Hepatocellular Carcinoma Invading Portal Venous System in Cirrhosis: Long-term Results of Percutaneous Radiofrequency Ablation of both the Nodule and Portal Vein Tumor Thrombus. A Case Control Study

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Abstract. *Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death. Portal vein tumor thrombus (PVTT) is one of the most dreadful complications of HCC and is associated with a median survival time of 2.7-4.0 months. The optimal treatment for HCC with PVTT has not yet been established. The aim of the present study was to report long-term results of percutaneous radiofrequency (RF) ablation of both HCC single nodule (up to 5 cm in diameter) and neoplastic main portal vein thrombus, compared to no-treatment. Patients and Methods: From January 2005 to January 2010, out of 2,847 consecutive cirrhosis patients, 672 had HCC and main portal vein tumor thrombus (MPVTT); among these, 57 had a single HCC with MPVTT. Thirty-five patients with 35 single HCC nodules (ranging from 3.7 to 5 cm in diameter) underwent percutaneous RF ablation of both the nodule and the thrombus (cases); 22 patients refused RF ablation or any other treatment (controls). Results: A complete necrosis of HCC nodules associated with re-canalization of main portal trunk (MPT) and its branches were observed in 26 patients (success rate=74%). The 1-, 3- and 5-year cumulative survival rates of patients were 63%, 30% and 20%, respectively. The 12-month cumulative survival rate of controls was 0% (p<0.0001). The difference was statistically significant (p<0.001; harzard ratio (HR)=2.88; 95% confidence interval (CI)=1.57-5.39). The 3- and 5-year cumulative disease-free survival rates of the patients were 35% and 22%, respectively. No deaths occurred. Conclusion: RF ablation of HCC and the accompanying MPVTT significantly prolongs long-term survival compared to no-treatment. The procedure is safe and should be considered as a new and effective tool in the treatment of advanced HCC.*

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide (1). It is by far the commonest sub-type of primary liver cancer and represents the second and the seventh most frequent cause of death from cancer in men and women, respectively (1). HCC arises in the setting of liver cirrhosis in 70-85% of cases and predominates among patients with chronic hepatitis B virus or hepatitis C virus infections (1, 2). HCC has a high predilection for portal vein invasion and this is found in 12.5%-39.7% of living patients with HCC and 64.7% of cases at autopsy (3, 4). Portal vein tumor thrombus (PVTT) is one of the most dreadful complications of HCC and is associated with a median survival time of 2.7-4.0 months in untreated cases (3). The optimal treatment for HCC with PVTT has not yet been established. Several treatment strategies have been attempted, including hepatic resection, trans-catheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) and, more recently, liver transplantation followed by systemic chemotherapy with sorafenib; however, the prognosis of HCC complicated by PVTT remains poor at present (5). In 2009 a new technique based on percutaneous radiofrequency (RF) ablation of both the HCC

single nodule (3-5 cm) and the intra-portal tumoral extension was described and was named "Percutaneous RF Thrombectomy" (6). Results of this case-control study after the first 3 years of experience were extremely encouraging, with a 3-year cumulative survival rate of 77% among treated patients and 0% among untreated controls (6).

The aim of the present study is to report long-term results of percutaneous RF ablation of both HCC intra-parenchymal single-nodule (up to 5 cm in diameter) and neoplastic main portal vein thrombus compared with no treatment.

Patients and Methods

Patients. This study was reviewed and approved by the Ethics Committee of our Institution. From January 2005 to January 2010, a consecutive series of 2,847 patients with HCC on liver cirrhosis were referred to the Interventional Ultrasound (US) Units of our Institutions for percutaneous ablation of a single or multiple HCC nodules under US guidance. Evidence of PVTT was found in 672 out of 2847 (23.6 %) patients. Of the 672 patients with PVTT, 615 (91.6%) were not considered for Percutaneous RF Thrombectomy due to either multiple nodules, a nodule diameter >5 cm, ascites or low hepatic functional reserve (Child-Pugh class >B7) and, therefore, were excluded from the study. The remaining 57 (8.4 %) were included. All included patients had a single HCC nodule up to 5 cm in diameter associated to tumoral invasion of the right or left branch of the portal vein and main portal trunk (MPT). Most (73.7%) of them were males; all had compensated liver disease (Child-Pugh class A or maximum B7). Cirrhosis was related to chronic HBV infection in 12 patients (21%) and to chronic HCV infection in the remaining 45 patients (79%). None of the included patients had received any treatment for the HCC nodule or the PVTT prior to being referred to our Unit. All patients diagnosed using US, were further studied with contrast-enhanced US, computed tomography (CT) or magnetic resonance imaging (MRI). Four HCC nodules were diagnosed by fine needle biopsy (FNB) under US guidance. In the remaining 53 cases, diagnosis was made on the basis of the alpha-fetoprotein (AFP) level and the contrast-enhanced US, CT or MRI appearance. However, the neoplastic nature of the portal vein thrombosis was confirmed histologically in all patients by FNB under sonographic guidance, using a 21-gauge needle (Ecoject, Tokio, Japan).

All study patients were offered percutaneous RF ablation of both the HCC nodule and the PVTT or, alternatively, TACE, hepatectomy-plus-TACE or systemic chemotherapy. The benefits and risks of each of the options were thoroughly discussed and informed consent was obtained for all treatment decisions.

Thirty-five patients with 35 single HCC nodules (ranging from 3.7 to 5 cm in diameter) and tumoral extension into the main portal vein (MPV) trunk accepted to undergo percutaneous RF ablation of both the nodule and the thrombus (group A, "cases"); the remaining 22 patients refused RF ablation or any other treatment (group B, "controls"). Table I reports the main clinical features of our series. Table II reports the tumor characteristics and extension of portal vein involvement. No significant differences between the two groups were found.

Procedure. The same operator, with more than 30 years of experience in interventional US, performed all RF ablations of both the intra-hepatic nodules and the portal thrombus under general anesthesia, using a perfused electrode needle (HiTT, Integra, city, county, USA), of 1.7- or 2.0-mm based on the diameter of the thrombus, below or above 2 cm, as described elsewhere (6). A 2-cm active needle tip was used when the diameter of the MPV tumor thrombus was greater than 2 cm. A 1-cm active needle tip was used when the diameter of the tumor thrombus in the MPV was less than 2 cm. For radiofrequency ablation of intra-parenchymal HCC nodules, a 2-mm-caliber perfused needle electrode with a 3 cm active needle tip was used in all instances.

The thrombus in the MPV was ablated first, followed by the thrombus in the right or left portal branch when present and the intra-parenchymal HCC nodule. The electrode needle was inserted percutaneously coaxial to the MPV and was passed through the whole thrombus. The needle tip was advanced until the posterior wall of MPV. When the length of neoplastic thrombus in the MPV exceeded 2 cm (7 patients), two needle electrodes were inserted in the thrombus, the first in the distal part of the MPV and the second in the proximal portion, leaving the needle in the liver in place.

Care was taken to avoid the hepatic artery and common bile duct during percutaneous insertion of the needle electrode in the main portal trunk. Color Doppler ultrasound was used to aid in identification of the hepatic artery. After inserting the needles the power generator was switched on. In cases of a second needle inserted in the thrombus, the generator remained on, leaving the liver electrode needle in place, until the second radiofrequency shock was delivered. Time for each application ranged from 10 to 15 min.

When the MPV appeared completely hyperechoic the procedure was considered to be completed and the electrode needle was withdrawn from the MPV thrombus, leaving the radiofrequency generator still in function. The time for the entire procedure (main portal trunk, right or left branch of the portal vein and the HCC nodule) was up to 45 minutes.

The procedure was considered to be successful when a complete re-canalization of MPV and both right and left branch and a complete necrosis of the HCC nodules were achieved. Re-canalization of the portal system was evaluated by color Doppler and contrast-enhanced ultrasound (CEUS). Necrosis of HCC nodules was confirmed by CEUS and contrast-enhanced CT.

Follow-up. All patients were closely monitored after the procedure. Color Doppler and CEUS examinations were both performed on the first day. Abdominal US and portal color Doppler were performed every week during the first 4 weeks. Contrast enhanced CT and CEUS were added at one month to assess patency of the MPV and its branches and to confirm necrosis of the HCC nodule and were repeated every six months. Laboratory tests, including AFP and abdominal US and color Doppler, were scheduled every two months. Untreated patients (Group B) received monthly clinical and laboratory assessment (including AFP) and US and color Doppler investigation.

Statistical analysis. The student's *t*-test for quantitative data and a Chi-square test for categorical data were used to compare baseline characteristics of the two groups of patients. Probability of survival was estimated by the Kaplan-Meier method and the difference was determined with the log-rank test. Overall survival was calculated by the time from the date of RF ablation (treated group) or date of diagnosis (untreated group) to the last follow-up examination for surviving patients or the day of exitus for fatal cases. Results were presented as hazard ratios (HR) with corresponding 95% confidence interval (CI) and p. Data processing and analysis were performed with the SAS software (version 8.2, SAS Institute, address).

Results

A complete necrosis of HCC nodules associated with complete recanalization of MPT and its branches was observed in 26 treated patients (success rate, 74%). Complete recanalization at color Doppler examination was recorded on the day after the procedure in 2 patients, after 1 week in 8 patients and after 1 month in 16 patients.

Complete necrosis of HCC nodules was achieved in 6 out of 14 patients receiving a single radiofrequency session, in 8 after two radiofrequency sessions and in 4 after three radiofrequency sessions. In all successful cases, recanalization of the MPV and its branches was always associated with a complete necrosis of the neoplastic intra-parenchymal nodule.

Among the 9 unsuccessful cases (26%), contrast-enhanced CT demonstrated an incomplete necrosis of HCC nodules (ranging from 70% to 90%) and incomplete recanalization of the MPV. No deaths were recorded after RF ablation procedures. No injuries to biliary tree were observed. Major complications were: one self-limited haemoperitoneum, mild ascites in 7 patients and transient increase of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in 9 patients. All these complications resolved within a week.

The follow-up period ranged from 8 to 60 months for the treated group and 2 to 10 months for the untreated group. Figure 1 shows the cumulative survival curves of the treated group compared to the untreated group. The 1-, 3- and 5-year cumulative survival rates of treated patients were 63%, 30% and 20%, respectively. The 12-month cumulative survival rate of untreated patients was 0% ($p<0.001$). The difference was statistically significant ($p<0.001$; HR=2.88; 95% CI=1.57–5.39). The 3- and 5-year cumulative disease-free survival rates of the treated patients were 35% and 22%, respectively (Figure 2). The mean survival time of treated patients was 28.3±3.8 (standard error) months and the mean survival time of untreated patients was 6.8 ± 0.5 months ($p<0.001$).

During the follow-up period, 17 patients in the treated group had one or more (up to three -1.4-3 cm in diameter) distant hepatic recurrences. These patients received a new RF ablation procedure and complete necrosis of the new nodules was observed with contrast-enhanced CT and CEUS in 74% of cases 1 month later. Eight patients showed only one distant recurrence and underwent a new RF ablation with complete necrosis in 65% of the cases. The remaining patients presented with a multi-nodular disease (>5 new nodules and/or segmental or multi-segmental portal venous neoplastic involvement) and underwent only supportive therapy.

All unsuccessfully-treated patients died within 5 months after the procedure. Infiltrative right lobe neoplastic disease developed in 4 of them and 5 patients had multiple nodules of HCC.

Table I. *Baseline patients' charachteristics.*

	Treated	Untreated
Number of patients	35	22
Age (years)	71±5	73±3
Sex (males)	22	15
Child-pugh		
A6	28	17
B7	7	5
HVB	7	5
HCV	28	17
Baseline clinical and laboratory variables		
Albumin (g/dl)	3.41±0.92	3.37±0.81
Bilirubin (mg/dl)	0.87±0.29	0.85±0.47
INR	1.02±0.3	1.05±0.14
Platelets (×1000/mm^3)	114.06±8.32	116.50±10.29
Alfa-fetoprotein mg/ml	78.84±91.61	78.46±1
Ascites%	0	0

HBV, Hepatitis B virus; HCV, hepatitis C virus.

Table II. *Baseline HCC charachteristics.*

	Treated	Untreated
Number of patients	35	22
HCC nodules	35	22
Diameter (cm)	4.2±0.6	4.3±0.4
Range of tumor diameter (cm)	3.7-5.0	3.6-5.0
Range of length of main PVTT from bifurcation (cm)	1.5-3.5	1.2-3.4
Range of diameter of main PVTT (cm)	1.5-2.2	1.4-2.1

HCC, Hepatocellular carcinoma; PVTT, portal vein tumor thrombus.

In the untreated group, 12 patients died of diffuse HCC and variceal bleeding, 7 patients died of diffuse HCC and hepatorenal syndrome and 3 of diffuse HCC and haemoperitoneum.

The cause of death in the treated patients was mesenteric thrombosis in 1 patient, decompensation of liver cirrhosis in 9 patients, multi-centric HCC recurrence with jaundice and spontaneous bacterial peritonitis in 15 patients and haemoperitoneum in 3 patients.

Discussion

Percutaneous RF ablation of both intra-parenchymal nodules and invading thrombus of MPV and its branches in cirrhotic patients with advanced HCC appears to improve the 5-year survival rate compared to no-treatment. These results confirm previous data about three-year cumulative survival rate (6).

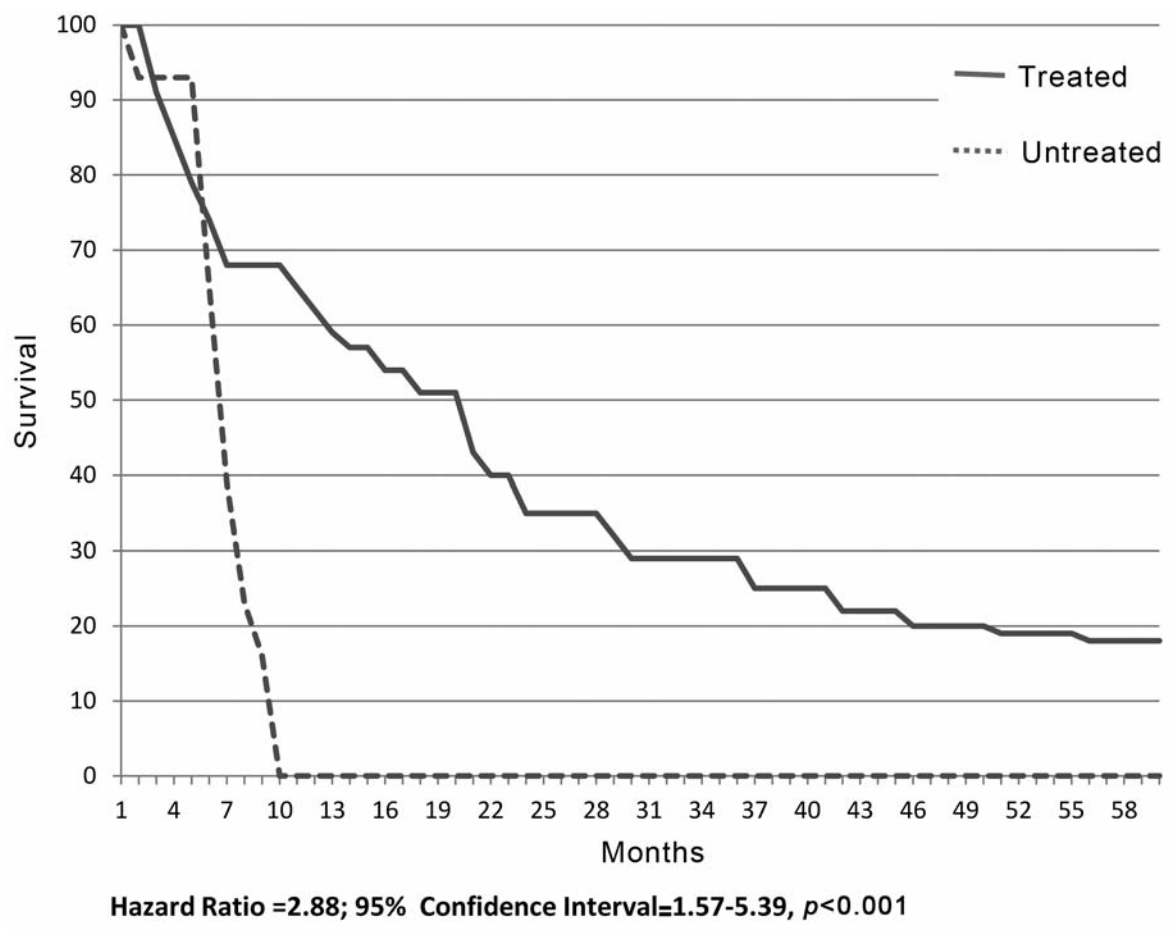

Figure 1. *Cumulative survival curves of the treated group compared with the untreated group.*

Our results obviously need to be compared with other HCC treatments, such as anti-angiogenetic treatment with oral sorafenib, chemoembolizzation, surgical removal of neoplastic trombus in MPV and Yttrium radioembolization. This comparison, however, appears to be quite difficult not in a setting of a randomized controlled trial including some of these therapeutic options.

At the time we started the present study, oral sorafenib was not yet available in our country. Moreover, the results that are available to date about the survival rate after oral sorafenib do not yet reach five years (7).

To our knowledge, the only published study reporting an approach to a cirrhotic patient population with HCC invading portal venous system that is similar to ours was conducted by Hirooka and coworkers (8). They used RF ablation for the treatment of intraparenchymal HCC nodules with coexisting invasion of the main portal vein trunk. In their study, RF ablation was associated to chemoembolization as a second step. The 2-year survival reported by Hirooka and colleagues appears to be far lower to that found in our cohort. However, these results could be due to the larger average size of the HCC nodules in their study. Finally, no long-term results are at the moment available from their series (8).

In our experience, RF ablation of PVTT offers better results compared to surgery. In a recent work by Chen *et al*., the clinical data and surgical outcomes of 88 HCC patients with PVTT and 211 patients without PVTT who underwent surgery were retrospectively reviewed (9). The median overall survival rate of HCC patients with PVTT after surgery was 9 months, with the 1-, 2- and 3-year overall survival rates being 31.1%, 18.3% and 15.2 %, respectively (9).

In another study, Shi *et al*. described their experience with 406 patients with HCC and PVTT who underwent partial hepatectomy (10). The complication rates and hospital mortality rates were 32.8% and 0.2%, respectively. After a median follow-up of 6.4 months, 128 patients (31.5%) died. The 1- and 3-year overall survival rates were 34.4% and 13.0%, respectively. Patients with PVTT located in the segmental, sectorial or right

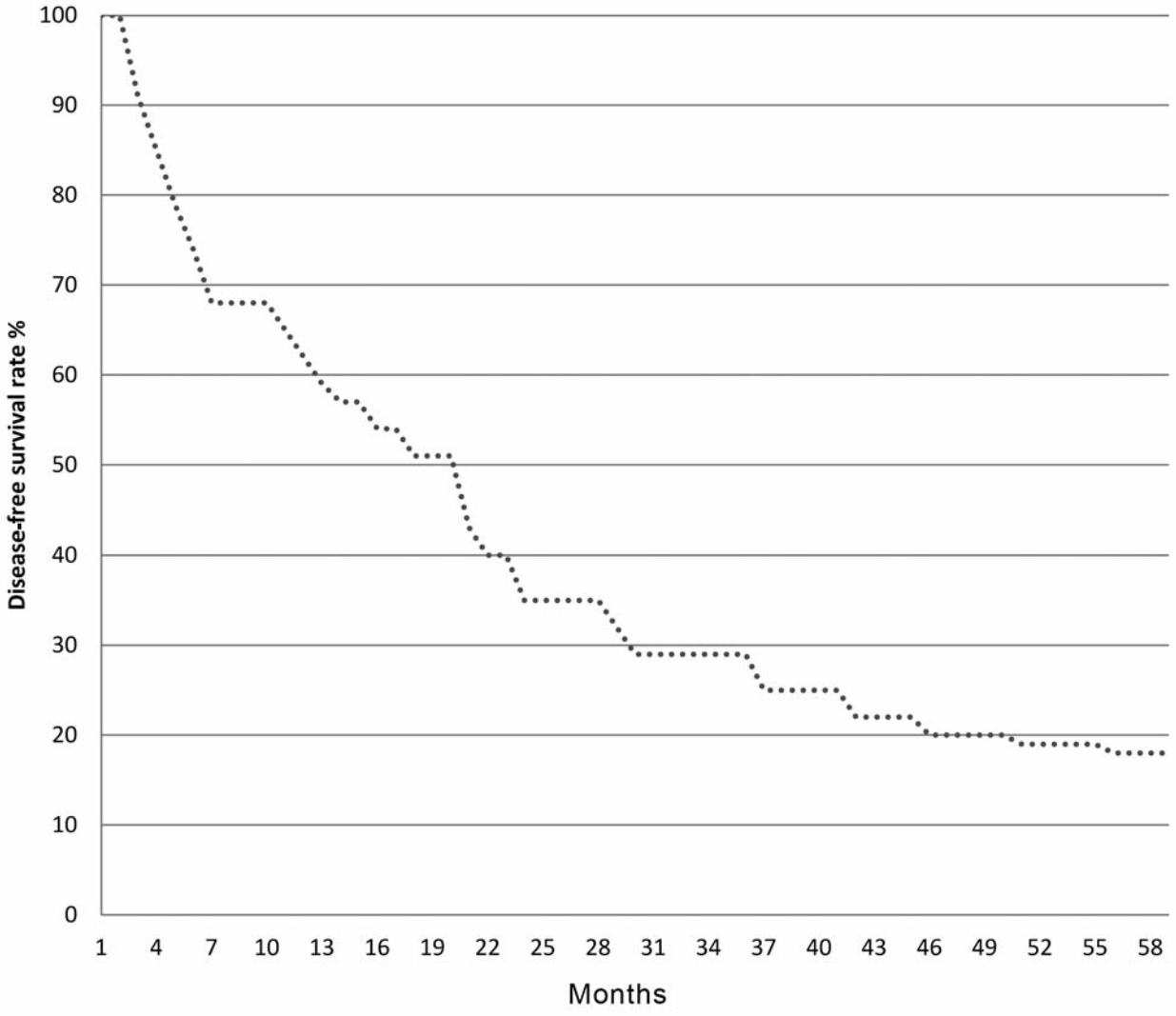

Figure 2. *The 3- and 5-year cumulative disease-free survival rates of treated patients.*

and/or left portal veins showed significantly better survival than those with PVTT extended to the main trunk of the portal vein or the superior mesenteric vein (10).

Inoue *et al*. described a surgical technique in which the PVTT was dissected from the portal venous wall and removed through the opening (PO) (N=20) (11). This procedure was compared with the en bloc resection of PVTT (N=29). No deaths occurred in either group. Both the 5-year overall survival and the recurrence-free survival rates of the PO group were comparable with those of the en bloc group (39% *vs*. 41% (p=0.90) and 23% *vs*. 18% (p=0.89), respectively). No local recurrences or re-growth of the PVTT occurred in either group (11).

Chen *et al*., on the other hand, reported that liver resection with thrombectomy yielded better outcomes in HCC patients with PVTT confined to the first or second branch of the main portal vein compared with PVTT extending into the main portal vein (12).

Memo *et al*. reported their experience with radio embolization for HCC with portal vein thrombosis and studied the impact of liver function on systemic treatment options at disease progression (13). They studied 63 patients with HCC and PVT and Child-Pugh (CP) score ≤7. Median survival and TTP were 13.8 and 5.6 months in CP-A and 6.5 and 4.9 months in CP-B7 patients, respectively. Out of the 29 CP-A patients who progressed, 45% maintained their CP status at progression (55% decompensated to CP-B). Out of the 15 CP-B7 patients who progressed, 20% improved to CP-A, 20% maintained their CP score and 60% decompensated (13).

Recently, the use of Yttrium-90 radioembolization for the treatment for advanced HCC accompanied by PVTT was introduced. In the study by Mazzaferro et al 58 treatments were performed on 52 patients (14). Median follow-up was 36 months. Median TTP was 11 months with no significant difference between portal vein thrombosis (PVT) *versus* no-PVT (7 *vs*. 13 months). Median survival was 15 months (95% CI 12-18) with a non-significant trend in favor of non-PVT *vs*. PVT patients (18 *vs*. 13 months). Five complete responses occurred (9.6%) and the 2-year progression rate was 62% (14).

Tsai *et al*. conducted a retrospective review of HCC with main (N=10) or first-branch (N=12) PVT treated with (90) yttrium microspheres (N=22) (15). Median survival for patients with cancer of the liver Italian program (CLIP) scores of 2/3 was 7 months *versus* 1.3 months for those with scores of 4/5 (p=0.04) (14). Although it is evident that it is difficult to compare the outcome of our treated patients with that reported after Yttrium-90 radioembolization, our results appear to be more encouraging.

We believe that a comparison between our results and those of surgery should be performed in order to find the best PVTT treatment and prolong HCC patients' survival rate.

Based on the results of this study, our approach to HCC nodules and portal extension seems to gain ground for adoption by other Centers too. In this hypothesis, it should be underlined that a hospital-based experienced operator with interventional US experience would be required in order to guarantee all the therapeutic steps of this percutaneous approach on the PVTT. Moreover, in future perspective, randomized clinical studies combining RF ablation of PVTT and sorafenib may be needed.

Conclusion

In conclusion, percutaneous RF ablation of both single intra-parenchymal medium-size HCC with MPV neoplastic thrombosis significantly prolongs survival of cirrhotic patients.

Compared to surgery, our proposed approach offers a lower invasive alternative treatment with a minimal rate of major complications and should be considered as a new and effective therapeutic option for advanced HCC.

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