Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma ≤ 4 cm

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Abstract

AIM: To determine which treatment modality - hepatectomy or percutaneous ablation - is more beneficial for patients with small hepatocellular carcinoma (HCC) (≤ 4 cm) in terms of long-term outcomes.

METHODS: A retrospective analysis of 149 patients with HCC ≤ 4 cm was conducted. Eighty-five patients underwent partial hepatectomy (anatomic in 47 and non-anatomic in 38) and 64 underwent percutaneous ablation (percutaneous ethanol injection in 37, radiofrequency ablation in 21, and microwave coagulation in 6). The median follow-up period was 69 mo.

RESULTS: Hepatectomy was associated with larger tumor size (P < 0.001), whereas percutaneous ablation was significantly associated with impaired hepatic functional reserve. Local recurrence was less frequent following hepatectomy (P < 0.0001). Survival was better following hepatectomy (median survival time: 122 mo) than following percutaneous ablation (median survival time: 66 mo; P = 0.0123). When tumor size was divided into ≤ 2 cm vs > 2 cm, the favorable effects of hepatectomy on long-term survival was seen only in patients with tumors > 2 cm (P = 0.0001). The Cox proportional hazards regression model revealed that hepatectomy (P = 0.006) and tumors ≤ 2 cm (P = 0.017) were independently associated with better survival.

CONCLUSION: Hepatectomy provides both better local control and better long-term survival for patients with HCC ≤ 4 cm compared with percutaneous ablation. Of the patients with HCC ≤ 4 cm, those with tumors > 2 cm are good candidates for hepatectomy, provided that the hepatic functional reserve of the patient permits resection.

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INTRODUCTION

Hepatectomy and percutaneous ablation are the treatments of choice for small hepatocellular carcinoma (HCC). Hepatectomy is recommended by surgeons, as this procedure removes portal venous thrombi in the adjacent liver, allows for better local control, and has better survival outcomes compared with percutaneous ablation. In contrast, gastroenterologists and interventional radiologists advocate percutaneous ablation techniques including ethanol injection, microwave coagulation, and radiofrequency ablation, as these methods are not as invasive as hepatectomy, have a lower incidence of morbidity and mortality, are more feasible in patients with impaired hepatic functional reserve, and have similar survival outcomes compared with hepatectomy. The aim of this study was to determine which treatment modality - hepatectomy or percutaneous ablation - is more beneficial for patients with small (≤ 4 cm) HCC in terms of long-term outcomes.

MATERIALS AND METHODS

Patients

From January 1990 to December 2002, 224 consecutive patients with HCC underwent either partial hepatectomy or percutaneous ablation therapy as an initial treatment at the Niigata University Medical and Dental Hospital. Of
these patients, 149 with HCC measuring ≤ 4 cm formed the basis of this retrospective study; they included 104 men and 45 women with a median age of 64 years (range: 29-83 years). Only HCCs measuring ≤ 4 cm were included in the current study, because percutaneous ablation therapy was the treatment modality mainly recommended for such tumors in our hospital. All patients were Japanese.

**Treatment modalities**

Of the 149 patients, 85 underwent a hepatectomy for HCC in the Division of Digestive and General Surgery. Hepatectomy. Procedures included non-anatomic hepatectomy in 38 patients, monosegmentectomy in 14, bisegmentectomy in 15, right hepatectomy in 14, and left hepatectomy in 4. In our department, the type of hepatectomy procedure selected was primarily based on the disappearance rate of indocyanine green (KICG[16-17]), which is an indicator of hepatic functional reserve. The selection criteria were KICG ≥ 0.12 for hemihepatectomy, KICG ≥ 0.10 for bisegmentectomy, KICG ≥ 0.08 for monosegmentectomy, and KICG ≥ 0.06 for non-anatomic hepatectomy (including the enucleation of hepatic tumors).

The remaining 64 patients underwent a percutaneous ablation procedure for HCC in the Division of Gastroenterology and Hepatology. Hepatectomy was considered as a feasible option for 51 of these 64 patients and was offered as an alternative. However, all these patients preferred to undergo percutaneous ablation treatment. Hepatectomy was not considered feasible in the remaining 13 patients due to impaired hepatic functional reserve (KICG < 0.06); therefore, these patients were only offered percutaneous ablation treatment. Percutaneous ablation procedures included percutaneous ethanol injection (PEI) in 37 patients, radiofrequency ablation (RFA) in 21, and microwave coagulation therapy (MCT) in 6. In these patients, adequacy of the ablation was assured with dual-phase dynamic computed tomography (section thickness of 5 mm) within a month of the procedure. A microwave tissue coagulator (Microtaze® OT-110M; Alfrresa-Pharma Co., Inc., Osaka, Japan) and an RF generator (Cool-tip® RF System, CMI Century Medical Co., Inc., Tokyo, Japan) were introduced in our hospital in 1995 and 2000, respectively.

**Post-treatment follow-up**

There were no mortalities 30 d post-treatment in the current study. Serum concentrations of alpha-fetoprotein were measured and abdominal ultrasonography and/or contrast-enhanced computed tomography was performed on all the patients approximately 1 mo after the treatment. Thereafter, patients were regularly monitored for recurrences in outpatient clinics every 3 mo by physical examination, laboratory tests, and imaging studies. When intrahepatic recurrences were detected, they were treated with either interventional radiological techniques, such as PEI, RFA, MCT, transarterial chemoembolization and hepatic arterial infusion, or repeat hepatectomy when indicated. Patients with disseminated recurrences and those in a debilitated state were treated with supportive care.

The follow-up period after the treatment was defined as the interval between the date of the initial treatment and that of the last follow-up, and ranged from 11 to 178 (median: 69) mo in the current study. The median follow-up period was 73 mo in patients who had undergone hepatectomy, and 61 mo in those who had undergone percutaneous ablation.

**Definition of local recurrence after treatment**

Local recurrence was defined as recurrences contiguous to resection margins in patients who had undergone hepatectomy; whereas in patients treated with percutaneous ablation, local recurrence was defined as recurrences contiguous to or within the ablated areas.

**Laboratory examination**

The following laboratory tests were performed before treatment: hepatitis B surface antigen; hepatitis C antibody; serum aspartate aminotransferase; serum alanine aminotransferase; the indocyanine green clearance test; and serum alpha-fetoprotein. Hepatitis B surface antigen and hepatitis C antibody in serum were detected by radioimmunoassay (Lumipulse II HBsAg Fujirebio Co., Inc., Tokyo, Japan) and a second-generation enzyme-linked immunosorbent assay (Lumipulse II Ortho HCV; Ortho-Clinical Diagnostics Co., Inc., Tokyo, Japan), respectively. Indocyanine green (Dyagnostreen; Daiichi Pharmaceutical Co., Inc., Tokyo, Japan) retention rate at 15 min after the injection of the dye (0.5 mg/kg) was used as an indicator of hepatic functional reserve, with a reference range of 10% or less[16-18]. Serum concentrations of alpha-fetoprotein were determined by enzyme immunoassay (Luminomaster AFP; Sankyo Yell Yakuhin Co., Ltd., Tokyo, Japan).

**Pathologic examination**

Resected specimens from all the patients who had undergone hepatectomy were submitted to the Department of Surgical Pathology in our hospital. Each specimen was examined to determine the number of hepatic tumors, tumor size, vascular invasion (gross or microscopic), and cirrhosis. Vascular invasion included both portal and hepatic venous invasion in the current study. Cirrhosis in the adjacent (non-tumorous) liver was diagnosed microscopically based on the presence of regenerative nodules surrounded by fibrous septa. The pathology of the liver was confirmed by fine-needle biopsy in all the patients undergoing percutaneous ablation. Among this group of patients, 41 patients had a fine-needle biopsy of the tumor.

**Factors influencing outcomes after treatment**

To determine the factors that may influence outcomes after the treatment, 13 conventional variables[19-22] were identified for univariate and multivariate analyses (Table 1). Vascular invasion and histologic grade were not chosen because they were often missed in patients undergoing percutaneous ablation.

**Statistical analyses**

Medical records and survival data were obtained for all the patients. The causes of death were determined from the medical records. Deaths from other causes were treated as uncensored cases. The Kaplan-Meier method was
used to estimate the cumulative incidences of events, and differences in these incidences were evaluated using the log rank test. The Cox proportional hazards regression model was performed to identify the factors that were independently associated with local recurrence and survival. In this model, a stepwise selection was used for variable selection with entry and removal limits of $P<0.1$ and $P>0.15$, respectively. The stability of each model was confirmed using a step-backward and step-forward fitting procedure, and variables identified as having an independent influence on local recurrence and survival were identical in both the procedures. Clinical features and pathologic tumor-related factors were compared between the two groups using Fisher’s exact test. All statistical evaluations were performed using the SPSS 11.5 software package (SPSS Japan Inc., Tokyo, Japan). All tests were two-sided and $P$ values of $<0.05$ were considered statistically significant.

RESULTS

Clinicopathologic characteristics according to treatment modality

A total of 125 hepatic tumors (median: one per patient; range: 1-14 tumors) were resected in patients undergoing hepatectomy, and a total of 100 tumors (median: one per patient; range: 1-5 tumors) were treated in patients undergoing percutaneous ablation.

Patients treated with hepatectomy had larger tumors than those treated with percutaneous ablation. Patients who had undergone percutaneous ablation were characterized by hepatitis C virus infection, cirrhosis, Child-Pugh classification B or C, an impaired indocyanine green retention rate at 15 min, and increased serum concentrations of aspartate aminotransferase and alanine aminotransferase, suggesting impaired hepatic functional reserve with active hepatitis in these patients (Table 1).

Factors influencing local recurrence

During the follow-up period, local recurrences developed in two patients who had undergone hepatectomy and 17 patients who had been treated with percutaneous ablation (10 treated with PEI and 7 treated with RFA). Univariate analysis revealed that treatment modality ($P<0.0001$), indocyanine green retention rate at 15 min ($P=0.0005$), Child-Pugh classification ($P=0.0012$), serum alpha-fetoprotein level ($P=0.0072$), hepatitis C virus infection ($P=0.0374$), and number of hepatic tumors ($P=0.0419$) were risk factors for local recurrence. Of these six variables, multivariate analyses revealed that treatment modality and serum alpha-fetoprotein level were the only independently significant variables (Table 2).

Factors influencing long-term survival

At the time of disease status assessment, 53 patients who had undergone hepatectomy were alive, and 32 had died. Thirty-four patients treated with percutaneous ablation were alive, and 30 had died. Univariate analysis revealed that Child-Pugh classification ($P=0.0010$), serum alpha-fetoprotein level ($P=0.0052$), treatment modality ($P=0.0123$), serum aspartate aminotransferase ($P=0.0278$), tumor size, hepatitis C virus infection ($P=0.0072$), and number of hepatic tumors ($P=0.0419$) were significant prognostic factors of long-term survival. Of these six variables, multivariate analyses revealed that treatment modality and tumor size were the only independent significant variables (Table 3).

Outcomes after treatment according to tumor size

Local recurrence was significantly less frequent in patients who had undergone hepatectomy than in those who had undergone percutaneous ablation ($P<0.0001$) (Figure 1). When the patients were divided into two groups according to their tumor size, local recurrence was significantly less frequent in patients with tumors less than 2 cm in diameter than those treated with percutaneous ablation. Patients treated with hepatectomy had larger tumors than those treated with percutaneous ablation. Patients who had undergone percutaneous ablation were characterized by hepatitis C virus infection, cirrhosis, Child-Pugh classification B or C, an impaired indocyanine green retention rate at 15 min, and increased serum concentrations of aspartate aminotransferase and alanine aminotransferase, suggesting impaired hepatic functional reserve with active hepatitis in these patients (Table 1).

### Table 1 Clinicopathologic characteristics of 149 patients with hepatocellular carcinoma according to treatment modality

| Variable                        | Hepatectomy | Percutaneous ablation |
|--------------------------------|-------------|-----------------------|
| Age (yr)                        | 65 or less  | 65 or more            |
| Gender (M/F)                    | Male        | Female                |
| Child-Pugh classification (A/B/C)| Present    | Absent                |
| Hepatitis C virus infection     | Positive    | Negative              |
| Number of hepatic tumors        | ≤ 20        | > 20                  |
| Tumor size (cm)                 | ≤ 2         | > 2                   |
| Treatment modality              | Hepatectomy | Percutaneous ablation |
| Serum alpha-fetoprotein level   | ≤ 50        | > 50                  |
| Indocyanine green retention rate| ≤ 15        | > 15                  |
| Hepatitis C virus infection     | Positive    | Negative              |
| Number of hepatic tumors        | ≤ 20        | > 20                  |
| Tumor size (cm)                 | ≤ 2         | > 2                   |
| Child-Pugh classification (A/B/C)| Present    | Absent                |
| Hepatitis C virus infection     | Positive    | Negative              |
| Number of hepatic tumors        | ≤ 20        | > 20                  |
| Tumor size (cm)                 | ≤ 2         | > 2                   |
| Treatment modality              | Hepatectomy | Percutaneous ablation |
| Serum alpha-fetoprotein level   | ≤ 50        | > 50                  |
| Indocyanine green retention rate| ≤ 15        | > 15                  |
| Hepatitis C virus infection     | Positive    | Negative              |
| Number of hepatic tumors        | ≤ 20        | > 20                  |
| Tumor size (cm)                 | ≤ 2         | > 2                   |

### Table 2 Independent risk factors for local recurrence

| Variable                        | Relative risk | 95% CI   | P value |
|--------------------------------|---------------|----------|---------|
| Treatment modality              | 1.000         |          | 0.001   |
| Hepatectomy                     | 13.442        | 3.102-58.254 | 0.014 |
| Percutaneous ablation           | 4.711         | 1.370-16.195 | 0.0454 |
| Serum alpha-fetoprotein level   | 1.000         |          |         |
| ≤ 20                            | 4.711         | 1.370-16.195 |         |
| > 20                            | 1.000         |          |         |

ICG R15: indocyanine green retention rate at 15 min. *P*<0.01 between groups.
Kaplan-Meier estimates of local recurrence. The incidence of local recurrence decreased and long-term survival increased independently after hepatectomy, indicating that this may partly be due to the fact that hepatic functional reserve was better in patients who had undergone hepatectomy.

Table 3: Independent factors influencing long-term survival

| Variable                | Relative risk | 95% CI       | P value |
|-------------------------|---------------|--------------|---------|
| Treatment modality      |               |              |         |
| Hepatectomy             | 1.000         |              | 0.006   |
| Percutaneous ablation   | 2.398         | 1.278-4.499  | 0.017   |
| Tumor size (cm)         |               |              |         |
| ≤ 2                     | 1.000         |              |         |
| > 2                     | 2.159         | 1.148-4.060  |         |
| Child-Pugh classification|              |              |         |
| A                       | 1.000         |              |         |
| B + C                   | 1.773         | 1.000-3.142  | 0.072   |
| AFP (ng/mL)             |               |              |         |
| ≤ 20                    | 1.000         |              |         |
| > 20                    | 1.713         | 0.952-3.084  |         |

Figure 1 Kaplan-Meier estimates of local recurrence. The incidence of local recurrence reached a plateau of 28% at 20 mo after percutaneous ablation, and a plateau of 3% at 22 mo after hepatectomy.

Incidence of vascular invasion according to tumor size

Vascular invasion was more frequent in patients with tumors > 2 cm (16/62, 26%) than in those with tumors ≤ 2 cm (1/23, 4%; P = 0.033, Table 4).

DISCUSSION

Selecting the correct treatment modality to suit individual patients with HCC remains a matter of debate. This prompted us to conduct the current study, which has revealed that hepatectomy provided better outcomes for patients with HCC ≤ 4 cm than percutaneous ablation. This may partly be due to the fact that hepatic functional reserve was better in patients who had undergone hepatectomy. Despite this, we found that the incidence of local recurrence decreased and long-term survival increased independently after hepatectomy, indicating that hepatectomy was found to be the more effective treatment for controlling local recurrence, but only in patients with HCC > 2 cm (P < 0.0001) (Figure 2). Survival after the treatment was significantly better in patients who had undergone hepatectomy than in those treated with percutaneous ablation (P = 0.0123, Figure 3). Again, hepatectomy was the more effective treatment in terms of long-term survival, but only in patients with HCC > 2 cm (P = 0.0001, Figure 4).

Figure 2 Kaplan-Meier estimates of local recurrence by tumor size. A: Among tumors ≤ 2 cm, the incidence of local recurrence reached a plateau of 12% at 15 mo after percutaneous ablation, whereas no recurrences had occurred after hepatectomy. B: Among tumors > 2 cm, the incidence of local recurrence reached a plateau of 61% at 21 mo after percutaneous ablation, whereas it reached a plateau of 4% at 22 mo after hepatectomy.

Figure 3 Kaplan-Meier estimates of survival. The median survival time was 122 mo with a 10-year survival rate of 53% in patients who had undergone hepatectomy. The median survival time was 66 mo with a 10-year survival rate of 31% in patients who had undergone percutaneous ablation.

Table 4: Incidence of vascular invasion according to tumor size

| Tumor size (cm) | Vascular invasion | P value |
|-----------------|-------------------|---------|
|                 | (−)               | (+)     |         |
| ≤ 2             | 22                | 1⁴      | 0.033   |
| > 2             | 46                | 1⁵      |         |

⁴Portal venous invasion was noted. ⁵Portal venous invasion in 10 patients, hepatic venous invasion in 3, and both portal and hepatic venous invasion in 3.
Vascular invasion is an established adverse prognostic factor of HCC\cite{9,21,28-30}, and the incidence of vascular invasion increases as the tumor enlarges\cite{30-33}. The current study confirmed this, with vascular invasion being more frequent in tumors \( \leq 2 \) cm. Recent authors have suggested that tumors \( > 2 \) cm are independently associated with local failure after RFA\cite{34,35}. Considering that vascular invasion was less frequent in tumors \( \leq 2 \) cm in our patients, percutaneous ablation appears to be an appropriate treatment modality for HCCs \( \leq 2 \) cm. Despite this, outcomes for patients with HCCs \( \leq 2 \) cm were better following hepatectomy than following percutaneous ablation. Due to the small sample size of this study, however, these differences were only marginally significant. We believe that hepatectomy may also be an appropriate treatment modality for HCCs \( \leq 2 \) cm, provided that the patient is robust and that the hepatic functional reserve of the patient is at a level permitted for the resection.

Recent evidence suggests that high pre-treatment serum alpha-fetoprotein levels are associated with both the presence of portal venous invasion and intrahepatic recurrences after the treatment in HCC\cite{26,36-41}. Serum alpha-fetoprotein levels were independently associated with local recurrences in the current study. The above findings suggest that high serum alpha-fetoprotein levels predict the presence of portal venous invasion, which may lead to treatment failure, in patients with HCC.

The current study has some limitations. First, it was a retrospective analysis of a small number of patients; second, the follow-up period in 64 patients was \( < 60 \) mo; and third, percutaneous ablation therapy included three different treatment modalities. However, we believe that these limitations do not significantly influence the outcome of the study, as the marked differences between each group appear to overcome these biases.

In conclusion, hepatectomy provides both better local control and better long-term survival for patients with HCC \( \leq 4 \) cm than percutaneous ablation, probably because hepatectomy eradicates both the primary tumor and venous tumor thrombi within the hepatectomy margin. Among the patients with HCC \( \leq 4 \) cm, those with tumors \( > 2 \) cm are good candidates for hepatectomy, provided that the level of hepatic functional reserve of the patient is suitable for resection.

REFERENCES

1. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; 35: 519-524
2. Poon RT, Fan ST, Tsang FH, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon’s perspective. *Ann Surg* 2002; 235: 465-486
3. Imamura H, Matsuyama Y, Miyagawa S, Makuuchi M, Kawasaki S. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. *Br J Surg* 1999; 86: 1032-1038
4. Montorsi M, Santambrogio R, Bianchi P, Donadon M, Moroni E, Spinelli A, Costa M. Survival and recurrences after hepatic resection or radiofrequency for hepatocellular carcinoma in cirrhotic patients: a multivariate analysis. *J Gastrointest Surg* 2005; 9: 62-7, discussion 67-8
5. Vivarelli M, Guglielmi A, Ruzzenente A, Cucchetti A,
Bellusci R, Cordiano C, Cavallari A. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. *Ann Surg* 2004; 240: 103-107.

6. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; 229: 790-79; discussion 790-79.

7. Livraghi T, Giorgio A, Marin G, Salimi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* 1995; 197: 101-108.

8. Kotoh K, Sakai H, Sakamoto S, Nakayama S, Satoh M, Morotomi I, Nawata H. The effect of percutaneous ethanol injection therapy on small solitary hepatocellular carcinoma is comparable to that of hepatectomy. *Am J Gastroenterol* 1994; 89: 194-198.

9. Shina S, Tagawa K, Niwa Y, Unuma T, Komatsu Y, Yoshiura K, Hamada E, Takahashi M, Shiratori Y, Terano A. Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. *AJR Am J Roentgenol* 1993; 160: 1023-1028.

10. Sato M, Watanabe Y, Ueda S, Iseki S, Abe Y, Sato N, Kimura S, Okubo K, Onji M. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology* 1996; 110: 1507-1514.

11. Seki T, Wakabayashi M, Nakagawa T, Itoh T, Shiro T, Kunieda K, Sato M, Uchiyama S, Inoue K. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994; 74: 817-825.

12. Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A, Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer* 1999; 85: 1694-1702.

13. Allgaier HP, Deibert P, Zuber I, Olschewski M, Blum HE. Percutaneous radiofrequency interstitial thermal ablation of small hepatocellular carcinoma. *Lancet* 1999; 353: 1676-1677.

14. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; 210: 655-661.

15. Tateishi R, Shina S, Teratani T, Obi S, Sato S, Koike Y, Fujishima T, Yoshida H, Kawabe T, Omata M. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer* 2005; 103: 1201-1209.

16. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuchu M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. *J Hepatobiliary Pancreat Surg* 2005; 12: 16-22.

17. Kawasaki S, Sugiyama Y, Iga T, Hanano M, Sanjo K, Beppu T, Idezuki Y. Pharmacokinetic study on the hepatic uptake of indocyanine green in cirrhotic patients. *Ann J Gastroenterol* 1985; 80: 801-806.

18. Moody FG, Rikkers LF, Aldrete JS. Estimation of the functional reserve of human liver. *Ann Surg* 1974; 180: 592-598.

19. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Manual, 6th edition. New York: Springer-Verlag, 2002: 131-138.

20. Izumi R, Shimizu K, Li T, Yagi M, Matsui O, Nonomura A, Miyagishima Y. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Gastroenterology* 1994; 106: 720-727.

21. Vauthey JN. Laurwers GY, Ennaola NF, Do KA, Belghiti J, Mirza N, Curley SA, Ellis LM, Regimbeau JM, Rashid A, Cleary KR, Nagorney DM. Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002; 20: 1527-1536.

22. Wakai T, Shirai Y, Nomura T, Nagakura S, Hatakeyama K. Computer tomographic features of hepatocellular carcinoma predict long-term survival after hepatic resection. *Eur J Surg Oncol* 2002; 28: 235-242.

23. Ohnishi K, Yoshioka H, Ito S, Fujiwara K. Prospective randomized controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. *Hepatology* 1998; 27: 67-72.

24. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; 228: 235-240.

25. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology* 2004; 127: 1714-1723.

26. Sasaki A, Kai S, Iwashita Y, Hiraoro S, Ohmoto K, Kitano S. Microsatellite distribution and indication for locoregional therapy in small hepatocellular carcinoma. *Cancer* 2005; 103: 299-306.

27. Shina S, Tagawa K, Unuma T, Takashani R, Yoshiura K, Komatsu Y, Hata Y, Niwa Y, Shiratori Y, Terano A. Percutaneous ethanol injection therapy for hepatocellular carcinoma. A histopathologic study. *Cancer* 1991; 68: 1524-1530.

28. Wakai T, Shirai Y, Yokoyama N, Nagakura S, Hatakeyama K. Hepatitis virus status affects the pattern of intrahepatic recurrence after resection for hepatocellular carcinoma. *Eur J Surg Oncol* 2003; 29: 266-271.

29. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg* 2003; 197: 753-758.

30. Tsai TJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, Hsiea CY, Wu CW. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. *Surgery* 2000; 127: 603-608.

31. Shi M, Zhang CQ, Zhang YQ, Liang MX, Li JQ. Micrometastases of solitary hepatocellular carcinoma and appropriate resection margin. *World J Surg* 2004; 28: 376-381.

32. Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K, Tsuneyoshi M. Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. *Cancer* 1996; 77: 2022-2031.

33. Ennosa NF, Laurwers GY, Mirza NQ, Nagorney DM, Doherty D, Iki I, Yamaoka Y, Regimbeau JM, Belghiti J, Curley SA, Ellis LM, Vauthey JN. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg* 2002; 6: 224-32; discussion 232.

34. Komorizono Y, Oketani M, Sako K, Yamashita S, Shibatou M, Maeda M, Kohara K, Shigenobu S, Ishihashi K, Arima T. Risk factors for local recurrence of small hepatocellular carcinoma tumors after a single session, single application of percutaneous radiofrequency ablation. *Cancer* 2003; 97: 1253-1262.

35. Yu HC, Cheng JS, Lai KH, Lin CP, Lo GH, Lin CK, Hsu PI, Chan HH, Lo CC, Tsai WL, Chen WC. Factors for early tumor recurrence of single small hepatocellular carcinoma after percutaneous radiofrequency ablation therapy. *World J Gastroenterol* 2005; 11: 1439-1444.

36. Fujioka M, Nakashima Y, Nakashima O, Kojiri M. Immunohistologic study on the expressions of alpha-fetoprotein and protein induced by vitamin K absence or antagonist II in surgically resected small hepatocellular carcinoma. *Hepatology* 2001; 34: 1128-1134.

37. Pompili M, Raspacchi GL, de Luca F, Caturelli E, Astone A, Siena DA, Villani MR, Grataglioni A, Celfroni A, Gasbarini G. Risk factors for intrahepatic recurrence of hepatocellular carcinoma in cirrhotic patients treated by percutaneous ethanol injection. *Cancer* 1997; 97: 1501-1508.

38. Ruzzenente A, Manzoni GD, Molfetta M, Pacher S, Genco B, Donatocci M, Guglielmi M. Rapid progression of hepatocellular carcinoma after Radiofrequency Ablation. *World J Gastroenterol* 2004; 10: 1137-1140.

39. Aoyagi Y, Oguro M, Yanagi M, Mita Y, Suda T, Suzuki Y, Hata K, Ichi K, Assakura H. Clinical significance of simultaneous determinations of alpha-fetoprotein and des-gamma-carboxy prothrombin in monitoring recurrence in patients with...
hepatocellular carcinoma. *Cancer* 1996; 77: 1781-1786

40 Aoyagi Y, Isokawa O, Suda T, Watanabe M, Suzuki Y, Asakura H. The fucosylation index of alpha-fetoprotein as a possible prognostic indicator for patients with hepatocellular carcinoma. *Cancer* 1998; 83: 2076-2082

41 Harrison LE, Koneru B, Baramipour P, Fisher A, Barone A, Wilson D, Dela Torre A, Cho KC, Contractor D, Korogodsky M. Locoregional recurrences are frequent after radiofrequency ablation for hepatocellular carcinoma. *J Am Coll Surg* 2003; 197: 759-764

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