

# Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey

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**Background.** Although a surgical resection is an important modality for the treatment of hepatocellular carcinoma (HCC), the impact of the operative method on both the patient survival and disease-free survival (DFS) still remains controversial.

**Methods.** Using a nationwide Japanese database, 72,744 patients with HCC who underwent a curative liver resection between 1994 and 2001 were divided into two groups based on whether an anatomical subsegmentectomy (AS) or a non-anatomical minor hepatectomy (MH) was performed. A total of 5,781 patients with single HCCs were selected for the study and divided into 3 subgroups based on the size of the HCCs (less than 2 cm, 2 to 5 cm, and greater than 5 cm in diameter). An AS was performed for 2,267 patients while an MH was performed for 3,514 patients.

**Results.** The overall DFS was significantly better after an AS ( $P = .0089$ ). When the patients were stratified according to the size of the HCC, a better DFS was seen in the patients with HCC from 2 to 5 cm after an AS ( $P < .0005$ ). Further stratification according to liver damage did not show any significant differences between an AS and an MH.

**Conclusion.** An AS is therefore recommended, especially when the size of HCC ranges from 2 to 5 cm. (Surgery 2008;143:469-75.)

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HEPATOCELLULAR CARCINOMA (HCC) is a common malignancy in Japan, especially in those with virally infected cirrhotic livers.<sup>1</sup> Although an anatomical liver resection is one of the curative treatment options available, a massive anatomical liver resection can be difficult to perform in diseased livers. Only 23% of the patients in the survey of the Liver Cancer Study Group of Japan (LCSGJ) underwent a hemi-hepatectomy.<sup>2</sup> For such cases of HCC in a diseased liver, especially for a single HCC, an anatomical subsegmentectomy (AS) to resect one Couinaud segment was advocated and reported to yield a good outcome.<sup>3</sup>

Another option to treat HCC in a diseased liver is a non-anatomical minor hepatectomy (MH) with a sufficient margin.<sup>4</sup> However, an absolute result of a comparison between an AS and an MH has not been reported, since the previous studies included a resection ranging from an extended hemi-hepatectomy to a subsegmentectomy in an anatomical resection group.<sup>3,4,7</sup> In addition, a comparison between an AS and an MH according to the size of the HCC and the liver function has not yet been fully demonstrated.

LCSGJ has been conducting a nationwide survey of the patients with primary liver carcinoma since 1969 in order to evaluate the epidemiologic and clinical characteristics, histopathologic features, diagnosis, treatment modalities, and outcomes.<sup>2</sup> Using the large-scale registration system of the LCSGJ, we herein evaluated the outcomes of an AS and an MH in order to clarify the impact of these two treatments on the survival of patients with a single HCC, and to identify which patients can benefit from these resections.

## MATERIALS AND METHODS

**Patients.** In a nationwide follow-up survey of primary HCCs conducted by LCSGJ, patients with primary malignant liver tumors who had been diagnosed by imaging studies, preoperative clinical data, and/or histopathologic studies at approximately 795 institutions in Japan were registered and followed prospectively every two years. This database contained 92,369 patients who were diagnosed with liver tumor and 72,744 patients who were finally diagnosed with HCC between 1994 and 2001. From this group, 5,781 patients with a single HCC who had undergone either an AS ( $n = 2,267$ ) or an MH ( $n = 3,514$ ) were enrolled. The indications for a hepatic resection and the types of operative procedures were usually determined based on the patients' liver functional reserved, mainly assessed by Makuuchi Criteria, which comprise preoperative

measurements of ascites, serum bilirubin level, and indocyanine green retention rate at 15 minutes.<sup>8</sup> This nation-wide study was prospectively performed but not randomly allocated, so this study is an "As treated" analysis and not an "Intention to treat" analysis.

**Operative methods.** In an AS, accurate determination of the resection area, i.e. one Couinaud segment, was typically performed with an intraoperative ultrasound and the complete resection of the portal territory containing the tumor was accomplished using either a dye puncture or the Glissonean method.<sup>9,10</sup> In a non-anatomical MH, a surgical margin from the tumor edge of at least 5 mm was secured whenever possible.<sup>11</sup> When it was not possible, however, liver parenchymal transection was performed without exposing the tumor surface, allowing the enucleation of the tumor. In all patients, the resection surface was histologically found to be free from HCC. Usually the liver parenchyma was divided with an ultrasonic dissector or the clamp-crushing method. The operation allocation depended on the policy of each surgeon in each facility. The median follow-up period was 789 days (range, 2 to 5860 days), the mean patient age was 63.1 years, and the male/female ratio was 76:24 (Table I). The patients were stratified according to the size of a single HCC. Specifically, the patients were divided into three subgroups; HCCs less than 2cm, HCCs 2 to 5 cm, and HCCs greater than 5 cm in diameter. In addition, the patients were further stratified according to the degree of liver damage, a procedure which was advocated by the LCSGJ as an alternative to the Child-Pugh score, which was defined by preoperative measurements of ascites, serum bilirubin level, serum albumin level, indocyanine green retention rate at 15 minutes, and prothrombin activity (Table II).<sup>12</sup> All recurrences were documented using computed tomography and/or magnetic resonance imaging with contrast media.

**Statistics.** The patient survival and the disease-free survival (DFS) curves of the AS and PH cases were generated using the Kaplan-Meier method and then were compared by the log-rank test. To investigate the hazard ratio of AS to MH, the Cox regression model was used. The major event of the model regarding patient survival was the cancer death of the patients, while for the DFS model it was the recurrence of HCC. *P* values of less than .05 were considered to be statistically significant. To accurately compare the effects of an AS with an MH, the outcomes were measured using the DFS because the patient survival after a recurrence could be affected by the subsequent treatment at other facilities.

**Table I.** Patient demographics

|                           | Operative methods |       |          |       |          |       |
|---------------------------|-------------------|-------|----------|-------|----------|-------|
|                           | AS                |       | MH       |       | Total    |       |
|                           | N = 2267          |       | N = 3514 |       | N = 5781 |       |
|                           | n                 | (%)   | n        | (%)   | n        | (%)   |
| Gender                    |                   |       |          |       |          |       |
| Male                      | 1764              | 77.81 | 2619     | 74.53 | 4383     | 75.82 |
| Female                    | 502               | 22.14 | 894      | 25.44 | 1396     | 24.15 |
| unknown                   | 1                 | 0.04  | 1        | 0.03  | 2        | 0.03  |
| Age (years old)           |                   |       |          |       |          |       |
| N                         | 1955              |       | 3079     |       | 5034     |       |
| Mean                      | 62.7              |       | 63.4     |       | 63.1     |       |
| SD                        | 9.23              |       | 9.02     |       | 9.11     |       |
| SE                        | 0.21              |       | 0.16     |       | 0.13     |       |
| unknown                   | 312               |       | 435      |       | 747      |       |
| Tumor size                |                   |       |          |       |          |       |
| N                         | 2213              |       | 3429     |       | 5642     |       |
| <=2cm                     | 622               | 28.1  | 1457     | 42.5  | 2079     | 36.8  |
| 2< <5cm                   | 1412              | 63.8  | 1798     | 52.4  | 3210     | 56.9  |
| >=5cm                     | 179               | 8.1   | 174      | 5.1   | 353      | 6.3   |
| Liver Damage              |                   |       |          |       |          |       |
| N                         | 2163              |       | 3286     |       | 5449     |       |
| unknown                   | 104               |       | 228      |       | 332      |       |
| A                         | 1615              | 74.7  | 2121     | 64.5  | 3736     | 68.6  |
| B                         | 530               | 24.5  | 1100     | 33.5  | 1630     | 29.9  |
| C                         | 18                | 0.8   | 65       | 2.0   | 83       | 1.5   |
| Observation period (days) |                   |       |          |       |          |       |
| N                         | 2267              |       | 3514     |       | 5781     |       |
| Mean                      | 951.6             |       | 948.2    |       | 949.5    |       |
| SD                        | 761.38            |       | 744.50   |       | 751.10   |       |
| SE                        | 15.99             |       | 12.56    |       | 9.88     |       |
| Operative mortality       | 16                | 0.71  | 30       | 0.86  | 46       | 0.79  |

**Table II.** Degree of Liver Damage Classified by the Liver Cancer Study Group of Japan

| Item                     | Degree of liver damage |              |                |
|--------------------------|------------------------|--------------|----------------|
|                          | A                      | B            | C              |
| Ascites                  | none                   | Controllable | Uncontrollable |
| Serum bilirubin (mg/dl)  | <2.0                   | 2.0-3.0      | >3.0           |
| Serum albumin (g/dl)     | >3.5                   | 3.0-3.5      | <3.0           |
| ICGR15(%)                | <15                    | 15-40        | >40            |
| Prothrombin activity (%) | >80                    | 50-80        | <50            |

NOTE. If 2 or more items scoring the same grade occurred in the 2 grades, the higher grade is adopted as the degree of liver damage. ICG R15(%), indocyanine green retention rate at 15 minutes

**RESULTS**

Table I shows the operative mortality by an AS and an MH as 0.71% and 0.86%, respectively. Fig 1 shows the overall survival of all patients with single HCCs treated either with an AS or an MH. The patient survival seemed to be better after an AS than after an MH but without statistical significance (hazard ratio 1.120,  $P = 0.0531$ ). The DFS was significantly better after an AS than after an MH (hazard ratio 1.121,  $P = .0089$ ).

After stratification according to the size of a single HCC, it was found that the HCCs measuring less than 2 cm in size numbered 2,079, HCCs ranging from 2 to 5 cm in size numbered 3,210, and HCCs greater than 5 cm in size totaled 353 cases, (size unknown 139 cases). When the survival was stratified according to above-mentioned size of HCC, the DFS was better after an AS as compared with the DFS after an MH for HCCs in the 2 to 5 cm diameter range (hazard ratio 1.216,  $P = .0005$ ,





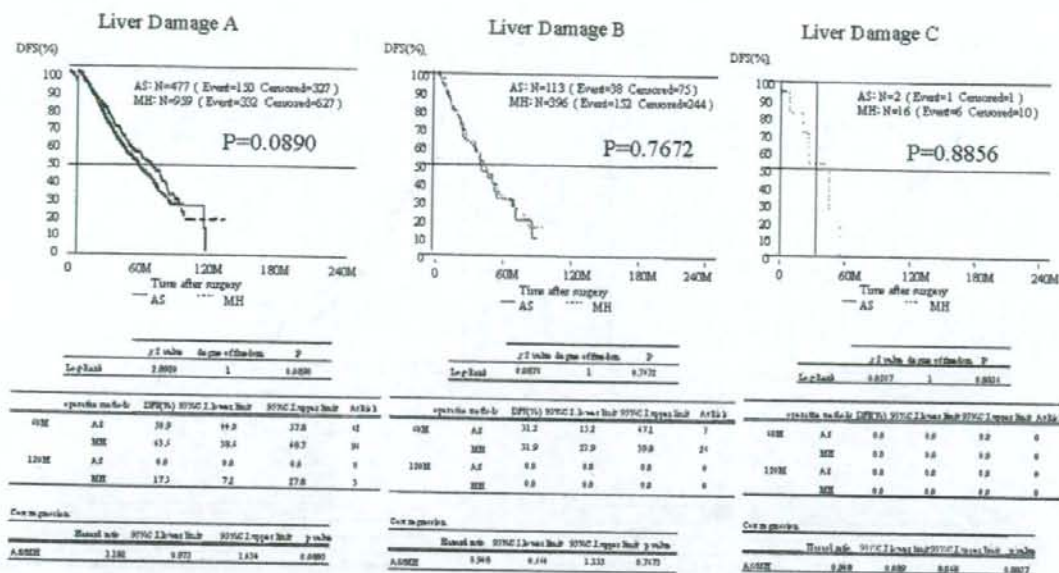


Fig 3. Disease-free survival after a curative resection for a single HCC measuring less than 2 cm in size.

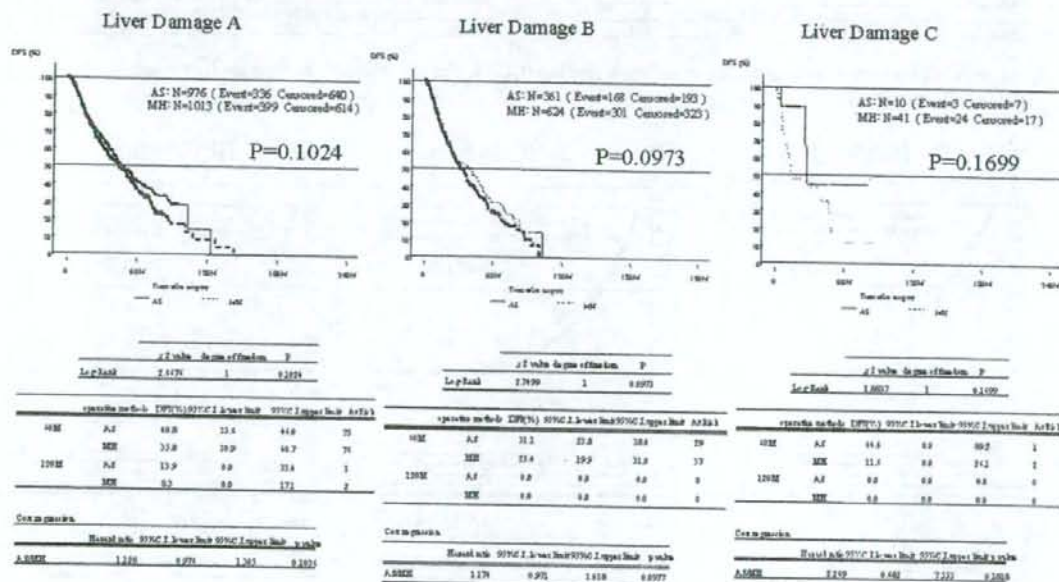


Fig 4. Disease-free survival after a curative resection for a single HCC of 2 to 5 cm.

extensive resections. In addition, the HCCs which developed in a Liver Damage C liver (n = 83, 1.5%), even those measuring less than 2cm in diameter, were not indicated for either AS or MH due to fear of inducing postoperative liver failure.

**DISCUSSION**

Using this large nationwide registration for HCC in Japan, we herein have demonstrated that an AS yielded a better DFS than did an MH for all single HCCs, especially for a tumor



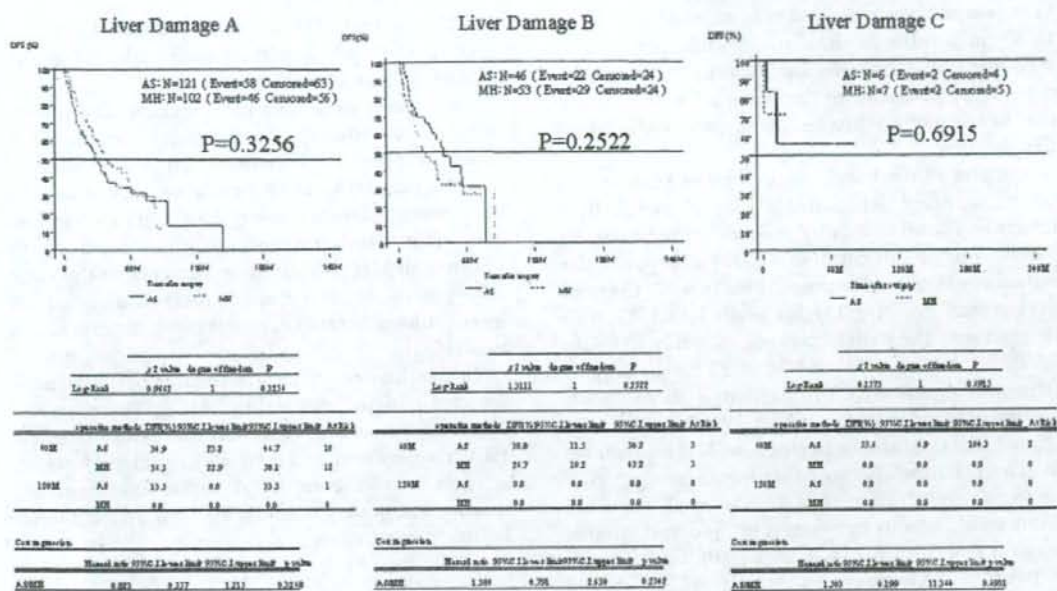


Fig 5. Disease-free survival after a curative resection for a single HCC larger than 5 cm in size.

between 2 and 5 cm in diameter. Although there was no statistical difference in the patient survival after an AS or an MH, it is important to note that, in this large scale study, even the patient survival only demonstrated a very slight statistically significant difference.

It seems reasonable that there was no statistical difference in the DFS between an AS and an MH because HCCs of less than 2 cm are generally effectively treated with other modalities such as local ablation therapy. In addition, for HCCs larger than 5 cm, an MH was comparable to an AS, because the stage of the HCC is elevated, and the oncological behavior of HCC is evident, and may offset the effects of the operative methods. Therefore, an AS became a strong prognostic factor, especially for HCCs measuring from 2 to 5 cm in size. In fact, the statistical probability of an AS on the DFS is greater for HCCs of measuring 2 to 5 cm in size ( $P = .0005$ ) in comparison with that seen in all HCCs before stratification ( $P = .0089$ ). It is also noteworthy to mention that the percentage of liver damage in patients within this group was not statistically higher than that occurring in the other groups (2 cm > HCC, 73.2%; 2 cm < HCC < 5 cm, 65.6%; 5 cm < HCC, 66.6%). Namely, the liver function could not account for the improved outcomes in the 2 cm < HCC < 5 cm group. For the patients with a preserved liver function, as in Child-Pugh A, a liver resection is a viable option for HCC

treatment. For this group of patients, various reports on the benefit of an AS or an MH show mixed results. In 1999 Nagasue et al<sup>13</sup> analyzed the outcome of extended (more than 2 subsegments) and partial liver resections for patients with HCCs less than 10 cm with preserved liver function (Child-Pugh A). They found no significant difference in the patient survival and the DFS between the methods of resection. On the other hand, in 2002, Regimbeau et al compared the outcomes of a curative MH in HCCs with at least 1 cm of surgical margin and of the anatomical liver resections for Child-Pugh A cirrhotic patients with HCCs measuring less than 4 cm in diameter.<sup>5</sup> The five- and eight-year patient survival rates were better in the anatomical resection group than in the MH group (five-year patient survival of 35% vs. 54%, eight-year patient survival of 6% vs. 45%), and the five- and eight-year DFS rates were also better in the anatomical resection group (26% vs. 45%, 0% vs. 21%). There were more local recurrences in the PH group. In 2004, Hasegawa et al<sup>3</sup> compared the outcomes of the anatomical and non-anatomical resections for a single HCC in Child-Pugh A and B groups (83% of the patients were Child-Pugh A) in a single center. The five-year patient survival and the DFS rates were better in the anatomical resection group (patient survival, 66% vs. 35%; DFS, 34% vs. 16%). In a multivariable analysis, an anatomical resection was one of the prognostic factors.



Our present study showed outcomes of the AS in DFS comparable to their study, while patient survival was not statistically significant. This might be due to the variability of the AS procedure between the nearly 800 Japanese institutions included in the database.

On the other hand, an extended resection is contraindicated for patients with impaired liver function, found mostly in cirrhotic patients. In the 1980s, one of our authors (T. K.) compared the outcome of limited liver resections ( $n = 37$ ) to major liver resections ( $n = 13$ ) for small HCCs.<sup>4</sup> In this comparison, the patient survival was only 79.9% to 78.7% at 1 year, and 32.6% to 22.5% at 5 years (thus not significant), while the mortality rate was higher after the major resections. We therefore concluded that it is valid to perform an MH for patients with liver cirrhosis because they have a poor prognosis to begin with. Recently, Kaibori et al<sup>6</sup> reported comparable results between a limited and an anatomical resection for HCC in a cirrhotic liver with hepatitis C. Therefore, although an AS should be performed to increase the survival of patients with HCC, an MH can be considered if an AS is not appropriate, especially for patients with poor liver function.

In this study, all resection margins were confirmed to be histologically free from HCC. In other words, only R0 (histologically curative) resections were included. However, no data regarding the distance from the resection margin and HCC were obtained in the LCSGJ study. Basically, this study was performed to see whether a resection of same portal territory of HCC (i.e. subsegment, namely, Couinaud one segment) has an impact on the disease free survival in a whole nation study in Japan rather than to clarify the impact of the distance from HCC to cut surface.

In the present study, there were no significant differences when the patients who underwent an AS or an MH were further stratified according to the degree of liver damage that is close to the Child-Pugh score, even in patients with HCCs of 2 to 5 cm in diameter. This might have been due to the decrease in the number of patients in each group of liver damage. For example, in patients with HCCs of 2 to 5 cm in diameter, 5 and 10 year survival rate after AS and MH were 37.4, 7.8% and 30.1, 4.6% with  $P$ -value of 0.0005 in Fig 2. When these patients were stratified with liver damage, 5 and 10 year survival rate after AS and MR were 40.8, 13.9% and 33.8, 8.3% with  $P$ -value of .1024 in patients with liver damage A ( $n = 1989$ ). It is quite possible that this statistical insignificance will be changed with increase in sample size. However, there is still a possibility that original cohort

of 3210 patients (HCCs 2-5cm) might have produced an overpowered study with statistical significance but little clinical relevance.

Since our present study provides Level 2a evidence using a large number of patients, it is considered to show the operative benefits of an AS for selected patients with HCC. In this study we did not analyze the patterns of recurrence of HCC after an AS or an MH. This needs further investigation to clarify whether an MH yields more recurrence in the same subsegment (i.e. intrahepatic metastasis) or in different subsegments (i.e. multicentric occurrence of new HCC).

In conclusion, an AS resulted in a better DFS for selected patients with a single HCC. Therefore, an AS is recommended, especially when the size of the HCC ranges from 2 to 5 cm in diameter. However, an MH is also considered to be an alternative treatment option for single HCC, if an AS cannot be performed safely.

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## Original Article

New chemotherapy for patients with advanced hepatocellular carcinoma: Pilot study of  $\beta$ -interferon and doxorubicin one-shot intra-arterial chemotherapyHirokazu Uyama,<sup>1</sup> Hiroaki Nagano,<sup>2</sup> Hideji Nakamura,<sup>3</sup> Takamichi Murakami,<sup>4</sup> Hironobu Nakamura,<sup>4</sup> Morito Monden<sup>2</sup> and Norio Hayashi<sup>1</sup>

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**Background:** Patients with advanced hepatocellular carcinoma (HCC) need an effective treatment modality because of the poor prognosis of the disease. From an *in vitro* study,  $\beta$ -interferon (IFN- $\beta$ ) has been reported to enhance the antiproliferative effects of doxorubicin on HCC cell lines. In the present study, we investigated the therapeutic effects of combined IFN- $\beta$  and doxorubicin intra-arterial injection therapy on patients with advanced HCC.

**Methods:** IFN- $\beta$  (3 MIU) and doxorubicin (10 mg/bodyweight) were given by one-shot intra-arterial injection through an arterial port to patients with advanced HCC. One treatment course consisted of three intra-arterial injections per week for 4 weeks. Three courses were conducted and evaluation was done monthly.

**Results:** Eleven patients with advanced HCC were treated with combined IFN- $\beta$  and doxorubicin. One patient entered

complete remission (CR), seven patients were evaluated as having stable disease (SD) and three as having progressive disease (PD). The mean overall survival was 10 months. The mean survival for CR and SD patients was 15 months, and that for PD patients was 6 months ( $P = 0.0464$ , log-rank test). Decrease of serum total bilirubin was observed for all patients.

**Conclusion:** Combined IFN- $\beta$  and doxorubicin intra-arterial therapy offers an effective chemotherapy option for patients with advanced HCC by improving liver function and having tolerable side-effects.

**Key words:** advanced hepatocellular carcinoma,  $\beta$ -interferon, doxorubicin, intra-arterial injection

## INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is principally associated with hepatitis B virus (HBV) or hepatitis C virus (HCV), and its incidence is especially high in Asia and Africa.<sup>1</sup> Recently, its incidence has been increasing in Europe and America.<sup>2,3</sup> There are various options for treatment of HCC, including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE) using inter-

ventional radiology (IVR), surgical resection, and liver transplantation.<sup>4</sup> However, the prognosis is poor for patients with advanced hepatic carcinomas, which develop in multiple segments in the liver and/or are accompanied by portal vein tumor thrombus, because no efficacious treatment modality has yet been developed.<sup>5</sup> Recently, for patients with advanced HCC without metastatic foci whose performance status (PS) is good, approximately 50% effectiveness has been reported for combined  $\alpha$ -interferon (IFN- $\alpha$ ) and 5-fluorouracil (5-FU) arterial injection therapy.<sup>6,7</sup> For patients with poor liver function who cannot accept IFN- $\alpha$  and 5-FU combination therapy, a new chemotherapy regimen is needed. Thus, we designed a protocol that minimizes hepatic toxicity and also enables one-shot arterial injection for patients with advanced HCC, who are not candidates for operation, liver

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transplantation, or local treatment such as IVR, PEIT or RFA due to the number of tumors, portal vein thrombosis, or liver dysfunction (BCLC staging system B or C).<sup>8</sup>

$\beta$ -interferon (IFN- $\beta$ ) is usually given by injection into the bloodstream and has fewer side-effects than IFN- $\alpha$ .<sup>9</sup> Recently, an *in vitro* study has shown that IFN- $\beta$  could suppress the proliferation of HCC more strongly than IFN- $\alpha$  both alone and in combination with anticancer agents.<sup>10</sup> In particular, the antitumor agent doxorubicin showed synergism with IFN- $\beta$  in the antiproliferation effect against HCC using HCC cell lines.<sup>11</sup> As myocardial damage and hepatic toxicity are the main side-effects of doxorubicin,<sup>12,13</sup> a small-volume one-shot arterial injection was selected for giving IFN- $\beta$ . This led us to design a new chemotherapy regimen of combined IFN- $\beta$  and doxorubicin intra-arterial injection therapy. The present study was conducted to determine whether this combined chemotherapy could be used for outpatient treatment after a short hospital stay in order to maintain the patient's quality of life (QOL) with fewer side-effects.

## METHODS

### Patient enrollment

PATIENTS WITH CIRRHOSIS and advanced HCC who were enrolled in this study were not eligible for surgical resection, liver transplantation or local treatment such as IVR, PEI or RFA because of diffuse or multiple tumors in both lobes with or without portal vein tumor thrombus and/or impaired liver function due to cirrhosis. To realize chemotherapy on an outpatient basis, patients with PS 0 or 1 were selected. Informed consent was obtained after explaining the purpose of the study and possible side-effects. Clinical tumor stages of patients with HCC were evaluated by abdominal contrast enhanced computed tomographic (CT) scans, magnetic resonance images (MRI) or angiography. Other criteria were a neutrophil count  $\geq 1000/\text{mm}^3$ , platelet count  $\geq 40\,000/\text{mm}^3$ , serum level of creatinine  $\leq 1.4\text{ mg/dL}$ , total bilirubin of  $\leq 3.5\text{ mg/dL}$ , and no abnormalities of cardiac function by ultrasound and electrocardiography. The exclusion criteria included intractable pleural effusion or ascites, severe infectious disease, severe myocardial damage, severe impairment of intelligence, encephalosis, metastasis to the central nervous system, hemorrhage from varicose veins within 1 month prior to enrollment, and pregnancy.

### Therapeutic design

All of the enrolled patients had a catheter placed by gastroduodenal artery (GDA) coil or other method and a port implanted subcutaneously. One course of chemotherapy consisted of one-shot intra-arterial injection of IFN- $\beta$  (3 MIU) and doxorubicin (10 mg/bodyweight) through the port, three times per week for 4 weeks. Three courses were conducted, when possible, and monthly evaluation of chemotherapy effects on HCC was based on serum tumor markers and CT scans.

### Evaluation of therapeutic effects

The antitumor effect was evaluated by tumor volumes using contrast enhanced CT scans every 4 weeks from the start of combined IFN- $\beta$  and doxorubicin intra-arterial injection therapy. The antitumor effect and toxicity were evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC)<sup>14</sup> and Response Evaluation Criteria in Solid Tumors (RECIST)<sup>15</sup> guidelines. Peripheral blood cells, biochemical tests, serum levels of  $\alpha$ -fetoprotein (AFP) and/or PIVKA-II were examined every 4 weeks. The overall survival was calculated from the first treatment until death or the final day of follow up. The primary end-point of the current study was the development of toxicity and overall survival.

The criteria of complete response (CR), stable disease (SD) and progressive disease (PD) were as follows: CR, complete disappearance of tumors and no evidence of new lesions; SD,  $< 50\%$  reduction or  $< 25\%$  increase of tumor volume and no evidence of new lesions; PD,  $\geq 25\%$  increase of tumor volume, evidence of new lesions, or rise in tumor markers.

### Statistics

The overall survival time from the start of the chemotherapy was analyzed by the Kaplan-Meier method and differences in survival were evaluated by log-rank tests.

## RESULTS

### Patient characteristics

ELEVEN PATIENTS WERE enrolled at Osaka University Hospital between November 2003 and August 2005. HCC was diagnosed by contrast-enhanced CT scan or MRI. Angiography and pathological diagnosis were not done. The serum levels of AFP and PIVKA-II were elevated. The pretreatment characteristics of enrolled patients are shown in Table 1.

Table 1 Pretreatment characteristics of patients with advanced hepatocellular carcinoma

| No. | Age (years) | Sex | Etiology    | Child-Pugh grade | Portal venous thrombosis (Vp) | Previous treatment |
|-----|-------------|-----|-------------|------------------|-------------------------------|--------------------|
| 1   | 56          | M   | HBV/HCV     | B                | +                             | TAE                |
| 2   | 78          | M   | HCV         | A                | +                             | TAE, RFA           |
| 3   | 73          | M   | HBV         | A                | -                             | Operation, TAE     |
| 4   | 58          | M   | HCV         | B                | -                             | TAE                |
| 5   | 71          | M   | HCV         | B                | -                             | TAE                |
| 6   | 49          | M   | HCV         | C                | +                             | TAE, RFA           |
| 7   | 69          | M   | Non B/non C | B                | +                             | None               |
| 8   | 63          | M   | HBV         | A                | +                             | TAE, RFA           |
| 9   | 62          | F   | HCV         | B                | -                             | TAE                |
| 10  | 61          | M   | HCV         | A                | +                             | TAE, RFA           |
| 11  | 56          | M   | HCV         | A                | -                             | None               |

HBV, hepatitis B virus; HCV, hepatitis C virus; RFA, radiofrequency ablation; TAE, transcatheter arterial embolization.

All patients were enrolled after being diagnosed as having liver cirrhosis by biochemical tests and/or radiological findings. Histological confirmation of liver cirrhosis was not done. The liver function of patients with cirrhosis was classified according to Child-Pugh grading criteria. Pretreatment tumor stages of patients with advanced HCC were classified according to the American Joint Committee on Cancer (AJCC) Tumor-Lymph Node Metastasis (TNM) classification system,<sup>16</sup> and according to the Cancer of the Liver Italian Program (CLIP) score<sup>17</sup> (Table 2). Seven patients had HCV infection, two had HBV, one had both HBV and HCV. One patient suffered from cirrhosis with neither HBV nor HCV infection.

### Tolerability and side-effects

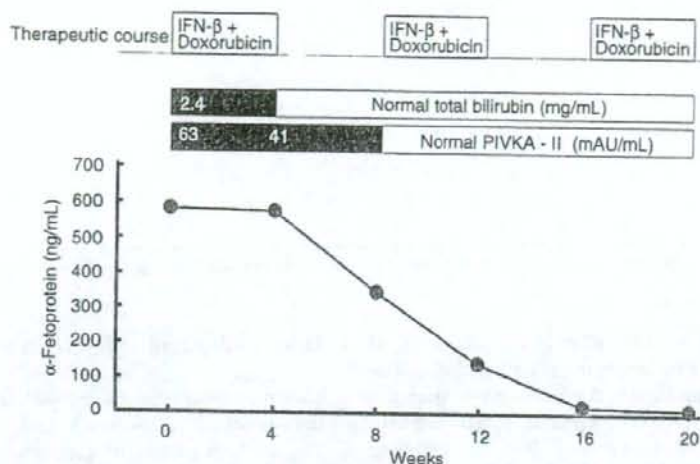
Eleven patients were started with intra-arterial administration of 3 MIU IFN- $\beta$  and 10 mg doxorubicin. The median period of combined chemotherapy was 11 weeks (range 8-12 weeks). The dose of doxorubicin was reduced from 10 mg/bodyweight to 5 mg/bodyweight for two patients (nos. 2 and 6) because of grade 3 and 4 neutropenia. A 78-year-old man (no. 2) developed grade 4 neutropenia after the first course, and doxorubicin was reduced to 5 mg/bodyweight and granulocyte-colony stimulating factor (G-CSF) was given, and then grade 4 stomatitis appeared after two courses leading to discontinuation of the chemo-

Table 2 Therapeutic effect according to RECIST on patients and tumor stages of HCC patients according to the CLIP score and TNM classification system

| No. | T-Bil (mg/mL) | AFP (ng/mL) | PIVKA II (mAU/mL) | CLIP score | TNM | Duration of therapy | Therapeutic effect | Prognosis  |
|-----|---------------|-------------|-------------------|------------|-----|---------------------|--------------------|------------|
| 1   | 1.9           | <5.3        | <40               | 4          | III | 3 cycles            | SD                 | 15 M Dead  |
| 2   | 1.7           | 2 145       | <40               | 4          | IVA | 2 cycles            | PD                 | 6 M Dead   |
| 3   | 0.6           | 24          | 148               | 1          | III | 3 cycles            | SD                 | 8 M Dead   |
| 4   | 3.3           | 24          | 140               | 2          | III | 3 cycles            | SD                 | 35 M Alive |
| 5   | 1.6           | 25          | 462               | 3          | III | 2 cycles            | SD                 | 6 M Dead   |
| 6   | 2.1           | 10 400      | 32 852            | 6          | IVB | 3 cycles            | SD                 | 6 M Dead   |
| 7   | 1.3           | 226 820     | 12 317            | 5          | IVA | 3 cycles            | PD                 | 5 M Dead   |
| 8   | 2.4           | 582         | 63                | 3          | IVA | 3 cycles            | CR                 | 20 M Alive |
| 9   | 2.9           | 41          | 1 397             | 2          | IVA | 2 cycles            | SD                 | 12 M Dead  |
| 10  | 0.7           | 255         | 1 341             | 3          | III | 3 cycles            | PD                 | 10 M Dead  |
| 11  | 2.4           | 309         | 13 900            | 1          | III | 3 cycles            | SD                 | 25 M Alive |

AFP,  $\alpha$ -fetoprotein; CLIP score, Cancer of the Liver Italian Program score; CR, complete remission; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; T-Bil, total bilirubin; TNM, Tumor-lymph Node Metastasis classification system.





**Figure 1** Time course of tumor markers in a complete remission case. A 63-year-old man with diffused type advanced hepatocellular carcinoma (HCC) (no. 8) was treated with three courses of combined  $\beta$ -interferon (IFN- $\beta$ ) and doxorubicin intra-arterial injection therapy without severe side-effects. Serum levels of PIVKA-II decreased after the first course of combined chemotherapy, entered the normal range during the second course and remained in the normal range after three courses. The serum level of  $\alpha$ -fetoprotein decreased after the second course and entered the normal range 1 month after three courses of combined therapy. No HCC lesions were detected in the patient's liver by contrast enhanced CT scans and MRI after three courses of combined chemotherapy and 6 months later.

therapy. A 71-year-old man (no. 5) and a 62-year-old woman (no. 9) with Child-Pugh grade B complained of severe fatigue after two courses, and the chemotherapy was stopped. They had been treated by TAE for the tumors more than five times previously. Previous treatments, especially transarterial chemoembolization (TACE) may have affected the severity of the toxicity of the present combined chemotherapy regimen, although other factors such as age and Child-Pugh grade can be considered as having affected the development of intolerable side-effects. Discontinuation of drug therapy led to quick recovery from the adverse reactions. Of the eight remaining patients, three dropped out of the study and five completed three courses of treatment.

#### Therapeutic effects of combined intra-arterial IFN- $\beta$ and doxorubicin injection therapy

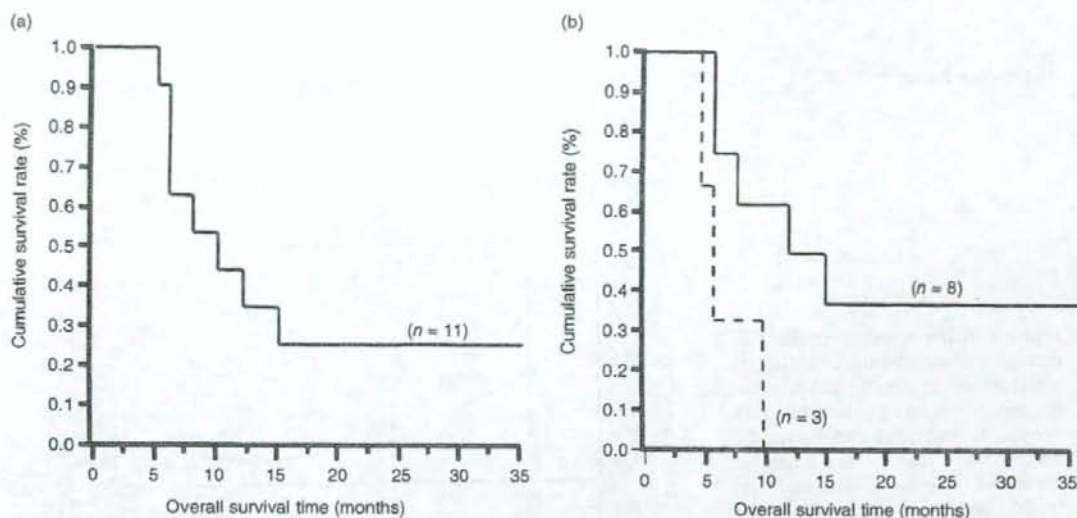
All patients had advanced HCC, seven with and four without portal thrombus. All HCC were evaluated for volume changes by contrast-enhanced CT scans after 8 or 12 weeks. A 63-year-old man (no. 8) with HBV infection showed significant reduction of AFP and PIVKA-II into the normal range. Diffuse HCC disappeared after three courses of combined IFN- $\beta$  and doxorubicin intra-

arterial injection therapy, being confirmed by contrast-enhanced CT scan and MRI. Thus, we concluded that patient no. 8 had attained CR (Fig. 1).

All patients showed a high serum level of AFP and/or PIVKA-II before treatment (Table 2). The serum levels of AFP and/or PIVKA-II decreased after one course of combined chemotherapy in all patients. However, the CT scans demonstrated no significant volume reduction of HCC in seven patients, and tumor enlargement in three. Seven patients were classified as SD and three as PD from contrast-enhanced CT scans (Table 1).

#### Overall survival

All of the patients were observed from November 2003 to October 2006. The estimated duration of overall median survival was 10 months (Fig. 2a). The mean survival time was 15 months for CR and SD patients, which is significantly longer than 6 months for PD patients ( $P = 0.0464$ , log-rank test) (Fig. 2b). The mean survival time of only SD patients (12 months) was not significantly longer than that for PD patients ( $P = 0.0786$ , log-rank test). The one-year survival rate for CR and SD patients was 62.5% (5/8) and that for PD was 0% (0/3). The progression-free survival time for CR or SD was longer than that for PD ( $P = 0.0004$ , log-rank test)



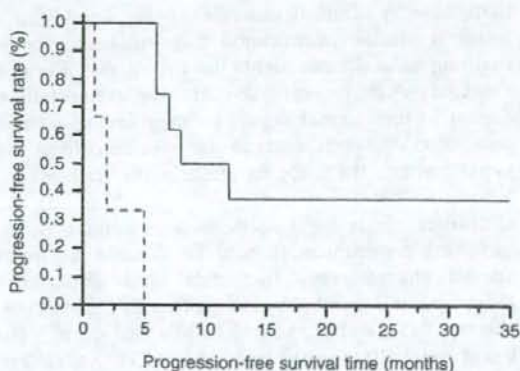
**Figure 2** Overall survival periods of patients with advanced hepatocellular carcinoma who received combined  $\beta$ -interferon (IFN- $\beta$ ) and doxorubicin intra-arterial injection therapy. (a) Overall survival periods of 11 patients who received combined IFN- $\beta$  and doxorubicin intra-arterial injection therapy. The mean survival period was 10 months. (b) Overall survival periods of seven patients with stable disease (SD) and three with progressive disease (PD) after combined IFN- $\beta$  and doxorubicin intra-arterial injection therapy. The mean survival period was 15 months for SD patients and 6 months for PD patients. (—), CR-SD; (---), PD. CR, complete response. ( $P = 0.0464$ , log-rank test).

(Fig. 3). Eight patients died of liver failure, including five SD and three PD patients. A 73-year-old man (no. 3) died of sepsis that developed from catheter problems, after completion of three cycles of treatment. Three patients are alive, including one CR patient (25 months) and two SD patients (35 and 20 months). The QOL of PD patients was maintained until the end of the treatment. The Eastern Cooperative Oncology Group (ECOG) performance status at the end of the treatment had not deteriorated.

Total bilirubin of the HCC patients who had received IFN- $\beta$  and doxorubicin intra-arterial combination therapy decreased significantly after one cycle ( $P = 0.0344$ ) and two cycles ( $P = 0.0051$ ) of treatment (Fig. 4). In all patients, anorexia and lassitude were alleviated, offering remarkable benefits for advanced HCC patients.

## DISCUSSION

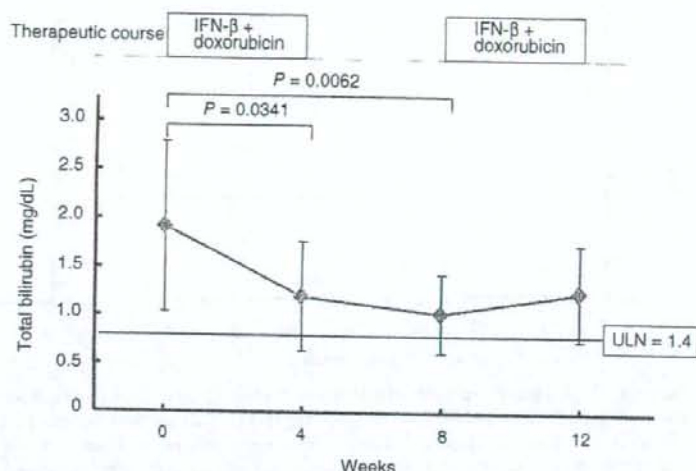
**H**EPATOCELLULAR CARCINOMAS RECEIVE nourishment from the hepatic artery, not the portal



**Figure 3** Progression-free survival times of patients with advanced hepatocellular carcinoma according to responses to  $\beta$ -interferon and doxorubicin combination therapy. One-year survival rate for CR or SD patients was 62.5% (5/8) and that for PD was 0% (0/3). The progression-free survival time for CR or SD was longer than that for PD. (—), CR-SD; (---), PD. CR, complete response. ( $P = 0.0004$ , log-rank test).



**Figure 4** Serum bilirubin ameliorated during combined  $\beta$ -interferon (IFN- $\beta$ ) and doxorubicin intra-arterial injection therapy. Serum levels of total bilirubin decreased significantly and entered the normal range after the first course of combined chemotherapy, and remained in the normal range during the further courses. Values are averages  $\pm$  SD. Upper limit of normal (ULN) serum values of total bilirubin, 1.4 mg/dL.



flow. Thus, a therapeutic effect should be attainable by giving antitumor agents via the hepatic artery. By direct delivery into the hepatic artery, the concentrations of anticancer agents in the liver increase to 10-fold or more than those by administration via the peripheral veins.<sup>18</sup> By direct injection of anticancer drugs into blood vessels draining to local areas, higher therapeutic effects can be expected when higher ratios of drug concentration appear in the internal organs on their first pass (first-pass effect).<sup>19</sup> When doxorubicin is infused from the hepatic artery, the first-pass effect in the liver is considered to be approximately 60% in rabbits. As the antitumor effects are dose dependent, anthracyclines, including doxorubicin, should be suitable for intra-arterial chemotherapy by single bolus injection.<sup>20</sup> Doxorubicin is metabolized in the liver by hepatic cytochrome P450 and is excreted in bile and urine.<sup>21</sup> On being metabolized by the typical P450 CYP3A4, 40% or more of doxorubicin is ultimately excreted via the bile. Its metabolism and excretion are delayed in patients with hepatic dysfunction such as cirrhosis or with obstructive jaundice, in whom the side-effects of anthracyclines tend to develop easily. In the present study, myelosuppression was observed in two patients (nos. 2 and 6), and in one case G-CSF had to be used. We have examined the concentration of doxorubicin of 10 patients including these patients. The blood concentration of doxorubicin was measured by high-performance liquid chromatography using patients' serum. In two patients with myelosuppression, the blood concentrations of doxorubicin exceeded 10 ng/mL at 60 min after

the start of administration. In these patients, no significant hepatic damages were observed. Another eight patients without significant myelosuppression, whose blood concentration of doxorubicin could be measured, showed lower blood concentration than 10 ng/mL. These findings suggested that patients, in whom the blood doxorubicin concentration is 10 ng/mL or more at 60 min after the start of administration, seem to be susceptible to the side-effects, especially hematological toxicity. In general, the serum concentration of doxorubicin at 60 min after its administration is less than 10 ng/mL in normal subjects. But it could be well considered that the serum concentration of doxorubicin at 60 min after its administration to the patients with liver dysfunction is more than 10 ng/mL due to the delayed metabolism and excretion of doxorubicin. The monitoring of serum concentration of doxorubicin seems to be important in patients with liver cirrhosis.

IFN- $\beta$  and doxorubicin intra-arterial combination therapy significantly reduced total bilirubin, but did not improve other liver function tests such as prothrombin time and albumin. This seems to be the most distinct hallmark of this therapy. In the present study, no patients had tumor thrombus in the bile duct. However, in the cases of advanced HCC, tumors may compress the small bile duct. After the treatment of combination therapy, compression of the small bile duct by tumors may be relieved because of the reduction of tumor size. However, giving IFN to bile duct-ligated rats has been reported to result in significant preservation of histology, inhibition of collagen accumulation and partial



improvement of serum markers of cholestasis.<sup>21</sup> Thus, IFN used with doxorubicin may bring about the partial improvement of cholestasis in patients with advanced HCC. However, the mechanism of reduction of serum bilirubin by this combination chemotherapy remains to be clarified. Marked improvement of total bilirubin by IFN- $\beta$  and doxorubicin therapy in HCC patients might offer clinical proof of the novel characteristics of interferon.

Yang et al. reported the efficacy of gemcitabine and doxorubicin for patients with advanced HCC, with median survival of 4.6 months for all patients and median progression-free survival of 2.5 months.<sup>22</sup> Obi et al. reported the efficacy of combination therapy of systemic IFN- $\alpha$  and intra-arterial 5-FU for HCC patients with portal vein invasion, with the survival rate at 12 months being 34% and median survival time of 6.9 months.<sup>23</sup> The 1-year survival rate for CR or SD patients was 62.5% and that for all patients, including PD patients, was 45%, and the mean survival time for all patients was 10 months in the present study, although the number of the patients was small. The present findings suggested that IFN- $\beta$  is more effective than gemcitabine or IFN- $\alpha$  for advanced HCC. This might explain the effectiveness of IFN- $\beta$  injected into the tumor site in the liver directly through the catheter. To confirm the superior effects of intra-arterial IFN- $\beta$  administration, further studies with more patients and longer treatment periods should be done.

All patients enrolled in the present study had extensively advanced HCC, with five cases including portal tumor thrombus Vp3. Patients with Child-Pugh grades A and B are also eligible for this combined chemotherapy regimen, but the dose and the interval of administration should be considered for patients with ascites or a serum level of total bilirubin at 3.0 mg/dL or more, such as Child-Pugh grade C.

Small amounts of IFN- $\beta$  and doxorubicin do not tend to cause severe side-effects. Under the new enrollment criteria, HCC patients need only 2 or 3 days of hospital stay for port implantation, and outpatient therapy can be started immediately. Moreover, this one-shot intra-arterial injection therapy can be conducted within a short time to minimize restriction of the patient. Based on these findings, one-shot intra-arterial combination chemotherapy of IFN- $\beta$  and doxorubicin could be recommended for outpatient therapy of patients with advanced HCC.

In conclusion, for patients with progressive hepatocellular carcinoma, this preliminary study shows that combined IFN- $\beta$  and doxorubicin intra-arterial chemo-

therapy has the potential of prolonging survival time while maintaining QOL in an outpatient clinic. This combination chemotherapy, with tolerable side-effects, has the potential of serving as an optimal treatment option for advanced HCC, by improving liver function and maintaining the QOL for outpatients.

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## Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: A preliminary report of the Japanese nationwide survey<sup>☆</sup>

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See Editorial, pages 502–504

**Background/Aims:** The treatment of choice for HCC remains controversial. We evaluated the therapeutic impact of surgical resection, PEI, and RFA for HCC on outcomes.

**Methods:** A database derived from a Japanese nationwide survey of 17,149 patients with HCC treated by resection, PEI, or RFA between 2000 and 2003 was used to identify 7185 patients with no more than 3 tumors ( $\leq 3$  cm) and a liver function of Child-Pugh class A or B. The patients classified into either a resection ( $n = 2857$ ), RFA ( $n = 3022$ ), or PEI group ( $n = 1306$ ) and their long-term outcomes were compared.

**Results:** The median follow-up period was 10.4 months. The 2-year time-to-recurrence rate was 35.5%, 55.4%, and 73.3% in the resection, RFA, and PEI groups, respectively, while the number of recurrences was 2410, 2368, and 862. Although the number of deaths was 55 (1.9%), 49 (1.6%), and 39 (3.0%), the overall survival rates were not different. In a multivariate analysis, surgical resection was a significant negative factor for recurrence as compared with RFA (relative risk, 0.62 [95% confidence interval, 0.54–0.71],  $P < 0.0001$ ) and PEI (0.45 [0.38–0.52],  $P < 0.0001$ ).

**Conclusions:** This preliminary report suggested that surgical resection may provide less time-to-recurrence rate than either RFA or PEI in patients with HCC.

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**Keywords:** Hepatocellular carcinoma; Surgical resection; Radiofrequency ablation; Percutaneous ethanol injection; Nationwide survey

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Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter hepatic arterial chemoembolization.

### 1. Introduction

Recent advances in the diagnosis and treatment of hepatocellular carcinoma (HCC) have improved short- and long-term outcomes [1]. Many treatments are now available for HCC, such as surgical resection, percutaneous ablation, and transcatheter hepatic arterial chemoembolization (TACE). Treatment for individual patients is selected on the basis of the stage of liver disease and tumor status, but clear-cut guidelines are lacking.

Since 1965, the Liver Cancer Study Group of Japan has conducted nationwide surveys of patients with HCC. In



2000, we reported the results of a study comparing survival after surgical resection, percutaneous ethanol ablation (PEI), and TACE, based on a large database including 30,000 patients registered between 1988 and 1996 [2]. Surgical resection was found to result in longer survival than PEI in clinical stage I [3] disease with a single tumor ( $\leq 5$  cm) and in clinical stage II disease with a single tumor ( $>2$  cm but  $\leq 5$  cm) or 2 tumors ( $\leq 2$  cm). TACE was inferior to both surgical resection and PEI. On the basis of these results, "Clinical practice guidelines for hepatocellular carcinoma", published in 2005 [4], recommended surgical resection and percutaneous ablation as first-line treatment and second-line treatment, respectively, in patients with good liver function, classified as liver damage A or B [3], and a single tumor or no more than 3 tumors each measuring  $\leq 3$  cm in diameter.

In the early 1990's, radiofrequency ablation (RFA) was introduced [5] and has since been widely used in place of PEI [6–8]. The results of randomized controlled trials have recently confirmed that RFA has better outcomes than PEI [9,10]. In view of these findings, the superiority of surgical resection over percutaneous ablation, supported by the results of our previous study comparing surgery with PEI [2], should now be re-evaluated by comparing surgery with RFA. We therefore compared long-term outcomes after surgical resection, RFA, and PEI based on data obtained in the latest Japanese survey.

## 2. Patients and methods

With the cooperation of 795 institutions in Japan, patients with primary liver cancer have been registered every 2 years and followed up prospectively in a nationwide survey conducted by the Liver Cancer Study Group of Japan. HCC was diagnosed on the basis of imaging studies, clinical data, and/or histopathological studies at each institution. Between 2000 and 2003, a total of 17,149 patients who underwent surgical resection, RFA, or PEI as a primary treatment for HCC were newly registered. Since 2000, RFA began to be more widely used in Japan, making the study period suitable for the assessment of this treatment. We studied outcomes in 7185 patients who met the following criteria, which are consistent with a common indication for RFA and PEI [10,11]: (1) no more than 3 tumors ( $\leq 3$  cm in diameter) and (2) a liver function of Child-Pugh class A or B. Patients for whom outcome data were not available were excluded. The 7185 patients were classified according to primary treatment into a resection group ( $n = 2857$ ), RFA group ( $n = 3022$ ), and PEI group ( $n = 1306$ ).

The patients were prospectively followed up at each institution. There is no definite follow-up protocol, however, most of the hepatologists and liver surgeons have observed the protocol, as shown in "Clinical practice guidelines for hepatocellular carcinoma" [4], in which ultrasonography and measurement of the tumor markers every 3 or 4 months and enhanced computed tomography or magnetic resonance imaging every 6 or 12 months is recommended.

The relevant clinical data were collected and analyzed. The baseline characteristics of the three groups (Table 1) were compared by analysis of variance for continuous variables, and by chi-square or Mantel-trend tests for categorical variables. The resection group had higher proportions of younger patients and male patients than did the RFA and PEI groups. Hepatitis C virus infection was less prevalent in the resection group than in the RFA and PEI groups. On the basis of Child-Pugh class, serum albumin and total bilirubin levels, platelet counts, and the indocyanine green retention rate at 15 min, liver function was better in the resection group than in

the RFA and PEI groups. As for tumor-related factors, the number of tumors was smaller and the maximum tumor diameter was larger in the resection group than in the RFA group or PEI group. The resection group had the lowest proportion of patients with an abnormally elevated alpha-fetoprotein level ( $\geq 15$  ng/mL) and the highest proportion of patients with an abnormal des- $\gamma$ -carboxy prothrombin level ( $\geq 40$  AU/mL).

Overall survival and time-to-recurrence curves were plotted by the Kaplan-Meier method and compared by the log-rank test. Recurrence was diagnosed on the basis of imaging studies, clinical data, and/or histopathological studies at each institution. When calculating time-to-recurrence, death without recurrence was defined as a censor.

The therapeutic impact of surgical resection, RFA, and PEI was estimated using a Cox proportional-hazards model, including the following 9 covariates: age, gender, Child-Pugh class, hepatitis C virus antibody, platelet count, tumor number, tumor size, alpha-fetoprotein level, and des- $\gamma$ -carboxy prothrombin level. The results of multivariate analysis are expressed as relative risks with 95% confidence intervals.  $P$  values of  $<0.05$  were considered to indicate statistical significance.

## 3. Results

The median follow-up period after treatment was 10.4 months, and the 25th percentile and 75th percentiles were 4.8 and 16.7 months, respectively. Overall survival rates at 1 and 2 years in the resection group, RFA group, and PEI group were 98.3%/94.5%, 98.5%/93.0%, and 98.2%/92.3%, respectively (Fig. 1). The differences between the groups were not significant. The number of deaths in the resection, RFA, and PEI groups was 55 (1.9%), 49 (1.6%), and 39 (3.0%), respectively. Time-to-recurrence rates at 1 and 2 years in the resection, RFA, and PEI groups were 17.0%/35.5%, 26.0%/55.4%, and 32.5%/73.3%, respectively, while the number of recurrences was 2410, 2368, and 862, respectively. The time-to-recurrence rate was significantly lower in the resection group than in the other two groups (Fig. 2,  $P < 0.0001$ ).

The multivariate analysis showed that the impact of treatment on overall survival did not differ significantly among the three groups (Table 2). Low tumor marker levels (alpha-fetoprotein  $<15$  ng/mL and des- $\gamma$ -carboxy prothrombin  $<40$  AU/mL), tumor size  $<2$  cm, better liver function (Child-Pugh class A), and the presence of hepatitis C virus infection were favorable factors for overall survival. Among the 3 treatments, surgical resection had the greatest negative impact on recurrence, because relative risk as compared with RFA and PEI was 0.62 (95% confidence interval: 0.54–0.71,  $P < 0.0001$ ) and 0.45 (0.38–0.52,  $P < 0.0001$ ), respectively. A single tumor, low tumor marker levels, a small tumor size, the absence of hepatitis C virus infection, and younger age were negative factors for recurrence.

## 4. Discussion

In this study, time-to-recurrence rate was lower after surgical resection for HCC than after RFA or PEI, and



**Table 1**  
Baseline characteristics

| Variables                                    | Resection (n = 2857) | RFA (n = 3022)  | PEI (n = 1306)  | P                    |
|--|----------------------|-----------------|-----------------|----------------------|
| Age (years)                                  | 67 (48, 77)          | 69 (52, 80)     | 69 (53, 80)     | <0.0001 <sup>a</sup> |
| Gender                                       |                      |                 |                 | <0.0001 <sup>b</sup> |
| Male   | 2114 (74.0%)         | 1937 (64.1%)    | 820 (62.8%)     |                      |
| Female                                       | 743 (26.0%)          | 1085 (35.9%)    | 486 (37.2%)     |                      |
| Hepatitis virus infection                    |                      |                 |                 | <0.0001 <sup>b</sup> |
| HBVsAg(+)/HCV-Ab(-)                          | 496 (17.4%)          | 261 (8.6%)      | 88 (6.7%)       |                      |
| HBVsAg(-)/HCV-Ab(+)                          | 1832 (64.1%)         | 2353 (77.9%)    | 1044 (80.0%)    |                      |
| HBVsAg(+)/HCV-Ab(+)                          | 56 (2.0%)            | 55 (1.8%)       | 27 (2.1%)       |                      |
| HBVsAg(-)/HCV-Ab(-)                          | 384 (13.4%)          | 256 (8.5%)      | 99 (7.6%)       |                      |
| Unknown                                      | 89 (3.1%)            | 97 (3.2%)       | 48 (3.7%)       |                      |
| Child-Pugh class                             |                      |                 |                 | <0.0001 <sup>b</sup> |
| A  | 2570 (90.0%)         | 2288 (75.7%)    | 939 (71.9%)     |                      |
| B  | 287 (10.0%)          | 734 (24.3%)     | 367 (28.1%)     |                      |
| Serum albumin (g/dL)                         | 3.9 (3.1, 4.6)       | 3.7 (2.8, 4.4)  | 3.6 (2.8, 4.4)  | <0.0001 <sup>a</sup> |
| Serum total bilirubin (mg/dL)                | 0.7 (0.4, 1.5)       | 0.9 (0.4, 2.0)  | 0.9 (0.4, 2.1)  | <0.0001 <sup>a</sup> |
| Platelet count ( $\times 10^4/\mu\text{L}$ ) | 12.8 (5.9, 23.9)     | 9.6 (4.4, 19.9) | 9.4 (4.2, 19.7) | <0.0001 <sup>a</sup> |
| ICG R <sub>15</sub> (%)                      | 15 (5, 35)           | 23 (7, 52)      | 24 (9, 54)      | <0.0001 <sup>a</sup> |
| Tumor number                                 |                      |                 |                 | <0.0001 <sup>c</sup> |
| Single                                       | 2410 (84.4%)         | 2189 (72.4%)    | 938 (71.8%)     |                      |
| Two  | 350 (12.3%)          | 624 (20.7%)     | 274 (21.0%)     |                      |
| Three  | 97 (3.4%)            | 209 (6.9%)      | 94 (7.2%)       |                      |
| Tumor size (mm)                              | 22 (12, 30)          | 20 (10, 30)     | 17 (10, 30)     | <0.0001 <sup>a</sup> |
| Alpha-fetoprotein (ng/mL)                    |                      |                 |                 | 0.005 <sup>b</sup>   |
| $\geq 15$                                    | 1473 (51.6%)         | 1678 (55.5%)    | 720 (55.1%)     |                      |
| <15  | 1288 (45.1%)         | 1243 (41.1%)    | 543 (41.6%)     |                      |
| Unknown                                      | 96 (3.4%)            | 101 (3.3%)      | 43 (3.3%)       |                      |
| Des- $\gamma$ -carboxy prothrombin (AU/mL)   |                      |                 |                 | <0.0001 <sup>b</sup> |
| $\geq 40$                                    | 1156 (40.5%)         | 867 (28.7%)     | 375 (28.7%)     |                      |
| <40  | 1415 (49.5%)         | 1813 (60.0%)    | 741 (56.7%)     |                      |
| Unknown                                      | 286 (10.1%)          | 342 (11.3%)     | 190 (14.6%)     |                      |

Data are shown as median (5 percentile, 95 percentile) unless specified.

HBVsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody.

ICG R<sub>15</sub>, indocyanine green retention rate at 15 min.

<sup>a</sup>ANOVA; <sup>b</sup>chi-square; <sup>c</sup>Mantel-trend test.

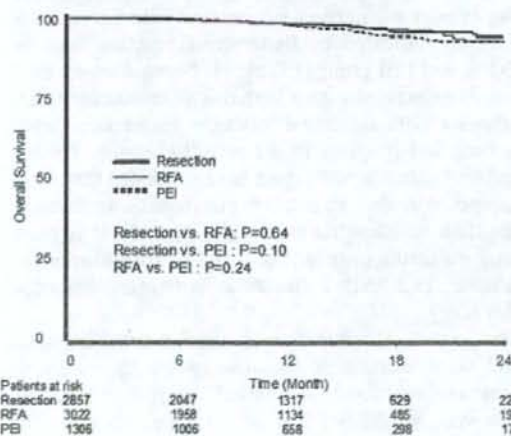


Fig. 1. Overall survival rates after surgical resection, RFA, and PEI.

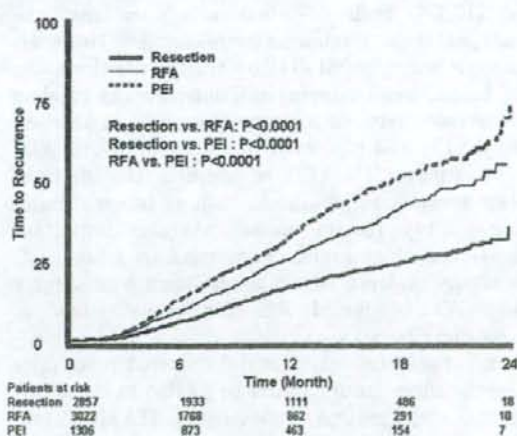


Fig. 2. Time-to-recurrence rates after surgical resection, RFA, and PEI.



**Table 2**  
Multivariate analysis

| Variables   | Relative risk | 95% Confidence interval | P                 |
|---|---------------|-------------------------|-------------------|
| <i>Overall death</i>  |               |                         |                   |
| Alpha-fetoprotein (<15 vs. 15=> ng/mL)                      | 0.43          | 0.27–0.64               | <0.0001           |
| Des-γ-carboxy prothrombin (<40 vs. 40=> AU/mL)              | 0.43          | 0.29–0.64               | <0.0001           |
| Tumor size (<2 vs. 2=> cm)                                  | 0.57          | 0.39–0.84               | 0.004             |
| Child-Pugh class (A vs. B)                                  | 0.57          | 0.38–0.85               | 0.007             |
| HCV-Ab (positive vs. negative)                              | 0.60          | 0.39–0.92               | 0.02              |
| <b>Resection vs. PEI</b>                                    | <b>0.67</b>   | <b>0.40–1.19</b>        | <b>0.12</b>       |
| <b>Resection vs. RFA</b>                                    | <b>0.78</b>   | <b>0.50–1.22</b>        | <b>0.27</b>       |
| Gender (female vs. male)                                    | 0.84          | 0.55–1.28               | 0.42              |
| <b>RFA vs. PEI</b>  | <b>0.86</b>   | <b>0.53–1.37</b>        | <b>0.52</b>       |
| Age (<65 vs. 65=> years)                                    | 0.87          | 0.58–1.30               | 0.48              |
| Tumor number (single vs. multiple)                          | 0.88          | 0.58–1.32               | 0.50              |
| Platelet count (>=10 <sup>4</sup> vs. <10 <sup>4</sup> /μL) | 0.94          | 0.63–1.40               | 0.76              |
| <i>Recurrence</i>   |               |                         |                   |
| <b>Resection vs. PEI</b>                                    | <b>0.45</b>   | <b>0.38–0.52</b>        | <b>&lt;0.0001</b> |
| <b>Resection vs. RFA</b>                                    | <b>0.62</b>   | <b>0.54–0.71</b>        | <b>&lt;0.0001</b> |
| Tumor number (single vs. multiple)                          | 0.65          | 0.58–0.73               | <0.0001           |
| Des-γ-carboxy prothrombin (<40 vs. 40=> AU/mL)              | 0.68          | 0.62–0.76               | <0.0001           |
| Alpha-fetoprotein (<15 vs. 15=> ng/mL)                      | 0.72          | 0.64–0.81               | <0.0001           |
| <b>RFA vs. PEI</b>  | <b>0.73</b>   | <b>0.64–0.83</b>        | <b>&lt;0.0001</b> |
| Tumor size (<2 vs. 2=> cm)                                  | 0.76          | 0.68–0.85               | <0.0001           |
| Age (<65 vs. 65=> years)                                    | 0.84          | 0.75–0.95               | 0.007             |
| Child-Pugh class (A vs. B)                                  | 0.88          | 0.77–1.00               | 0.05              |
| Gender (female vs. male)                                    | 0.89          | 0.78–1.00               | 0.05              |
| Platelet count (>=10 <sup>4</sup> vs. <10 <sup>4</sup> /μL) | 0.89          | 0.79–1.01               | 0.06              |
| HCV-Ab (positive vs. negative)                              | 1.27          | 1.09–1.48               | 0.002             |

PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

Bold indicates the values of the relative ratios concerning the treatments, because the comparison of the effects of the three treatments for HCC on long-term results.

the multivariate analysis showed that surgical resection was an independent favorable factor for recurrence, as compared with percutaneous ablation. These results of the preliminary analyses suggested that surgical resection may be superior to ablation with respect to the prevention of recurrence.

Whether surgery or ablation is the better treatment for HCC has long been debated. The results of two randomized controlled trials have recently been published [12,13], both of which concluded that the impacts of these treatments were similar. However, both trials were flawed [14] by critical drawbacks in study design, small sample sizes, differences in baseline characteristics between the surgery group and ablation group [12,13], and high rates of conversion from ablation to surgery (21%) [13]. In addition, the effects of ablation-specific complications, such as tumor dissemination [15,16], remain unclear. Another important issue is that ablation has been used to treat HCC without any evidence to support ablation over surgery [17,18]. We conducted this prospective study to address these points.

In our study, the significant different recurrence rates among the three groups would be related to the differences of the background characteristics. The proportion of the multinodular HCC patients in the resection group was lower than the proportions in the RFA and PEI

groups, whereas the tumor size in the resection group was larger than the other two groups (Table 1). Because both multiple nodules and large tumor size are major risks of recurrence in theory, it is difficult to discuss the effects of the different tumor-related factors on the differences of the recurrence rates among the three groups.

As for the liver-related factors, the significant lower recurrence rate in the resection group might be related to the smaller proportion of patients with severe liver fibrosis, as indicated by better liver function than in the RFA and PEI groups (Table 1). Because severe liver fibrosis is associated with a high risk of multicentric carcinogenesis [19], a second primary recurrence might have been less frequent in the resection group. On the other hand, some investigators have suggested that early recurrence is mainly caused by intrahepatic metastasis, rather than multicentric carcinogenesis [20]. It is quite difficult to distinguish between these two pathways of recurrence, and further discussion is beyond the scope of this study.

The overall survival curves were nearly the same for all three treatments. Because of the short follow-up period (median 10.4 months), mortality from all causes was low (1.6–3.0%) in all three groups. The extent to which the clinical impact on recurrence affects overall survival is the most important question



that arose in this study. Treatment-related mortality rates after surgery and ablation are recently lower than 1% [6–8,21]. Most cancer-related deaths within 1 year after treatment occur in patients with highly malignant HCC. In such patients, the impact of treatment is probably negligible, regardless of whether surgery or ablation is performed. As follow-up extends beyond 1 year, treatment-related effects on outcome are expected to emerge and become more apparent. Future studies with a sufficiently long follow-up period would be needed to examine whether the superiority of surgery in preventing recurrence contributes more to longer overall survival, as compared with that after ablation.

As for the comparison of the therapeutic effects between RFA and PEI, RFA seems to be superior to PEI in preventing recurrence (Fig. 2), which supports the results of the previous randomized controlled trials [9,10]. In this study, the overall survival rates were not different between them (Fig. 1), however, further investigation with a long follow-up period is also expected to support the superiority of RFA over PEI to prolong overall survival.

Although this was a large study of more than 7000 patients, there are important limitations in the generalizability of our results, which should be interpreted carefully. For example, clinical characteristics that can strongly influence outcomes differed significantly among the three treatment groups (Table 1). This problem arose despite the fact that we had established inclusion criteria to make tumor- and liver-function-related factors roughly similar among the groups. Another limitation was that we performed multivariate analysis to assess the impact of different baseline characteristics on outcomes; however, there are limits to such a statistical approach.

The presence of hepatitis C virus antibodies had different impacts on overall and recurrence-free survival (Table 2). The absence of hepatitis C virus antibodies in the study population was mainly associated with the presence of hepatitis B virus infection (Table 1). Potential differences in the effects of hepatitis B and C virus infections on outcomes after treatment for HCC remain unclear; nonetheless, the conflicting results are another limitation of our study. Although the underlying reason is unknown, the relation between hepatitis C virus infection and recurrence (Table 2) should theoretically result in poorer overall survival after further follow-up.

In conclusion, this large prospective study based on data derived from a nationwide survey in Japan suggested that surgical resection may offer some advantage over percutaneous ablation in terms of the time-to-recurrence rate of patients with HCC. However, the results should be regarded as preliminary, because of the short follow-up.

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