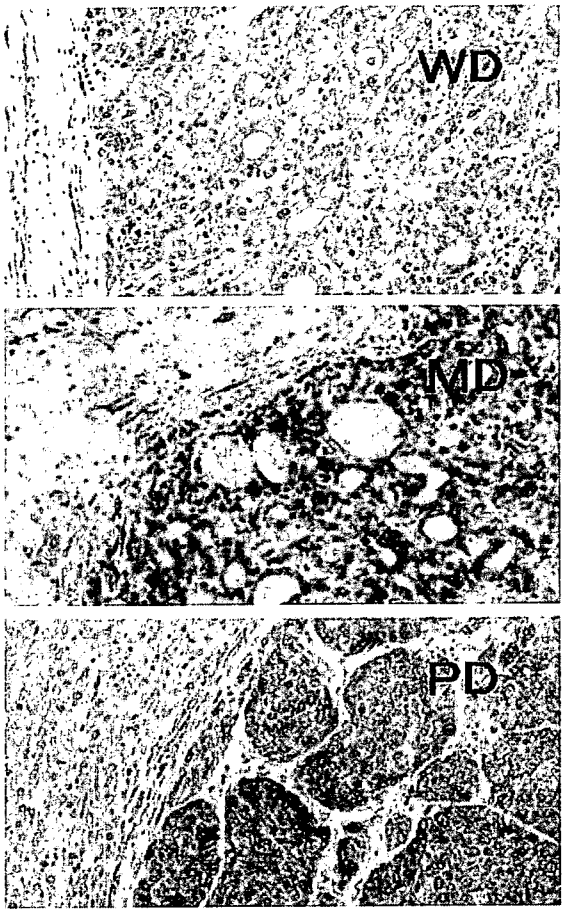

Fig. 3. Expression of mPGES-I in different histological grades of hepatocellular carcinoma (HCC) tissues. HCC cells demonstrated an enhanced expression of microsomal prostaglandin E synthase-1 (mPGES-1) in different histological grades of HCC tissues. Representative samples of different histological grades of HCC tissues are shown (original magnification, × 100).

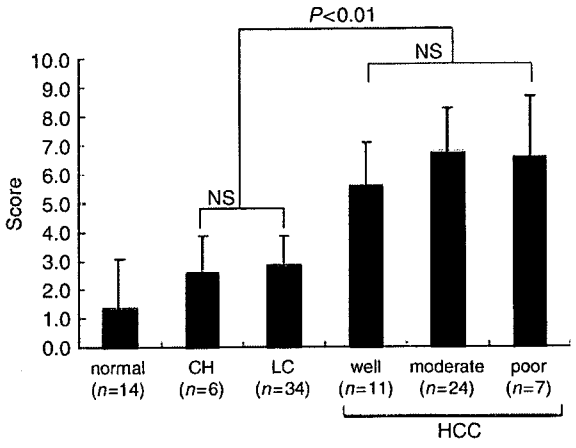

Fig. 4. Scores representing immunoreactivity for mPGES-1 in different histological grades of (HCC) cells and in hepatocytes in control livers, Data are expressed as means ± SD. WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated; NS, not significant; HCC, hepatocellular carcinoma; mPGES-I, microsomal prostaglandin E synthase-1.

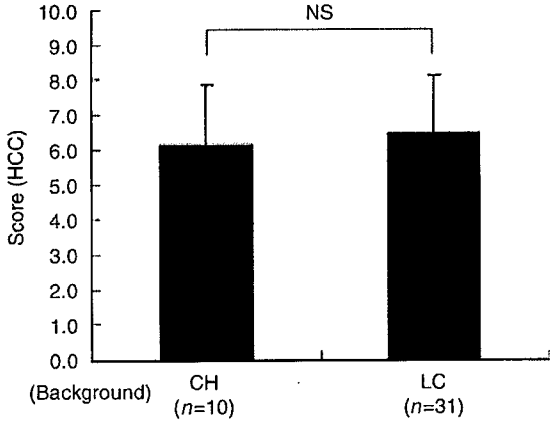

Fig. 5. Scores representing immunoreactivity for mPGES-1 in HCC cells with different background liver histology. Data are expressed as means ± SD. CH, chronic hepatitis; LC, liver cirrhosis; NS, not significant; HCC, hepatocellular carcinoma; mPGES-1, microsomal prostaglandin E synthase-1.

mPGES-1 mRNA expression levels in HCC tissues

Using a semiquantitative RT-PCR method, we investigated whether mPGES-1 mRNA is expressed in HCC tissues. As shown in Fig. 7, mPGES-1 mRNA was detected in the HCC tissues, while the non-tumorous tissues displayed very low levels of mPGES-1 mRNA. To further analyse differences in mPGES-1 mRNA expression levels between the HCC tissues and the non-tumorous liver tissues, we used the quantitative real-time PCR method. The mPGES-1 and GAPDH mRNA expressions were examined using normal liver tissues ($n = 14$), liver tissues with viral hepatitis ($n = 28$), and HCC tissues ($n = 33$). mPGES-1 mRNA expression was up-regulated in chronic hepatitis or cirrhotic liver tissues compared with the tissues in the control normal livers, while mPGES-1/GAPDH ratios were significantly higher in the HCC tissues than in the non-tumorous tissues (Fig. 8).

Discussion

In the present study, we demonstrated the marked expression of mPGES-1 in HCC tissues with various differentiation grades. We found that the expressions

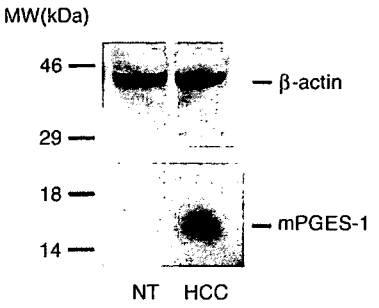

Fig. 6. Western blot analysis for microsomal prostaglandin E synthase-1 (mPGES-1). Tumorous (T) and non-tumorous (NT) liver tissue samples from a hepatocellular carcinoma (HCC) patient were lysed, and lysates were subjected to electrophoresis. Separated proteins on Hyfond PDF membranes were probed with anti-mPGES-1 and anti-β-actin antibodies.

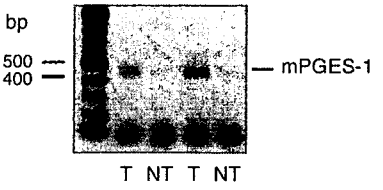

Fig. 7. Reverse transcriptase-polymerase chain reaction (RT-PCR) assays for microsomal prostaglandin E synthase-1 (mPGES-1) mRNA using non-tumorous (NT) and tumorous (T) tissues from an HCC patient. Total RNA was isolated from tumorous (T) and non-tumorous (NT) liver tissues and RT-PCR was performed using the method described in 'Patients and methods'.

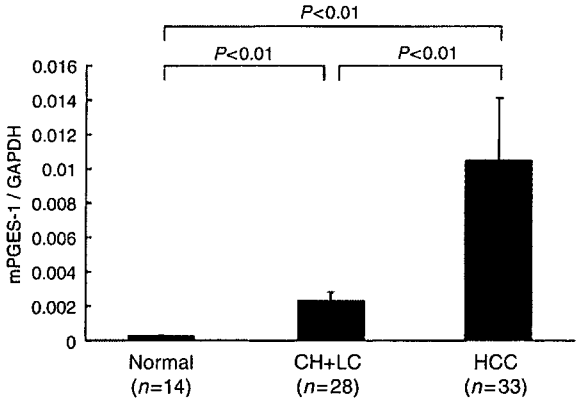

Fig. 8. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of microsomal prostaglandin E synthase-1 (mPGES-1) mRNA expression in HCC tissues and control liver tissues. Total RNA was isolated from tumorous and non-tumorous control liver tissues and real-time RT-PCR was performed using the method described in 'Patients and methods'. Data are expressed as means ± SD.

of mPGES-1 mRNA and mPGES-1 protein were markedly increased in HCC tissues compared with the expressions in non-tumorous liver tissues. Some expressions of mPGES-1 were also observed in non-tumorous liver tissues from patients with liver cirrhosis or chronic hepatitis. PGE_2, produced at sites of inflammation by up-regulated mPGES-1, could contribute to the perpetuation of inflammation and following tumorigenesis (5). Therefore, the elevated expression of mPGES-1 in the inflammed liver tissues might be linked to the predisposition to hepatocarcinogenesis.

Hepatocarcinogenesis is described as a continuity of regeneration, proliferation, dysplasia and malignant transformation (18). PGE_2 has been shown to stimulate cell proliferation, induce angiogenesis and suppress immune surveillance (19). Inhibition of PGE_2 synthesis protects against both tumour formation and growth (20). One recognized strategy for inhibiting carcinogenesis is to suppress PGE_2 production in premalignant tissues (21). The synthesis of PGE_2 from arachidonic acid requires two enzymes that act in sequence. COX catalyses the conversion of arachidonic acid to PGH_2 (22). In general, COX-1 is constitutively expressed, and COX-2 is not expressed in normal tissues but is induced by cytokines, growth factors, oncogenes and tumour promoters (23). COX-2 is a key enzyme that is involved in prostanoid biosynthesis at sites of inflammation (24). Terminal PGE_2 synthases (PGES) are of special interest because of their ability to convert COX-2-delivered PGH_2 to PGE_2 (25).

An inducible PGES has been identified as a 16 kDa, glutathione-dependent integral membrane protein and is referred to as microsomal PGES-1 (mPGES-1). mPGES-1 is induced by proinflammatory stimuli (26). In addition to the inducible mPGES-1, cytosolic protein processing PGES activity (cPGES) has been characterized and found to be constitutively expressed and not to be generally induced by proinflammatory stimuli (15). A possible linkage of mPGES-1 with tumoriogenesis has been provided by recent observations that mPGES-1 is expressed in several cancers (27–29). Cells overexpressing mPGES-1 produce more PGE_2 and grow faster (30). Kamei et al. (30) reported that cotransfection of COX-2 and mPGES-1 into HEK 239 cells resulted in cellular transformation and tumour formation when injected into nude mice. These results demonstrated that the aberrant expression of mPGES-1 could be associated with cellular transformation.

With the use of immunohistochemical methods, COX-2 was detected in HCC tumorous tissues. Koga

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et al. (11) examined the COX-2 expression in liver tissues in patients with HCC. A significant increase in COX-2 expression was observed in non-tumorous liver tissues in parallel with disease progression from chronic hepatitis to cirrhosis. Histologically, well-differentiated HCC shows a profound expression of COX-2, whereas less-differentiated HCC expressed little or no COX-2 (11). These findings suggest that COX-2 expression is differentiation-dependent in HCC and that COX-2 is involved in early stage hepatocarcinogenesis.

In contrast to these previous findings, the aberrant expression of mPGES-1 was detected in poorly differentiated HCC as well as in well-differentiated HCC in our study. The differential expressions of mPGES-1 and COX-2 in poorly differentiated HCC suggest that the expression of these two enzymes may not localize to the same cells and that the mechanisms controlling the expression of these two enzymes differ. COX-2 is regulated by both transcriptional and post-transcriptional mechanisms (31, 32), whereas transcriptional control appears to be the primary mechanism regulating the expression of mPGES-1 (33). Transcription factors, such as activating protein-1 (AP-1), nuclear factor κB (NF-κB), NF-IL-6 and PEA3, control COX-2 gene expression (34), whereas Egr-1 is critical for regulating the transcription of mPGES-1 (35). The mechanisms for mPGES-1 transcriptional regulation have not yet been completely elucidated. Additional studies are needed to further delineate the similarities and differences in the regulation of mPGES-1 and COX-2. In our study, there were some discrepancies between mPGES-1 mRNA expression and protein expression in HCC tissues. The reason for these discrepancies between mPGES-1 mRNA and protein expression in our data is unclear. In addition to the transcription of mPGES-1 gene, it is possible that mRNA stability or mRNA translocation mRNA, stability or mRNA translocation could participate in the mPGES-1 protein synthesis as reported previously (36).

In conclusion, our data demonstrate the increased expression of mPGES-1 in HCC tissues from patients with viral hepatitis and suggest its involvement in hepatocarcinogenesis. mPGES-1 might be a potential new target for a treatment to control both PGE_2 synthesis and hepatocarcinogenesis without the systemic side effects associated with COX-2 inhibitors (37, 38). However, further large-scale studies are needed to define the relationship between mPGES-1 expression and clinical parameters such as progression, metastasis, and prognosis in patients with HCC.

Acknowledgement

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Recurrence-free Survival after Radiofrequency Ablation of Hepatocellular Carcinoma. A Registry Report of the Impact of Risk Factors on Outcome

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Background: Despite the high complete necrosis rate of radiofrequency ablation (RFA), tumor recurrence, either local tumor recurrence or new tumor formation, remains a significant problem. Purpose of this study is to evaluate the pattern and risk factors for intrahepatic recurrence after percutaneous RFA for hepatocellular carcinoma (HCC).
Methods: We studied 40 patients with 48 HCCs ($\leq$ 3.5 cm) who were treated with percutaneous RFA. The mean follow-up period was 24.1 $\pm$ 15.7 months. We evaluated the cumulative disease-free survival of overall intrahepatic recurrence, local tumor progression (LTP) and intrahepatic distant recurrence (IDR). Thirty host, tumoral and therapeutic risk factors were reviewed for significant tie-in correlation with recurrence: age; gender; whether RFA was the initial treatment for HCC or not; severity of liver disease; cause of liver cirrhosis; contact of tumor to major hepatic vessels and liver capsule; degree of approximation of tumor to the liver hilum; ablation time; degree of benign pre-ablational enhancement; sufficient safety margin; tumor multinodularity; tumor histological differentiation; tumor segmental location; maximum tumor diameter; degree of tumor pre-ablational enhancement at arterial phase CT, MRI or CT-angiography; and laboratory markers pre- and post-ablation (AFP, PIVKA II, TP, AST, ALT, ALP and TB).
Results: The incidence of overall recurrence, LTP and IDR was 65, 23 and 52.5%, respectively. The cumulative disease-free survival rates were 54.6, 74.8 and 78.3% at 1 year, 27.3, 71.9 and 46.3% at 2 years and 20, 71.9 and 29.4 at 3 years, respectively. Univariate and multivariate analysis showed that the significant risk factors for LTP were: tumor size $\geq$ 2.3 cm, insufficient safety margin, multinodular tumor, tumors located at segments 8 and 5, and patient's age > 65 years ($P < 0.05$). No significant risk factor relationship for IDR could be detected.
Conclusion: Our results would have clinical implications for advance warning and appropriate management of patients scheduled for RFA. Patients at risk of LTP should be closely monitored in the first year. Furthermore, regular long-term surveillance is essential for early detection and eradication of IDR.

Key words: recurrence-free survival – risk ratio – RFA, radiofrequency ablation – HCC

INTRODUCTION

Hepatocellular carcinoma (HCC) is the cause of 250 000 deaths worldwide each year. HCC is often advanced at first manifestation, and without treatment the 5-year survival rate is less than 5% (1). Only 9–27% of the patients with HCC are eligible for surgical resection. There are many limiting factors for successful surgical resection in patients with HCC such as severe impairment of hepatic functional reserve, bilobar distribution of the tumors, extra hepatic metastasis or involvement of the portal vein (2,3). Hence, different locoregional

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therapies have been developed for irresectable liver tumors with an attempt to achieve local tumor control. These include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), and various thermal ablation therapies such as cryotherapy, interstitial laser therapy, microwave coagulation and radiofrequency ablation (4–7). Although these ablation therapies can achieve complete necrosis of small HCC, recurrence is still common. Most HCCs are associated with liver cirrhosis, and total prevention of recurrence might not be achieved even in the future (8). The intrahepatic recurrence rate is 20% during a mean follow-up period of 18 months (9). However, it is still unclear which factors influence intrahepatic recurrence (10).

Among the local methods for tumor control, radiofrequency ablation (RFA) is considered a promising alternative to surgery (11). For irresectable tumors, RFA seems to be the most effective treatment among other locoregional therapies. The main advantages of RFA include low morbidity and mortality rates, effective tumor ablation and preservation of maximal normal liver parenchyma (12). However, despite the high complete necrosis rate of RFA, early tumor recurrence within one year, either local tumor recurrence or new tumor formation, remains a significant problem. A series of studies discussed the factors for tumor recurrence, including the tumor size, subcapsular lesion, operative procedure, underlying liver disease and alpha-fetoprotein (AFP) levels, but the results were not well documented (13–17).

There are two types of intrahepatic recurrence found in patients with HCC after RFA, local tumor progression and intrahepatic distant recurrence. Local tumor progression (LTP) occurs along the peripheral margin of the ablative lesion and intrahepatic distant recurrence (IDR) is a new HCC tumor remote from the margin of the ablative lesion. Evaluation of overall recurrence as well as LTP and IDR may provide important information for the management of HCC patients receiving RFA therapy (18).

Therefore, the purpose of this study was to determine the pattern of cumulative recurrence-free survival rate after percutaneous RFA of hepatocellular carcinoma and to determine the risk factors and the incidence of intrahepatic recurrence according to each type. To assign that task, many potential risk factors were reviewed for significant tie-in correlation to intrahepatic recurrence.

PATIENTS AND METHODS

Study Population

From February 2000 to November 2005, a total of 40 patients with 48 HCC nodules underwent percutaneous RFA for the treatment of HCC by a multidisciplinary team consisting of hepatobiliary physicians and interventional radiologists. Ultrasound-guided ablation was performed in the Hepatobiliary Oncology Department and CT-guided ablation in the Radiology Department, National Cancer Center Hospital East, Japan.

In all patients, a written informed consent was obtained. This study was approved by our institutional review board. Ablation performed in inpatient participants after they had fasted for 6 h. Laboratory examinations including complete blood count, blood coagulation test, blood typing and tumor marker for HCC (AFP) were performed before each procedure. Inclusion criteria for performing RFA in patients with HCC are as follows: the tumor or tumors should be visualized with ultrasonography (US) or CT and accessible via the percutaneous route; a single tumor no greater than 5 cm in the largest dimension; multiple tumors (<3) with each tumor measuring no greater than 3 cm; no portal venous thrombosis and extrahepatic metastasis; prothrombin time ratio over 50% (prothrombin time with international normalized ratio, INR < 1.7) and a platelet count greater than 50 000/μl without transfusion support.

For all patients, proof of HCC malignancy was attained by the typical imaging features at US, triphasic CT, triphasic MRI, celiac angiography or CT-angiography along with a serum AFP, PIVKA II tumor markers and US-guided biopsy. The imaging criteria for HCC were a newly presenting, residual or recurrent tumor at follow-up US or CT in patients with chronic liver disease or a characteristic enhancement pattern on contrast-enhanced multi-phase CT and/or MRI (hypervascularization on hepatic arterial phase and wash-out pattern on delayed phase), filling defect at CTAP or tumor staining at DSA and CTA.

The patients were predominantly elderly (mean age 65.6 ± 8.5) and male (77.5%). Five patients had a past history of HCC therapy with transcatheter arterial chemoembolization ($n = 3$), surgical resection ($n = 1$) or percutaneous microwave ablation ($n = 1$), prior to RFA for the recurrent tumor. All the tumors in these five patients included in our study were newly developed lesions, and there was no evidence of viability of the tumors that had been treated previously. Mean value of the period between the latest previous treatment and RFA was 18 ± 12.8 months with a range of 3–34 months.

Severity of the underlying cirrhosis was classified in accordance with the Child–Pugh classification. The etiology of cirrhosis was chronic hepatitis C virus (HCV) infection in 33 (82.8%) patients, hepatitis B virus (HBV) infection in four (10%) patients and cirrhosis due to hepatitis of non-viral causes in three (7.5%) patients. Clinical features of patients and tumors are summarized in Table 1.

Radiofrequency Ablation

The RF system used in this study was the RF 2000 (RadioTherapeutics, Mountain View, CA, USA), which included a 100 W generator, a 15-gauge monopolar electrode array with 10 hook-like arms and needle electrodes of 2 and 3 cm diameter (LeVeen; RadioTherapeutics). Hot withdrawal was performed to prevent oozing and tumor seeding. When the ablation was started, we often ablated the deepest parts first and the superficial parts last to avoid

Table 1. Baseline demographics of the patients ($n = 40$)

Number of patients	40
Number of HCC nodules	48
Age (years)	
Mean (range)	65.6 ± 8.5 (45–79)
Gender	
Male/female	31/9
History of HCC treatment	
TACE/PMCT/surgical	3/1/1
Etiology of cirrhosis	
HCV/HBV/other	33/4/3
Severity of liver disease	
Child–Pugh class A/B	32/8
Multiplicity of tumors	
Single/multiple	33/7
Tumor diameter	
Mean (range)	2.02 ± 0.55 (1–3.5) cm
Serum AFP	
Mean (range)	110 ± 178.2 (9–305)
Imaging tool utilized to guide RFA	
US/CT	44/4[a]
Follow-up period (months)	
Mean (range)	24.1 ± 15.7 (1–50)

[a]Numerical data states the number of HCC nodules ($n = 48$).
Numerical data were expressed as mean ± SD.
TACE, transcatheter arterial chemoembolization; PMCT, percutaneous microwave coagulation therapy; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein enzyme; RFA, radiofrequency ablation; US, ultrasonography; CT, computed tomography.

imaging disturbances caused by hyperechogenic gas artifacts generated from boiling tissue. The average time required for ablation ranged from 3 to 51.11 min with a mean value of 20.6 ± 11.8 min. The goal of radiofrequency thermal ablation is to kill the target tumor as well as a 5 mm circumferential cuff of adjacent normal hepatic parenchyma as a safety margin.

RF ablations were performed via the percutaneous route under US-guidance ($n = 44$) or CT-guidance ($n = 4$). Image guided ablation was performed using a real-time US (GE Logiq 5 Expert) scanner with 3.5–5.0 MHz convex probes equipped with attachments for biopsy and electrode insertion. For CT-guided tumor ablation a Toshiba Aquilion multislice-CT (MS-CT) scanner with 16 row detector channels was used. The patients received 35 mg of pethidine hydrochloride (Opystan, Tanabe, Tokyo, Japan) intravenously before RFA for analgesia. Antibiotics were administered before and 2–3 days after each PEI and RFA procedure. Local infiltration anesthesia was induced by using 5–10 ml of 1% lidocaine.

Evaluation of Therapeutic Efficiency

To evaluate the tumor response to ablation therapy, contrast-enhanced CT was performed 1 month after the treatment. Additional CT scans were obtained in all patients within 1 day after completion of therapy to determine whether there was any remaining malignant tissue that would require a second ablation session and also for early detection of complication. The ablation was considered a success on the basis of all of the following findings at follow-up CT: (a) no contrast enhancement detected within or around the tumor; (b) the margins of the ablation zone clear and smooth; and (c) the ablation zone extended beyond the previously estimated tumor borders.

If any residual HCC was noted, we repeated the RFA as soon as possible ($n = 5$) and then performed a second immediate follow-up CT scan. We confirmed that there was no evidence of residual tumor that went untreated in all patients. As a follow-up rule thereafter, contrast-enhanced CT, US scan and measurement of serum AFP were performed regularly every 3–4 months.

Risk Factors for Recurrence

Intrahepatic recurrence was divided into LTP and IDR based on standardization of terminology and reporting criteria by the international working group of image-guided tumor ablation (19). Local tumor recurrence of an HCC nodule was defined as the development of an enhanced area on the CT scan in the same sub-segment as the primary nodule and was found along the peripheral margin of the ablative zone. Intrahepatic distant recurrence of HCC was defined as a lesion with typical enhancement characteristics for HCC but distant from the original ablative zone. IDR was evaluated for patients for whom complete coagulation was achieved without recurrence in the same sub-segment as the primary nodule. In case of recurrence, other supplemental examinations like MRI, hepatic DSA and angio-CT were performed to confirm not only local but also distant recurrence of HCC. When tumor recurrence was confirmed, patients were hospitalized and an additional treatment cycle was administered if the patient's physical condition was strong enough for him or her to safely undergo another ablation session(s). Patients who developed diffuse HCC were shifted to transarterial embolization (TAE), hepatic artery infusion (TAI), radiotherapy or proton beam therapy.

Statistical Analysis

After review of the follow-up CT, we assessed the incidence and the cumulative recurrence-free survival rate of overall recurrence, LTP and IDR, respectively. Data analyses were performed using MedCalc statistical software for Biomedical research (version 9 for Windows).

For analysis of the significant risk factors for LTP, 30 host, tumoral and therapeutic variables were reviewed: (1) age, (2) gender, (3) whether RFA was the initial treatment

for HCC or not (previous history of interventional or surgical), (4) severity of liver disease according to standard Child–Pugh classification, (5) cause of liver cirrhosis (hepatitis C or B or non viral hepatitis), (6 and 7) contact of tumor to major hepatic vessels and liver capsule, (8) degree of approximation of tumor to the liver hilum, (9) ablation time, (10) the degree of benign periablational enhancement at immediate follow-up CT (grade 0, no enhancement; grade 1, disrupted non-continuous enhancement; grade 2, continuous rim enhancement), (11) ablation safety margin is sufficient or not (sufficient 5 mm, pre- and post ablation CT were as reference), (12) number of primary HCC nodules at the time of ablation (single or multiple), (13) tumor histological differentiation (well, moderate or poorly differentiated), (14) tumor segmental location (in segments 5 and 8 or others), (15) maximum tumor diameter (we divided the tumors into small and large groups with the cutting value of 2.3 cm), (16) degree of tumor pre-ablational enhancement at arterial phase CT, MRI or CT-angiography (strongly or poorly enhanced), (17–30) laboratory markers pre- and post-ablation within normal limits or not (alpha-fetoprotein, des-gamma carboxy prothrombin, total protein, aspartate transaminase enzyme, alanine transaminase enzyme, alkaline phosphatase enzyme and total bilirubin).

For the IDR, 21 host, tumoral and therapeutic variables were reviewed: (1) age, (2) gender, (3) whether RFA was the initial treatment for HCC or not (previous history of interventional or surgical), (4) severity of liver disease according to standard Child–Pugh classification, (5) cause of liver cirrhosis (hepatitis C or B or non viral hepatitis), (6) number of primary HCC nodules at the time of ablation (single or multiple), (7) tumor histological differentiation (well, moderate, or poorly differentiated), (8–21) laboratory markers pre- and post-ablation within normal limits or not (alpha-fetoprotein, des-gamma carboxy prothrombin, total protein, aspartate transaminase enzyme, alanine transaminase enzyme, alkaline phosphatase enzyme and total bilirubin). These risk factors were analyzed retrospectively.

The unpaired Student's *t*-test was used to compare averages between groups and the $\chi 2$-test and Fisher's exact probability test were used to compare independence. Cumulative disease-free survival was estimated using the Kaplan–Meier method and the significance of the hazard ratio for LTP and IDR was evaluated with univariate analysis using the log-rank test. If multiple hazard ratios were proven to be significant by this test, we performed multivariate analysis using a stepwise Cox proportional hazard regression model to search for independently significant risk factors. The results were reported as ratios with 95% CI. A *P*-value <0.05 was considered statistically significant.

RESULTS

Intrahepatic Recurrence

In 26 of 40 patients (65%), intrahepatic recurrence (LTP, $n = 5$; IDR, $n = 15$; LTP + IDR, $n = 6$) was found during the follow-up period of 24.1 ± 15.7 months (range 1–50). These were found 2–39 months (3–18 for LTP, 2–39 for IDR) after RFA with a median of 11 months (6 for LTP, 18 for IDR), 95% confidence interval (CI), 10.5–18 months (3.4–11.4 for LTP, 7.8–24.5 for IDR). The 12, 24 and 36 month cumulative recurrence-free survival rates were 54.6% (95% CI, 37.5–71.7%), 27.3% (95% CI, 11.4–43.2%) and 20% (95% CI, 5.4–34.5%) respectively (Fig. 1a). LTP was found in 11 of 48 tumors (23%) and occurred 3–18 months after the procedure with a median of 6 months (95% CI, 3.4–11.4 months). Thirty-seven treated tumors had no LTP during the entire follow-up period up to 50 months. For all patients ($n = 40$), the mean LTP-free survival was 36.9 ± 18.5 months. However, the mean LTP-free survival in those patients with LTP ($n = 11$) was 7.5 ± 4.4 months. The 12, 24 and 36 month cumulative LTP-free survival rates were 74.8% (95% CI, 61.3–88.4%), 71.9% (95% CI, 57.6–86.1%) and 71.9% (95% CI, 57.6–86.1%), respectively (Fig. 1b). IDR was found in 21 of 40 patients (52.5%) during the follow-up period. These recurrent tumors occurred from 2.0 to 39 months after RFA with a median of 18 months (95% CI, 7.8–24.5 months). The 12, 24 and 36 month cumulative IDR-free survival rates were 78.3% (95% CI, 64–92.6%) 46.3% (95% CI, 28.1–64.4%), and 29.4% (95% CI, 11.5–47.2%), respectively (Fig. 1c). We summarize these data in Table 2.

Risk Factors Analysis of Intrahepatic Recurrence

Tables 3 and 5 summarize the results of the hazard ratio analysis for each type of intrahepatic recurrence associated with HCC after percutaneous RFA. Data expressed in Tables 3 and 5 was analyzed using the *t*-test, one-way Anova test, Kaplan–Meier method and log-rank test.

Local Tumor Progression

When we set the criterion for large tumors to be ≥2.3 cm in the greatest dimension, the incidence of LTP was 3/32 (9.4%) in small tumors and 8/16 (50%) in large tumors. The Kaplan–Meier estimates of the 12, and 24 month recurrence-free survival after RFA were 87.7% (95% CI, 74.6–100%), same ratio, for small tumors and 55% (95% CI, 30.1–79.9%) and 47.1% (95% CI, 21.5–72.8%) for large tumors, respectively. Small tumors had a statistically significant longer LTP-free survival compared with large tumors ($P = 0.0054$; Fig. 2a).

We determined statistical significance ($P = 0.0313$) for LTP between HCC nodules ablated with sufficient safety margin (7/41; 17%), and nodules ablated with insufficient safety margin (4/7; 57.1%). The Kaplan–Meier estimates of the 12, and 24 month recurrence free survival after RFA were 78.4% (95% CI, 64.1–92.6%), same ratio, for sufficient ablation margin and 57.1% (95% CI, 20.5–93.8%) and 42.9% (95% CI, 6.2–79.5%) for insufficient ablation margin, respectively (P=0.0313; Fig. 2b).

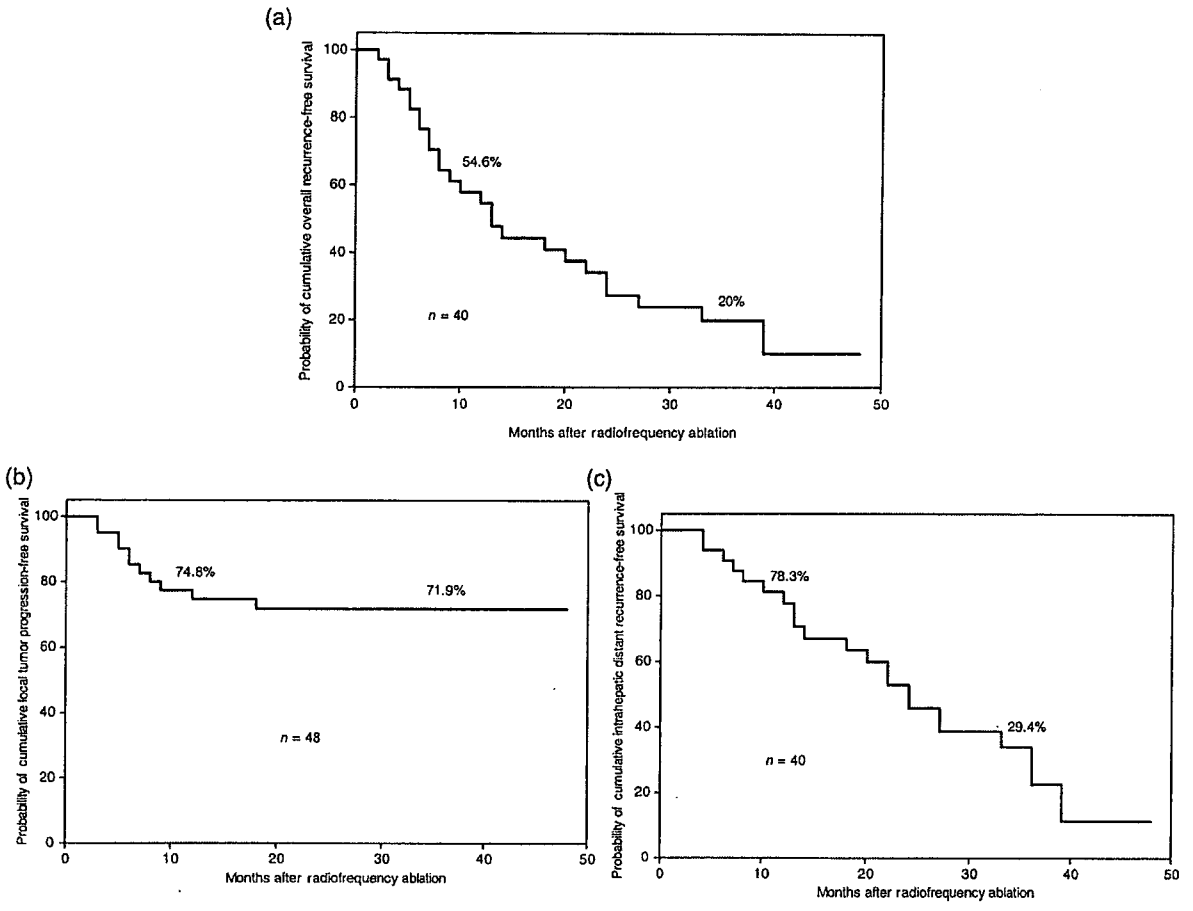

Figure 1. Kaplan–Meier survival curves for (a) overall recurrence ($n = 40$), (b) local tumor progression ($n = 48$), and (c) intrahepatic distant recurrence ($n = 40$) after percutaneous radiofrequency ablation of hepatocellular carcinoma; 12 and 36 month survival rates are expressed as survival percentages.

Statistical analysis of the number of primary HCC nodules at the time of ablation revealed that the LTP incidence was 4/34 (11.8%) for primary uninodular HCC and 7/14 (50%) for primary multinodular HCC. The Kaplan–Meier estimates of the 12, and 24 month recurrence-free survival after RFA were 85.8% (95% CI, 72.8–98.7%), same ratio, for primary uninodular HCC and 50% (95% CI, 21.7–78.3%) and 41.7% (95% CI, 13.8–69.6%) for primary multinodular HCC, respectively. The primary multinodular HCC was significantly associated with a higher LTP rate compared with primary uninodular HCC ($P = 0.0045$; Fig. 2c).

Statistical analysis for the risk factors associated with LTP, determined significant ($P = 0.0305$) high LTP ratio for tumors located at segments 8 and 5 (9/26; 34.6%), more than other segments (2/22; 9.1%). The Kaplan–Meier estimates of the 12 and 24 month recurrence-free survival after RFA were 66.7% (95% CI, 47.8–85.5%) and 61.9% (95% CI, 42.2–81.6%), for segments 8 and 5 and 86.9% (95% CI, 69.8–100%), same ratio, for other segments, respectively (P=0.0305; Fig. 2d).

When we set the criterion for the age to be 65 years, the incidence of LTP was 2/21 (9.5%) in patients ≤ 65 years old and 9/27 (33.3%) in patients >65 years old. The Kaplan–Meier estimates of the 12 and 24 month recurrence-free survival after RFA were 94.7% (95% CI, 89.5–100%) and 88% (95% CI, 72.1–100%) for age ≤ 65 years and 59.1% (95% CI, 38.5–79.6%) same ratio for 12 and 24 months for age >65 years, respectively. Patients ≤ 65 years old had a statistically significant longer LTP-free survival compared with patients >65 years old ($P = 0.0366$) (Fig. 3).

Statistical analysis determined high hazard ratio for elevated AFP post-ablation (2.476) and low total protein (TP) pre-ablation (2.411); however, the P-value was not significant for both ($P = 0.2368$ and 0.3946 respectively).

We could not determine a significant correlation between the incidence of LTP and gender, previous HCC therapy, severity of liver disease, cause of liver cirrhosis, contact of tumor to major hepatic vessels and liver capsule, degree of approximation of tumor to liver hilum, ablation time, the

Table 2. Recurrence pattern of hepatocellular carcinoma after percutaneous radiofrequency ablation

Type	Incidence	Median	Mean	12 month	24 month	36 month	48 month
Overall recurrence	26/40 (65%)	13 months (12.6–14.6)	14 months (10–18.1)	54.6% (37.5–71.7%)	27.3% (11.4–43.2%)	20% (5.4–34.6%)	10% (0–25.6%)
LTP	11/48 (23%)		19.6 months (15.1–24)	74.8% (61.3–88.4%)	71.9% (57.6–86.1%)	71.9% (57.6–86.1%)	71.9% (57.6–86.1%)
IDR	21/40 (52.5%)	24 months (23.5–25.5)	18 months (7.8 –24.5)	78.3% (64–92.6%)	46.3% (28.1–64.4%)	29.4% (11.5–47.2%)	14.7% (0–36.9%)

LTP, local tumor progression; IDR, intrahepatic distant recurrence; median, median of recurrence-free survival after percutaneous radiofrequency ablation of hepatocellular carcinoma; mean, mean of recurrence-free survival after percutaneous radiofrequency ablation of hepatocellular carcinoma; 12, 24, 36 and 48 months, 12, 24, 36 and 48 month cumulative recurrence-free survival rate. Parentheses, 95% confidence interval (95% CI).

degree of benign pre-ablational enhancement, tumor histological differentiation, degree of tumor enhancement pre-ablation or laboratory markers. Also the hazard ratios for all were low, except for elevated AFP post-ablation and low TP pre-ablation.

To evaluate independent risk factors proven to be significant based on univariate analysis, we performed a multivariate analysis by a stepwise Cox hazards regression model. We found that tumor diameter $\geq$ 2.3 cm (risk ratio 8.4, 95% CI 1.7–41.7, $P = 0.0096$), insufficient ablation of safety margin (risk ratio 6.3, 95% CI 1.1–35.7, $P = 0.0396$), tumor multiplicity at the time of ablation (risk ratio 5.2, 95% CI 1.0–26.3, $P = 0.0482$), tumors located at segments 8 and 5 (risk ratio 4.6, 95% CI 1.9–11.3, $P = 0.0007$) and patient's age >65y (risk ratio 4.3, 95% CI 1.8–10.3, $P = 0.0011$) were statistically significant risk factors for LTP after percutaneous RFA for HCC (Table 4).

Intrahepatic Distant Recurrence

IDR occurred in 21 of 40 patients (52.5%). Among the 21 risk factors investigated for IDR, no significant correlation could be described with the length of the IDR-free survival. The highest hazard ratio (2.274) was recorded for elevated AFP pre-ablation in spite of the correlation not being significant ($P = 0.0777$; Table 5).

DISCUSSION

We categorized intrahepatic recurrence of HCC after percutaneous RFA into local tumor progression and intrahepatic distant recurrence; each type of recurrence has a specific mechanism of pathogenesis and is thought to occur independently. Generally, LTP occurs early and is considered to be related to residual tumor cells that have spread microscopically beyond the ablative margin, although there is a possibility of *de novo* occurrence at that site. Pathogenesis of IDR is thought to be the result of an intrahepatic metastasis of a primary HCC or due to a multicentric origin of the HCC (20,21). Therefore, LTP may be associated more with a treatment methodology or result, local environment of the tumor such as a vessel contact and characteristics of the tumor itself rather than the systemic condition of the patient. By contrast, IDR may be related more to systemic factors rather than local factors (18). Therefore, we analyzed a variety of potential local and systemic risk factors for LTP and IDR associated with HCC, independently.

There have been several studies reporting on the incidence and risk factors of LTP or IDR after RFA for HCC. Komorizono et al. (13), who studied LTP after a single application of RF energy for relatively small HCC, reported a tumor-free survival rate at 12 and 15 months of 76 and 74%, respectively. Significant risk factors for LTP were reported to be a large tumor size over 2 cm in the greatest dimension and a subcapsular location. Hori et al. (22), who also studied a similar group of subjects, reported that the cumulative local

Table 3. Univariate analysis for potential hazard ratio associated with local tumor progression of HCC after percutaneous RFA

	Recurrent ($n = 11$)	Not recurrent ($n = 37$)	P-value	Hazard ratio
Host factors				
Age				
$> 65/\leq 65$ years	9/2	18/19	0.0366[S]	4.397
Gender				
Male/female	7/4	32/5	0.0918	0.2528
Severity of liver disease				
Child–Pugh class B/A	3/8	6/31	0.6886	1.368
Cause of liver cirrhosis				
HCV/HBV/other	10/0/1	31/4/2	0.5209	1.284
TP				
Pre-RFA	7.1 ± 0.6	7.1 ± 0.6		
Low/normal	3/8	6/31	0.3946	2.411
Post-RFA	7.0 ± 0.5	7.0 ± 0.6		
Low/normal	2/9	9/28	0.8859	1.164
AST				
Pre-RFA	93.6 ± 56.3	86.5 ± 59.6		
Elevated/normal	8/3	28/9	0.3415	0.4729
Post-RFA	82.3 ± 44	85.5 ± 59.5		
Elevated/normal	9/2	27/10	0.6067	1.712
ALT				
Pre-RFA	95.5 ± 71.9	86.6 ± 70.6		
Elevated/normal	7/4	23/14	0.7954	0.8294
Post-RFA	69.6 ± 48.9	78.5 ± 63.9		
Elevated/normal	7/4	22/15	0.8471	1.149
ALP				
Pre-RFA	342.8 ± 125.7	348.4 ± 186.0		
Elevated/normal	5/6	13/24	0.3683	1.698
Post-RFA	349.0 ± 131.2	340.0 ± 146.2		
Elevated/normal	6/5	16/21	0.2822	1.887
Total bilirubin				
Pre-RFA	1.03 ± 0.4	1.3 ± 0.5		
Elevated/normal	5/6	13/24	0.2944	1.854
Post-RFA	1.4 ± 0.6	1.3 ± 0.6		
Elevated/normal	5/6	19/18	0.9385	0.9559
Tumor and therapy factors				
History of previous treatment of HCC by interventional or surgical modality				
Present/absent	1/10	7/30	0.0366[S]	4.397
Contact of the tumor to major hepatic vessels				
Contact/no contact	4/7	8/29	0.5665	1.426
Contact of the tumor with hepatic capsule				
Contact/no contact	2/9	8/29	0.7484	0.7804

Continued

Table 3. *Continued*

	Recurrent ($n = 11$)	Not recurrent ($n = 37$)	*P*-value	Hazard ratio
Degree of approximation to hepatic hilum				
Peripheral/intermediate/central	7/4/0	28/7/2	0.2382	0.5410
Ablation time (min)	23.2 ± 3.5	19.8 ± 2.0	0.4080	
Degree of benign periablational hyperemia at immediate follow-up CT				
Grade 0/1/2	1/4/6	10/18/9	0.2322	0.3909
Sufficient safety margin at immediate follow up CT				
Insufficient/sufficient	4/7	3/34	0.0313[S]	3.503
Number of primary HCC at the time of radiofrequency ablation				
Multinodular/Uninodular	7/4	7/30	0.0045[S]	4.904
Histological differentiation				
PD/MD/WD	2/4/5	4/18/15	0.7237	1.399
Segmental location				
8, 5/7, 6, 4, 3, 2	9/2	17/20	0.0305[S]	3.488
Nodule diameter (cm)	2.3 ± 0.5	1.9 ± 0.6		
≥2.3/ <2.3 cm	8/3	8/29	0.0054[S]	5.291
Tumor enhancement at arterial phase CT/MRI/CTA				
Strong/poor	9/2	28/9	0.5158	1.641
AFP				
Pre-RFA	173.9 ± 96.2	87.9 ± 24.6		
Elevated/normal	8/3	24/13	0.7482	1.289
Post-RFA	117 ± 49.8	65 ± 21.9		
Elevated/normal	8/3	21/16	0.2368	2.476
PIVKA II				
Pre-RFA	30.1 ± 49	40.6 ± 64		
Elevated/normal	2/9	11/26	0.4720	0.4738
Post-RFA	20 ± 20.7	69 ± 246		
Elevated/normal	2/9	8/29	0.7502	1.395

S, significant; PD, poorly differentiated; MD: moderately differentiated; WD, well differentiated; PIVKA II, protein induced by vitamin K absence or antagonist-II (Des-gamma carboxy prothrombin); TP, total protein; AST, aspartate transaminase enzyme; ALT, alanine transaminase enzyme; ALP, alkaline phosphatase enzyme.

recurrence rates were 9.7, 15.4 and 20.4% at 1, 2 and 3 years, respectively. Significant risk factors for LTP were tumor size and tumor location. Izumi et al. (23) reported that the IDR, after RFA or microwave ablation for HCC, was found in 22 out of 84 patients (26.2%; median follow-up period, 22 months); significant risk factors for IDR were an increased level of serum AFP, a hepatitis C virus infection and multifocal HCC at the time of treatment. Harrison et al. (14) reported that the LTP rate was 39.1% and the IDR rate was 30.4% in their 3-year follow-up study, and that the significant risk factors for overall recurrence were a large tumor size, an increase in serum AFP level and the presence of hepatitis. Yamanaka et al. (10) reported, in their study of RFA for HCC in patients with hepatitis C, that the cumulative recurrence rates after 1 and 2 years were 30.8 and 86.8% for multinodular HCC and 15.4 and 29.5% for uninodular HCC; the investigators found significant risk factors to be associated with the number of HCC nodules, low serum platelets and albumin level. Kim et al. (18) recently estimated the incidence of the cumulative disease-free survival for the overall recurrence, LTP and IDR. In his study, the incidence of overall recurrence, LTP and IDR was 62.9, 26.4 and 53.2%, respectively. The cumulative disease-free survival rates were 52, 82 and 56% at 1 year, and 26, 63 and 30% at 2 years, respectively. The significant risk factors for LTP were a tumor with a diameter > 3 cm, contact of HCC with a vessel and an insufficient safety margin. Only the increased serum alpha-fetoprotein was a significant risk factor for IDR.

Concerning this current study, the incidences of overall recurrence, LTP and IDR were 65, 23 and 52.5%,

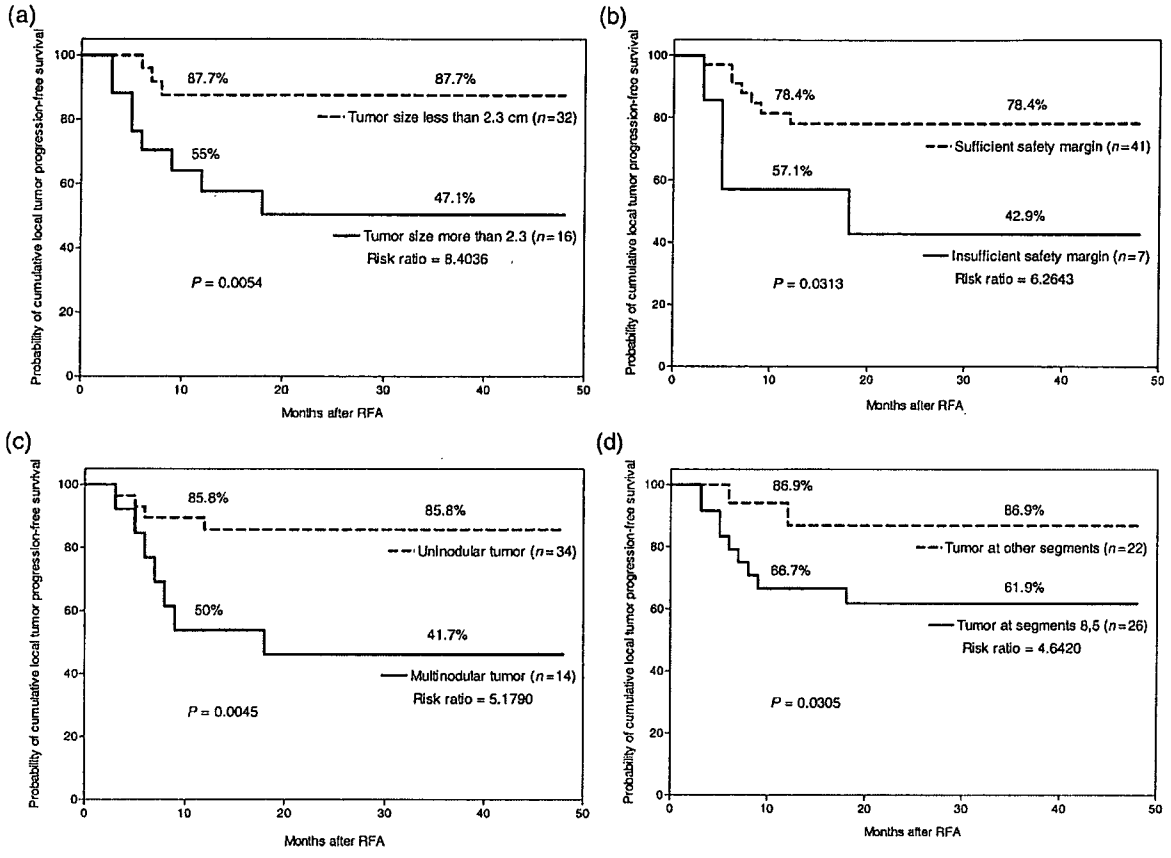

Figure 2. Significant risk factors for local tumor progression after percutaneous radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC). Tumor size $\geq$ 2.3 cm in its greatest dimension ($P = 0.0054$) (a), failure to establish a sufficient ablative safety margin at the immediate follow-up computed tomography (CT) scan over 5 mm in all directions ($P = 0.0313$) (b), tumor multiplicity at the time of ablation ($P = 0.0045$) (c), and tumors originated at segments 8 and 5 ($P = 0.0305$) (d), were proven to be significant by Kaplan–Meier method and log-rank test. Risk ratio was analyzed by stepwise Cox proportional hazard regression model

respectively. The cumulative disease-free survival rates were 54.6, 74.8 and 78.3% at 1 year, and 27.3, 71.9 and 46.3% at 2 years, respectively. The significant risk factors for LTP were a tumor with a diameter $\geq$ 2.3 cm, an insufficient safety margin, a multinodular tumor at the time of ablation, tumors located at segments 8 and 5, and patient's age >65 years. We could not ascertain significant risk factors for IDR. Our results are in line with those of Kim et al. (18), who reported that overall recurrence rate after RFA is two-thirds of treated patients; IDR occurs more frequently than LTP and LTP almost always occurs during the first 24 months postablation; IDR could occur at any time during the first 24 months postablation or later on (Table 6).

In two patients included in our study, residual tumors were found on immediate follow-up CT scans. In those cases, we repeated the procedures as soon as possible to achieve complete ablation. Then, we confirmed complete treatment on another immediate follow-up CT scan after the additional RFA. We included these cases in our study population and analyzed them as the same as those cases with a single complete ablation; this is because there was no reason to differentiate them from the other cases with a single-session ablation.

Hori et al. (22) reported that recurrence is low in HCC $\leq$ 2.3 cm and increased if the tumor is $\geq$ 2.5 cm in its maximum diameter. Our results in harmony with Hori et al. Reported in other series as well as our study, that the most important variable which influences the LTP, is tumor size (10,22). In the present study, large tumor size (larger than or equal to 2.3 cm) proved the highest risk ratio for LTP (8.4036, $P = 0.0096$). Matching our results is the large study conducted by Nakashima et al. (33). Nakashima et al. investigated the relationship between macroscopic types of HCC and intrahepatic metastasis in 209 surgically resected small HCC nodules less than 3 cm in diameter. Vaguely nodular and single nodular types (mean diameter 1.36 and 2.28 cm, respectively) were found to have lower prevalence of intrahepatic metastasis (0 and 4.1%, respectively) than single nodular with extranodular growth and confluent multinodular types (mean diameter 2.31 and 2.39 cm, intrahepatic

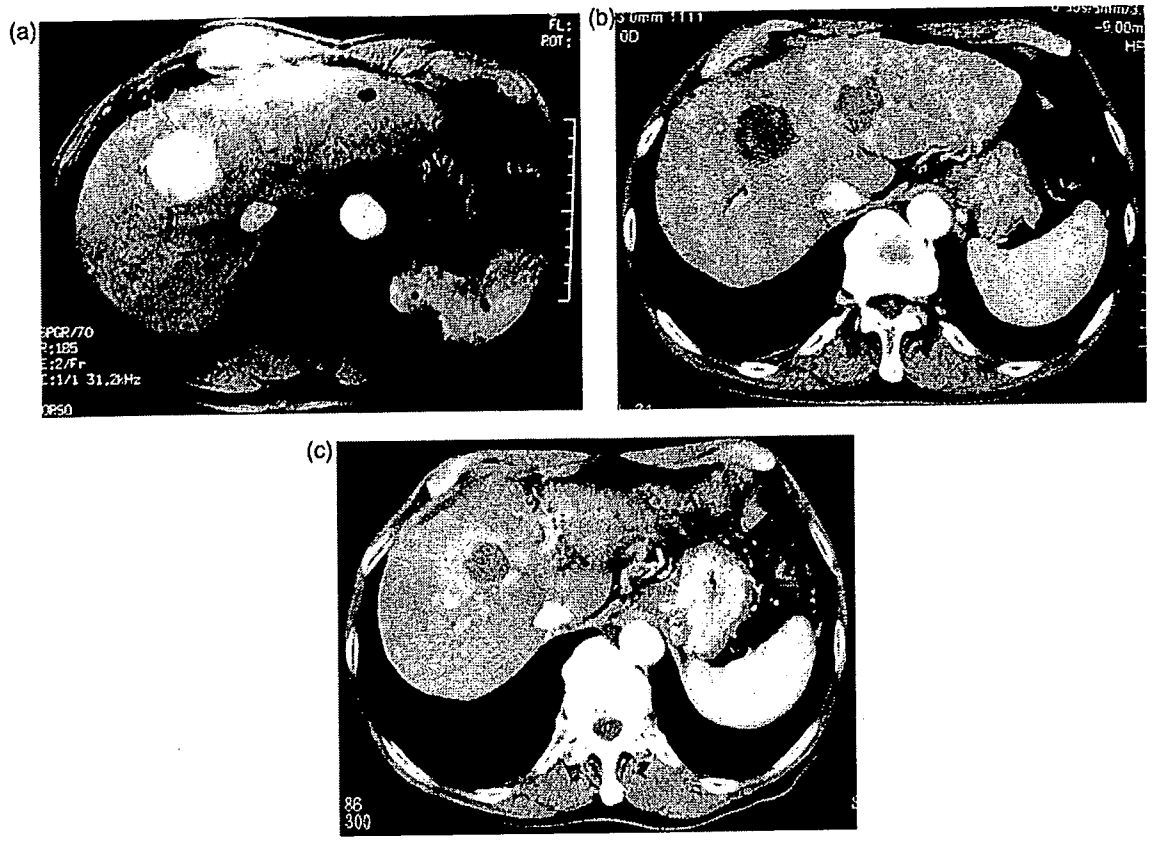

Figure 3. A 71-year-old man with multinodular hepatocellular carcinoma at segment S8-5 and segment S2-3. (a) Pre-RFA, arterial phase dynamic magnetic resonance (MR) imaging reveals two enhanced masses measuring 2.5 cm in segment S8-5 and 1.2 cm in segment S2-3 (arrows). (b) Immediate post-RFA arterial phase dynamic CT imaging reveals periablational hyperemia with complete tumor necrosis. No residual viable tumor could be discerned. Safety margin ablation was sufficient for segment S2–3 mass, although insufficient for segment S8–5 mass because of the hazard of inferior vena cava (IVC) injury. (c) Fifth-month follow-up arterial phase dynamic CT imaging reveals enhanced area along the peripheral margin of segment S8–5 ablative zone, consistent with local recurrence. Note that five risk factors are associated: tumor size >2.3 cm; insufficient safety margin ablation; tumor multiplicity; segmental location S8–5; and age >65 years.

Table 4. Independent risk factors associated with local tumor progression after percutaneous RFA of HCC identified by multivariate analysis using stepwise stepwise Cox's hazard regression model

No. of tumors (% recurrence)	Covariate coefficient	Standard error	*P*-value	Risk ratio (95% confidence interval)	Overall model chi-square (*P*-value)
Tumor diameter ≥2.3 cm					
7/16 (50%)	2.1287	0.8218	0.0096	8.4036 (1.6923–41.7304)	8.4509 (0.0036)
Insufficient safety margin ablation					
4/7 (57.1%)	1.8349	0.8918	0.0396	6.2643 (1.1006–35.6563)	4.5393 (0.0331)
Multiple primary tumors at the time of ablation					
7/14 (50%)	1.6446	0.8324	0.0482	5.1790 (1.0216–26.2540)	4.7976 (0.0285)
Tumors at segment 8, 5					
9/27 (34.6%)	1.5352	0.4548	0.0007	4.6420 (1.9125–11.2674)	10.8329 (0.0044)
Age >65 years					
9/27 (33.3%)	1.4561	0.4468	0.0011	4.2890 (1.7946–10.2504)	9.2746 (0.0023)

Table 5. Univariate analysis for potential hazard ratio associated with intrahepatic distant recurrence of HCC after percutaneous RFA

	Recurrent ($n = 21$)	Not recurrent ($n = 19$)	*P*-value	Hazard ratio
		Host factors		
Age				
>65/ ≤65 years	12/9	10/9	0.5098	0.7500
Gender				
M/F	17/4	14/5	0.8173	1.2510
Severity of liver disease				
Child–Pugh class B/A	3/18	5/14	0.7100	0.7988
Cause of liver cirrhosis				
HCV/HBV/other	18/2/1	15/2/2	0.9064	0.9315
Total protein (TP)				
Pre-RFA	7.3 ± 0.4	7 ± 0.8		
Low/normal	4/17	6/13	0.7230	0.8241
Post-RFA	7.1 ± 0.1	6.9 ± 0.2		
Low/normal	3/18	6/13	0.1252	0.4162
AST				
Pre-RFA	97.6 ± 62.5	77.7 ± 53.8		
Elevated/normal	18/3	14/5	0.2715	1.936
Post-RFA	93.1 ± 62.3	73.2 ± 45.1		
Elevated/normal	18/3	13/6	0.2890	1.890
ALT				
Pre-RFA	94.7 ± 70.5	94.7 ± 70.5		
Elevated/normal	14/7	12/7	0.5012	1.337
Post-RFA	86.4 ± 70.2	63.3 ± 42.2		
Elevated/normal	14/7	11/8	0.6798	1.206
ALP				
Pre-RFA	357.4 ± 171.3	318.5 ± 183.0		
Elevated/normal	10/11	7/12	0.7370	1.4783
Post-RFA	349.2 ± 149.7	339.8 ± 158.3		
Elevated/normal	10/11	8/11	0.8634	1.2426
Total bilirubin				
Pre-RFA	1.1 ± 0.4	1 ± 0.4		
Elevated/normal	9/12	5/14	0.1602	1.888
Post-RFA	1.5 ± 0.6	1.2 ± 0.5		
Elevated/normal	13/8	9/10	0.1412	1.838
		Tumor and therapy factors		
History of previous treatment of HCC by interventional or surgical modality				
Present/absent	2/19	3/16	0.7370	0.8588
Number of primary HCC at the time of radiofrequency ablation				
Multinodular/uninodular	4/17	3/16	0.08976	1.0356
Histological differentiation				
PD/MD/WD	4/13/4	2/6/11	0.9138	1.2475

Continued

Table 5. *Continued*

	Recurrent ($n = 21$)	Not recurrent ($n = 19$)	*P*-value	Hazard ratio
AFP				
Pre-RFA	144.7 ± 227.9	67.5 ± 82.1		
Elevated/normal	12/9	9/10	0.0777	2.274
Post-RFA	88.8 ± 130.7	68.1 ± 101.8		
Elevated/normal	14/7	11/8	0.1682	1.839
PIVKA II				
Pre-RFA	28.22 ± 35.50	49.80 ± 80.29		
Elevated/normal	4/17	5/14	0.4346	0.6644
Post-RFA	7.1 ± 0.4	6.9 ± 0.6		
Elevated/normal	3/18	3/16	0.9460	0.9606

metastasis 26.7 and 26.3%, respectively) (33). It was reported that the coagulated necrotic area produced by RFA conformed to the size of the tumor and was smaller than expected in the surrounding cirrhotic tissue, and larger than expected within the tumor (called the 'oven effect') (24). In the present study, 16 of 48 tumors were ≥2.3 cm in diameter with LTP incidence 8/16 (50%). Several small satellite nodules might have existed around tumors larger than 25 mm in diameter and these satellite nodules could not be completely treated by single-session RFA in tumors larger than 25 mm since they are difficult to detect by transcutaneous US, dynamic CT or dynamic MRI (22,25).

Although there have been studies on a safe tumor-free margin of a surgical resection for hepatic tumors, this remains an unresolved problem (21,26,27). A gross tumor-free margin of 1 cm in all directions around the tumor in the resected specimen is generally accepted by most surgeons and pathologists. Local recurrence was more frequently observed after limited resections than after anatomic resections that included the tumor and its portal territory (50 vs 10%). Patients undergoing anatomic resection for HCC achieved better disease-free survival than those undergoing limited resection (26). RFA in our study was performed percutaneously; evaluation could be done with CT images pre- and post-procedure. We set and evaluated a safe ablative margin as 5 mm in all directions around the tumor and two CT scans before and after the RFA were analyzed. We showed that the establishment of a 5 mm ablative margin was effective in suppressing LTP after RFA of HCC and, without this safety margin ablation, LTP incidence was 57.1% (risk ratio = 6.2643, $P = 0.0396$).

Tumor multiplicity is a strong indicator of tumor recurrence after curative resection of HCC (8), microwave (23) or radiofrequency ablation (10,23). We obtained the same end result; statistical analysis of the number of primary HCC nodules at the time of ablation revealed that the LTP incidence was 7/14 (50%) for primary multinodular HCC. The primary multinodular HCC was significantly associated with a higher LTP (risk ratio = 5.1790, $P = 0.0482$).

Tumor location is one of the most important factors influencing LTP. Eleven LTP tumors showed segmental distribution as follows: S8 ($n = 4$), S5 ($n = 2$), S8 + 5 ($n = 3$) and S6 ($n = 2$). One of the reasons why segment 8 + 5 showed a higher LTP rate may be that there were more chances for dual arterial feeders from segmental arteries. The other possible reason may be the greater probability for collateral vessels developing from the adjacent segmental arteries after ablation. This agrees with the conclusion of Yun et al. (28), concerning significant risk for local recurrence after chemoembolization for HCC in tumor located in segmental border zone. If tumor located in S8 attained a sub-diaphragmatic location, then LTP was significantly higher compared with that in tumors situated more deeply within the liver parenchyma. When the tumors were located close to the liver surface beneath the diaphragm, it was not easy to insert the RFA electrode and open the multiple-array at the center of the tumor. In the present study, three of four S8 locally recurrent tumors were located beneath the diaphragm. Recently, it was reported that the laparoscopic approach and artificial ascites method for percutaneous treatment were effective techniques for the treatment of patients with HCC located just beneath the diaphragm (24,29–31). These techniques are recommended for the treatment of tumors located close to the surface (22). In the same way, tumors in segment 5 have a greater chance of being near to the gall bladder and consequently in this location it is complicated to achieve complete ablation by RFA. In this study, one of two tumors at S5 was located near to the gall bladder. Percutaneous ethanol injection was recommended in such patients (risk ratio = 4.6420, $P = 0.0007$).

The patient's age was confirmed as an independent prognostic variable, perhaps representing a surrogate for declining host defense mechanism associated with advancing age.

Table 6. Recurrence-free survival outcome and risk factors for recurrence of hepatocellular carcinoma after radiofrequency ablation

Study	No. of Patients	No. of Tumors	Tumor type (no. patients)	RFA approach	Time frame (months)	Recurrence	Recurrence free survival	Risk factors	Risk ratio
Komorizono et al. (13)	56	65	HCC	Percutaneous	24	LTP	12 months, 76%	Tumor size >2 cm[b]	4.9
							15 months, 74%	Subcapsular location[b]	5.2
Hori et al. (22)	99	104	HCC	Percutaneous	30	LTP	12 months, 90.3%	Tumor diameter ≥2.5 cm[b]	7.396
							24 months, 84.6%	Subcapsular location[b]	5.909
							36 months, 79.6%		
Izumi et al. (23)	84	16 RFA	HCC	Percutaneous	36	IDR	12 months, 82%	HCV[c]	5.31
		68 PMCT		laparoscopic			36 months, 48%	Multinodular tumor[c]	3.89
						LTP	12 months, 92.5%	Elevated serum AFP[c]	N/A
Harrison et al. (14)	50		HCC	Percutaneous	36	Overall	36 months, 28%	Hepatitis[a]	N/A
				open		LTP	36 months, 64%	Large tumor size[a]	N/A
						IDR	36 months, 72%	Elevated serum AFP[a]	N/A
Yamanaka et al. (10)	26	26	HCC	Percutaneous	31	LTP	12 months, 100%	Multinodular tumor[c]	6.970
								Low serum platelets[c]	2.426
						IDR	12 months, 46.2%	Low serum albumin[c]	
Kim et al. (18)	62	72	HCC	Percutaneous	49.1		12 months, 24 mo	Insufficient safety margin[b]	9.281
						Overall	52 months, 26%	Tumor diameter >3 cm[b]	2.899
						LTP	82 months, 63%	Tumor contact with vessel[b]	
						IDR	56 months, 30%	Elevated serum AFP[c]	
Current study	40	48	HCC	Percutaneous	50		12, 24, 36 months	Tumor diameter ≥2.3 cm[b]	8.4036
						Overall	54.6, 27.3, 20%	Insufficient safety margin[b]	6.2643
						LTP	74.8, 71.9, 71.9%	Multinodular tumor[b]	5.1790
						IDR	78.3, 46.3, 29.4%	Tumors at segments 8 + 5[b]	4.6420
								Age > 65 years[b]	4.2890

[a]Overall recurrence risk factors; [b]LTP risk factors; [c]IDR risk factors.

The incidence of LTP was 9/27 (33.3%) in patients >65 years old (risk ratio 4.6420, $P = 0.0011$).

Theoretically, a tumor that is contiguous to a large vessel has more chance of allowing some tumor cells to survive local thermal therapy because there is a significant tissue cooling effect caused by blood circulation of normal body temperature (32). However, previous studies (13,18,22) showed that it was not a significant risk factor for LTP after RFA for HCC and our results agree with them; we could not ascertain that contiguity to a large vessel is a significant risk factor for LTP.

Previous studies proved that an increased level of serum AFP was associated with IDR after RFA for HCC (14,16,18,23). In our study the correlation between serum AFP and IDR was not significant ($P = 0.0777$); however the pre-ablation elevated AFP level recorded the highest hazard ratio (2.274) among all other risk factors investigated for IDR.

In our study, 91% of LTP occurred after 12 months and after 18 months; tumors that did not recur during that interval did not show any LTP during the residual follow-up period of up to 50 months. This time interval has great clinical significance because it can affect the follow-up CT schedule as well as patient prognosis. It is an important explanation for why the close follow-up protocol is indispensable during the first year. Kim et al. (18) support our standpoint; in his study, the incidence of LTP after 24 months is 0%.

CONCLUSION

We can conclude that, after percutaneous RFA for HCC, overall recurrence rate after RFA reaches two-thirds of the treated patients. IDR occurs more frequently than LTP and LTP almost always occurs during the first 18 months post-ablation; IDR could occur at any time earlier during the first 24 months post-ablation or later on. Although less frequent, LTP tended to occur when we ablated a large HCC tumor $\geq$2.3 cm in dimension, or when we could not establish a sufficient safety margin. Tumor multinodularity, tumors located at segments 8 and 5, and patients over 65 years are further significant risk factors. Our findings of different risk factors and prognostic factors for intrahepatic recurrence after RFA of HCC may have clinical implications in determining rational strategies in post-ablation surveillance, prevention and management of recurrence. Patients at risk of LTP should be closely monitored in the first year. Furthermore, regular long-term surveillance is essential for early detection and eradication of IDR.

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Conflict of interest statement

None declared.

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Factors predicting survival in advanced T-staged hepatocellular carcinoma patients treated with reduction hepatectomy followed by transcatheter arterial chemoembolization

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Abstract

Aims: To evaluate the efficacy of reduction hepatectomy followed by transcatheter arterial chemoembolization (TACE) for advanced T-Staged hepatocellular carcinomas (HCCs).
Methods: A retrospective analysis of 39 consecutive patients who underwent reduction hepatectomy followed by TACE for advanced T-Staged HCCs was undertaken.
Results: Reduction hepatectomies, including 20 major ones, were performed. After a median interval of 30 days, the hepatectomies were followed by TACE using farmorubicin. Actual overall 3-year survival after surgery was 32%. Indocyanine green $R_{15} \geq 15\%$, preoperative AFP ≥ 2000 ng/ml, and tumour reduction rate $<98\%$ were predictive of decreased overall survival. When the three prognostic factors were used in a scoring system, with one point assigned for each factor, the 3-year survival rates of patients with scores of 0, 1, 2, and 3 were 71%, 40%, 0%, and 0% respectively.
Conclusions: Reduction hepatectomy followed by TACE is effective in patients with advanced T-Staged HCCs who have none of the 3 poor prognostic factors. Reduction surgery followed by TACE is one of the options for controlling advanced T-Staged HCCs in patients who are not candidates for curative resection or TACE alone.

Keywords: Hepatocellular carcinoma; Resection; Transcatheter arterial embolization; Transcatheter arterial chemoembolization; Prognosis

Introduction

Multiple hepatocellular carcinomas (HCCs) with huge tumours or tumour thrombi are associated with a poor prognosis.[1–3] No effective treatment for the disease has yet been identified. Although surgical resection offers the best chance for long-term survival,[4–6] many of the patients are not candidates for curative resection due to underlying liver dysfunction or the extent of the tumour. Moreover, transcatheter arterial chemoembolization (TACE), which is thought to be the first option for unresectable HCC,[7,8] is sometimes ineffective for controlling such advanced T-staged HCCs, since a large tumour burden or portal tumour thrombi can frequently coexist with the disease.[9,10]

Reduction surgery is a potential treatment for advanced T-staged HCCs that cannot be treated by either curative resection or TACE alone. Several studies have reported long-term survivors after reduction surgery.[11–16] Previously, we reported the results of reduction surgery followed by TACE for treatment of advanced T-staged HCC patients with tumours greater than 10 cm in size with preserved liver function and residual tumour accounting for less than 10% of the remnant liver.[17] However, the efficacy of this strategy is still uncertain, since the optimal patient selection criteria for the strategy have not been determined.

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