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Short Communication

Psychiatric and psychological outcomes of Japanese living donors following liver transplantation

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This study indexed the mental status in six living donor liver transplantations (LDLT) performed at the Juntendo University Hospital between 2005 and 2007. The donors' preoperative and postoperative psychiatric and psychological status was assessed using the Profile of Mood States (POMS) and the State–Trait Anxiety Inventory (STAI). The present study found that the donors' POMS anger/hostile score decreased significantly following transplantation. In addition, the STAI score suggested that donors had little anxiety or depression following the operation. Although the present study was limited due to the small number of donors, the findings suggest that a successful operation stabilizes donor mentality. The studied donors will be reassessed for their mental and physical condition in the future.

Key words: donor, living donor liver transplantation, psychological assessment, Profile of Mood States, State–Trait Anxiety Inventory.

THE NUMBER OF living donor liver transplantations (LDLT) has recently increased in Japan. More than 3000 LDLT have been performed in Japan until 2005, and 20 were carried out at the Juntendo University Hospital. Donors were evaluated for their preoperative and postoperative psychiatric and psychological status. Because healthy LDLT donors feel anxiety about the operation and their postoperative recovery, they often have conflicts with other family members.

Studies on the preoperative psychological status of donors using psychological tests have been reported.[1] Although most donors are highly motivated to donate, some have a high level of anxiety (with an increased State–Trait Anxiety Inventory [STAI] score) and depression.[2] There are few studies that have evaluated both the preoperative and postoperative psychological status of Japanese donors. In the present study we assessed the postoperative psychological status of donors and discuss how clinical treatment by psychiatrists could be improved.

METHODS

Participants

The psychosocial suitability and mental status of potential living donors was assessed by the authors at the Juntendo University Hospital. Between 2005 and 2007, six hepatectomies and transplantations were performed with living donors. Two of the six donors were female and both were aged 32 years. The average age of the four male donors was 34.5 years. One donor was the son of the recipient, one the husband, one the brother-in-law, one the father and two the mothers.

Procedures

A semi-structured interview was performed by a psychiatrist in order to make a comprehensive evaluation of the mental status of the donors before

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transplantation. Psychological tests, including the Profile of Mood States (POMS) and STAI in Japanese (STAI-JYZ) were performed on all donors to confirm that none had any symptoms of psychiatric disorders. All six donors had no history of psychiatric illness and did not conform to any ICD-10 criteria. The postoperative psychometric data were collected between 10 days and 4 weeks after each operation and once the recovery of the recipients was verified. We also confirmed that all donors were physically stable prior to the re-test. Donor moods were measured with the POMS, which consists of 65 questions, and rates six moods. To assess donor anxiety and the tendency to be anxious the STAI, which consists of 40 questions, was utilized. Because Trait Anxiety (T-A) indicates the tendency toward anxiety and does not depend on time, only the State Anxiety (S-A) was re-tested. The purpose and significance of this study was explained in detail to each donor and all subjects provided their informed consent. The study protocol was approved by the Ethics committee of the Juntendo University School of Medicine.

Statistical analysis

Preoperative and postoperative status was compared using Wilcoxon's signed rank test. Statistical significance was set at $P < 0.05$ (two-tailed). Statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, IL, USA).

RESULTS

POMS

According to the standard T-scores from a healthy population, a score >60 is suggestive of a clinical disturbance for all moods. Table 1 shows the mean preoperative T-scores for each mood. All mean preoperative scores were within the standard range for healthy individuals. A comparison of the postoperative scores with the preoperative scores showed that there was a statistically significant decrease in the anger/hostile score. No other moods showed any significant difference between the preoperative and postoperative states. Among the donors, two presented with negative scores for all moods prior to the operation and two presented with negative scores for all moods following operation.

State–Trait Anxiety Inventory

The mean preoperative T-A and S-A scores for the donors was 44.7 ± 10.5 and 46.0 ± 8.3, respectively. These scores are not different from that of a normal population. The mean postoperative S-A score was 39.5 ± 9.8. Although the postoperative S-A score was found to be lower than that of the preoperative state, it did not reach statistical significance.

DISCUSSION

The present results showed a significant decrease in the POMS anger/hostile score. To the best of our knowledge, this study is the first to use POMS to evaluate LDLT donors. Although some previous studies have suggested that donors suffer from severe psychiatric complications,[3,4] others indicate that donors feel a sense of satisfaction through the course of the procedure.[5]

We re-tested the psychological parameters almost 1 month after the transplantation. We found that LDLT donors displayed feelings of sacrifice and agi-

Table 1. Donor mood status

		Before operation (Mean score)	After operation (Mean score)	*P*
POMS	Anxiety–tension	51.83	45.83	0.47
	Depression–dejection	50.00	46.00	0.50
	Anger–hostility	48.83	40.33	0.03*
	Vigor	44.00	49.00	0.41
	Fatigue	47.83	41.00	0.25
	Confusion	47.50	44.33	0.31
STAI	State anxiety	46.00	39.50	0.16

*$P < 0.05$ (Wilcoxon signed rank test).
POMS, Profile of Mood States; STAI, State–Trait Anxiety Inventory.

tation prior to the operation and of achievement following the operation. These changes decreased the mean anger/hostile score. Fortunately, because all six donors were physically stable, they were not troubled about their physical condition. As with personal operations, donor S-A scores increase before transplantation and decrease after. The increase in donor anxiety prior to transplantation could possibly be reduced through the support of family members and medical staff. If additional donors were included in the study, the preoperative POMS anger/hostile score and STAI score might exceed the normal range.

The present results suggest that reducing donor anxiety and agitation during the operation procedure by reviewing psychometric data is crucial. The authors willingly support donors and are available for consultation when requested. Additionally, clinical psychologists (HS) regularly counsel donors. Support is also provided to assist donors to maintain healthy relationships with other family members. The present study was limited due to the small number of the donors studied and the short follow-up time span. Therefore, more LDLT donors should be evaluated in the future. It was reported that the physical and mental status of donors return to their previous levels in 3–12 months[6,7] and that some donors have negative moods after LDLT.[8] We plan to re-assess these six donors for their mental status and psychosocial situations in the future. As the families return to their original situations, conflict, anger and anxiety sometimes re-appear, but these may be moderated by receiving psychiatric and psychological care. It would be important to conduct extended follow-up studies of Japanese LDLT donors.

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Donor Complications Associated With Living Donor Liver Transplantation in Japan

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Background. The Japanese Liver Transplantation Society presented its first report on donor morbidity in 2003. The Society has been continuing to survey outcomes in living liver donors in Japan.
Methods. By using a uniform comprehensive medical record review process, data were collected on 3565 living liver donors who had donated grafts by the end of December 2006 at 38 Japanese centers.
Results. Preoperative problems were reported in 2 donors, intraoperative problems in 27, and postoperative complications in 270. In total, 299 donors (8.4%) suffered complications related to liver donation. Postoperative complications included biliary complications in 3.0%, reoperation in 1.3%, severe after-effects in two (0.06%), and death (apparently related to donor surgery) in one donor (0.03%). The incidence of postoperative complications in left and right lobe donors was 8.7% and 9.4%, respectively.
Conclusions. The accumulated experience indicates a reduction in the incidence of donor complications, especially for right lobe resection. One donor death and two cases of severe after effects related to liver donation have been reported during 18 years of living donor liver transplantation experience in Japan.

Keywords: Living donor liver transplantation, Donor morbidity, Donor mortality, Donor complication.

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In the face of the critical shortage of cadaveric donors for liver transplantation, living donor liver transplantation (LDLT) provides an alternative source of liver grafts for patients with end-stage liver disease (*1–10*). However, reports of donor deaths (*11–14*) have underlined the need to consider that the benefit of LDLT should not undermine concern for the safety of healthy living donors (*15–17*). We, the Japanese Liver Transplantation Society, have conducted a multicenter survey of the safety and outcome of living liver donors in Japan. In 2003, the Society presented its first report on donor morbidity, which was 12% overall, and 19% among right lobe donors (*18*). Subsequently, the Society has been continuing to survey outcomes in living liver donors. This report details the results for donors, including preoperative and intraoperative problems, the severity of postoperative complications, and the incidence of reoperation, severe after effects, and death, based on retrospective study of the cohort in the Society's registry. Although the data include the results for the donors presented in the first report (*18*), the data have been assorted newly in accordance with Clavien grades II to V (*19*).

PATIENTS AND METHODS

To study donor complications associated with LDLT, we sent a questionnaire to all centers with liver transplantation programs in Japan. Data on the donor hepatectomy procedures and the results for donors, including preoperative and intraoperative problems, postoperative complications, and the incidence of reoperation, severe after effects, and death were collected. In addition, the questionnaire asked whether the centers had changed any institutional policy related to preoperative evaluation, operative techniques, or postoperative management. Aborted donations were not in-

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cluded in this study. Centers that did not respond were contacted up to three times by e-mail and telephone. Data were collected on transplantations that had been performed by the end of December 2006 and followed up for at least 1 year (by the end of December 2007). For assessing the severity of postoperative complications, the uniform reporting of adverse outcomes of surgery proposed by Clavien and coworkers (*19*) was adopted. We collected postoperative complications corresponding to Clavien grades II to V, because inclusion of grade I incidents among this large population was considered unfeasible. The preoperative and intraoperative problems were examined and reported separately.

This study was designed carefully on the basis of the registration database of the Japanese Liver Transplantation Society to which all LDLT centers in Japan are obliged to report the characteristics and results for all LDLT donors and recipients. All the LDLTs were approved by the respective institutional review boards, and this study was approved by the Japanese Liver Transplantation Society.

RESULTS

Data Collection

Questionnaires were returned by 38 of the 55 centers (69%), describing the outcomes for 3565 (83%) of the 4294 living donors who had donated liver grafts by the end of December 2006 in Japan. Table 1 shows the numbers of each type of donor hepatectomy procedure.

Among the 3565 living liver donors, preoperative problems were reported in 2, intraoperative problems in 27, and postoperative complications in 270. In total, 299 donors (8.4%) suffered complications related to liver donation.

Preoperative problems (n=2) included bleeding from a duodenal ulcer in one donor and anemia due to chronic inflammatory bowel disease in another. Intraoperative problems (n=27) included homologous blood transfusion in 16 donors, biliary stricture in six, and malignant hyperthermia, bronchial asthma, thrombosis in the inferior vena cava, injury to the cervical vein, and ventricular tachycardia in one each. In most of the cases requiring homologous blood transfusion, the cause was intraoperative injury to the hepatic vein. Injury to the branch from segment 8 to the middle hepatic vein was reported in three cases. Injury to the short hepatic vein and inferior vena cava was reported in three cases. Trouble with clamping forceps caused bleeding from the hepatic vein in two cases. In one case, the middle hepatic vein flowed into the inferior vena cava at a lower position than usual and was injured from the left side. This anatomic variant was confirmed by retrospective examination of the preoperative computer tomography scan.

TABLE 1. Graft types and number

Graft type	Number
Lateral segment	1045
Left lobe	1088
Right lobe	1378
Right lateral sector	54
Total	3565

TABLE 2. Postoperative complications in 3565 living liver donors

Bile leakage	94
Wound infection	44
Gastric outlet obstruction	27
Biliary stricture	13
Homologous blood transfusion	10
Small bowel obstruction	10
Brachial plexus palsy	9
Gastro-duodenal ulcer	9
Pleural effusion	9
Intra-abdominal abscess	6
Psychological problems	5
Alopecia	4
Incisional hernia	4
Atelectasis	3
Hoarseness	3
Liver dysfunction (necessitating admission to intensive care unit)	3
Intestinal perforation	2
Portal vein thrombosis	2
Pneumothorax	2
Achalasia recurrence	1
Cardiac failure	1
Chylous ascites	1
Hepatitis C	1
Hypertrophic scar	1
Peroneal nerve palsy	1
Pneumonia	1
Severe wound pain	1
Temporary multiorgan failure	1
Paralysis of the lower body	1
Death	1
Total	270

Table 2 shows the incidence of postoperative complications, which included bile leakage in 2.6%, wound infection in 1.2%, gastric outlet obstruction in 0.8%, biliary stricture in 0.4%, and homologous blood transfusion in 0.3%. With regard to the incidence of postoperative donor complications in relation to the hepatectomy procedure used, the difference between right and left hepatectomies was small (Fig. 1). The incidences of bile leakage were 3.6% in right lobe donors and 2.0% in left lobe donors. The incidence of biliary stricture was 0.7% for both hepatectomy procedures. Table 3 shows the numbers of postoperative complications classified according to Clavien grade. When we compared the severity of postoperative complications between right lobe and left lobe donors, the differences were also small (Fig. 2).

Among 299 donors with perioperative complications, 277 returned to work, 17 had temporary after-effects, four had chronic after-effects (of which two were Clavien grade IVb), and one died. All of the 299 LDLT procedures were completed without discontinuation.

Reoperation

Reoperations were required in 48 donors, including repeat biliary reconstruction, adhesiolysis, and closure of bile duct leakage, as shown in Table 4.

Life-Threatening Complications

Two instances of life-threatening complications (Clavien grade IVb) were reported. One involved biliary stricture and infection leading to temporary multiorgan failure. The other case, which was more severe, led to paralysis of the lower body. This donor was a 55-year-old woman with liver steatosis and diabetes, and a body mass index of 34. She was accepted as a donor but considered to have a higher risk of thrombotic complications. An overdose of heparin was administered without appropriate coagulation tests. The catheter for epidural anesthesia was inserted before surgery, and epidural hematoma was confirmed on the first postoperative day. Now, more than 2 years after liver donation, the patient still has paralysis of the lower body.

Donor Mortality

There was one case of donor death (Clavien grade V) (*12*). A woman in her late 40s who donated her right lobe to her daughter died 6 months after donation. She had nonalcoholic steatohepatitis and an excessively small remnant liver, which was estimated at 26% by computer tomography. She underwent domino liver transplantation at 5 months and died 1 month later.

Changes in Donation Policy

Thirty-one of the 299 experiences (10.4%) in this series led to changes in policy for donor operations. These involved changes or attempts to improve preoperative evaluation, hepatic resection technique, and postoperative care (Table 5).

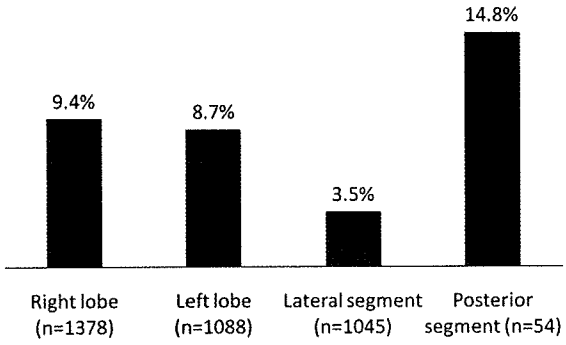

FIGURE 1. Incidences of postoperative mortality and morbidity according to graft type. Lateral segment graft group includes 11 cases of monosegment graft.

TABLE 3. Clavien's classification for postoperative complications (n=270)

Clavien grade	Number
II	125
IIIa	86
IIIb	56
IVa	0
IVb	2
V	1

TABLE 4. Reoperations in donors

Repeat biliary reconstruction	9
Adhesiolysis	9
Closure of bile duct leakage	8
Abdominal drainage	8
Hemostasis	4
Drainage of the bile duct	3
Hernioplasty	3
Plasty of the bile duct	2
Liver transplantation	1
Pleural drainage	1
Total	48

TABLE 5. Changes in institutional policy

Hepatic resection technique	11
Intraoperative bile leakage test	9
Preoperative evaluation	7
Prevention of adhesion	3
Postoperative care	1
Total	31

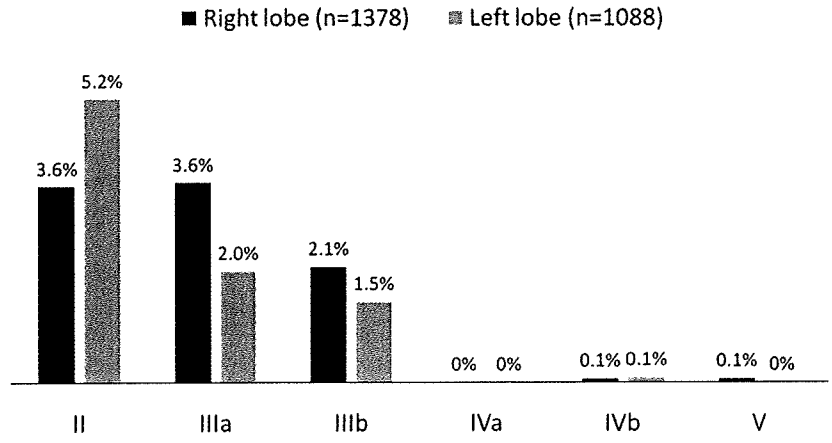

FIGURE 2. Comparison of the severity of postoperative complications according to Clavien grade between right lobe and left lobe graft donors.

DISCUSSION

The risks for live liver donors are small but real (*14*). LDLT was applied initially in pediatric patients, using left lobe or left lateral segment donation usually from an adult parent to a child or small adult. Adult-to-adult LDLT was introduced in 1993 (*20*), and the use of LDLT with a right liver graft has increased (*21, 22*). Along with these developments, concerns over donor safety have increased (*23–33*), and a major reassessment of the risks of right lobe liver donation has led to a more cautious approach to the use of this procedure (*32*). The Japanese Liver Transplantation Society has been conducting an ongoing survey with the specific aim of gathering accurate information on the risks and benefits of LDLT for donors. In comparison with our previous report (*18*), the results of the present survey show that accumulated experience may have led to a reduction in the incidence of donor complications, especially for right lobe resection (please note that this survey did not include Clavien grade I postoperative complications). The difference in the incidence of complications between right lobe and left lobe hepatectomy has now become small. However, one donor death and two cases of severe after-effects have been reported during 18 years of LDLT experience in Japan.

Reliable information about risks must be provided to prospective donors. The first multicenter study on this issue was described by Lo (*30*) in Hong Kong in 2003, incorporating the results of 1508 cases at five Asian centers. In that report, comparison among the types of donor hepatectomy showed that a high proportion of right lobe donors (28%) suffered hyperbilirubinemia and intraabdominal fluid collection as complications. As most of these complications have been assumed to be temporary, right lobe liver transplantation for adult patients has become accepted worldwide. A systematic review (*14*) reported that donor morbidity ranged from 0% to 100%, with a median of 16.1%. The median-reported rate of biliary complications, most commonly biliary leakage and biliary stricture, was 6.2%, and the rate of infections, commonly wound infection, was 5.8%.

There have been an estimated 12 to 13 donor deaths, at least seven involving adult-to-adult donation, at least three involving adult-to-child donation, and three late donor deaths. The 10 early donor deaths probably involved five right lobe donations, one left lobe, one left lateral segment, and three unspecified graft types. In 9 of the 10 early donor deaths, the causes were specified as sepsis in three, pulmonary embolism in two, massive bleeding, liver insufficiency and sepsis due to unrecognized congenital lipodystrophy, anesthetic complications, and multiple organ failure, in one case each. The estimated donor mortality for LDLT is approximately 0.2% (*14*).

In 2008 at Istanbul, The Transplantation Society issued a declaration that the provision of care for living donors before, during, and after surgery is no less essential than taking care of the transplant recipient, and that a positive outcome for a recipient can never justify harm to a live donor. All countries require a legal and professional framework to govern organ donation and transplantation activities, as well as a transparent regulatory oversight system. Furthermore, the declaration addresses the importance of the informed consent process (*34*).

The Japanese Liver Transplantation Society have been making it obligatory to register all the characteristics of LDLT donors and recipients and the results obtained at all liver transplantation centers, including severe donor complications and deaths. This study was carried out to obtain further information about all the donors by using a detailed questionnaire. The complexity of this questionnaire may have been one of the reasons for the lower response rate (83%) among the donors. We accepted this rate, and confirmed that all of the large LDLT centers in Japan were included in this study, as shown in the list of Contributors. Most importantly, we considered it of paramount importance not to underestimate the incidence of severe donor complications or death. Details of all donors and any severe complications have been reported faithfully to the Society's database, and the Committee of the Society investigates cases when this is judged necessary. This system has been established since the inception of LDLT in Japan. We consider that, at least, the incidence of Clavien grade IV to V complications was not underestimated. This study still had limitations due to the lack of a complete reporting system, especially for Clavien grade II to III complications, and thus donor morbidity may have been underestimated. However, we will need to continue this survey with maximal effort to provide accurate information for prospective donors, and also for transplant centers, to minimize the learning curve process for donor hepatectomy. Most of the intraoperative and postoperative complications might have been avoided with wider experience of hepatic resection conducted on a daily basis. Furthermore, specific training of the surgical team at an experienced center is also indispensable. Even though 20 years have now passed, since the introduction of LDLT, a cautious attitude toward donors is still essential, and the importance of this approach should continue to be stressed.

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肝細胞癌 治療の実際

Hepatocellular carcinoma: Current management and recent advances

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key words：肝細胞癌，肝切除，肝移植，経皮的局所療法，TACE

はじめに

肝細胞癌（HCC）の治療はこの25年の間に飛躍的に進歩してきた。現在HCCに対して有効な治療法として確立されているのは，①肝切除，②肝移植，③経皮的局所療法，④肝動脈化学塞栓療法（TACE），である。HCCの多くは肝硬変，慢性肝炎を基礎的病変として発生するため，HCCの進展度（腫瘍因子）と背景肝の障害度（肝機能因子）のバランスを考えて治療法を選択しなければならない。したがって，同一の腫瘍病期でも背景肝病変が異なれば治療法の選択が施設によって異なることもあり，これまで治療法に対するコンセンサスがなかなか得られなかった。DDW-Japan 2003 OSAKA（Digestive Disease Week-Japan）において肝癌治療に対するrecommendation[1]がまとめられ，さらに2005年にわが国初の『科学的根拠に基づく肝癌診療ガイドライン』(2005年版)[2]が刊行された。これらの治療指針は肝癌治療にかかわる多くの臨床医が治療方針を立てるうえで役立つものと期待されている。本稿では各治療法の適応，実際成績につき概説した。

わが国における肝癌治療の現況

日本肝癌研究会による第17回全国原発性肝癌追跡調査報告によれば，2001～2002年に17159例のHCC症例が新規登録された[3]。肝切除は33.6%に施行され，腫瘍径2cm以下が17.4%，3～5cmが52.9%，5～10cmが19.8%であり，単発例が73.1%であった。また肝移植は45例に施行された。局所療法は31.2%に施行され，第16回調査報告の26.8%に比べ増加していた。その内訳はエタノール局注療法（PEI）が21.4%，マイクロ波凝固壊死療法（MCT）が11.6%，ラジオ波焼灼療法（RFA）が68.8%であり，第16回調査報告ではそれぞれ41.2%，17.7%，40.2%であったのと比較するとPEIに代わってRFAの頻度が増加していた。TACEが29.6%に施行され，第16回調査報告の36.4%に比べ減少していた。内訳はリピオドールのみが15.3%，リピオドール＋塞栓物質によるものが73.8%であった。また90.7%に抗癌剤が併用されていた。そのほか，化学療法が4.9%に実施され，その90.0%は経肝動脈的に施行されていた。

『肝癌診療ガイドライン』

2005年3月に，国際的な標準となっているEBM（evidence based medicine）の手順に従ったわが国初の『肝癌診療ガイドライン』が刊行された。本ガイドラインは予防，診断（サーベイランス，腫瘍マーカー，画像診断），手術，化学療法，TACE，経皮的局所療法の6つの章からなり，58件のリサーチクエスチョンが設定され，それぞれに対応する科学的根拠（scientific statement），それから導かれる推奨（recommendation）が記述されている[4]。さらにHCC治療のアルゴリズムが示されており，病態に応じた治療法の選択基準が示されている（図1）。本基準は肝障害度，腫瘍数，腫瘍径の3因子をもとに設定されている。日本肝癌研究会による肝障害度分類は国際的分類として普及したChild-Pugh分類（図2）から肝性脳症を除き，ICG検査を加えており，より肝切除の適応を考慮した分類となっている（図3）。肝障害度A，B症例では，①単発ならば腫瘍径にかかわらず肝切除が推奨される。ただし，肝障害度Bで2cm以下なら経皮的局所

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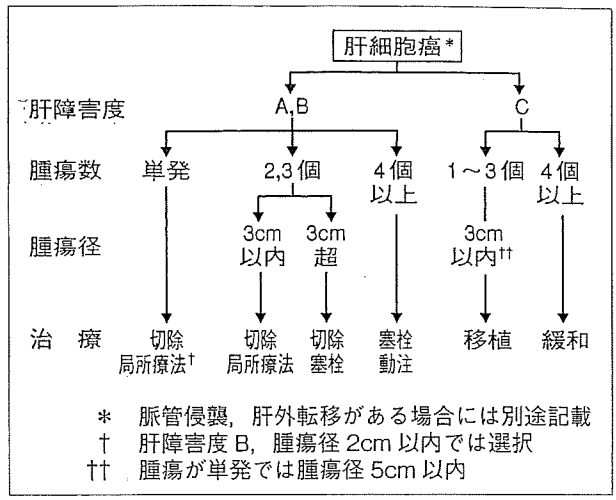


〔文献2)より引用〕

図1　肝細胞癌治療アルゴリズム

項目＼ポイント	1点	2点	3点
脳　症	な　い	軽　度	ときどき昏睡
腹　水	な　い	少　量	中等度
血清ビリルビン値(mg/dl)	2.0未満	2.0～3.0	3.0超
血清アルブミン値(g/dl)	3.5超	2.8～3.5	2.8未満
プロトロンビン活性値(%)	70超	40～70	40未満

各項目のポイントを加算しその合計点で分類する

Child-Pugh分類	A	5～6点
	B	7～9点
	C	10～15点

註：Child分類ではプロトロンビン活性値の代わりに栄養状態（優，良，不良）を用いている

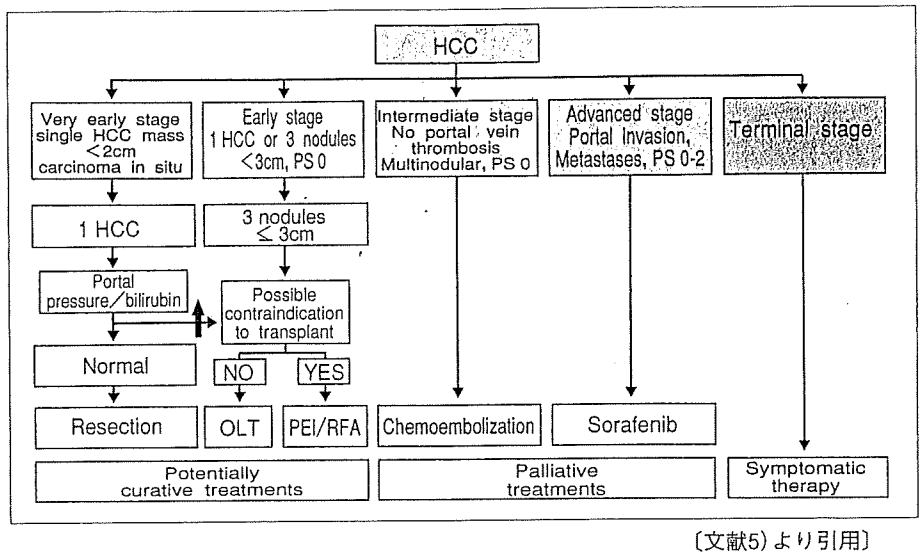
図2　Child-Pugh分類

臨床所見，血液生化学所見により3度に分類する。各項目別に重症度を求め，そのうち2項目以上が該当した肝障害度をとる

項目＼肝障害度	A	B	C
腹　水	な　い	治療効果あり	治療効果少ない
血清ビリルビン値(mg/dl)	2.0未満	2.0～3.0	3.0超
血清アルブミン値(g/dl)	3.5超	3.0～3.5	3.0未満
ICG R_{15}(%)	15未満	15～40	40超
プロトロンビン活性値(%)	80超	50～80	50未満

註：2項目以上の項目に該当した肝障害度が2カ所に生じる場合には高いほうの肝障害度をとる。たとえば，肝障害度Bが3項目，肝障害度Cが2項目の場合には肝障害度Cとする。また，肝障害度Aが3項目，B，Cがそれぞれ1項目の場合はBが2項目相当以上の肝障害と判断して肝障害度Bと判定する

図3　肝障害度（liver damage）



〔文献5)より引用〕

図4　BCLC のガイドライン

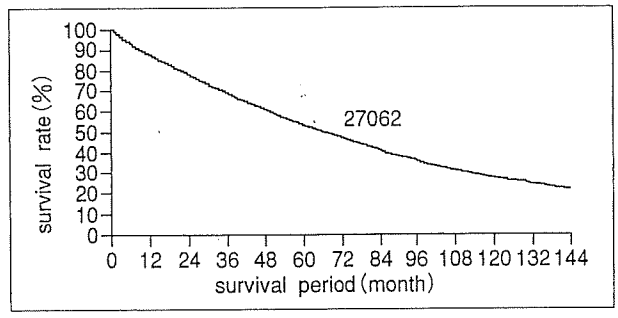


図5　肝切除の生存率（日本肝癌研究会）

療法も選択される。②2個または3個で3cm以下なら肝切除または経皮的局所療法が推奨される。③2個または3個で3cm超なら肝切除またはTACEが推奨される。④4個以上ならばTACEまたは肝動注が推奨される。肝障害度C症例では単発5cm以下，3個以下で3cm以下ならば肝移植が推奨され，それ以外の症例では緩和治療が推奨されている。

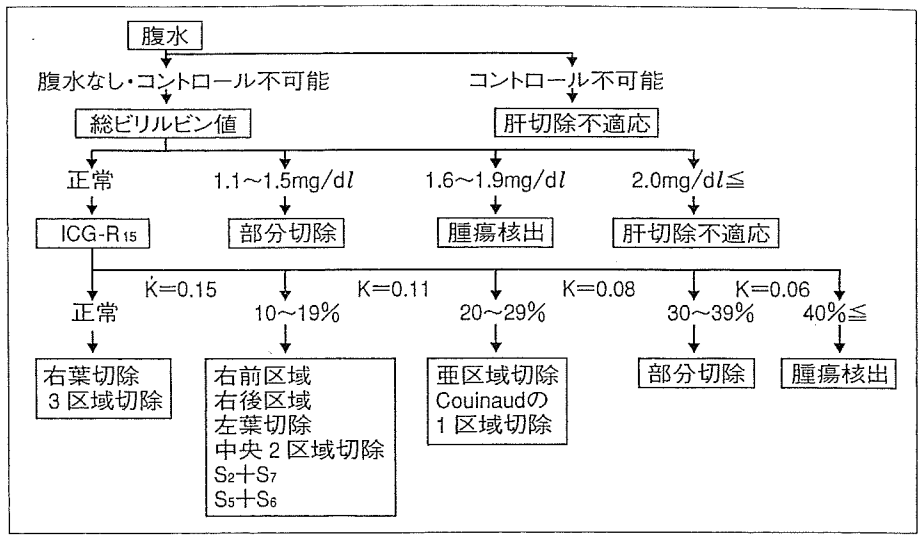
欧米のガイドライン[5](図4)ではまず外科的切除，つまり肝移植や肝切除が治療の第一選択である。腫瘍条件として5cm以下単発，3cm以下3個までが外科的治療の適応とされている。わが国の治療方針との大きな違いは，わが国では肝移植の適応の多くが肝障害度C症例であるのに対して，欧米では上記の腫瘍条件を満たしたHCCは肝障害度A，Bでも肝移植の適応となることである。これは欧米とわが国でのHCCの発生頻度の差，肝硬変合併症例に対する肝切除成績の差，移植方法の相違（生体肝移植vs脳死肝移植）を反映しているものと考えられる。

肝切除

肝切除の安全性は術前評価，手術手技，周術期管理の改善により，以前と比べ著しく向上している。日本肝癌研究会による25年前の全国調査では，原発性肝癌における肝切除症例の手術死亡率は27.5%，5年生存率は11.8%であったのに対して，最新の第17回調査（2001～2002年）では手術死亡率は0.8%，5年生存率は53.4%と飛躍的に改善している（図5)。

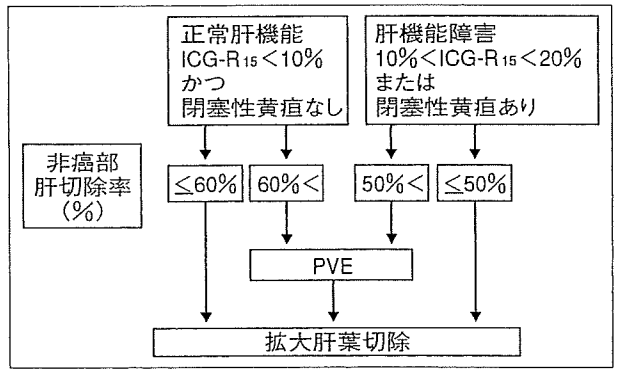
障害肝でどの程度肝臓を切除できるかの判断は難しく，さまざまな指標が提唱されている。われわれは幕内基準を用いて肝切除範囲を決定している（図6)[6]。つまり肝機能が正常であれば2/3程度の肝実質を切除することが可能であり，ICG-R_{15}が10%台であれば1/3，20%台では1/6，30%台ではわずかな肝実質を腫瘍とともに切除することが可能である。40%以上では核出術を施行する。

大量肝切除が必要とされる症例では術後に残肝容積が過小となり，肝不全が危惧される。これを回避するために考案されたのが術前門脈枝塞栓術（portal vein embolization；PVE）である。術前に切除予定側の



〔文献6)より引用，改変〕

図６　肝切除範囲の決定



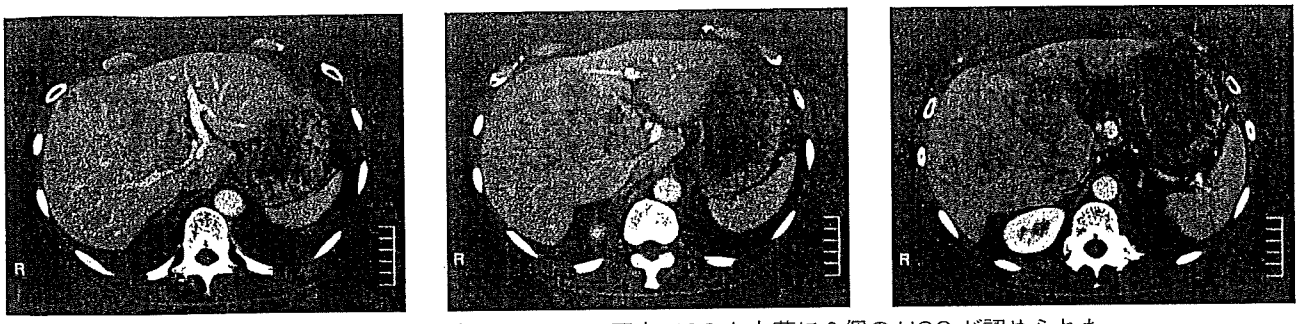
〔文献7)より引用，改変〕

図７　門脈枝塞栓術の適応

PVE を施行することにより，予定切除肝の萎縮，予定残肝の代償性肥大を促進し，術後肝不全のリスクを軽減することが可能となる。当科の PVE の適応は Makuuchi らの適応基準に準じて行っている（図 **7**）[7]。正常肝機能症例（ICG-R_{15}＜10%）で予定残肝容積が全肝容積の40%未満の場合，肝機能低下例（10%≦ICG-R_{15}≦20%）では50%未満の場合を PVE の適応としている。HCC の90%は慢性肝炎，肝硬変などの慢性肝疾患が背景肝であるため，肝切除後の肝不全を回避するためには残肝容積がより重要な要素となる。問題は HCC の多くは動脈血により栄養されており，切除予定肝の門脈を塞栓すると代償性に動脈血流が増加し HCC の増大を招くことである。このため，PVE に先行してまず肝動脈塞栓療法（TAC）を行い，その後に PVE を施行することが推奨されている（図 **8 a～d**）。また慢性肝疾患は正常肝に比べ，PVE 後の非塞栓葉の代償性肥大の程度が低いとされ，TAE を併用することにより肥大の程度が増加することが報告されている。

系統的肝切除

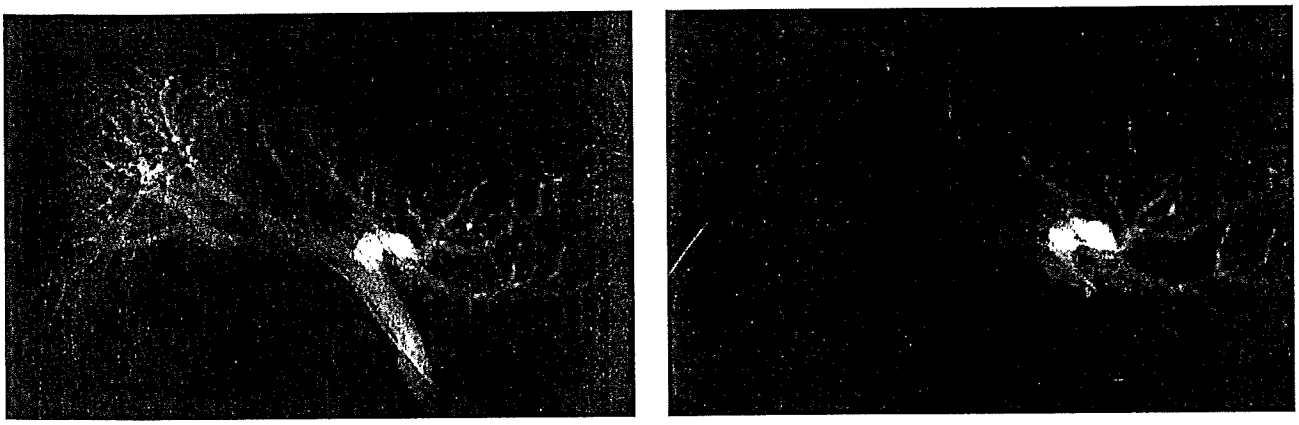
肝切除は解剖学的血行支配に基づいた系統的肝切除と，非系統的肝切除である肝部分切除に大別できる。系統的肝切除は担癌領域門脈の支配領域をすべて切除することであり，葉切除，区域切除，亜区域切除がこれに相当する。亜区域切除は US ガイド下に門脈を穿刺して色素を注入することにより肝表面より亜区域を同定し，これを切除することが可能となる。一般的には系統的切除が推奨され，部分切除よりも良好な成績が報告されている[8)9)]。東京大学の報告によれば系統的亜区域切除の１，３，５年生存率97%，87%，67%，１，３，５年無再発生存率82%，55%，28%は，部分切除の１，３，５年生存率93%，66%，35%，１，３，５年無再発生存率69%，20%，16%に比べ良好であった（図 **9**）[10]。肝機能により系統的切除が困難な場合には部分



a：右葉から内側区域を占める17cmの巨大HCCと左葉に3個のHCCが認められた

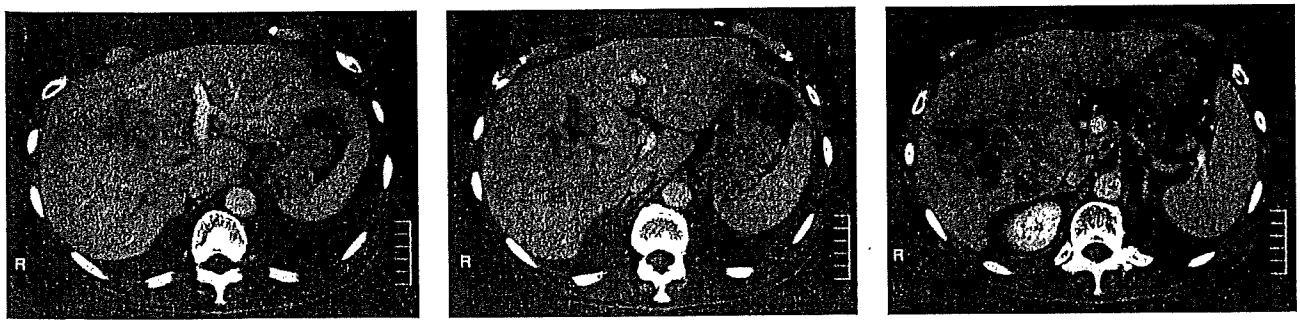
塞栓前　　塞栓後

b：SMAより分岐した右肝動脈からのfeeding arteryにTAE施行



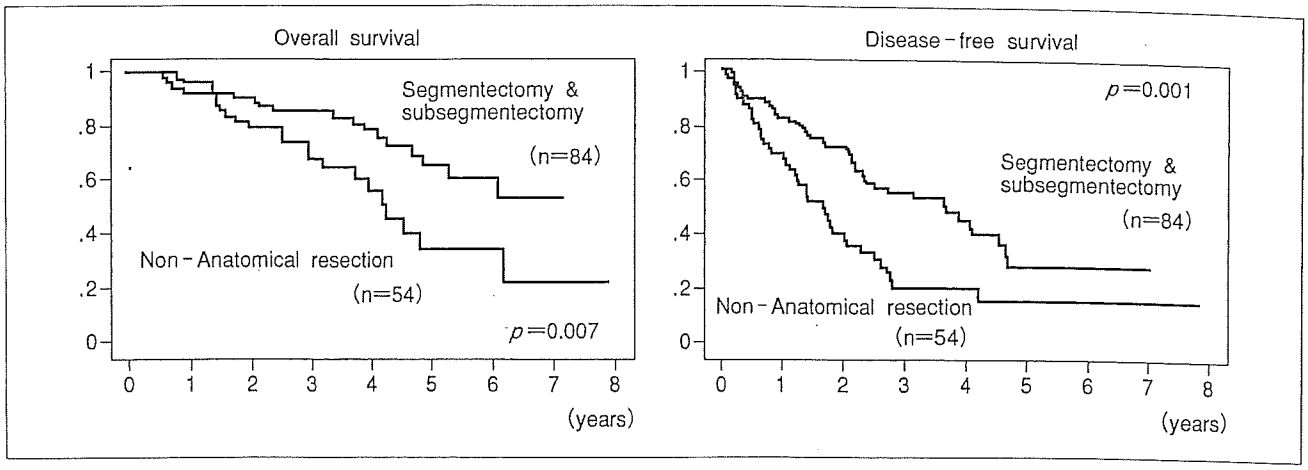
塞栓前　　塞栓後

c：TAEの4週間後に右門脈枝塞栓術施行



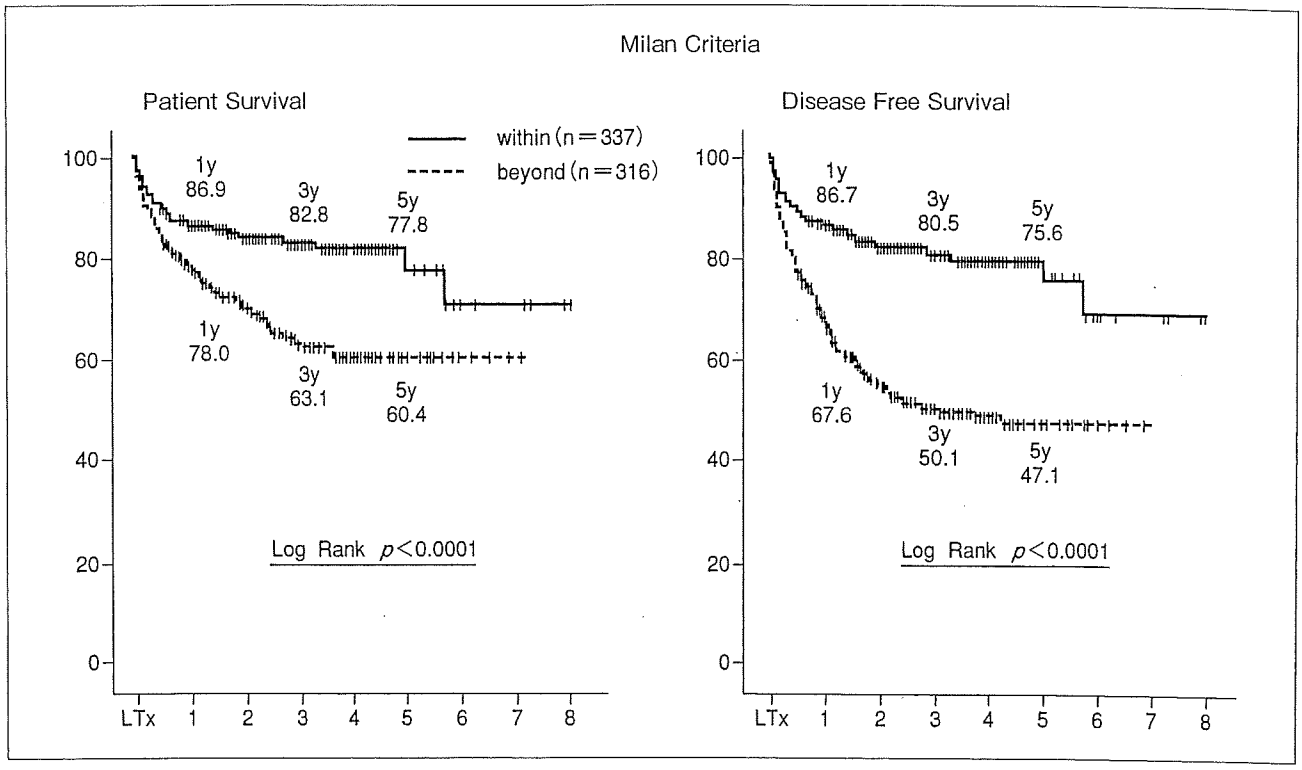
d：門脈枝塞栓術2週間後のCTではHCCの縮小化と左葉の腫大が認められた。一連の操作で予定残肝容積は30.7～38.3%に増加し，拡大右葉切除，左葉の部分切除を施行

図8　HCC症例（61歳，男性）



〔文献10)より引用〕

図９　系統的亜区域切除 vs 部分切除



〔文献11)より引用〕

図10　HCC に対する生体肝移植

切除が考慮される。肝切離断端距離は予後に寄与する可能性は低く，必要最小限の距離がとれれば問題ないと考えられている。

肝移植

HCC に対する肝移植は適応基準のスタンダードであるミラノ基準（腫瘍径５cm 以下単発，３cm 以下３個以内）を満たせば良好な予後が期待でき，５年生存率は70％以上，再発率は15％以下である。最近はミラノ基準逸脱例でも長期生存例の報告があり，UCSF 基準（腫瘍径6.5cm 以下単発，腫瘍径4.5cm 以下２個または３個で腫瘍径の合計が８cm 以内）など適応基準の拡大が提唱されている。脳死肝移植では移植待機中に腫瘍が進展して待機リストからはずれることがあるため，待機中に HCC に対して経皮的局所療法や TACE などの前治療を行い癌の進行を遅らせたり，すでにミラノ基準を逸脱した症例に対して，ほかの治療による downstaging を行ってから移植を施行する試みがなされている。

わが国では2004年１月より肝硬変および劇症肝炎の15歳以下の年齢制限が廃止され，ミラノ基準内の

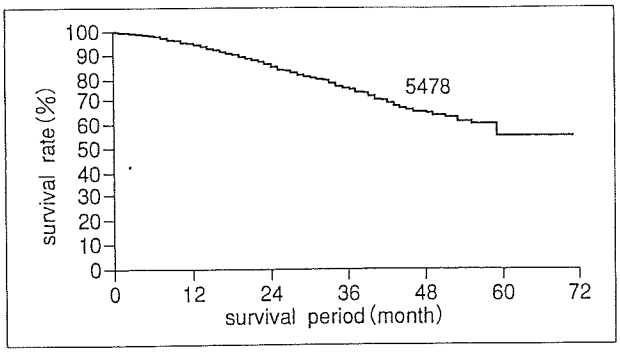
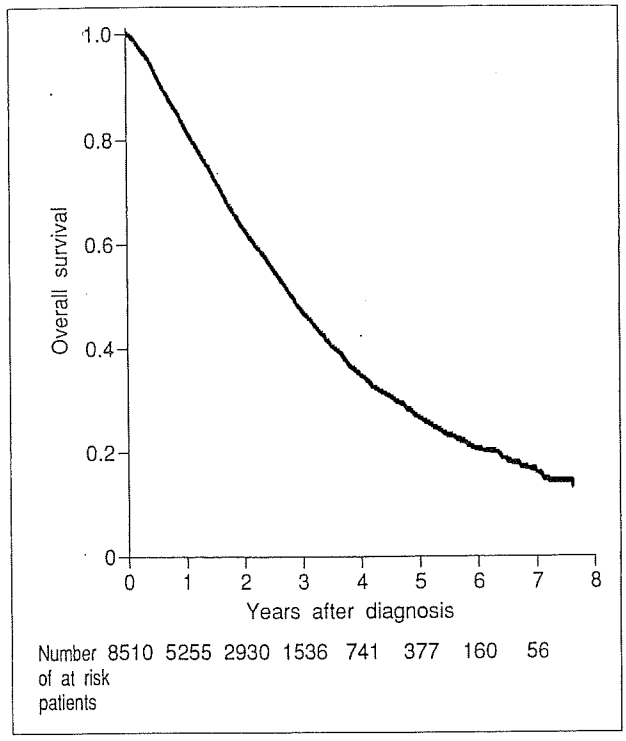


図11　HCC に対する RFA（日本肝癌研究会）

HCC が保険適応となり，以後 HCC に対する移植例が急増し，1989～2005年までに行われた成人生体肝移植初回治療例2190例において，移植の適応が HCC であった症例は649例（29.6%）に達している。わが国では生体肝移植が主流であり，脳死肝移植における提供肝の公平分配という原則にとらわれないため，ミラノ基準にこだわらずにほかに有効な治療法がない症例を適応とする施設が多いのが特徴である。HCC に対する生体肝移植の成績はミラノ基準合致例では3年，5年生存率82.8%，77.8%と良好であった。一方，ミラノ基準逸脱例では3年，5年生存率は63.1%，60.4%と合致例に比べて低いものの，ほかの治療法による成績を考慮すると比較的よい成績と考えられる（図10）[11]。また HCC の腫瘍マーカーである AFP と PIVKAII は移植成績と相関することが明らかとなっており，これらを移植適応の基準に含めるかどうかが今後の検討課題である。

経皮的局所療法

肝予備能の低下している患者では，局所的に治療できる経皮的治療は HCC 以外の正常な肝細胞に対する影響が少なく，有用な治療法となる。経皮的局所療法はまず PEI が開発された。その後，腫瘍を熱凝固させる MCT から RFA へと発展し，最近では RFA が肝癌治療の主療法となりつつある。RFA は1回焼灼時間での凝固範囲が広いことから，ほかの経皮的治療に比べて局所のコントロールが優れ，少ない回数での治療が可能とされる。RFA 後2～3年の局所再発率は8～14%と PEI の局所再発率23～34%に比べて低い[12]。日本肝癌研究会の集計で RFA の治療成績をみると，1年，3年，5年生存率はそれぞれ94.9%，76.7%，57.3%と良好である（図11）。2004年4月より RFA が保険適応となり，今後，肝癌の治療法として広く普及することが予想される。しかしながら，長期成績に関しては HCC の大きさや悪性度に応じて局所再発の頻度が高くなるとされ，効果に関する十分なエビデンスが得られていないのが実情で今後の解析が期待される。治療のアルゴリズムでも示されているように，局所療法の適応となる症例は同時に肝切除の適応となることが多い。経皮的局所療法後の局所再発は肝内転移の遺残を多く含むと考えられ，肝内転移が経門脈性の進展により生じることを考慮すると，門脈支配領域を含む系統的肝切除が局所療法より合理的な治療法であると考えられる。



〔文献13）より引用〕

図12　HCC に対する TACE

TACE

TACE は主に肝切除や経皮的局所療法の適応のない大きさが3 cm 以上の比較的大型の HCC や4個以上の多発した症例において適応となる。肝動脈造影で腫瘍濃染像を有する，いわゆる古典的 HCC もしくは一部の early advanced hepatocellular carcinoma が対象である。本治療により30～50%の患者で抗腫瘍効果が認められるものの，完治する HCC は2%以下である。切除不能の HCC　8510例に対するわが国の cohort 研究では TACE の生存期間中央値は34カ月，1，3，5，7年生存率はそれぞれ82%，47%，26%，16%であった（図12）[13]。現在主に行われている TACE は，抗癌剤とリピオドールをエマルジョン化

して担癌区域動脈に注入後，ゼラチンスポンジ細片にて塞栓するTACEである。抗癌剤はdoxorubicin, mitomycin, cisplatinなどが主に用いられている。さらに癌の存在する領域の動脈に超選択的にマイクロカテーテルを挿入し，担癌領域だけの区域，亜区域に対するTACEが行われ，治療成績，安全性はいっそう向上している。肝機能障害が高度の場合には治療効果は低くなるが抗癌剤とリピオドールのエマルジョンのみで塞栓術が施行される場合もある。

おわりに

肝炎ウイルスの汚染地帯の一地域であるわが国は，肝癌の基礎および臨床研究における世界のリーダーである。肝癌に対する治療方法は，さまざまな背景因子を考慮して選択される必要があり，診療ガイドラインを参考に臨床医が一定の治療方針をたてることが肝要である。

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特集 CTHA/CTAPの今日的意義を考える

コロナ濃染の今日的意義*

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Key Word 肝細胞癌，AP shunt，コロナ濃染，被膜

要旨

コロナ濃染は注入された造影剤が病変を通過した後，隣接する背景肝の類洞を通過する際，現れる濃染である．多血性肝細胞癌(以下，多血性肝癌)のsingle-level dynamic CTHA(以下，D-CTHA)で発見された[1)]が，D-CTHA以外，例えばCTHA，造影超音波，経静脈性ダイナミックCT，あるいは経静脈性ダイナミックMRIでもみられる[2~6)]．本稿ではコロナ濃染の由来を振り返り，本濃染描出に必要な条件，ならびに発見から13年を経た今日における意義を概説する．

肝胆膵画像 2009；11：25-31

コロナ濃染の由来

1995年，C型慢性肝炎を背景に脂肪を含有する肝腫瘤を検診で指摘された40歳代の男性が受診された．血管筋脂肪腫と脂肪を含有した肝細胞癌の鑑別が必要であった．血管筋脂肪腫の診断に有用な腫瘍内静脈瘤の描出を企図して造影剤を数秒間動注し，動注開始直前から40秒間CTを撮影するsingle-level dynamic CTHA(以下，D-CTHA)で撮影すると流出静脈が描出された(図1)．

当時は動脈-門脈短絡(arterio-portal shunt，以下，AP shunt)と肝癌の鑑別法を模索していた時期でもあった．D-CTHAを行えばAP shuntに特徴的な門脈の早期描出が得られ，その結果，肝癌との鑑別が可能になると考え，両者の鑑別が困難な際，本法を施行した．

すると，本法では企図したAP shuntにおける門脈の早期描出に加え，肝癌とAP shuntは以下のような互いに異なる所見を呈したため，両者の鑑別が容易であることがわかった[7)]．すなわち，D-CTHAを行うと，肝癌はAP shuntに先んじて濃染し，その後，特徴的な輪状濃染を呈するのに対し，AP shuntは肝癌に遅れて濃染したのち，濃染域の形状を変えることなく，そのまま経時に従い濃染が消退した(図2)．これに組織学的所見とD-CTHAの所見を組み合わせて肝癌の血液流出路を解明した．初稿では肝癌のD-CTHA後期相にみられた輪状濃染に対してring enhancementを充てたが，転移を示唆する“ring”以外の命名に変更するようにとの指示が査読者からあった．それに応じて，腫瘍の外にみ

* Current significance of corona enhancement

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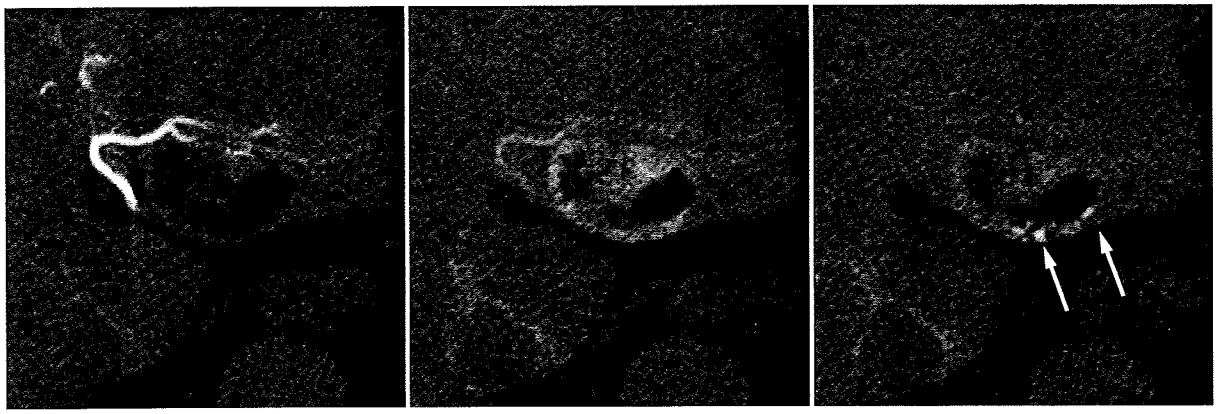

図1　血管筋脂肪腫の D-CTHA
左から右へ動注開始後 5, 10, 15 秒. 5 秒, 10 秒では造影されない点状濃染が 15 秒で出現する(⇨). これにより, D-CTHA では流出静脈が描出されることがわかった.

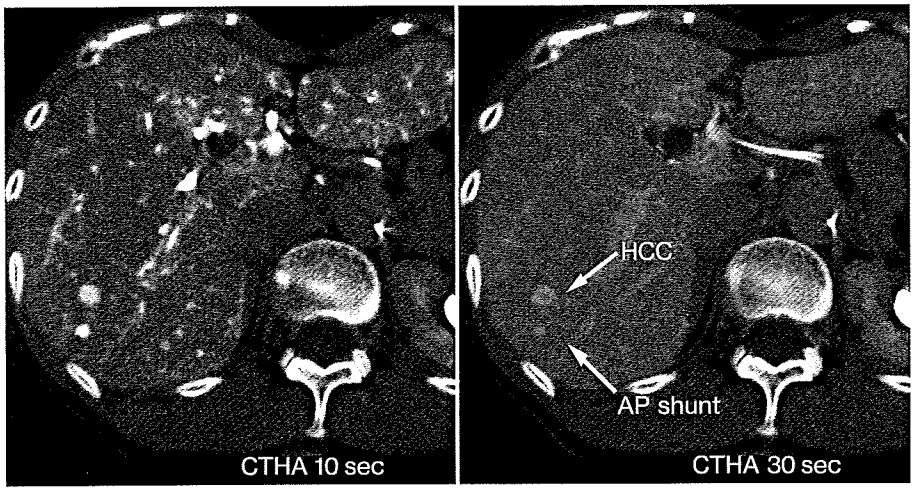

図2　肝癌と AP shunt の CTHA
左, 早期相；右, 晩期相. 早期相では肝癌も AP shunt も早期濃染を示し, 区別できないのに対し, 晩期相では肝癌が輪状濃染を呈するのに対し, AP shunt は呈さないことから鑑別できる.

られるこの輪状濃染を日食時にみられる太陽の外のコロナになぞらえ“corona enhancement”と命名したのがコロナ濃染の由来である[1].

コロナ濃染の定義

注入された造影剤が病変を通過した後, 隣接する背景肝の類洞を通過する際, みられる濃染をいう.

コロナ濃染描出に適した撮影条件

1. 造影剤がコロナ濃染域に到達してから撮影がなされること

病変を通過した造影剤が隣接する背景肝類洞を通過している最中に撮影がなされる必要がある. 具体的には造影剤が肝動脈を通過したのち 10 秒で病変を通過した造影剤が周囲の門脈枝に到達し, そののち 12 秒(＝肝動脈通過後 22 秒)以降にコロナ濃染が出現する.

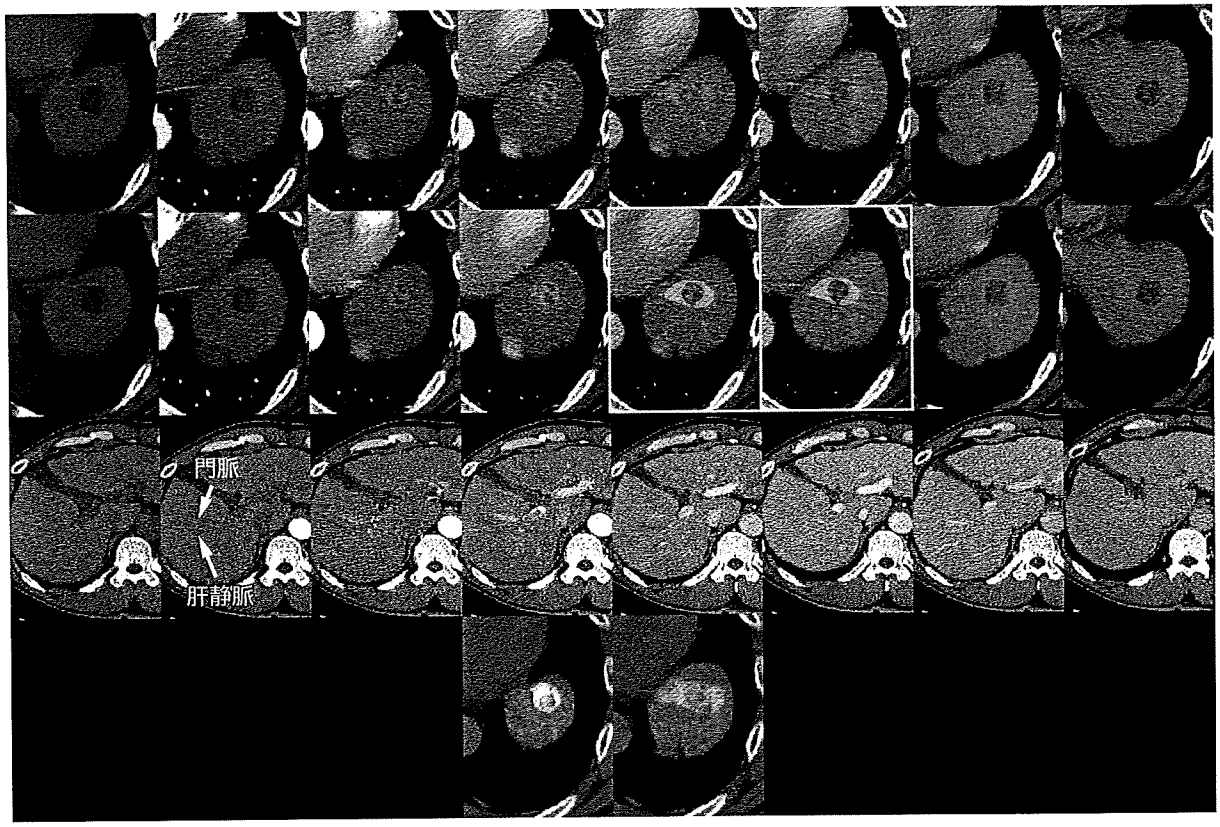

図3　肝癌のダイナミックCT
最上段から第3段まで左から右へそれぞれ造影前，静注開始後15，22，30，37，45，90，210秒(毎秒8 m*l*，総量100 m*l*)；最下段D-CTHA動注開始後12秒，30秒；最上段と第2段は同一画像で第2段の桃色の影はコロナ濃染；第3段は最上段と第2段と同一撮影時相の肝門近傍の画像，門脈と肝静脈の背景肝との相対的濃度に注目ください．
本例は脂肪沈着の目立つ多血性肝癌例．コロナ濃染が明瞭なのは静注開始後37秒と45秒．腫瘍の左右に蝶の羽に似たコロナ濃染を認める(第2段，桃色のオーバーレイ)．
コロナ濃染が明瞭な時相は門脈が背景より高吸収，肝静脈が低吸収～等吸収を呈し，肝の濃度がピークを迎える直前の時相に一致する(第3段)．それは腫瘍の濃度がピークを迎えた直後に一致する．
コロナ濃染がいつ明瞭に描出されるか注目すべきは背景肝の濃度，次いで門脈，肝静脈の濃度であり，造影開始からの秒数に意味はない．加えて，コロナ濃染が描出されるようであれば腫瘍が最も見やすい時相より遅れ気味で撮影されたことを意味する．

2. コロナ濃染域が背景肝の濃度よりも高いこと

造影剤が肝動脈に注入されるのであれば，背景肝の濃度はコロナ濃染が消退するまでコロナ濃染域の濃度より低い．具体的には肝動脈動注開始後22秒以降に撮影されれば1分後でもコロナ濃染はみられる．肝癌でコロナ濃染を輪状濃染として描出したいのであれば，造影剤動注停止が必要で，動注停止後30～60秒後に撮影するとよい．

一方，造影剤を静注し，門脈を経由して背景肝類洞に造影剤が還流した後はコロナ濃染域と隣接する背景肝の濃度が等濃度になるため，コロナ濃染は視認できなくなる．それゆえ，コロナ濃染が出現したのち，かつ背景肝の濃度がピークを迎える前に撮影すればコロナ濃染は静注でもみられる(図3)．なお，動注で造影剤注入停止した後の撮影と異なり，静注CTではコロナ濃染が出現する時期に病変の濃染が消退しないためコロナ濃染は輪状にはみえず，病変の濃染とコロナ濃染が一体となって高吸収を呈する．静注MRIではCTに比べ，造影剤注入のボーラス性が高いため，輪状にみられることがある[4]．

3. 動注CTにおける造影剤量とスライス厚

動注CTでは動注される造影剤の総量が大きいほどコロナ濃染は明瞭になる．CTが高速になると

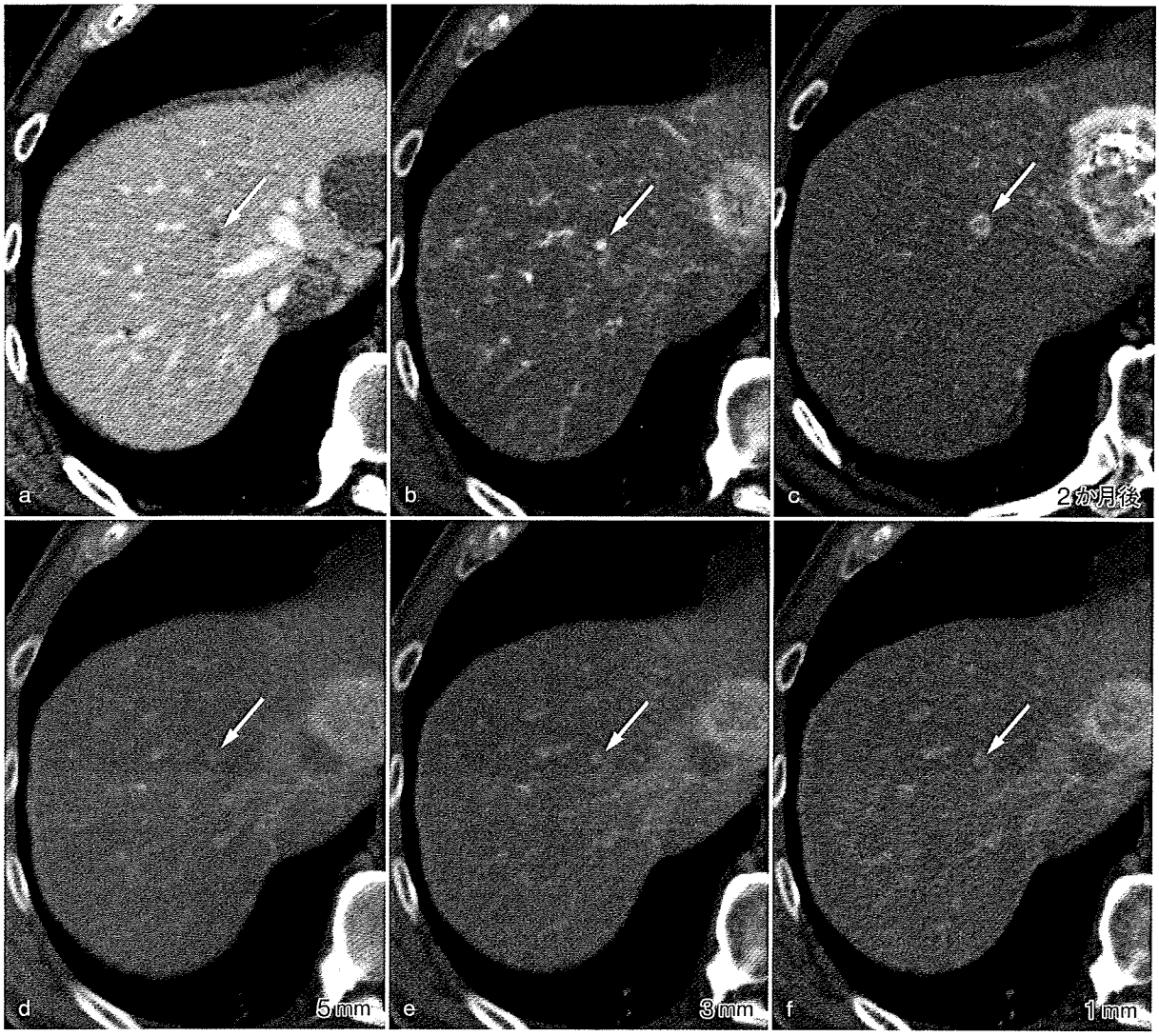

図4　コロナ濃染描出に適した動注CTのスライス厚
a. CTAP　b. CTHA早期　c. CTHA晩期2か月後　d. CTHA晩期5mm　e. 同3mm　f. 同1mm
肝癌のCTHA(2か月後増大)CTAP，CTHA早期では肝癌か動門脈短絡か判定できない．CTHA晩期5mm，3mmでは輪状濃染と判断しづらいが，1mmでは輪状にみえる．CTHAでは動注による造影効果がノイズによる画像の劣化を補う．CTHA早期で微小濃染をみた場合は1mmのCTHA晩期相で肝癌か動門脈短絡かを判断するのがよい．

CTHAの第1相撮影終了時に造影剤注入を停止すると造影剤の総量が小さくなるので注意が必要である．スライス厚に関しては動注による造影効果がスライス厚が薄くなると増えるノイズによる画像の劣化を補う(図4)．スライス厚1mm，3mm，5mmの画像を作成し比較すると，1mmでコロナ濃染が最も明瞭であった．筆者らは肝動脈より造影剤(300 mgI/m*l*，30 m*l*)を毎秒1m*l*で注入後，10秒，60秒(＝造影剤注入停止後30秒)に撮影し，1mm厚画像を作成している．

コロナ濃染の臨床意義

1. 画像診断への寄与

1) 肝癌とAP shuntの鑑別

コロナ濃染の最も重要な臨床的意義が肝癌とAP shuntの鑑別にある[7,8](図2)．1990年代はもっぱら動注CTにおいて古典的肝癌の確実な拾い上げに