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Original Article / Оригинални рад

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Radiofrequency ablation for hepatocellular carcinoma – analysis of the clinical outcome

Радиофреквентна аблација хепатоцелуларног карцинома: Анализа клиничког исхода

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SUMMARY

Introduction/Objective Radiofrequency ablat-ion (RFA) is a minimally invasive treatment modality for primary and metastatic liver tumors. It can be performed percutaneously or as a laparoscopic or open surgical procedure under ultrasound or CT guidance.
The aim of this work was to evaluate the clinical outcome of the initial 16 patients with hepatocellular carcinoma (HCC) managed by percutaneous RFA at a tertiary institution and to assess the efficacy of this procedure in the management of selected patients with HCC.
Method From June 2011 until December 2013, 16 patients with early stage HCC were managed by percutaneous radiofrequency ablation. We analyzed the clinical outcome and the biologic effect of this treatment by comparing the pre and post treatment levels of alpha-fetoprotein (AFP).
Results Post-treatment values of liver transaminase levels returned to the pretreatment values from Day 3. Post-treatment hospital stay was 2 days (2–8). Post-procedural complications included: mild pain in all patients, skin necrosis at the site of the electrode puncture in 5 patients and transient hepatic decompensation in 1 patient. In all patients the AFP level correlated with the findings of liver imaging (US and/or MRI with liver-specific contrast agent) indicating viability of the treated tumor.
Conclusion RFA is a feasible and effective procedure providing favorable clinical outcome in patients with early stage HCC.
Keywords: radiofrequency ablation; hepatocellular carcinoma; biologic effect; percutaneous approach

САЖЕТАК

Увод/Циљ Радиофреквентна аблација (РФА) је минимално инвазиван начин лечења примарних и метастатских тумора јетре. Може се извести перкутано, лапароскопски или отворено хируршки, под контролом ултразвука или КТ.
Циљ овог рада је да прикаже клинички исход лечења првих 16 болесника са хепатоцелуларним карциномом (ХЦК), третираних перкутаном РФА у терцијаној установи и да процени ефикасност ове процедуре у лечењу селектованих болесника са ХЦК.
Метод У периоду од јуна 2011. до децембра 2013. године, 16 болесника са раним ХЦК третирани су перкутаном РФА. Анализирали смо клинички исход и биолошки ефекат лечења поредећи ниво алфа-фетопротеина (АФП) пре и после третмана.
Резултати Ниво трансаминаза након интервенције се је враћао на вредности пре третмана од 3. дана. Останак у болници је био два дана (2–8). Постпроцедуралне компликације су биле: благи бол код свих болесника, некроза коже на месту пункције електродом код пет болесника и пролазна декомпензација јетре код једног. Код свих болесника ниво АФП је корелирао са налазом на јетри (ултразвук и/или МР са специфичним контрастом за јетру), указујући на вијабилност третираног тумора.
Закључак РФА је изводљива и ефикасна процедура која обезбеђује повољан клинички исход код болесника са раним ХЦК.
Кључне речи: радиофреквентна аблација; хепатоцелуларни карцином; биолошки ефекат; перкутани приступ

INTRODUCTION

Radiofrequency ablation (RFA) is a minimally invasive treatment modality for primary and metastatic liver tumors. It can be performed as percutaneous or as laparoscopic or open surgical procedure under ultrasound (US) or computerized tomography (CT) guidance. When performed percutaneously patients can be managed using local analgosedation avoiding general anesthesia. Radiofrequency ablation is an alternative treatment option to hepatic resection for patients with small, primary liver tumors [1–3]. It is a safe procedure achieving survival as long as 10 years in the latest reports [4] and it is considered a curative treatment modality. For selected patients with early-stage hepatocellular carcinoma (HCC) RFA can be used as a first-line treatment option. However, the results of the treatment are dependent on operator experience [5].

The advantages of RF ablation are the following: a) it is an effective treatment for primary and metastatic liver tumors in selected patients who are unsuitable for surgical resection; b) treatment-related serious complications are infrequent and discomfort is minimal; c) the procedure may be used

repeatedly to treat recurrent liver tumors; d) the percutaneous approach is minimally invasive, produces few complications, and may be applies in ambulatory settings; e) it is a relatively quick procedure associated to quick recovery so chemotherapy may be resumed almost immediately if required; f) it is less expensive than other treatment options; g) no surgical incision is needed.

The clinical outcome of patients treated by RFA can be assessed using laboratory analysis and imaging modalities. Several studies confirmed that alpha-fetoprotein (AFP) measurement indicate the necrotic effect of loco-regional thermal ablation [6-8] while other studies confirmed the biologic role of AFP in a neoplastic growth [9]. Alpha-fetoprotein (AFP) is a fetal specific glycoprotein normally produced primarily by the fetal liver. Normally, AFP levels decline rapidly after birth, reaching undetectable levels (< 10 ng/ml) within several months after birth [6-8]. Increased AFP levels indicate the presence of cancer, most commonly liver cancer, ovarian cancer, or germ cell tumor of the testicles. However, not every liver, ovarian, or testicular cancer will produce significant quantities of AFP [8.9].

In the present study we analyzed the clinical outcome of the first 16 patients with early-stage HCC treated by RFA at a tertiary institution and we assessed the efficacy of this procedure using post-procedural imaging and measuring pre and post treatment levels of AFP.

The study objective was to evaluate the clinical outcome of the first 16 patients with an early-stage hepatocellular carcinoma managed by a percutaneous radiofrequency ablation and to assess the efficacy of this procedure using post-procedural imaging and serum levels of AFP.

METHOD

From June 2011 until December 2013, 16 patients with an early stage hepatocellular carcinoma were managed by percutaneous radiofrequency ablation at the Clinic for Digestive Surgery, Clinical center of Serbia, Belgrade. During the same period 5 additional patients were managed by the same procedure for a solitary metastatic tumor in the liver as they were not eligible for open surgery due to their co-morbidities. All patients were managed by the same team composed of an interventional radiologist and a liver surgeon. According to revised version of the Barcelona Clinic Liver Cancer system endorsed by the American and European Association for Study of the Liver, patients diagnosed at early stage are defined as follows [10]: *"very early"* with a single node less than 2 cm in size, in Child-Pugh A class, with no symptoms and no change in performance status; and *"early"* when single node, smaller than 5 cm, or up to 3 nodes <3 cm each, in Child-Pugh A-B class, with no symptoms and no change in performance status.

All patients included in this study met the following criteria: (a) no extrahepatic spread of a disease; (b) liver tumor less then 5cm in diameter; (c) adequate functional liver parenchyma; (d) no obstructive jaundice; and (e) no simultaneous operative procedures on other organs.

The preoperative workup of the patients included: (a) accurate liver imaging utilizing multi-detector CT or MRI; (b) the assessment of hepatic functional reserve; (c) AFP measurement.

In all patients, biochemical liver function tests were monitored before and on the first day after the RFA. Since all patients had liver cirrhosis static biochemical liver function tests were used to assess hepatic functional reserve. Liver abscess, subphrenic abscess, bile leakage, sepsis, chest involvement, and post-procedural bleeding were considered procedure-related complications. Follow-up protocol included laboratory analysis, AFP measurement and US examination 1, 3 and 9 months after the RFA and laboratory analysis, AFP measurement and MRI with a liver-specific contrast agent (Primovist®, Bayer), 6 and 12 months following RFA. After the first year patients were followed on 6 months bases using abdominal MRI and AFP level. The follow-up period for patients included in the study ranged from 24–42 months.

In all patients, RFA was performed using Cool-tip® (Valleylab, Tyco) water-cooled, single, RF tumor ablation electrode, with 30mm non-insulated tip, connected to a 480 kHz 200 watt generator (Valleylab Cool-tip® RF System). RF energy was applied by gradually increasing the output to maximum power achieving thermal ablation of tumor tissue. Under US guidance the electrode was repositioned until the complete tumor ablation was performed.

Table 1. Patient and tumor characteristics.

Variable	RFA, n=16 pts
Sex (M/F)	11/5
Age	60.5 (47–79)
Cirrhosis etiology	
Hepatitis B	5
Hepatitis C	9
Co-infection hepatitis B and C	1
Hepatitis B and ethylic	1
Liver function status	
Child-Pugh A	13
Child-Pugh B	3
Tumor number	
1	15
2	1
Tumor size (mm)	**25.5 (21-40)**
Tumor localization	
Segment II/III	2
Segment IVB	1
Segment V	4
Segment VI	5
Segment VII	3
Segment VIII	2

Four patients were treated under the local analgosedation and twelve patients were treated in general anesthesia. Other patients' data are presented in Table 1.

All patients had liver cirrhosis of viral origin with Child status A or B. Child B patients had either lower albumin level (30–35 g/l)/, moderate ascites responsive to diuretics treatment and/or increased bilirubin level (Child-Pugh B8). However, only Child B patients with sufficient remnant liver volume and compensated liver function were considered for RFA. All patients managed by percutaneous RFA in this study had compensated liver function. All patients included in this study were not candidates for liver resection due to their co-morbidites, liver function or due to tumor localization that would require major liver resection with insufficient liver remnant.

The patients were diagnosed either by liver biopsy (histological confirmation of HCC and cirrhosis during the previous surgery /liver resection/ or by ultrasound guided biopsy performed in another institution) or by typical radiological findings of HCC (arterial enhancement and wash-out on portal phase) on CT or MRI imaging in combination with an increased level of AFP (normal range up to 10 ng/ml).

Inform consent was obtained from all patients before RFA.

All data were prospectively collected and entered into a computerized data base. All data are expressed as median with the range.

RFA procedure

All RFA treatments were performed under a standard protocol using the cool-tip® RF needle with 3 cm exposed tip. In all patients ablation was performed with a curative intent, aiming to achieve a margin of 1 cm. After completing the procedure a safe margin of 1cm was assessed by measuring the ablated zone. In all patients the ablated zone was at least 1cm larger than the size of the tumor. All patients were reviewed by a multidisciplinary team before the approach of RFA was decided (intercostal in 10 and subcostal in 6 patients). The percutaneous ablation was performed by ultrasound guidance under local analgosedation (4 patients) or under the general anesthesia (12 patients). The ablation was performed using the manual mode with continuous monitoring of the impedance, RF current and the temperature (Figure 1–3). The electrode non-insulated tip was continuously perfused with cold saline via internal channels inside the needle throughout the ablation to maintain the tip temperature below 15°C, preventing charring around the electrode tip.

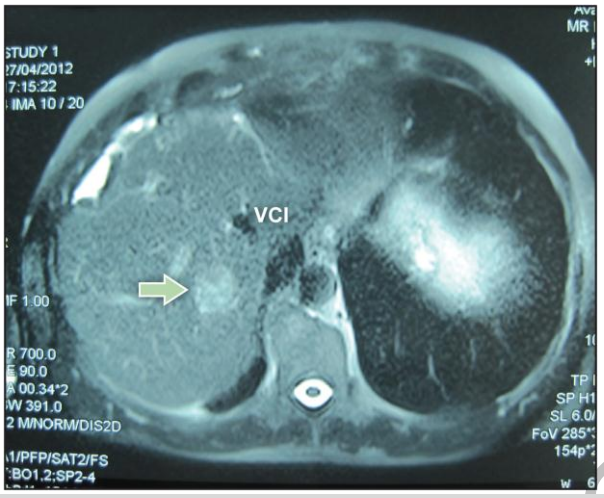

Figure 1. Pretreatment abdominal MRI demonstrating tumor in liver segment VIII.

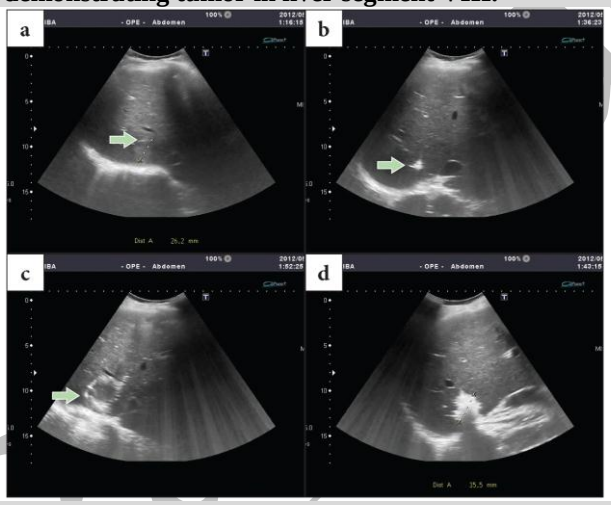

Figure 2. US guided RFA procedure for HCC in liver segment VIII. a) US tumor measurement, localization and positioning of the needle b) Start of ablation c) Progress of ablation d) End of procedure, ablation zone.

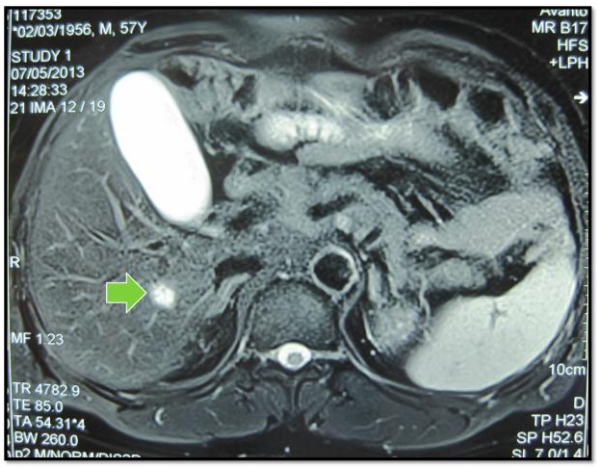

Figure 3. Post-treatment abdominal MRI using a liver-specific contrast agent demonstrating complete tumor ablation.

RESULTS

Sixteen patients with an early-stage HCC in cirrhotic livers underwent curative-intent RFA. Peri-procedural transfusion was not required in any patient.

Table 2. Pre- and post- treatment profile of liver enzymes and hemoglobin/platelets.

Variable	Before RFA	After RFA
Bilirubin (μmol/L)	24.1 (8.6–92.3)	28.1 (18.2–80.4)
AST (U/L)	56.5 (34–227)	226.5 (87-529)
ALT (U/L)	46.5 (22–137)	147.5 (33–411)
Prothrombin time	147.5 (33–411)	14 (11.3–24.3)
Hemoglobin (g/L)	129 (107–158)	116.5 (97–156)
Platelet (10^9/L)	113 (40–178)	89.25 (40–162)

The pretreatment and post-treatment profile of liver enzymes (bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time (PT)) and hemoglobin and platelets is presented in Table 2. The post-treatment values of AST and ALT returned to pretreatment values from Day 3.

Table 3. Post-procedural complications.

Variable	n (%)
Pain (mild)	14 (87)
Nausea	0
Vomiting	0
Fever	0
Skin necrosis	5 (31)
Transit liver decompensation	1 (6)

The post-treatment hospital stay was 2 days (2–8). Post-procedural complications included mild pain in 14 patients, skin necrosis at the site of the needle puncture in 5 patients and transit hepatic decompensation in 1 patient (Table 3).

During the follow-up period, two patients were managed by transarterial chemoembolization (using a mixture of lipiodol/cisplatin) as the tumor size exceeded 3cm (42mm) or due to tumor recurrence. Mortality was not recorded during the follow-up period.

In one patient one month following RFA alpha-fetoprotein level had increased from pretreatment levels of 145.1ng/ml to 366.6ng/ml. An abdominal US examination confirmed incomplete tumor ablation and the patient was re-treated using the same procedure. At 6-month follow-up AFP measured 11.8ng/ml. This result correlated with the finding of complete ablation verified by the abdominal MRI using liver specific contrast agent.

In one patient at 6-month follow up AFP level significantly increased to more than 20,000 ng/ml. This result correlated with the finding of recurrent tumor adjacent to the ablation zone verified on abdominal MRI using a liver specific contrast agent. The tumor recurrence was managed by liver resection and intraoperative exploration has demonstrated new incapsulated tumor adjacent to the ablation zone. At the time of surgery the patient liver function has improved to Child A status.

Table 4. Pre- and post-procedural measurement of AFP. Correlation with liver imaging.

Patient	Pre-AFP	AFP 1M	AFP 6M	MR/Primovist
1	21.9	6.5	5.9	Complete ablation
2	26	10.6	7.7	Complete ablation
3	1,703	24.1	11.1	Complete ablation
4	147.2	5.7	7.2	Complete ablation
5	145.1	366.6	11.8	Complete ablation
6	4,848.8	22.9	14.3	Complete ablation
7	1,216.7	55.1	11.4	Complete ablation
8	13.4	8.7	8.8	Complete ablation
9	1,746	33.1	21,748	Incomplete/Recurrence
10	30.1	4.7	5.2	Complete ablation
11	12.5	5.5	4.9	Complete ablation
12	14,964	8,232	-	-
13	13.2	15.6	9.9	Complete ablation
14	40.5	12.8	10.1	Complete ablation
15	13.8	10.6	11.2	Complete ablation
16	409.4	55.1	14.8	Complete ablation

AFP – alfa-fetoprotein; 1M – one month after the treatment;
6M – six months after the treatment.

In the two presented patients with recurrent tumor the AFP level correlated with the findings of liver imaging (abdominal US and/or MRI with liver-specific contrast agent) indicating viability of the treated tumor (Table 4).

DISCUSSION

Radiofrequency ablation for small HCC demonstrated a survival benefit comparing to percutaneous ethanol injection as indicated by randomized controlled trials [11] and meta analysis and systemic reviews [12]. For many years, these results established RFA as a standardized local thermal ablation technique for treating small liver tumors.

Novel ablation thermal and non-thermal techniques, including microwave ablation and irreversible electroporation, have some potential to overcome the limitations of RFA but further clinical investigations are required [13].

The complete ablation rate of RFA for liver tumors was found to vary from 50% to 95% in different reports [14]. In the present study a complete ablation was achieved in 14 out of 16 patients (87%) after the initial RFA and in 94% of patients after the repeated procedure in one patient having a recurrent tumor. Only one patient required surgical treatment due to recurrent tumor adjacent to the ablation zone.

Significantly different results of RFA are usually attributed to the differences in the electrode design, generators and application techniques. The importance of operator experience was reported by Poon RT et al [5]. In Poon and co-workers report in the first 50 patients managed by RFA, complete ablation was achieved in 84% of patients while in the following 50 patients 100% ablation rate has been achieved. In the present study the success rate for initial 16 patients with small HCC managed by RFA was 87%.

In the same study Poon at al. suggested close collaboration between the surgeons and radiologists in order to shorten the learning curve and plan the best strategy for ablation. In the present study pretreatment analysis, deciding on the RFA approach, RFA procedure and post-treatment follow up were performed in a multidisciplinary team approach by an interventional radiologist and a liver surgeon.

Complication rates following RFA of liver tumors range from 0–27% [15,16]. Reported RFA treatment-related complications include pneumothorax; symptomatic pleural effusion; bleeding from the needle track or into the treated tumor; biliary fistula; biliary stricture; biloma; abscess in the treated tumor; skin burn; cholecystitis; thermal injury to adjacent structures including the diaphragm, stomach, duodendum, and transverse colon; liver failure; segmental hepatic infarction; paralysis of the hemidiaphragm; arterial-portal venous fistula; systemic hemolysis; tumor lysis syndrome; myoglobinemia or myoglobinuria; transient acute renal failure; and prolonged post treatment pain for lesions near the hepatic capsule [15]. According to Livraghi et al and Mulier et al the complication rates are higher after open or laparoscopic RFA compared to the percutaneous approach [17,18]. A

possible explanation is that more difficult cases are treated by open or laparoscopic approach and due to surgery-related complications.

In the present study during the follow up period early and late post procedure complications did not occur. This is mainly due to proper patient selection and due to collaboration between an interventional radiologist and liver surgeon which is rarely reported in the literature [5].

In the present study 2 out of the first 16 patients had HCC in seg. VIII (and one more patient with metastatic liver tumor not included in this series) not eligible for open surgery. In the reviewed literature this tumor localization is considered difficult for percutaneous approach or associated with serious complications [19,20]. The two patients had uneventful post-procedural course and demonstrated no complications in the follow up period.

The most common complication in the present study was skin burns at the site of the electrode puncture detected in the first 5 patients treated by RFA. In the reviewed literature the majority of reported skin burns after percutaneous radiofrequency ablation occur along the edge of the grounding pads [14] or during the tract ablation phase [21,22]. In the present study skin burns resulted from an excessive tract ablation to prevent tract seeding, however in the following 11 patients this complication did not occur.

The most important result of the study is related to the comparison of alpha-fetoprotein measurement and liver imaging indicating the biologic effect of the applied treatment.

There is a consensus in the literature that AFP regulates neoplastic growth through the presence of an alpha-fetoprotein cell surface receptor that undergoes internalization to the cell interior growth [9].

In hepatocellular carcinoma there is a strong correlation between AFP values, tumor dimensions and microvascular invasion, as predictors of HCC recurrence [23]. According to reports from the literature AFP is a surrogate of tumoral activity and vascular invasiveness. AFP-mRNA concentration is used as a marker of HCC cell dissemination into the circulation, what is an additional proof of this correlation [24,25].

In the present study the AFP level increased from pretreatment level of 145.1ng/ml to 366.6ng/ml one month after the RFA in 1 out of 16 patients. Abdominal US examination confirmed incomplete tumor ablation and the patient was re-treated using the same procedure. At 6-month follow-up AFP measured 11.8 ng/ml correlating with the finding of complete ablation on abdominal MRI using liver specific contrast agent.

In another patient at 6-months follow up, the AFP level significantly increased to more than 20.000ng/ml correlating with the finding of recurrent tumor adjacent to the ablation zone on abdominal MRI using liver specific contrast agent. The tumor recurrence was managed by liver resection. The pathology finding has demonstrated a new incapsulated tumor adjacent to the ablation site.

In other patients normal AFP values correlated with complete tumor ablation verified by liver imaging techniques. Therefore, in all patients the AFP level correlated with the findings of liver imaging (abdominal US and/or MRI using liver-specific contrast agent) indicating viability of the treated tumor.

New tumor markers are continuously discovered and investigated, but they are still far from the routine clinical practice.

The present study confirmed the need for development of a new predictive model combining radiological and biological features based on biological markers as already indicated by Giovanni B et al [26].

CONCLUSION

In conclusion, percutaneous RFA is a first-line treatment option for carefully selected patients with small-sized/early-stage HCC in a cirrhotic liver when performed at a tertiary institution by a multidisciplinary team. The procedure is associated with a minimal morbidity offering curative treatment for this difficult category of patients.

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