Radiofrequency ablation of hepatocellular carcinoma in patients with and without cirrhosis

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KEYWORDS

Hepatocellular carcinoma;
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Cirrhosis.

Abstract *Introduction:* Hepatocellular carcinoma (HCC) is a leading cause of death in patients with cirrhosis. Around 12% of all cases are associated with chronic liver disease without cirrhosis. The aim of our study was to compare primary tumor ablation rates, local tumor progression, safety, and long-term outcomes of radiofrequency ablation for single (less than 3.5 cm in diameter) or multiple HCC nodules (up to three nodules, each less than 3 cm) in both types of patients.

Methods: We treated 200 consecutive HCC patients recruited from a local sonographic screening program: 175 with cirrhosis and 25 with non-cirrhotic chronic liver disease.

Results: Complete ablation was achieved in 150 of the 175 patients (85.7%) (174 of the 206 nodules treated, 84.4%) in the cirrhotic group and in 24 of the 25 patients (96%) (27 of the 29 nodules treated; 93%) in the non-cirrhotic group. The two groups were not significantly different in terms of local tumor progression rates 1, 3, and 5 years after treatment (11%, 23%, and 24% among cirrhotics vs. 4%, 14%, and 14% among non-cirrhotic patients). Multifocal disease was more frequent among the cirrhotics. One-, three- and five-year survival rates were also similar in the cirrhotic (93%, 77%, and 61%) and non-cirrhotic groups (92%, 72%, and 64%). There were no treatment-related deaths. Severe complications occurred only in the cirrhotic group (2.2%).

Conclusions: Radiofrequency ablation is safe and effective treatment for HCC in patients with or without cirrhosis. The latter group has a significantly lower rate of multifocal disease.

Sommario *Introduzione:* L'epatocarcinoma è una delle più frequenti cause di morte per cirrosi ed è associato ad epatopatia cronica non cirrotica nel 12% dei casi.

Scopo: Valutare l'efficacia terapeutica, la ricorrenza di malattia, la "sicurezza" della procedura e la sopravvivenza dei pazienti sottoposti a radiofrequenze di epatocarcinoma singolo (di diametro inferiore o uguale a 3,5 cm) oppure multiplo (fino a tre lesioni con diametro inferiore a 3 cm) in entrambi i gruppi.

Metodi: Sono stati trattati 200 pazienti consecutivi, 175 affetti da cirrosi epatica e 25 da epatopatia cronica non cirrotica, reclutati da un programma locale di screening ecografico.

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Risultati: È stata ottenuta una risposta completa in 150 dei 175 pazienti (85,7%) (174/206 noduli, 84,4%) nel gruppo dei cirrotici, in 24 dei 25 pazienti (96%) (27/29 noduli, 93%) nel gruppo dei non cirrotici.

Il tasso di recidiva locale a 1, 3, 5 anni dalla procedura non era differente tra i cirrotici (11, 23 e 24% rispettivamente) e i non cirrotici (4, 14 e 14%), mentre il tasso di malattia multicentrica era più elevato nei cirrotici.

Il tasso di sopravvivenza a 1,3,5 anni non era differente tra il gruppo dei cirrotici (93, 77 e 61% rispettivamente) e dei non cirrotici (92,72 e 64% rispettivamente). Nessun paziente è deceduto a causa del trattamento e solo il 2,2% dei pazienti nel gruppo dei cirrotici ha presentato complicanze maggiori.

Conclusioni: La termoablazione con radiofrequenze è una tecnica efficace e affidabile in pazienti con o senza cirrosi; nei pazienti senza cirrosi l'insorgenza di malattia multicentrica è significativamente inferiore.

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Introduction

Surveillance programs aimed at the early detection of small, hepatocellular carcinoma (HCC) nodules in patients with chronic liver diseases are increasing the eligibility for local or surgical treatments [1–3]. Radical treatment options, which are feasible in up to 30% of all cases, include surgical resection, orthotopic liver transplantation (OLT), and ultrasound (US)-guided percutaneous ablation methods based on ethanol injection or radiofrequency energy [1,4]. The availability of different approaches allows the clinician to tailor the treatment to the individual patient's needs, the general clinical features of the case, the presence of underlying diseases, and the stage and location of the tumor(s).

In a small proportion of HCC patients with underlying cirrhosis, surgical resection is possible, and liver transplantation is considered even more effective [5]. Patients who are not candidates for surgery may be eligible for percutaneous ablative treatments. Radiofrequency ablation (RFA) is currently considered the best way to produce complete destruction of the neoplastic nodules [5–11], and it is a cost-effective solution for patients expected to remain on waiting lists for OLT for more than 6 months [12].

Current guidelines for HCC screening and indications for curative therapy are based exclusively on studies performed on patients with cirrhosis [1,4]. However, in clinical practice, HCC may also be encountered in patients with chronic viral liver disease with no evidence of cirrhosis. Patients with chronic hepatitis B or C are generally followed with a yearly US examination [3] because the transition from bridging fibrosis to cirrhosis cannot be detected clinically, and HCC develops with stepwise progression of hepatic fibrosis [13].

In HCC patients with non-cirrhotic CLD, surgical resection is considered the best treatment. It is also preferred over OLT, which is not associated with any benefits in terms of survival [14].

The aim of this study was to evaluate the efficacy and safety of RFA for nodular HCC in patients with and without cirrhosis who were not eligible for surgery or OLT. We therefore evaluated complete ablation rates, local progression, the development of new lesions, safety, and survival in these two groups of HCC patients.

Materials and methods

In accordance with our local US screening protocol, patients with Child-Pugh class A or B cirrhosis and those with non-cirrhotic CLD had abdominal ultrasound examinations every 6 and 12 months, respectively. Patients with newly diagnosed HCCs that were ineligible for surgical resection (due to the location of the tumor lesions, poor liver function, and/or comorbidity) or OLT were scheduled for RFA, provided their tumors consisted in a single nodule smaller than 3.5 cm or no more than three nodules, each measuring less than 3 cm. (Our treatment protocol calls for transarterial chemo-embolization [TACE] for patients with good liver function who have more than three nodules or at least one intermediate-stage (2) over 3.5 cm in diameter.) Exclusion criteria were Child C cirrhosis, eligibility for surgical resection or OLT, and previous treatments with either PEI or TACE. In our district, there is no liver transplant unit. Therefore, all patients regarded as potential candidates for OLT were evaluated in regional hospitals with liver transplant programs. Three patients included in the study had previously undergone hepatic resection. Written informed consent was obtained from all the patients, in accordance with the provisions of the local ethics committee. None of the patients refused the proposed treatment.

Patients and HCC characteristics

From July 1, 1997 to June 30, 2006, we enrolled 200 consecutive patients who met the criteria specified above. Their characteristics and the main features of their tumors are summarized in Table 1.

The HCC diagnosis was histologically confirmed in 108 cases (92 [52.5%] of the 175 cirrhotic patients and 16 [64.0%] of the 25 without cirrhosis). In the remaining cases, the diagnosis was based on concordant findings consistent with HCC on two or more diagnostic imaging examinations (ultrasonography, contrast-enhanced spiral computed tomography, and, when doubts persisted, magnetic resonance imaging) or findings strongly indicative of HCC on a single imaging study together with alpha fetoprotein levels exceeding 400 ng/mL [3].

In the 25 cases of CLD without cirrhosis, an extranodular biopsy was collected at the time of the nodular biopsy (16

Table 1 Characteristics of patients with hepatocellular carcinoma (HCC) and cirrhosis or non-cirrhotic chronic liver disease (CLD) treated with radiofrequency ablation (RFA).

Characteristics	HCC/cirrhosis	HCC/CLD without cirrhosis
Patients	<i>N</i> = 175 ^a	<i>N</i> = 25
Females — no. (%)	65 (37.2)	6 (24)
Age (years)		
Mean	70.26 ± 7.12	70.28 ± 7.07
Range	43–84	55–84
Cause of cirrhosis		
HCV	150 (85.7)	21 (84)
HBV	9 (5.1)	1 (4)
ETOX	9 (5.1)	1 (4)
Others	7 (4.0) ^b	2 (8) ^b
AFP levels (ng/mL) ^b		
0–20	116 (77.8)	16 (80)
21–100	19 (12.8)	3 (15)
>100	14 (9.4)	1 (5)
Patients with		
1 nodule	145 (82.8)	21 (84)
2 nodules	29 (16.6)	4 (16)
3 nodules	1 (0.6)	0 (0)
Mean		
Nodules	<i>N</i> = 206	<i>N</i> = 29
Mean no. per patient	1.17	1.04
Size of main tumor		
Mean	25.34 ± 6.31 mm	25.4 ± 6.48 mm
Range	10–35 mm	12–35 mm
1–20 mm (No. %)	53 (30.1)	8 (32.0)
>20 mm	123 (69.9)	17 (68.0)
US pattern of main tumor		
HYPER	31 (15)	3 (12)
HYPO	106 (51.4)	23 (76)
ISO	4 (1.9)	0 (0)
MIX	65 (31.5)	3 (12)
Histology		
Well differentiated	69 (39.4)	13 (52)
Poorly differentiated	9 (5.1)	3 (12)

Abbreviations: AFP, alpha fetoprotein; ETOX, alcohol abuse; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HYPER, hyperechoic; HYPO, hypoechoic; ISO, isoechoic; and MIX, mixed.

^a Child class A (*N* = 143), Child class B (*N* = 32).

^b Subsample only.

cases) or within the 2 years preceding the nodular biopsy (9 cases). In 16 (64%) of these 25 cases, the HCC diagnosis was histologically confirmed.

In 5 cases (2 treated with RFA during laparotomy, 2 that had previously undergone surgical resection, and 1 treated with resection for the development of a new HCC lesion), intraoperative examination of the tumor morphology was also possible.

The nature of the underlying liver disease is reported in Table 1. The causes classified as “others” were (for the non-cirrhotic group) hepatitis C viral infection associated with alcohol abuse (1 case) and metabolic steatosis (1 case) and (for the cirrhotic group) hemochromatosis (1 case), steatohepatitis (3 cases), and cryptogenic (3 cases).

The group with cirrhosis included 5 patients with borderline histological findings characterized by what appeared to be regenerative tissue associated with intense fibrosis (F 3–4 according to the Knodell classification) [15]. As for the other 170 patients in this group, the diagnosis of cirrhosis was histologically confirmed in 78 cases and based on standardized clinical or imaging criteria (US, CT, endoscopy) [16] in the remaining 92 cases.

Routine liver function tests, prothrombin time, and platelet counts were checked before each treatment. None of the patients were excluded for coagulation deficits. Platelet infusions were administered to patients with platelet counts of 30,000–50,000/mm³ (4 cases). In 140 cases, percutaneous treatments were performed under US guidance with a 3.5-Mhz transducer and one of the following scanners: Ultra Mark 9 Plus (ATL USA) or HDI 5000 (Philips USA). Sixteen patients (10.2%) had HCC nodules in areas difficult to reach with percutaneously inserted electrodes. Laparoscopy was performed in 11 of these cases (all members of the cirrhosis group): in 6 cases ultrasound guidance was also used for tumors located in deep sites, and in 5 cases nodules located on the bulging surface of the liver or in areas adjacent to the bowel or gallbladder were punctured under direct laparoscopic vision. Laparotomy was performed in the remaining 5 cases. These included 3 patients with cirrhosis who had originally been scheduled for surgical resection.

The equipment used included monopolar systems produced by RITA (Medical System, Mountain view, CA, USA): Model 500 consisting in a 50-watt generator and a 15-G 4-hook needle electrode and Model 1500 consisting in a 150-watt generator and a 9-hook needle electrode.

The Invatec system (Brescia, Italy) was also used with an expandable-tip electrode (1 mm in diameter) or an internally cooled electrode 4-mm in diameter with a 3-cm-long exposed metallic tip. The Radionic system (Valley Lab, USA) was used with an 18-gauge internally cooled electrode 20 cm long with a 2–3-cm-long exposed metallic tip.

During all treatments, impedance and the amount of energy delivered were constantly monitored with the generator, and the intrahepatic needle-insertion track was ablated at the end of the treatment. When appropriate and feasible, the needle was reinserted one or more times to produce additional thermal lesions, thus ensuring complete ablation of nodule, including the peripheral regions. Additional details of the treatment method have been described elsewhere [17].

All patients were monitored in the hospital for 24 h after the procedure. In a few cases (6 out of 200, 3%), treatment was performed under general anesthesia induced with petidine (Molteni, Scandicci, Italy) and midazolam (Roche, Milan, Italy) infusions in a day-hospital setting. Major complications and side effects were recorded.

All RFA procedures were performed by the operator with the most experience in PEI (A.S.) or under his supervision.

The surveillance protocol included a primary ablation rate and early treatment response assessment. Contrast-enhanced spiral CT was performed within 1 month after treatment.

Long-term responses were evaluated with measurements of alpha fetoprotein levels and hepatic ultrasound every 3 months and by spiral CT every 6 months. The follow-up ranged from 6 to 107 months, but in the statistical analysis the maximum observation time was set at 60 months for all patients in order to avoid problems arising from weighting differences. The mean follow-up was 35.7 months in the group with cirrhosis and 35.9 months in the non-cirrhotic group.

Elderly patients with contraindications to the use of iodinated contrast agents underwent magnetic resonance imaging (MRI) or contrast-enhanced ultrasonography with SonoVue (Bracco, Italy).

The aim of the follow-up examinations was to detect signs of local tumor progression and/or the development of new lesions outside the margins of the previously treated nodule. Intra-nodular/peripheral enhancement at CT scan and/or an increase in nodule size were considered evidence of local progression. In these cases, the recurrence was retreated with RFA unless the patient no longer met the inclusion criteria listed above. Multifocal disease was defined as the development of more than 3 nodules without portal thrombosis or extrahepatic disease. In these cases, patients were treated with TACE or received exclusively symptomatic treatment, as indicated.

The primary efficacy rate was calculated as the percentage of treated nodules that displayed no viable tumor tissue after 1 or 2 treatment sessions. Tumor necrosis was considered complete (complete response) when no area of enhancement was seen within the margins of the original nodule on CT scan. A tumor persistence of 30% or more after up to 2 treatment sessions was considered as incomplete ablation or treatment failure respectively. In cases of treatment failure, tumors were treated with PEI or TACE when feasible. An ablation zone beyond the borders of the tumor was defined as the *ablation margin*.

Statistical analysis

Survival rates were assessed with the Kaplan–Meier method. Differences between curves were analyzed with the Log Rank test (Mantel–Cox). None of the patients withdrew from the study, so the only “dropout event” considered was death.

For the analysis of new events that occurred during observation, i.e. local tumor progression, the appearance of new lesions, and multifocal disease, we performed a survival analysis with the calculation of the actuarial probability of new events. The factors were compared with the Wilcoxon–Gehan test (in which the significance threshold is usually set at 0.10 instead of 0.05).

The maximum observation time was set to 60 months (5 years) for all patients, including those undergoing longer observation, in order to avoid problems related to weighting differences.

The Student *t*-test was used to investigate differences between the two groups in terms of the main patient characteristics.

Results

The groups of patients with and without cirrhosis were similar in terms of sex, age, type of CLD, size of the main

tumor, location of tumors, US patterns, and alpha fetoprotein levels (Table 1).

The RFA efficacy rate, defined as the percentage of treated nodules in which complete ablation was achieved, was 84.4% (174/206) in the cirrhotic group and 93% (27/29) in the non-cirrhotic group with no statistically significant difference ($p = 0.271$).

In the cirrhotic group, 239 treatments were performed on 206 nodules in 175 patients (mean, 1.16 treatments per nodule). Complete ablation was obtained in 84.4% of nodules: 169 required a single treatment session, and the remaining 5 required 2 treatment sessions. Incomplete ablation was observed after the second treatment session in 29 nodules (14%), and treatment failure was observed in the remaining 3 (1.4%).

In terms of patients rather than nodules, complete clinical responses were obtained in 150 (85.7%) of the participants with one (145 patients) or two (5 patients) treatments. Partial responses were observed in 22 others (12.5%), and failures were observed in the remaining 3 (1.7%). In 25 (16.6%) of the 150 patients with complete ablation, an ablation margin was detected on arterial phase CT.

In the non-cirrhotic group, 30 treatments were performed on 29 nodules in 25 patients (mean, 1.03 treatments per nodule). Complete ablation was obtained in 27 nodules (93%): 26 required a single treatment, and the remaining one required 2 treatment sessions, leading to 100% necrosis. No incomplete ablations or failures were recorded after the second treatment session. In 3 cases, an ablation margin was detected. At the patient level, complete clinical responses were observed in 96% of patients after 1 (23 cases) or 2 (1 case) treatments. A partial response was recorded in the 25th case, and further treatment was precluded by the development of multifocal disease.

Within the observation time, local progression occurred in 20% of the cirrhotic patients (35 cases) and 12% of those without cirrhosis (3 cases). Local tumor progression rates 1, 3, and 5 years after treatment were not significantly different in the cirrhotic (11%, 23%, and 24%, respectively) and non-cirrhotic (4%, 14%, and 14%, respectively) groups (Fig. 1). The onset of one or more new HCC lesions 1, 3, and 5 years after treatment were observed in 14%, 38%, and 52% of the patients with cirrhosis and in 4%, 33%, and 41% of those with non-cirrhotic CLD (Fig. 2).

The actuarial probability analysis revealed no statistically significant differences between the two groups of patients in terms of local progression ($p = 0.30$ Wilcoxon–Gehan test) or the onset of new lesions (up to 3 nodules) outside the margins of the primary nodule ($p = 0.55$ Wilcoxon–Gehan test) (Figs. 1 and 2).

In the non-cirrhotic group, the 3 cases of local progression were treated with RFA (2 cases) or PEI (1 case); 7 of the 8 new lesions were treated with RFA (6 cases) or surgical resection (1 case); and no treatment was possible for the remaining patient, who had multifocal liver disease with bone metastases.

The 5-year probability of developing multifocal disease was significantly lower in the non-cirrhotic group (16% vs. 41% in the cirrhotic group) ($p = 0.052$ Wilcoxon–Gehan test) (Fig. 3).

Fig. 1 Local recurrence rates for main HCC nodules in patients with cirrhosis and with non-cirrhotic CLD. Differences between the two groups were not significant ($p = 0.30$ at the Wilcoxon-Gehan test).

Actuarial survival rates after 1, 3, and 5 years were 93%, 77%, and 61% in the cirrhotic group and 92%, 72%, and 64% in patients with CLD without cirrhosis (Fig. 4).

Kaplan–Meier analysis showed no statistically significant difference between the two groups ($p = 0.85$).

During the follow-up period, 46 of the 175 patients in the cirrhotic group died. None of the deaths were related to RFA complications. Causes of death were determined in 45 cases. The most frequent causes were liver failure due to the spread of the neoplastic liver disease (26 cases, 56.5% of patients) and decompensated cirrhosis (11 patients, 23.9%). Death was related to a second primary tumor in 5 cases (1 patient with lymphoma, 1 with gastric cancer, 3 with lung

Fig. 2 Overall actuarial probability curves for new HCCs in patients with cirrhosis and with non-cirrhotic CLD. Differences between the two groups were not significant ($p = 0.55$ at the Wilcoxon-Gehan test).

Fig. 3 Overall actuarial probability curve for multifocal HCC after RFA in patients with cirrhosis and with non-cirrhotic CLD. Differences between the two groups were significant ($p = 0.052$ at the Wilcoxon–Gehan test).

cancer) and to cerebral hemorrhage in one. Two patients developed distant metastasis (to the celiac and periaortic lymph nodes in one case, to the pelvis in the other). In the remaining case, the cause of death was unknown.

In the non-cirrhotic group, 7 of the 25 patients died. Causes of death were progression of the neoplastic disease (3 cases, including one with bone metastases), myocardial infarction (1 case), acute leukemia (1 case), and were unknown in the remaining 2 cases.

In the cirrhotic group, major complications were recorded in 4 cases (2.2%). They included 1 liver abscess (treated

Fig. 4 Overall actuarial survival rates in patients with HCC associated with cirrhosis or with CLD without cirrhosis. Differences between the two groups were not significant ($p = 0.85$ at Log Rank test).

by ultrasound-guided drainage), 1 case of hemobilia with obstruction (treated with endoscopic sphincterotomy), and 2 cases of tumor seeding in the abdominal wall (detected 17 and 35 months after treatment, respectively [mean, 23 months] and surgically removed). None of the major complications had any long-term consequences. Side effects severe enough to prolong the hospital stay were recorded in 5 of the 175 (2.8%) patients. They included local skin burns (1 case), right pleural effusion (1 case), and fever due to the post-ablation syndrome (3 cases). Both in the 11 cases treated during laparoscopy and in the 3 cases treated during laparotomy no major complications or side effects were recorded in the cases treated with RFA during laparoscopy (11 cases) or laparotomy (3 cases).

In the non-cirrhotic group, there was only one major complication. It involved subcutaneous tumor seeding, which was detected 24 months after treatment and surgically removed. In the 2 cases treated during laparotomy, no major complications were recorded.

Fig. 5 (a) Hypoechoic nodule in segment VII of a non-cirrhotic liver; normal hepatic vein. (b) The same nodule after RFA.

Figs. 5 and 6 show HCC nodules in cirrhotic and non-cirrhotic livers before and after RFA.

Discussion

In patients with non-cirrhotic CLD, RFA ablation rates for primary HCCs were very high (96%) and statistically speaking, not significantly different from rates observed in cirrhotic patients (85.7%). In terms of local tumor progression, new lesion onset, and overall survival, treatment outcomes were also comparable in the two groups. However, the onset of multifocal disease was more frequent in the cirrhotic group ($p = 0.052$ Wilcoxon-Gehan test), showing that HCC onset is correlated with more advanced stages of liver disease [13].

There were no significant differences between the two groups in terms of sociodemographic features, etiology,

Fig. 6 (a) Hypoechoic nodule in segment IV of a cirrhotic liver; the left portal vein is enlarged. (b) The same nodule after RFA. The hyperechoic area is related to microbubble formation during RF ablation.

nodules size and location, and mean alpha fetoprotein levels (Table 1).

The prevalence of HCC associated with non-cirrhotic CLD without in our study population (12.5%) is comparable to that reported in a previous local case-control study [18]. Two recent Japanese reviews on RFA of HCC revealed prevalence rates of 12% and 18% [8,19]. However, outcomes in the non-cirrhotic subgroup of HCC patients were not described in either of the articles. We can assume that similar prevalence rates have been observed (albeit not reported) in studies on surgical treatment of HCC.

In a recent meta-analysis of RFA efficacy, factors related to the tumor (e.g., diameter, pathology, proximity to large vessels, subcapsular location) or to treatment (e.g., RFA electrode type and other physician-dependent factors) were considered, but the disease status of the surrounding liver tissue was not analyzed [20].

Some investigators have suggested that the presence of cirrhotic tissue enhances thermal ablation through a specific mechanism known as the "oven effect" [7,21]. The presence of thick, fibrotic tissue around the nodule is believed to insulate the lesion, preventing the dispersion of heat generated around the RFA needle electrode. In our study, however, complete ablation rates were actually higher for nodules located in non-cirrhotic livers (93% vs. 84.4% in the cirrhotic group) although this difference was not statistically significant.

At the moment, other studies of RFA of HCC in patients with CLD but no cirrhosis are not available, and the validity of current guidelines is therefore limited to HCC patients with cirrhosis. Our findings naturally need to be confirmed in larger groups of patients.

Surgical resection is the ideal treatment for HCC associated with non-cirrhotic CLD, even when the tumors are large. However, in some cases this approach may not be feasible or safe owing to the location of the nodule location or other types of comorbidity, and it may even be associated with an increased risk of mortality.

In conclusion, our findings suggest that for patients with cirrhotic or non-cirrhotic CLD, RFA may be the treatment for choice for HCC tumors less than 3.5 cm in diameter.

Conflict of interest statement

The authors have no conflict of interest.

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References

- [1] Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–36.
- [2] Bolondi L, Sofia S, Siringo S, Gaiani S, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001;48:251–99.
- [3] Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *J Hepatol* 2003;39:1076–84.
- [4] Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002;35: 519–24.
- [5] Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 2008 Jan; 47(1):82–9.
- [6] Rossi S, Buscarini E, Garbagnati F, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. *AJR Am J Roentgenol* 1998;170:1015–22.
- [7] Gazelle S, Goldberg N, Solbiati L, et al. Tumor ablation with radiofrequency energy. *Radiology* 2000;217:633–46.
- [8] Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129: 122–30.
- [9] Lin SM, Lin C-J, Lin C-C, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005;4:1151–6.
- [10] Ebara M, Okabe S, Kita K, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20 years observation. *J Hepatol* 2005;43:377–80.
- [11] Sutherland LM, Williams J, Padbury R, et al. Radiofrequency ablation of liver tumors A systematic review. *Arch Surg* 2006; 141:181–90.
- [12] Lu DSK, Yu NC, Raman SS, Lassman C, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005;41:1130–7.
- [13] Takano S, Yokosuka O, Imazeki F, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995;21:650–5.
- [14] Otto G, Heuschen U, Hofman WJ, et al. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. *Ann Surg* 1998;227:424–32.
- [15] Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994;19:1513–20.
- [16] Leevy CM, Sherlock S, Tygstrup N, Zetterman R, editors. Diseases of the liver and biliary tract. Standardization of nomenclature, diagnostic criteria and prognosis. New York: Raven Press; 1994. p. 61–2.
- [17] Salmi A, Turrini R, Lanzani G, et al. Long-term effectiveness of radiofrequency ablation for hepatocellular carcinoma of 3.5 cm or less. *Hepatogastroenterology* 2008;55:191–6.
- [18] Chiesa R, Donato F, Tagger A, et al. Etiology of hepatocellular carcinoma in Italian patients with and without cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2000;9(2):213–6.
- [19] Hong SN, Lee SY, Choi MS, et al. Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well preserved liver function. *J Clin Gastroenterol* 2005;39:247–52.
- [20] Mulier S, Ni Y, Jamart J, Ruers T, et al. Local recurrence after hepatic radiofrequency coagulation. Multivariate meta-analysis and review of contributing factors. *Ann Surg* 2005;242: 158–71.
- [21] Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 2000;210:655–61.