arising from hepatocellular damage. A reduction in body weight with exercise has been reported to be advantageous in obese patients with chronic liver disease.[33] The present study had a short postoperative observation period, so no differences in the recurrence of HCC or of mortality were detected between the 2 groups (data not shown), but longer follow-up is necessary to confirm this finding.

When we divided the exercise group into standard and high-frequency subgroups on the basis of the weekly number of exercise sessions, AT Vo_2 and peak Vo_2 were significantly higher in the high-frequency group after 6 months. In addition, whole body mass and fat mass were significantly lower in the high-frequency group compared with the standard group at 6 months. Furthermore, the platelet count and branched-chain amino acid/tyrosine ratio were increased and the serum insulin/insulin resistance index ratio was significantly improved in the high-frequency group.

Table 4 Comparison of exercise tests, DEXA parameters, and laboratory data between the standard and high-frequency exercise subgroups

Variable	Standard (n = 11)	High frequency (n = 14)	*P*
Exercise parameters			
AT Vo_2 at 6 mo (% of baseline)	102 ± 14	115 ± 18	.0379*
Peak Vo_2 at 6 mo (% of baseline)	103 ± 12	118 ± 11	.0015*
DEXA parameters			
Whole body mass at 6 mo (% of baseline)	97 ± 4	93 ± 6	.0314*
Whole body fat mass at 6 mo (% of baseline)	98 ± 16	80 ± 15	.0075*
Whole body fat-free mass at 6 mo (% of baseline)	98 ± 6	103 ± 5	.0628
Laboratory data			
Albumin (g/dL)			
Pre	3.79 ± .52	3.98 ± .37	.3077
Post	4.09 ± .38	4.13 ± .31	.8055
Platelet count ($\times 10^4/\mu L$)			
Pre	18.8 ± 10.8	17.6 ± 4.9	.7362
Post	11.3 ± 2.5	14.8 ± 4.6	.0288*
ALT (U/L)			
Pre	56 ± 22	45 ± 37	.3898
Post	35 ± 33	31 ± 27	.7529
Insulin (μU/mL)			
Pre	9.1 ± 4.5	8.5 ± 5.8	.8099
Post	10.7 ± 4.6	5.8 ± 2.8	.0193*
Glucose (mg/dL)			
Pre	111 ± 16	117 ± 24	.5079
Post	101 ± 20	102 ± 10	.8991
HOMA-IR			
Pre	2.43 ± 1.12	2.59 ± 2.21	.8488
Post	2.71 ± 1.23	1.47 ± .68	.0232*
BCAA			
Pre	438 ± 102	462 ± 58	.4958
Post	474 ± 114	604 ± 214	.0960
AAA			
Pre	91 ± 19	80 ± 16	.1888
Post	102 ± 26	87 ± 13	.1184
BTR			
Pre	5.08 ± .84	5.43 ± .90	.4263
Post	4.78 ± 1.02	6.92 ± 2.20	.0091*

Data are expressed as mean ± SD.

AAA = aromatic amino acids; ALT = alanine aminotransferase; BCAA = branched-chain amino acids; BTR = branched-chain amino acid/tyrosine ratio; DEXA = dual-energy x-ray absorptiometric; HOMA-IR = homeostasis model of assessment of insulin resistance; Vo_2 = oxygen consumption.

*Statistically significant ($P < .05$).

One limitation of the present study was the selection of patients. The patients taking part in the study were less sick than many patients who might undergo this protocol, and patients with more advanced disease may not respond as well.

In conclusion, perioperative and postoperative exercise for patients with HCC with hepatic impairment led to weight loss (because of a decrease in fat mass) and improvement in insulin resistance but had no effect on skeletal muscle mass. Maintenance of postoperative physical strength and earlier resumption of daily activities could be possible by intensifying perioperative and postoperative exercise. We recommended that patients continue to exercise for 6 months after surgery. However, because some failed to continue to exercise long term for various reasons, patients should be followed up carefully after hepatectomy and encouraged to perform continuous long-term exercise.

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4. その他の肝腫瘍

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最近の動向

肝臓には種々の腫瘍が発生するが，約90%以上を占める肝細胞癌，また約5%の胆管細胞癌が代表的な腫瘍である．しかし近年の検診の普及およびMRIを中心とする画像診断の進歩により，無症状で発見される腫瘍が増加している．その中には，日常診療ではあまり遭遇しないが肝細胞癌や胆管細胞癌との鑑別のうえで重要な腫瘍である混合型肝癌，胆管嚢胞腺癌や原発性肝肉腫，また肝良性腫瘍のうち，鑑別が重要と思われる肝細胞線種，血管腫，限局性結節性過形成などが含まれている．これらを的確に診断するためには，稀な腫瘍を鑑別疾患として念頭に置くことが重要となる．

その他の肝腫瘍：概説

『原発性肝癌取扱い規約』第5版補訂版では，肝臓に原発する上皮性悪性腫瘍は肝細胞癌，肝内胆管（胆管細胞）癌，胆管嚢胞腺癌，混合型（肝細胞癌と肝内胆管癌の混合）肝癌，肝芽腫，未分化癌に分類される[1]．第18回全国原発性肝癌追跡調査報告（2004～2005年）[2]によると20,753例の登録症例中，肝細胞癌は19,499例（93.96%），肝内胆管癌905例（4.36%），混合型肝癌160例(0.77%)，胆管嚢胞腺癌27例(0.13%)，肝芽腫14例(0.07%)，肉腫9例(0.04%)，未分化癌8例（0.04%），その他131例（0.63%）となっている．すなわち，肝細胞癌以外の悪性腫瘍は比較的稀であり，治療に関するガイドラインが確立していない疾患が大部分である．本稿では肝細胞癌，肝内胆管癌を除く原発性悪性腫瘍である**混合型肝癌，原発性肝肉腫（類上皮性血管内皮腫，血管肉腫，未分化肉腫，平滑筋肉腫），小児に特徴的な肝芽腫**，また肝良性腫瘍のうち，肝細胞癌や胆管細胞癌との鑑別が重要と思われる**肝細胞腺腫，血管腫，限局性結節性過形成**について，最新の文献的考察を加えて診断・治療法などを概説する．

混合型肝癌（Combined hepatocellular and cholangiocarcinoma）

同一腫瘍内に肝細胞癌と肝内胆管癌の成分が混在するもので，両腫瘍が離れ

1) 日本肝癌研究会 編：原発性肝癌取扱い規約，第5版補訂版．金原出版，2009
2) 日本肝癌研究会 編：第18回全国原発性肝癌追跡調査報告（2004～2005）．日本肝癌研究会，2009

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1884-8508/12/¥100/頁/JCOPY

て存在する場合は重複癌とみなす．混合型肝癌ではAFPやPIVKA-IIに加えCEAやCA19-9の上昇を伴う場合がある．第18回全国原発性肝癌追跡調査報告[2]によると，原発性肝癌20,753例中，混合型肝癌は160例で原発性肝癌の0.8%である．混合型肝癌症例において，HBsAg陽性が18.9%，HCV抗体陽性が46.7%であり，6割以上は**肝炎ウイルス**に感染しており，**肝細胞癌**の背景と類似する傾向を示す．画像所見としては基本的に肝細胞癌組織内の造影効果に乏しい部分が胆管癌成分を示すことが多く，低分化型肝細胞癌との鑑別が問題となる．**肝内胆管癌**と同様に**リンパ節転移**をきたす場合がある．組織所見は同一腫瘍内に**肝細胞癌組織と胆管癌組織が混在**する．両癌腫成分の性格を有する細胞も認められることから，癌幹細胞の観点から考えると肝細胞や胆管細胞の双方向性を有する幹細胞や前駆細胞由来の腫瘍から発生し，各々の成分の方向に最終分化した状態が混合型とも考えられる．肝細胞癌と胆管細胞癌はその予後に差がある．一つの腫瘍の治療において予後の異なる癌が両者存在する場合，予後不良な腫瘍に焦点を当てた治療をしなければ予後向上にはつながらない．治療方針としては肝細胞癌と同様に切除可能であれば根治切除を目標とするが，術前に混合型と確定することが困難であるため，一般的に肝細胞癌と比較し**予後不良**であるといわれている[3]．最近，矢野ら[4]は混合型肝癌6例，肝細胞癌377例，肝内胆管癌36例の三群間における外科切除後長期成績を報告した．混合型肝癌切除例は全例男性，6例中5例がウイルス肝炎マーカー陽性および組織学的血管浸潤陽性であり，全例stage III以上であった．術後1年，2年生存率はそれぞれ66%，16%であり，肝細胞癌および肝内胆管癌のそれらと比較し不良であった（累積生存率；混合型肝癌 vs 肝細胞癌　$p = 0.008$，混合型肝癌 vs 肝内胆管癌　$p = 0.373$）．また，混合型肝癌は，患者背景因子は肝細胞癌と類似しているが，予後や再発形式は肝内胆管癌と類似していた．一方，Zhanら[5]は27例の混合型肝癌に対して肝切除術25例および肝移植術2例を行った．男性24例，女性3例であり，術前血清α-fetoprotein > 20 ng/mLの高値を示した患者は37%であった．術後1年，2年生存率はそれぞれ73%，49%であり，術後1年，2年無再発生存率は54%，41%であった．肝切除および肝移植例それぞれ1例が手術時死亡となっているが，術死に対する予後因子は診断時有症状および**所属リンパ節転移陽性**，また再発に対する予後因子においても，**所属リンパ節転移陽性**および切除断端癌浸潤陽性が同定された．

原発性肝肉腫（Primary hepatic sarcoma）

原発性肝肉腫は肝臓の支持組織としての間葉系組織や血管系より発生する**非上皮性悪性腫瘍**であり，原発性肝癌取扱い規約[1]ではWHOの肝腫瘍組織分類（1994年）に沿い非上皮性悪性腫瘍に分類され，**①類上皮性血管内皮腫，②血管肉腫，③未分化肉腫，④横紋筋肉腫，⑤その他（平滑筋肉腫など）**に細

3) 中野雅行：【肝・胆道系症候群（第2版）その他の肝・胆道系疾患を含めて】 肝臓編 肝細胞癌　特殊型肝細胞癌　混合型肝癌（肝細胞癌と肝内胆管癌の混合）．“日本臨牀 別冊 肝・胆道系症候群II” pp127-129, 2010

4) 矢野公一，千々岩一男，近藤千博 他：混合型肝癌切除例の臨床病理学的検討　—肝細胞癌，胆管細胞癌との比較—．胆道 25：163-168, 2011

5) Zhan Q, Shen BY, Deng XX et al : Clinical and pathological analysis of 27 patients with combined hepatocellular-cholangiocarcinoma in an Asian center. J Hepatobiliary Pancreat Sci 2011 (Jul 9) [Epub ahead of print]

分化されている．我が国における頻度は，第18回全国原発性肝癌追跡調査報告[2]によると，2004～2005年の2年間の原発性肝癌登録20,627例中9例(0.04%，男7：女2）であった．なお，第16回，第17回の同調査報告では，それぞれ11例（0.06%，男6：女5）．19例（0.10%，男11：女8）と男性にやや多く，原発性肝癌の0.1%以下の頻度である[6]．治療においては，これまでに成人の肝原発肉腫の治療法についてのまとまった報告は少ない．治療の基本は外科切除と考えられるが，多くの症例で診断時 既に進行しており**完全切除は困難**なことが多い．

1．類上皮性血管内皮腫（Epithelioid haemangioendothelioma）

一般的に軟部組織に発生する**血管内皮細胞由来**の腫瘍であるが，その他**骨，肺，肝臓，腹膜**にも発生する．性差は**肺・肝臓**の場合には**女性優位**であるとされている．30～50歳に好発し，再発や転移をきたすことがある．通常自覚症状を訴えることは少なく腫瘍が増大したための症状によることが多い．画像所見では約20%に**石灰化巣**がみられ，腫瘍の血流は乏血性，多血性等様々な報告があり一定したものはない．**多結節型**と**単結節型**の2型に分類されるが，約80%が**多結節型で両葉**にわたり腫瘍径は種々である．稀にCEA陽性例を認める．組織所見では腫瘍の中心部は壊死，梗塞，出血と様々であり，腫瘍細胞は好酸性の胞体を有し，中等度の核異型を伴う短紡錘形の上皮細胞が篠状あるいは小胞巣を形成した未分化な血管腔を形成している．これらの腫瘍細胞は第8因子関連抗原が陽性となる．治療方針は，偶然発見された腫瘤では肝生検を行い，signet-ring cell carcinoma様の細胞がみられ，**第8因子関連抗原**，CD31，UEA1のいずれかが陽性の場合には診断がつけられる．効果的な化学療法の報告はなく，切除可能であれば切除が望ましい．多発する場合は**肝移植**の適応となる[7]．Mehrabiら[8]は，肝移植128例（44.8%），肝切除27例（9.4%），化学療法60例（21%），無治療71例（24.8%）の計286例の治療成績を検討した．化学療法に関しては，5-Fu，MMCなどの動注や，IL-2，IFNα-2bの全身投与などの報告が散見され，その他にも肝動脈塞栓療法も報告されている．治療法別の5年生存率は，肝切除75%，肝移植54.5%，化学療法30%，無治療4.5%の順となっている．同疾患の進展形式上，切除が可能となるのは約10～15%ではあるが，安全に施行可能であれば外科的切除が最も成績が良い．また，他の腫瘍性肝疾患と異なり，本疾患は肝外病変を伴っていても肝移植を含めた外科的切除の適応と考えられている．小児の類上皮性血管内皮腫に対する脳死肝移植治療に関する論文が，Guiteauら[9]より報告されている．1987年から2007年までのUNOSデータベースより，366人の小児の肝腫瘍に対する脳死肝移植症例において，肝芽腫237例，肝細胞癌58例，類上皮性血管内皮腫35例，その他36例であった．移植後5年生存率は，類上皮性血管内皮腫が61%で，肝芽腫72%やその他肝腫瘍79%と比較し不良であったが，肝細胞癌54%より

6) 宇都宮　徹，島田光生，居村　暁 他：[肝・胆道系症候群（第2版）　その他の肝・胆道系疾患を含めて] 肝臓編　肝細胞癌以外の肝腫瘍　原発性肝肉腫．“日本臨牀 別冊 肝・胆道系症候群 II” pp276-280, 2010

7) 上村顕也，須田剛士，青柳　豊：【肝・胆道系症候群（第2版）】 肝臓編（下）肝細胞癌　以外の肝腫瘍　肝類上皮血管内皮腫．“日本臨牀 別冊 肝・胆道系症候群 II” pp225-228, 2010

8) Mehrabi A, Kashfi A, Fonouni H et al : Primary malignant hepatic epithelioid hemangioendothelioma : a comprehensive review of the literature with emphasis on the surgical therapy. Cancer 107 : 2108-2121, 2006

9) Guiteau JJ, Cotton RT, Karpen SJ et al : Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma : The UNOS experience. Pediatr Transplanation 14 : 326-331, 2010

良好であった．グラフト生着率においても同様の結果であった．小児類上皮
血管内皮腫に対する肝移植治療は，これまでの諸家の報告と比較し移植後生
率が不良であったことを指摘している．

2. 血管肉腫（angiosarcoma）

血管肉腫は第二次大戦中に用いられた放射性造影剤である二酸化トリウム
トロトラスト）や塩化ビニルの工業性曝露によって誘発されることが知られ
いる．**60歳代**に好発し**男性**に多い．**血管内皮細胞由来**の腫瘍で，原発性肝
腫の中では類上皮性血管内皮腫とならんで頻度が高い．腫瘍が血管に富むた
血栓形成や腹腔内出血をきたしやすく，貧血や血小板減少を伴うこともある．
像所見はCT，MRIでは周囲との境界明瞭な腫瘍として描出され，造影にて
行に富み一部は濃染像が遷延し，画像上は海綿状血管腫の所見に類似するた
鑑別は困難な場合が多い．組織所見は核の異型・分裂を伴う血管内皮類似の
瘍細胞が類洞に沿う形で浸潤・増殖する像が認められる．治療方針は外科的
除が基本であるが，**術後1年以内の再発**が多い．化学療法に関しては
sfamide, 5-fluorouracil, doxorubicin, paclitaxel, carboplatin, methotrexate
どが単独あるいはその組合せで試みられているが標準的なものはない．肝血
肉腫の**予後は極めて不良**であり，診断からの平均生存期間は6ヵ月，2年以
生存することは稀である[10]．手術は現時点で肝血管肉腫を根治しうる唯一
治療法であり，根治切除可能であった場合には予後の改善が期待できる．し
し特異的な症状がなく，画像所見のみから診断することも困難であり，根治
除可能な症例は約20%と，発見時には既に手術不能である場合が多い．

3. 未分化肉腫（undifferentiated sarcoma, embryonal sarcoma）

好発年齢は6～10歳であるが成人例での報告も散見される．性差はない．
腹部の膨隆と腹痛が初発症状であることが多い．巨大な単発腫瘍であることが
く，境界は明瞭であるが内部に出血，壊死，嚢胞形成を認める．Liら[11]は，
例のうち，肝動脈塞栓化学療法を先行し肝切除行った2例の平均生存期間は
0Mであり，肝切除単独2例の21Mより良好であったと報告している．

4. 平滑筋肉腫（leiomyosarcoma）

50歳代に好発し性差は認めない．肝静脈または胆管の**平滑筋由来**と考えら
れる．多くは**巨大な単発腫瘍**として診断され，そのため腹痛や体重減少を認め
ることがある．平滑筋腫との組織学的鑑別は必ずしも明確ではないが，核分裂
数や核異型を中心に評価する．また他臓器，特に肝以外の腹腔内原発巣からの
転移性平滑筋肉腫との鑑別も要する．発育は比較的緩徐であるが腹腔内破裂の
報告もある．年齢は6～10歳であるが成人例での報告も散見される．最近，
Shivathirthanら[12]は原発性平滑筋肉腫に関する自験例を含めた英語論文記載
4例の集計を報告している．男性13例女性20例（不明1例）であり，診断
時年齢中央値61歳（12～86歳）であった．治療法は肝切除22例，肝移植3例，

10) 三浦智史，高橋　達：【肝・胆道系症候群（第2版）】 肝臓編（下）肝細胞癌　以外の肝腫瘍　肝血管肉腫．“日本臨牀 別冊 肝・胆道系症候群II” pp283-286, 2010

11) Li XW, Gong SJ, Song WH et al : Undifferentiated liver embryonal sarcoma in adults : a report of four cases and literature review. World J Gastroenterol 16 : 4725-4732, 2010

12) Shivathirthan N, Kita J, Iso Y et al : Primary hepatic leiomyosarcoma : Case report and literature review. World J Gastrointest Oncol 3 : 148-152, 2011

化学療法2例，経過観察1例，記載なしが6例であった．転帰に関しては観察期間中死亡20例と報告されており，同疾患は非常に珍しく，また腹痛などの症状発現も遅く早期発見が困難であり，予後不良であると指摘している．

肝芽腫（Hepatoblastoma）

原発性の肝腫瘍は**小児悪性腫瘍**の1%で，このうちの80%以上は肝芽腫である．**5歳未満**での発生が多い．小児悪性新生物全国登録では，原発性肝悪性腫瘍は年間20～30例の発症と報告され，主たる症状は腹部膨満，腹部腫瘤触知である．腫瘍マーカー**AFP**が極めて高値を示し，診断，術後，治療後の経過追跡にも重要である．画像所見は超音波・CT・MRIでは隔壁を有する分葉状の形態と粗大石灰化が特徴とされ，造影では種々の程度の濃染像を認める．血行動態は肝細胞癌と異なり門脈相でのwashoutが認められない症例もある．血管造影上では腫瘍血管は肝細胞癌より小さく腫瘍濃染も淡いといわれる．腫瘍内には骨・軟骨のような類骨組織が認められる場合がある．周囲への浸潤傾向は少ないが，肺などへの遠隔転移を生じる場合がある．肝芽腫では**外科的切除**が重要であり，その適応決定には病期分類が必要である．予後と病期も強く関連しており，我が国ではPRETEXT（Pre-Treatment Extent of Disease）による病期分類が使用されている．治療方針は，一般的には完全切除された症例の予後は極めて良好であり，その一環として肝に限局する腫瘍で切除不能例に対する**肝移植**も施行されている．最近，Lautzら[13]は，化学療法が既に施行された病期分類POSTTEXT IIIもしくはIVの14人の小児肝切除例を検討した．診断時年齢中央値は生後8ヵ月であった．肺転移3症例は2例肺切除，1例は化学療法にて治癒となった．本来肝移植適応患者であった14人中13人（93%）が積極的な肝切除を施行，13人全例生存しており無再発中央期間は57ヵ月であった．累積1年/2年/5年生存率は93/91/88%，イベントフリー1年/2年/5年生存率は93/91/75%と良好であった．Lautzらは化学療法後に4セクター肝全域に残存，もしくは主要脈管浸潤となっている治療抵抗性進行肝芽腫に対しては，肝移植手術および積極的な肝切除の両者の外科的治療戦略が必要であると強調している．肝移植は本邦でも2008年4月より保険適応となり，一次的肝移植を中心に，徐々に症例数が増加しつつある．日本肝移植研究会による肝移植症例登録報告[14]では，2009年12月までに42例行われており，1年，3年および5年累積生存率はそれぞれ86%，81%，70%と報告されている．外科的に切除可能かどうかの判断には多くの経験を必要とするが，一次的肝移植に比べ，再発後のレスキューとしての肝移植の予後は不良であるため，初期段階から移植施設へコンサルトを行い移植適応の有無を評価することが必要である．

13) Lautz TB, Ben-Ami T, Tantemsapya N et al：Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. Cancer 117：1976-1983, 2011

14) 日本肝移植研究会：肝移植症例登録報告．移植 45：621-632, 2010

肝細胞腺腫
(Hepatocellular adenoma, liver cell adenoma)

我が国では稀な**良性腫瘍**約30％は**多発例**であり，10結節以上有する場合は肝腺腫症とよばれている．エストロゲンを含有した経口避妊薬やアンドロゲン含有アナボリックステロイドの服用，I型糖原病（von Bierke）やIII型糖原病も肝細胞腺腫発症の危険因子といわれている．肝細胞腺腫の自然発症率は女性100万人に1人の割合であるが，エストロゲンを含有した**経口避妊薬**を長期間にわたって服用すると，その発症率は30～40倍になるといわれている．非硬変肝に発症することや**若年女性**に多いことが特徴である[15]．臨床症状は腫瘍の破綻による腹腔内出血，腹部腫瘤，腹痛などであり，小さい場合などは偶然に発見されることが多い．画像診断では超音波で不均一な高エコーを呈する．単純CTでは，出血，壊死などを反映して低～高吸収域の多彩な像を呈する．造影CTでは，早期像で豊富な血流を反映して強い濃染像を呈し，後期像では等あるいは低吸収域を示す．MRI像も出血，壊死などを反映して多彩な像を呈する．組織学的には線維性の被膜を有し，細胞異型に乏しく，肝細胞が索状・管腔状に配列し，門脈域を認めないが，高分化型肝癌との鑑別が難しいときもあり，併存肝病変の有無が重要な鑑別点となる．治療は腫瘍が小さければ**経過観察**にとどめてもよいが，確立された基準はない．一般的に腫瘍が大きく増大傾向にあれば，腹腔内破裂や，肝細胞癌との鑑別困難例もあり，外科的切除の適応となる．Mohammedら[16]の腹腔鏡下肝切除13例の検討では，外科的切除適応において有症状12例，悪性所見の疑い症例が2例，巨大腫瘍が1例であった．有症状は腫瘍出血に伴うものが10例，腫瘍に対する肝動脈塞栓術後の肝膿瘍からの敗血症が1例，腫瘍による腹部圧迫が1例であった．腫瘍破裂により出血を伴っていた5例は緊急肝動脈塞栓術を要した．腹腔鏡下肝切除においては，8例（62％）が系統的切除（5例右葉切除，3例左葉切除），5例（38％）が部分切除を行い，全例開腹手術への移行はなかった．手術時間中央値は270分，腫瘍径中央値は85 mmであった．術後死亡は認めず，術後入院期間中央値は4日であった．以上より，肝細胞腺腫に対する系統的切除を要する腹腔鏡下肝切除は安全で推奨される術式であると結論づけている．また，Bunchorntavakulら[17]は肝細胞腺腫と**肥満**との相関を検討した．60例中56例が女性，年齢中央値36歳，75％が経口避妊薬服用の既往があった．18％が超過体重，55％が肥満（BMI ≥ 30 kg/m^2）であった．腺腫単発28％，多発72％であった．肥満は，腺腫の多発（85％ vs 48％，p = 0.005）および両葉分布（67％ vs 33％，p = 0.01），術前低アルブミン血症（p = 0.007），脂肪肝併存（p = 0.006），糖尿病（p = 0.003），高血圧（p = 0.006），脂質異常症（p = 0.03）と有意な相関を認めた．治療は17例に肝切除，9例に肝動脈塞栓術，

15) 鳥村拓司，佐田通夫：【肝・胆道系症候群（第2版）】 肝臓編（下）肝細胞癌　肝細胞癌の類似病変（肝細胞の結節性病変）　肝細胞腺腫．“日本臨牀 別冊 肝・胆道系症候群II” pp154-157, 2010

16) Mohammed AH, Francesco DF, Robert DW et al : Laparoscopic liver resection for hepatocellular adenoma. World J Gastrointest Surg 3 : 101-105, 2011

17) Bunchorntavakul C, Bahirwani R, Drazek D et al : Clinical features and natural history of hepatocellular adenomas : the impact of obesity. Aliment Pharmacol Ther 34 : 664-674, 2011

8例に肝切除および塞栓術を行った．腺腫の完全切除の割合は肥満患者で有意に低率（8% vs 69%，p = 0.004）であった．また無治療で経過観察中の26例において腫瘍サイズ増大は肥満患者に有意に多かった(33% vs 0%，p = 0.05)．以上より，肥満は肝細胞腺腫患者に頻繁に認められ，また経過観察している腺腫患者において腫瘍増大は肥満と関連があると報告している．

血管腫（Haemangioma）

肝血管腫は1層の血管内皮に覆われた血管腔から成り，線維性隔壁で分割されている．肝良性腫瘍の中では**最も頻度が高い**．本症は**女性**に多く，好発年齢は**30～50歳**，**単発性**が多く，**緩徐に発育**する．多くは**無症状**であるが腫瘍が大きい肝外突出型では右季肋部痛や腹部腫瘤を主訴とすることが稀にある．血小板減少やフィブリノーゲン減少などの凝固異常を伴ったものは**Kasabach-Merritt症候群**といわれ，その多くは**小児例**である．病理学的には嚢状に拡張した多数の血管の集族と線維性の支持組織からなり，石灰化や血栓形成を伴うこともある．画像検査ではCT造影前の低濃度域がbolus静注により血管腫周辺から濃染され，時間の経過とともに内部まで濃染されるのが特徴である．またMRIのT2強調画像で明らかな高信号として描出されるのが特徴的であり，ガドリニウム（Gd）-DTPA造影MRIではT1強調像で辺縁部から中心部に充満していく造影パターンを呈する．肝切除術の適応はKasabach-Merritt症候群合併，破裂の可能性がある巨大血管腫などであるが，破裂による腹腔内出血が5～20%にみられると以前は報告されていたが，実際には極めて稀なものと考えられてきている．Choiら[18]は，8例の巨大肝血管腫に対する肝切除を報告している．男性1例，女性7例，平均年齢48.5歳（33～58歳）であり，主訴は腹痛62.5%，腹部腫瘤触知37.5%，Kasabach-Merritt症候群合併25%，血管腫サイズ増大が25%であった．多発87.5%，両葉分布75%であり，腫瘍径中央値は14.5 cm（7～29 cm）であった．手術手技において全例に対してGlissonean pedicle transaction method（GPTM）とliver hangin maneuver（LHM）を用いて実質切離時早期より肝流入血コントロールを行い，またtotal vascular exclusion（TVE）の準備を行った．術後合併症および死亡は認めず，輸血率は37.5%と良好な手術成績であった．手術時出血量の本文記載はないが，肝切除時出血コントロールが非常に困難な巨大肝血管腫に対してGPTM，LHM，TVEの有用性を強調している．最近，エホバの証人32歳女性の巨大肝血管腫に対して，ロボット手術による肝右葉切除術を術中出血量300 mLにて行ったとする症例が報告されている[19]．

限局性結節性過形成（Focal nodular hyperplasia）

限局性結節性過形成（FNH）は血管腫に次いで2番目に多い良性の肝腫瘍で，

18) Choi J, Lee YJ, Hwang DW et al : Surgical treatment of giant hepatic hemangiomas : technical point of view. Am Surg 77 : 48-54, 2011

19) Giulianotti PC, Addeo P, Bianco FM : Robotic right hepatectomy for giant hemangioma in a Jehovah's Witness. J Hepatobiliary Pancreat Sci 18 : 112-118, 2011

1958年にEdmondsonによって初めて報告された．WHOによる肝腫瘍の組織学的分類では，過誤腫，先天性胆管嚢胞などとともに腫瘍類似病変に分類されている．新生物（neoplasm）というより，動脈奇形や血栓などの先行する脈管障害によるものを主とした限局性の血流増加に対する肝細胞の反応性過形成と考えられている．**40歳前後の女性**に多く，腫瘍は**5 cm以下の単発，肝表面**に存在することが多く，多発例は約20％である．合併症の頻度は低く，肝細胞腺腫や高分化型肝癌との臨床上，病理学的に類似点が多く鑑別診断が問題となることはあるが，**悪性化することはない**[20]．画像診断では，腫瘍は線維性隔壁で小結節に分かれて，中央の放射状の線維化（**central scar**）が特徴的である．このcentral scarを反映するソナゾイドを用いた造影超音波，CT，MRIさらには肝動脈造影で中心静脈の拡張と放射状の末梢静脈の存在（spoke-wheel sign）が鑑別診断に有効といわれている．病理学的にはFNHに特徴的なcentral scarも実際には約半数にしか認められず，非典型例も多い．FNHの腫瘍増大は極めて稀であり，悪性化の可能性もなく，確定診断がつけば外科治療の対象になることは少ない．外科治療は画像診断が不確実な場合に実施されていることが多い．稀ではあるがFNHの破裂に伴う腹腔内出血が報告されており，腫瘍が大きく，肝表面に局在するときは注意を要する．Dardenneら[21]60例において経過観察47例，肝切除術13例に行った．手術適応は有症状3人（23％），術前診断不明2人（15％），術前診断相違8人（62％）であった．多発腫瘍は経過観察群16人，手術群3人，腫瘍径平均は経過観察群52 mm，手術群60 mmであった．術前診断の正診率は経過観察群40人（85％），手術群2人（15％）であり（$p < 0.00001$），経過観察群は診断方法として典型的画像所見27人（57％），腫瘍生検13人（28％）であった．著者らは手術施行例の術前診断正診率の低さから，治療は腫瘍径にかかわらず腹部圧迫，腹痛などの症状がない限り**経過観察**を推奨している．

20）田中基彦，佐々木　裕：[肝・胆道系症候群（第2版）　その他の肝・胆道系疾患を含めて] 肝臓編　肝細胞癌　肝細胞癌の類似病変（肝細胞の結節性病変）　限局性結節性過形成．“日本臨牀 別冊 肝・胆道系症候群 II”pp141-145, 2010

21）Dardenne S, Hubert C, Sempoux C et al : Conservative and operative management of benign solid hepatic tumours : a successful stratified algorithm. Eur J Gastroenterol Hepatol 22 : 1337-1344, 2010

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ソラフェニブ投与進行肝細胞癌患者に対する人参養栄湯の併用効果の検討

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要　旨

ソラフェニブ投与中の進行肝細胞癌患者12例に対し，副作用軽減効果を期待し，漢方薬の人参養栄湯を12週間併用投与した。併用後の自他覚所見の推移を開始時，4週，8週，12週後に調査した。その結果，ASTは4週後，ALTは4，8週後で有意に低下し，血小板数は12週後に正常範囲まで有意に回復した。自覚所見については中止を必要とする増悪はみられなかった。これらの結果より，ソラフェニブ投与患者における人参養栄湯の併用は，ソラフェニブの副作用軽減に有用であることが示唆された。

緒　言

ソラフェニブは進行肝細胞癌に対して延命効果が証明された世界初の分子標的薬である。しかし肝機能障害，手足症候群，消化器症状および貧血などの副作用のために減量・中止を余儀なくされる場合が多数あり[1]，ソラフェニブ継続の可否が予後に大きな影響を与える。そこで，体力低下や疲労倦怠，食欲不振および貧血に対する効能効果があり，肝疾患に対しても数多くの報告[2)-4)]がなされている漢方薬の人参養栄湯を用いたソラフェニブによる副作用の軽減効果を検討した。

Ⅰ．対象と方法

2011年4月～7月に当科にてソラフェニブ投与中の切除不能進行肝細胞癌患者のうち，クラシエ人参養栄湯エキス細粒1日7.5 gの服用を希望し，12週間まで併用投与できた12例（男性7例 女性5例，平均年齢70.9±5.0歳）を解析対象とし，4，8，12週併用後の自他覚所見の変化について検討した（**表1**）。自覚所見については，手足症候群の症状や出血の有無，食欲や排便の状態，精神症状について，患者自身が記入するアンケートにより調査した。血液生化学検査については血清AST，ALT，アルカリフォ

Therapeutic effects of combination therapy of traditional Japanese medicine, ninjinyoueito, and sorafenib in recipients with advanced hepoatocellular carcinoma

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Key words：ソラフェニブ（sorafenib），人参養栄湯（ninjinyoueito），漢方薬（traditional Japanese medicine），分子標的薬（molecular target drug），副作用軽減（side effect reduction）