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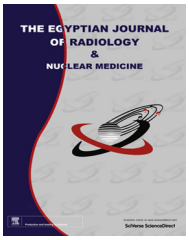

ORIGINAL ARTICLE

Impact of thrombocytopenia on radiofrequency ablation therapy of hepatocellular carcinoma in patients with liver cirrhosis

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KEYWORDS

Radio frequency ablation;
Heaptocellular carcinoma;
Thrombocytopenia

Abstract *Objective:* The objective of our study was to assess the impact of thrombocytopenia on percutaneous radiofrequency ablation (RFA) therapy of Hepatocellular carcinoma (HCC) in patients with liver cirrhosis.
Material and methods: We analyzed retrospectively 64 patients with liver cirrhosis and thrombocytopenia, defined as a platelet count of less than $100 \times 10^3/mm^3$ that had undergone percutaneous RFA to treat 86 HCCs. The Kaplan–Meier and Cox regression methods were used to predict hemorrhage, and time to the first decompensation event, defined as the development of ascites, hepatic encephalopathy, variceal hemorrhage, and deterioration of liver function to Child-Pugh class B/C.
Results: There were no significant risk factors of hemorrhage. Univariate and multivariate analyses revealed that liver decompensation was clearly linked to prothrombin activity ($p = 0.010$ and $p = 0.006$, respectively) and a $\leqslant 63\%$ of prothrombin activity was found as significant threshold for the occurrence of liver decompensation ($p = 0.003$) confirmed by the Cox model ($p = 0.05$).
Conclusion: Percutaneous RFA for HCC can be performed safely without the need for support, in patients with liver cirrhosis and thrombocytopenia up to $37 \times 10^3/mm^3$.

1. Introduction

Hepatocellular carcinoma (HCC) is now treated with invasive therapies, such as resection and, minimally invasive therapies as radiofrequency ablation (RFA) (1). In either case, thrombocytopenia as the most essential abnormality in hypersplenism with liver cirrhosis seems to adversely affect patient's tolerance of these HCC treatments (2).

RFA has been accepted as a safe and effective technique, for the treatment of an unresectable HCC. An advantage of the use of RFA includes low mortality (0–0.5%), morbidity,

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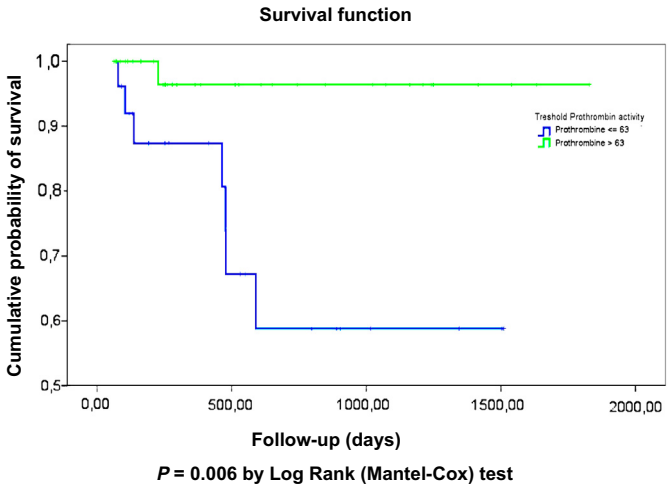

Fig. 1 Kaplan–Meier survival curves by risk score: the difference in survival between these two risk groups was significant ($P = 006$). The estimated prothrombin group > 63% (38 patients) and prothrombin group ⩽ 63 (26 patients) survival rates were 97.4% (95% confidence interval: 16–18) and 73.1% (95% confidence interval: 13–77), respectively.

and repeatability in recurrent lesions. This therapeutic method, has largely replaced surgical resection for the treatment of patients with small (< 3 cm) HCCs, and poor hepatic reserve, because of underlying liver cirrhosis (3).

However, the real incidence of thrombocytopenia-related limitation for RFA of HCC treatment is unclear. In several institutions, HCC patients with severe thrombocytopenia received platelet transfusion or splenectomy to improve their thrombocytopenic status. These measurements may be available in some institutions than that in other general institutions especially that have no designated oncology center specializing in HCC (4).

In Egypt, we have a relatively high proportion of severe end stage patients desiring intensive care, and a small number of specialized hospitals in the treatment of HCC. Although splenectomy and arterial splenic embolization are efficient methods for treating HCC patients with severe thrombocytopenia, these treatment options are not always available for patients with advanced cirrhosis. Thus, severe thrombocytopenia is still a major unresolved issue affecting HCC treatment, and eltrombopag, a thrombopoietin-receptor agonist, is expected to improve HCC treatment (2).

The absolute value of the platelet count in liver cirrhosis may not be crucial in determining the risk of bleeding, as it is well recognized that even those patients with normal prothrombin times and platelet counts can have severely deranged bleeding times (5). Nevertheless, for a percutaneous RFA of HCC in the patient with liver cirrhosis, the platelet count was felt to be safe without the need for support, in need for identification.

The effect on bleeding of thrombocytopenia due to hypersplenism resulting from liver cirrhosis following RFA of HCC has, to our knowledge, not been studied in detail.

The purpose of this study was to assess whether percutaneous RFA for HCC is a safe procedure in patients with liver cirrhosis and thrombocytopenia, and try to reach the minimum platelet count felt to be safe without the need for support.

2. Patients and methods

2.1. Study design

In accordance with a protocol approval by our institutional review board, radiology reports, laboratory and medical records were retrospectively reviewed in all patients with HCCs, who initially managed by percutaneous RFA. From June 2008 through September 2011, among HCCs, 256 patients were treated with RFA in our center, we identified 64 with cirrhosis and thrombocytopenia as reflected by a platelet count of 37–$99 \times 10^3/mm^3$. Statistical analysis was performed for factors suggested to contribute to bleeding or liver decompensation.

2.2. Selection criteria for RFA procedures

In our department, the decision of treatment is individualized for each patient by a medico-surgical staff after staging the disease. Selection criteria for RFA of the HCC were (i) tumor size less than 5 cm in diameter, (ii) no portal or segmental invasion adjacent to the tumor, (iii) less than four concomitant tumors in the whole liver, and (iv) contraindications to resection as first-line treatment. Patients were not eligible for RF treatment in cases of extra hepatic metastasis, severe liver dysfunction (Child-Pugh class C), or significantly abnormal coagulation test results with prothrombin activity < 40% and platelet count < $30 \times 10^3/mm^3$.

2.3. Pretreatment work-up

Pre-treatment work-up included gray-scale and color Doppler ultrasound (US) examination, by using 3.5-MHz probes with (SONOLINE G20 Ultrasound, Germany), as well as non enhanced and dual-phase contrast material–enhanced computed tomography (CT) using Multislice CT unit, a GE Light Speed Ultra (General Electric Healthcare, Milwaukee). The first non-enhanced scanning over the entire liver with 8-mm collimation, a pitch of 1.5, and reconstructions every 8 mm was followed by

two contrast material–enhanced passes with 5-mm collimation, a pitch of 1.5, and reconstructions every 5 mm for 20 s during the arterial phase and for 60 s during the portal venous phase of the intravenous injection of iodinated contrast medium. A 170-mL volume of the contrast medium (iohexol, Omnipaque [300 mg of iodine per milliliter]; Amersham, Cork, Ireland) was systematically injected, at a rate of 5 mL/min, through an 18-gauge catheter inserted into a forearm vein.

All patients underwent the following laboratory tests before RFA: Complete blood count, serum aspartate aminotransferase, serum alanine aminotransferase, serum total bilirubin, serum albumin, blood urea nitrogen, serum creatinine, prothrombin time, hepatitis B surface antigen and hepatitis C antibody, and serum levels of alpha-fetoprotein. All laboratory tests were performed within 48 h before RFA procedure.

2.4. RFA procedure

RFA was performed with a percutaneous approach by using 3.5-MHz probes for real-time US guidance with (SONOLINE G20 Ultrasound, Germany). All procedures were performed in the operative suite under strictly aseptic conditions, by one author, who had 7 years of experience in performing US-guided interventional procedures. As the safety and efficacy of the procedure depended on the patient being absolutely still during puncture and treatment, general anesthesia with tracheal intubation and assisted ventilation was used. The anesthetic protocol was 0.1–2 μg/kg intravenous injections of sufentanil (Sufenta; Janssen-Cilag, Issy-les-Moulineaux, France), 1.5–2.5 mg/kg of propofol (Diprivan; AstraZeneca, Rueil-Malmaison, France). For percutaneous RFA, patients were treated using the RITA 1500 generator (RITA Medical Systems Inc., Mountain View, CA, USA). This system consists of a generator that supplied up to 150 W of power and a multitined expandable electrode (StarBurst XL, RITA). The multitined expandable electrode consisted of a 15-gauge insulated cannula, 15–25 cm in length that contains nine individual electrode tines deployed in situ after ultrasound-guided placement of the needle electrode into the liver tumor. Depending on tumor size, shape, and location, a defined treatment strategy was adopted that consisted of a mathematical protocol, an individualized protocol, and adjunctive measures. The strategy to achieve complete necrosis of the tumor was to ablate a peripheral margin of 0.5–1 cm of normal hepatic tissue surrounding the tumor as well as the entire tumor itself so; multiple overlapping ablation techniques were used whenever necessary according to the volume of the tumor and to the spread of hyperechogenic area induced by RF energy deposition during the procedure.

2.5. Post treatment assessment and follow-up

All patients were outpatients before the procedure, and admitted two hours before the procedure. After RFA, the patients underwent close medical observation, 1–2 h to detect any bleeding in the liver or the peritoneal cavity. All patients stayed in the hospital overnight, and any adverse event was evaluated and recorded. Patients were discharged from the hospital, and were followed at the outpatient clinic with physical examination and laboratory tests at one week, one month, and then three-month intervals thereafter. All follow-up images included CT imaging of the abdomen before and after the intravenous administration of contrast. Response to treatment was assessed one month after ablation by the same CT scan technique previously described. The ablation was considered as complete on the basis of all of the following findings: (a) no contrast enhancement was detected within or around the tumor, (b) the margins of the ablation zone were clear and smooth, and (c) the ablation zone extended beyond the tumor borders (14). Follow-up of patients was updated consulting a prospective data base.

2.6. Study endpoints and definitions

Complications were defined as immediate ($\leqslant$24 h after the procedure), periprocedural (within 30 days), delayed (after 30 days) and minor or major according to the recommendations of The Working Group on Image-Guided Tumor Ablation (6). Bleeding complications were classified as major (any hemodynamically significant or life-threatening hemorrhage) or minor (superficial hematoma, either visible or palpable, or superficial oozing from the puncture site but without hemodynamic consequence). Because the natural courses of cirrhosis direct usually toward the liver decompensation, we selected the end point 30 days within the start time of the procedure, during which the appearance of at least one episode of ascites, jaundice, encephalopathy, or variceal bleeding was considered to be related to RFA (6). More than 30 days after ablation, other events might further compromise the liver functional reserve and confound the results. A per ablative death was defined as death in hospital or within 30 days in the case of patients discharged from hospital (6).

The observation end point for tumor progression was either, (1) local, defined as re-appearance of any focal or nodular peripheral enhancement in the ablated lesion, or (2) distal which was recognized when new nodules at other sites of the liver showing contrast enhancement during CT-arterial phase (7).

2.7. Statistical analysis

The risk factors for bleeding or liver decompensation after RFA included (i) patient factors such as age, gender, Child-Pugh classification, etiology of cirrhosis, blood platelet count, and prothrombin time; (ii) tumor factors such as, maximum tumor size and number of tumor nodules, and (iii) RF technical factors such as type of electrode. The variables found significant by univariate analysis were further analyzed by multivariate analysis using the Cox proportional hazard regression model. All P values were two-sided and the significant level was <0.5.

3. Results

3.1. Treatment outcome

RFA was successful in 57 (89.1%) patients and 7 (10.9%) patients had residual unablated tumor in the ablation zone. Four patients underwent a successful second RFA procedure (with the same RFA device) and the remaining three patients could not complete the treatment because one patient had extra hepatic metastasis, and the other two patients developed severe hepatic decompensation. The post-treatment follow-up varied

approximately from 2 to 70 months (mean: 19 ± 2); during follow-up, local tumor progression developed in nine patients (14.1%), distant tumor progression observed in 6 (9.4%) patients, and both local and distant tumor progressions developed in 7 (9.94%) patients.

3.2. Complications

No patients were excluded from analysis owing to ablation mortality or being lost to follow-up. Each category of risk factors related to patient demo-graphics, lesions, and the electrode are shown in Table 1, and overall complications including bleeding and liver failure are shown in Table 2. Hemorrhage occurred in 2 of 64 patients (3.1%). The cause of hemorrhage in both patients was sub capsular hematoma that was discovered by an US examination after the disabling pain persisted more than 3 days after the RFA procedure. The first patient (1.6%), was Child Pugh A, and had a 3.3-cm subcapsular HCC located in segment 3. After RFA procedure a 1–3 cm hematoma in front of the ablation zone developed and resolved conservatively within 4 weeks. The second patient, was Child-Pugh B, and had two HCCs measuring 2 cm and 4 cm and located at segments 7 and 3, respectively. The hematoma was 2 × 3 cm and resolved spontaneously within 4 weeks. No need for blood transfusion or drainage of both patients.

Univariate analysis revealed no significant variable contributor to the risk of hemorrhage. There was a tendency for hemorrhage with Child-Pugh class; the incidence of hemorrhage for Child-Pugh A, was 1.8% (1 of 57); the incidence for Child-Pugh B was 14.3% (1 of 7), but the difference was not statistically significant (χ^2 test; $p = 0.072$). Platelet count and prothrombin activity did not significantly affect the occurrence of hemorrhage ($p = 0.819$, and $p = 0.348$, respectively).

Hepatic decompensation defined as development of ascites, hepatic encephalopathy, variceal hemorrhage, and deterioration of liver function to Child-Pugh class B/C, developed in 8 of 64 patients (12.5%) along the course of follow-up. We recorded a case of encephalopathy developed immediately (1.6%), this case had 4 HCCs totally measuring 6 cm, and the remaining seven (10.9%) patients had it periprocedural; two patients had variceal bleeding and five patients had ascites. All ascites were mild to moderate, and there was no need for intervention.

Table 3, shows the existence of clearly significant links, between liver decompensation and the prothrombin activity (%) ($p = 0.017$). Other factors such as, age, sex, etiology of cirrhosis, Child-Pugh class, blood platelet count, maximum tumor size, number of tumor nodules and type of electrode did not have a relationship with liver decompensation.

Table 1 Patient characteristics ($n = 64$).

Category	Mean (range) (%)
Age (y)	62 (35–83)
Male sex	49 (76%)
Platelet count	76 (37–99) × 10^3/mm^3
Prothrombin activity (%)	66 (42–100)
Etiology of cirrhosis	
HCV	35 (54.7%)
HBV	3 (4.7%)
B/C	2(3.1%)
Alcohol	21 (32.8%)
Metabolic	3 (4.7%)
Child-Pugh class	
A	57 (89.1%)
B	7 (10.9%)
Number of tumor nodules	
1	47 (73.4%)
2	13 (20.3%)
3	3 (4.7)
4	1 (1.6%)
Mean tumor size (mm)	26 (10–60)

Note—Values in parentheses are percentages (%), or range.

Table 2 Overview of complications including bleeding and liver decompensation.

Types of complications	Frequency	Bleeding	Liver decompensation
	21	2	8
Immediate complication	2	1	1
Encephalopathy	1	–	1
*Hematoma and right pleural effusion	1	1	–
Peri procedural complication	14	1	7
Spleen infarction	3	–	–
Septicemia	1	–	–
Ascites	4	–	4
Sub capsular hematoma	1	1	–
*Ascites and portal thrombosis	1	–	1
Portal vein thrombosis	1	–	–
Right pleural effusion	1	–	–
Variceal bleeding	2	–	2
Delayed complication	5	0	0
Ascites	–	–	–
Hepatic aneurysm	1	–	–
Biliary stricture	3	–	–
Arterio-portal fistula	1	–	–

* One patient developed immediate and periprocedural complication.

3.3. Analysis of interaction between significant variables

Factors found significant in contributing to risk of liver decompensation after univariate analysis were evaluated for possible association and interaction. Significance attached to prothrombin, ($p = 0.006$) was confirmed, taking into account strengthens its intensity. The use of a regression tree made us able to put a significant threshold: prothrombin = 63%; $p = 0.003$. The simultaneous introduction in a Cox model revealed that in a more limiting way the calculated threshold of prothrombin ($p = 0.053$), was a predictive factor for liver decompensation. In Figure 1, Kaplan–Meier survival curves by risk score revealed significant difference in survival between these two risk groups. The estimated prothrombin group > 63% (38 patients) and prothrombin group ⩽ 63 (26 patients) survival rates were 97.4% (95% confidence interval:

Table 3 Relationship between variables and bleeding/hepatic decompensation in 64 sessions of RFA therapy according to univariate and Cox regression.

	Bleeding		*P* value	Liver decompensation		*P* value
	No ($n = 62$)	Yes ($n = 2$)		No ($n = 56$)	Yes ($n = 8$)	
Sex			0.368			0.911
Male	48 (98)	1 (2)		43 (87.8)	6 (12.2)	
Female	14 (93.3)	1 (6.7)		13 (86.7)	2 (13.3)	
Age			0.319			0.533
Platelet			0.819			-0.015
Prothrombin activity			0.348			
Prothrombin < = 63				26 (40.6)	7 (87.5)	0.017
Prothrombin > 63				38 (59.4)	1 (12.5)	0.053*
Etiology of cirrhosis			0.376			0.314
HCV	35(100)	0(0)		32(91.4)	3(8.6)	
HBV	3 (100)	0(0)		3 (100)	0(0)	
B/C	2(100)	0(0)		1(50)	1(50)	
Bilharzial	19(90.5)	2(9.5)		17(81)	4(19)	
Metabolic	3(100)	0(0)		3(100)	0(0)	
Child-Pugh class			0.072			0.173
A	56 (98.2)	1 (1.8)		51 (89.5)	6 (10.5)	
B	6 (85.7)	1 (14.3)		5 (71.4)	2 (28.6)	
Mean tumor size (mm)			0.165			0.414
Number of tumor nodules			0.758			0.657
1	46 (97.9)	1 (2.1)		41 (87.2)	6 (12.8)	
2	12 (92.3)	1 (7.7)		12 (92.3)	1 (7.7)	
3	3 (100)	0(0)		2 (66.7)	1 (33.3)	
4	1 (100)	0(0)		1 (100)	0 (0)	
Type of electrode			0.637			0.408
Monopolar radionics	15 (93.8)	1 (6.3)		16 (100)	0 (0)	
Monopolar cluster	14 (100)	0 (0)		12 (85.7)	2 (14.3)	
Monopolar berchtold	12 (92.3)	1 (7.7)		11 (84.6)	2 (15.4)	
Bipolar berchtold	19 (100)	0 (0)		15 (78.9)	4 (21.1)	
Bipolar celon	2 (100)	0(0)		2 (100)	0 (0)	

Note. Numbers in parentheses are percentages.
* Cox model test for trend of: 1-Prothrombin activity $\leqslant 63$ vs. > 63.

16–18) and 73.1% (95% confidence interval: 13–77), respectively.

4. Discussion

In the present study, the platelet count felt to be safe without the need for support during RFA therapy for HCC was $37 \times 10^3/mm^3$. For a percutaneous liver biopsy the minimum platelet count felt to be safe without the need for support is $60 \times 10^3/mm^3$ (5).

A number of investigators have shown that the degree of bleeding from the liver puncture site bears no correlation to peripheral blood coagulation parameters, and hemorrhage may result from laceration of the liver caused by deep inspiration or patient movement during biopsy, or result from the penetration of distended vein, aberrant arteries or branch of the hepatic artery or portal vein (8).

It should, however, be borne in mind that during a percutaneous RFA of HCC, the liver is not the only structure to be punctured and the skin and subcutaneous tissues (and occasionally other organs) can bleed. Thus, peripheral indices of clotting must still be taken into consideration. During percutaneous liver biopsy, some of the investigators have postulated that this discrepancy in liver bleeding time may be due to the inherent elasticity of the biopsy track collapsing down after the core has been taken, together with the high local concentrations of clotting factors within the hepatic parenchyma (8).

During RFA therapy of HCC, a lower rate of hemorrhage is observed although the needle electrodes of large diameter (17–14 gauge) are used due to, traversing sufficient normal hepatic parenchyma as well as cauterization of the needle tract after ablation. In addition to, the operator's skill in placing the RF needle electrode safely without traversing major vessels and in minimizing the amount of needle repositioning (9). Also, as long as there is difference in efficiency of practice, the operators of RFA should have a lower rate of hemorrhage.

Several large studies suggested that about 90% of the bleeds occurred in patients with an INR < 1.3 and reinforce the fact

that having a normal INR or prothrombin time is no reassurance that the patient will not bleed after the procedure of liver biopsy (8). Our study agreed with these studies and revealed no increased risk of bleeding associated with prothrombin activity up to 42%.

Although worsening of liver function in patients with cirrhosis is less common following RFA for HCC in comparison with surgical resection, the incidence of such adverse effect after RFA has been reported in a range from 0.14% to 0.6% in multicenter studies (10). Eight patients (8/64, 12.5%) of liver decompensation were observed in our study, one patient (1/64, 1.6%) had encephalopathy and seven patients (7/64, 10.9%) suffered from transient ascites. The reported high overall percentage of liver decompensation can be explained firstly because in the literature transient ascites are not always regarded as liver decompensation related to RFA (11), secondly the number of Child-Pugh B patients (10.9%) included in our study was especially high, and thirdly in contrast to previous studies reporting lower incidence of liver decompensation after RFA, all patients in our series had cirrhosis and thrombocytopenia. It is known that patients with cirrhosis and thrombocytopenia related to portal hypertension, have an increasing risk of liver decompensation especially after surgical resection (2). An analysis of 1222 patients, who underwent hepatectomy, demonstrated that thrombocytopenia was a significant risk factor for postoperative morbidity and hospital mortality (12).

Low platelet count is a marker of portal hypertension but is not routinely included in the standard preoperative evaluation of patients with hepatocellular carcinoma (HCC) because it pertains to liver function (Child/model for end-stage liver disease [MELD] score) and tumor burden (Milan criteria). Bennett and Blumgart hypothesized that low platelet count less than $100 \times 10^3/mm^3$, was independently associated with increased major complications, postoperative liver insufficiency, and mortality after resection of HCC, even when accounting for standard criteria, such as Child/MELD score and tumor extent, used to select patients for resection (13).

Our results revealed that the platelet count was not an independent predictive factor for the development of liver decompensation after RFA of HCC, likely because RFA spares much more non tumoral liver than resection. We found also that patients with thrombocytopenia and a prothrombin time $\leqslant 63\%$ had a significant higher risk of occurrence of liver decompensation following RFA therapy of HCC. Prothrombin time is in fact a well known marker of liver function and on this account it is commonly used in the main prognostic scores of chronic liver disease as the Child-Pugh or Model of End-Stage Liver Disease (MELD) scores (14). In a prospective analysis of risk factors of morbidity and mortality following the surgical resection for Hepatocellular carcinoma, Kim and Colleagues reported that an increased prothrombin time was one of the most sensitive indicators of peri-operative mortality independent of the Child-Pugh score and hypothesized that intraoperative transfusion, which is mainly related to intraoperative bleeding, should be reduced if possible to decrease morbidity (15).

Some limitations of this study must be addressed. First, this was a retrospective study of a small sample of subjects. Because thrombocytopenia was considered a relative contraindication for performing RFA in our institution, patients with thrombocytopenia $60 \times 10^3/mm^3$ were not commonly referred to planning sonography of RFA. Second, we could not evaluate objectively the response of patients to medications administered to control thrombocytopenia before RFA. Finally, accurate assessment of the safe account of platelets and the optimal time to perform RFA after thrombocytopenia control should be investigated with further prospective studies.

In summary, for patients with cirrhosis and HCC treated by RFA, mild thrombocytopenia above $37 \times 10^3/mm^3$ platelets per liter is not an independent risk factor of bleeding or liver decompensation. However when thrombocytopenia is associated with a prothrombin time $\leqslant 63$, % the risk of liver decompensation after RFA significantly increases. Therefore in such conditions, caution is required in indication of RFA especially if large volume of tissue ablation is planned and in the perspective of the future improvements of the destructive capacities of radiofrequency devices.

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