RESEARCH ARTICLE

Transarterial Chemoembolization Combined with Either Radiofrequency or Microwave Ablation in Management of Hepatocellular Carcinoma

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Abstract

Introduction: Local ablative therapy and trans arterial chemoembolization (TACE) are applied to ablate non resectable hepatocellular carcinoma (HCC). Combination of both techniques has proven to be more effective. We aimed to study combined ablation techniques and assess survival benefit comparing TACE with radiofrequency (RFA) versus TACE with microwave (MWA) techniques. **Methods:** We retrospectively studied 22 patients who were ablated using TACE-RFA and 45 with TACE-MWA. All were classified as Child A-B and lesions did not exceed 5 cm in diameter. TACE was followed within two weeks by either RFA or MWA. We recorded total and partial ablation rates and complication rates. Survival analysis was then performed. **Results:** TACE-MWA showed a higher tendency to provide complete response rates than TACE-RFA (P 0.06). This was particularly evident with lesions sized 3-5 cm (P 0.01). Rates of complications showed no significant difference between the groups. Overall median survival was 27 months. The overall actuarial probability of survival was 80.1% at 1 year, 55% at 2 years, and 36.3% at 3 years. The recurrence free survival at 1 year, 2years and 3 years for the TACE-RFA group was 70%, 42% and 14% respectively and for TACE-MWA group 81.2%, 65.1% and 65.1% without any significant difference (P 0.1). In relation to the size of focal lesions, no statistically significant difference in the survival rates was detected between the groups. **Conclusion:** TACE-MWA led to better response rates than TACE-RFA with tumors 3-5 cm, with no difference in survival rates.

Keywords: Hepatocellular carcinoma- microwave ablation- radiofrequency ablation

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Introduction

Hepatocellular carcinoma (HCC) is a challenging tumor that usually develops on top of chronic liver disease and liver cirrhosis (Elbaz et al., 2013). Liver cirrhosis has been reported in many studies as the most predominant pathological lesion behind the development and progression of HCC. Generally, HCC has a bad prognosis so that its incidence is nearly equivalent to its mortality rate (Abdelaziz et al., 2014).It is the third common cause of deaths related to cancer all over the world. Due to the hyper vascularity of HCC, it can show rapid progression, direct invasion of the surrounding tissues and vessels or spontaneous rupture (Zhang et al., 2015). Curative therapy is considered lonely in restricted number of cases with early HCC lesions and who can succeed to perform surgical resection or liver transplantation. Of course, both lines of management are clearly not simple procedures and can`t be offered to all such patients, certainly in countries with restricted financial supports. Otherwise, large lesions are considered for palliation. For patients with acceptable performance status and good liver reserve, it is truly hard to accept the aim of tumor palliation and true enthusiasms are to achieve curative end points whenever possible (Abdelaziz et al., 2015).

Many studies proved that local ablative therapies are a good solution for non-surgical patients and early lesions (Lin et al., 2003). Thermal ablative techniques are generally safe and should be as effective as surgical resection (Kuang et al., 2011). These techniques include radiofrequency ablation (RFA) and microwave ablation (MWA). Although patients who are managed their lesions by MWA showed a lower incidence of local recurrence than lesions managed by RFA, this was not really translated in terms of survival benefit (Abdelaziz et al., 2014). As compared to trans-arterial chemoembolization (TACE), MWA better ablated HCC lesions in a lesser number of needed sessions that aimed to achieve complete ablation, lower incidence of tumor recurrence and better survival benefit (Abdelaziz et al., 2015). Trans-catheter

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intra-arterial therapies allow for selective delivery of the chemotherapeutic agent to hepatic tumors and protects against ischemic necrosis of the rest of the liver. Recent data revealed that highly selective approach may be safe in patients with portal vein thrombosis. There after, many studies reported another clear benefit to combine TACE with one of both thermal ablative techniques. This combined ablation proved to offer better ablation rates than using lone TACE or local ablation; both in small and large lesions (Seki et al., 2000, Tanaka et al., 2014).

However, very scarce studies looked for a comparison between both local thermal techniques when combined to TACE (Ginsburg et al., 2015). So, we aimed to perform this retrospective study to search for any survival advantage and higher curative ablation rates that can be provided to HCC patients through either using TACE-RFA or TACE- MWA techniques.

Materials and Methods

Patients

This study was performed in a multidisciplinary HCC clinic located in Kasr Al-Aini Hospital, Cairo University, Egypt. It is a retrospective study that included 67 patients who suffered from hepatocellular carcinoma on top of liver cirrhosis and who presented to the clinic since March 2012. As microwave ablative technique was a relatively newer technique that was introduced to the clinic after long experience with radiofrequency ablation, we previously assessed a comparative study between both of them and we aimed at the current study to look if it matters to choose a certain local ablative technique when combined with trans-arterial chemoembolization (TACE). All patients were diagnosed and managed according to international guidelines for HCC (Bruix et al., 2001, Bruix et al., 2011) and in compliance with ethics principles of the declaration of Helsinki for GCP guidelines. All patients signed an informed consent that was ethically approved by our local ethical committee.

All studied patients were Child Pugh class A or B with focal lesions that are three or less in number and the largest lesion not exceeding 5 cm in diameter. We excluded patients with worse Child Pugh score (Child class C). Also, we excluded patients with advanced stages (larger lesions, more numerous lesions and those with portal vein thrombosis, metastases or considerable lymphadenopathy). If patients had technical difficulties such as inappropriate coagulation profile or if they did previous ablative procedures to their lesions, they were similarly excluded.

Methodology

Timing of the procedures and the follow up: In all studied patients, we started ablation using TACE that was followed within two weeks by radiofrequency or microwave ablation. We assessed the ablative procedures for any complications either that occurred early post-ablation or later. Any evidence of hepatic decompensation is reported. Then, Triphasic CT imaging is performed 4 weeks later (post ablation) and every 3 months during the first year then bi-annually if proved well ablated. Follow up was done for 3 years.

Response to treatment: It is considered "complete" if CT scans showed no evidence of intra-lesional contrast enhancement in the arterial phase, and "Partial" if CT scans provided areas of enhancement within the boundaries of the lesions in the arterial phase. Any evidence of tumor progression or development of de novo lesions is reported. Also, we assessed the overall survival and the recurrence free survival in relation to lines of management.

Trans-arterial chemoembolization (TACE): The procedure approaches the common femoral artery by catheterization that is followed by super-selective catheterization of the tumoral-feeding artery (arteries). Then, injection of intra-arterial doxorubicin (50 mg) that is mixed with lipiodol (5–10 ml) is performed. Injection of embolic materials (such as gelfoam or PVA particles) is performed to completely occlude tumor shunting if needed. Lipiodol allows the injected drug to concentrate in the tumor to be retained for weeks. Immediately after ending the TACE procedure, a non-contrast CT scan is done to affirm the intra-lesional presence of the chemotherapy/lipiodol.

Local ablation techniques (RFA and MWA): Both local ablative procedures are ultrasonography guided using 3.5–5 MHz probe connected to Hitashi EUB-5500 machine. In radiofrequency ablative technique, we used 18 gauge (200 mm) internally Cool tip electrodes (Radionics®) that are connected to a 500-KHz radiofrequency generator (Series CC-1; Radionics®). In microwave ablation, it was performed using an HSAMICA® microwave machine (HS Hospital service S.P.A. Roma, Italy) called AMICA GEM machine. This machine operates at frequency of 2.450 MHz. Fourteen gauge (150 and 200 mm) cooled shift electrodes (AMICA probes) are used to deliver the microwave energy into the liver tissue.

Statistical analysis

In our study, we represented the numerical data as mean ± standard deviation (SD) while the categorical data are reported as counts and percentages. Student t test and Chi square test are used when needed. Statistically significant difference is considered if probability of occurrence by chance is 5 % or less ($p<0.05$). Survival analysis is calculated using Kaplan–Meier method from the date of primary diagnosis till the date of last follow up or death of the patient.

Results

In the current study, 67 patients were divided into 2 groups: TACE-RFA (n=22) and TACE-MWA (n=45). Looking for any statistical difference that can bias the comparison between both groups, we found no statistical difference either in their demographic characteristics (age, gender, Child Pugh score, performance status and serum AFP) or ultrasonography features of managed tumors (number, site and size of tumors) (Table 1). All our patients had HCC on top of chronic HCV infection.

Then, we studied the success rates of both lines of management. TACE-MWA line of treatment showed a higher tendency to provide complete response rates than

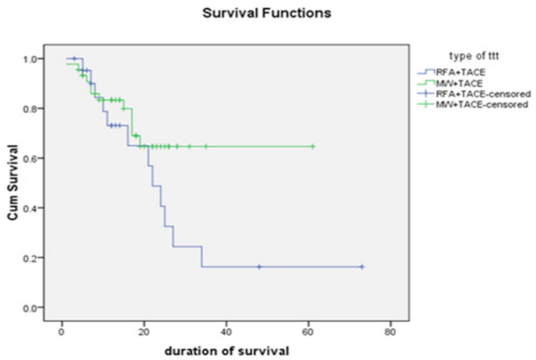

Figure 1. Kaplan-Meier Survival Analysis: Overall Survival of the Studied Groups.

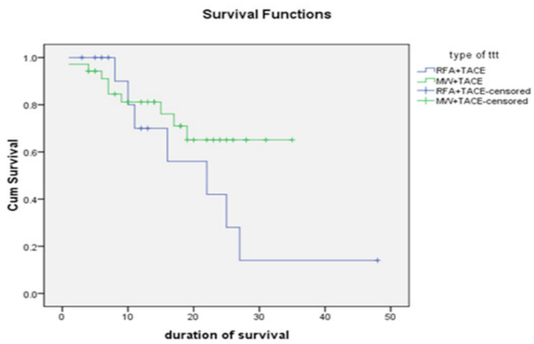

Figure 2. Kaplan-Meier Survival Analysis: Recurrence Free Survival of the Studied Groups.

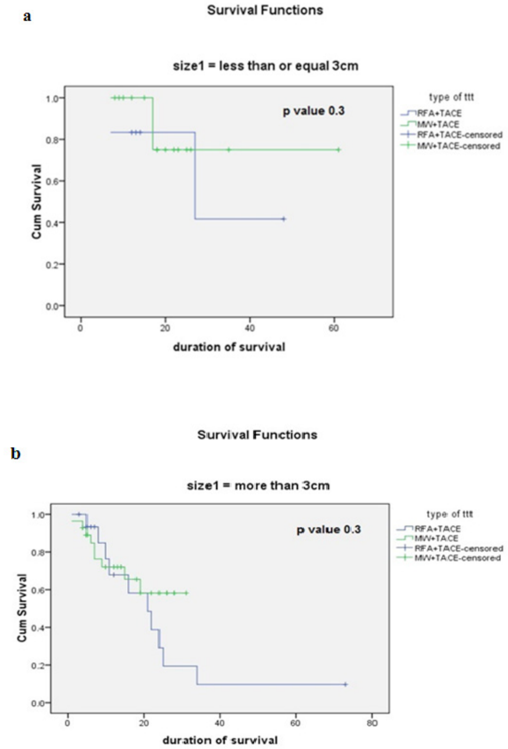

Figure 3. (a) Kaplan-Meier Survival Analysis: Survival of the Patients with Focal Lesion Equal or Less than 3cm, (b) Kaplan-Meier Survival Analysis: Survival of the Patients with Focal Lesion More than 3cm.

Table 1. General Characteristics and Ultrasonographic Features of the Studied Groups

	TACE+RFA (n. 22)	TACE+Microwave (n. 45)	P value
Age (years)	58.9+ 6.4	58.3+ 7.8	0.7
Gender			
Male	18 (81.8%)	38 (84.4%)	0.7
Female	4 (18.2%)	7 (15.6%)	
Child-Pugh class			
Class A	13(59.1%)	25 (55.6%)	0.7
Class B	9 (40.9%)	20 (44.6%)	
Performance status			
0	8 (36.4%)	19 (42.2%)	0.7
1	12 (54.5%)	20 (44.4)	
2	1 (4.5%)	5 (11.1%)	
3	1(4.5%)	1 (2.2%)	
Serum AFP† U/ml	49(3.7-5,470)	35.1 (1-2,823)	0.5
Number of tumors			
Single	9 (40.9%)	26 (57.8%)	0.2
Two	6 (27.3%)	5 (11.1%)	
Three	7 (31.8%)	14 (31.1%)	
Site of tumors			
Left lobe	3 (13.3%)	5 (11.1%)	0.9
Right lobe	15 (82.2%)	32 (71.1%)	
Both lobes	4 (4.4%)	8 (17.8%)	
Size of tumors (cm)	4.6+1.9	4.2+1.9	0.4
Size of tumors			
≤ 3cm	6 (28.6%)	17 (37.8%)	0.4
3-5cm	15 (71.4%)	28 (62.2%)	

†median and range

Table 2. Success Rate and Outcome of Both Procedures

	TACE+RFA	TACE+Microwave	P value
Complete response	18/22 (81.8%)	43/45 (95.6%)	0.06
Partial response	4/22 (18.2%)	2/45 (4.4%)	
Tumors ≤ 3cm			
Complete response	5/6 (83.3%)	15/17 (88.2%)	0.7
Partial response	1/6 (16.7%)	2/17 (11.8%)	
Tumors 3-5cm			
Complete response	13/16 (81.2%)	28/28 (100%)	0.01*
Partial response	3/16 (18.8%)	0(0%)	

*p value ≤ 0.05 is significant

Table 3. Procedure Related Complications and Follow up Data of the Studied Groups

	TACE+RFA (n.22)	TACE+Microwave (n.45)	P value
Recurrence	4 (18.2%)	8 (17.8%)	0.9
PV thrombosis	0 (0.0%)	1 (2.2%)	0.5
Abdominal LNs	0 (0.0%)	0 (0.0%)	-
Bone metastases	1 (4.5%)	0 (1.5%)	0.7
Ascites	3 (13.6%)	6 (13.3)	0.9
Variceal bleeding	5 (22.7%)	4 (8.9%)	0.2

TACE-RFA treatment (P 0.06). So, we discriminated between tumors that measured less than or equal to 3 cm and those tumors that are 3-5 cm in diameter. No difference existed between both lines while managing small tumors while a clear and statistically significant difference was well appreciated for the favor of TACE-MWA while ablating tumors measuring 3-5 cm (P 0.01) (Table 2). Otherwise, follow up of all patients didn`t show significant difference in rates of complications between both groups. This included recurrence, portal vein thrombosis, bone metastases, development of ascites and occurrence of variceal bleeding (Table 3).

At the end of the follow up period, 24 patients (35.8%) died; equally divided between both groups. Recorded causes of death were hepatic failure (n=7), gastrointestinal hemorrhage (n=4), spontaneous bacterial peritonitis (n=2) while the cause of death was unknown for the rest of died patients.

Since the date of diagnosis, the overall median survival was 27 months. The overall actuarial probability of survival was 80.1% at 1 year, 55% at 2 years, and 36.3% at 3 years. For patients managed with combined TACE and microwave, the actuarial probability of survival at 1, 2 and 3 years was 83.3%, 64.7%, 64.7% respectively. For patients treated with combined TACE and RFA, they were 73.1%, 40.6% and 16.2% respectively with no statistically significant difference (P 0.08). Figure 1(Table 4).

The recurrence free survival at 1year, 2years and 3 years for patients treated with combined TACE-RFA was 70%, 42% and 14% respectively and for patients treated with combined TACE-MWA was 81.2%, 65.1% and 65.1% respectively with no statistically significant difference (P 0.1). Figure 2 (Table 4).

There was no statistically significant difference in the survival rates between both groups in relation to the size focal lesions. The median survival of patients with focal lesion ≤3cm treated with TACE-MWA or TACE-RFA was 50 months vs. 27 months respectively. For focal lesions

Table 4. Overall Survival (OS) and Recurrence Free Survival (RFS) of Studied Patients

	Total patients	TACE+RFA	TACE+Microwave	P value
Overall survival				0.08
(27 months)				
1 year	80.10%	73.10%	83.30%	
2 years	55%	40.60%	64.70%	
3 years	36.30%	16.20%	64.70%	
Overall survival in relation to tumor size				0.3
focal lesion ≤ 3cm		27 months	50 months	
focal lesion > 3cm		21 months	22 months	
Recurrence Free Survival				0.1
1 year		70%	81.20%	
2 years		42%	65.10%	
3 years		14%	65.10%	

3-5 cm, recorded median survival was 22 months and 21 months respectively (P 0.3). Figure 3a,3b (Table 4).

Discussion

We retrospectively studied our patients to compare between RFA and MWA when combined with TACE ablation to manage tumors that are up to 5 cm. Different studies proved that local thermal ablations provided better survival rates than TACE (Liu et al., 2014) and that the co-management of lesions using both TACE and local ablation is better than using TACE alone (Liu et al., 2014, Bharadwaz et al., 2015, Xu et al., 2015) or local ablation alone (Liu et al., 2014, Chen et al., 2015). Even more, a recent meta-analysis found that TACE combined to whatever procedure (percutaneous ethanol injection, radiotherapy, 3D-CRT or HIFU) is better than TACE alone (Liao et al., 2013). Noticeably, we found large differences between studies in terms of their inclusion criteria and space timing between procedures. Studied tumors were small lesions (Seki et al., 2000,Yang et al., 2009), up to 5 cm [8,22] and even more exceeding 7 cm (Fan et al., 2011,Yi et al., 2014). Studies timed MWA after TACE by 1-2 days (Seki et al., 2000, Ginsburg et al., 2015) while other studies performed MWA 1-3 weeks post TACE (Yang et al., 2009) To avoid distraction by multiple confounding factors, we focused our search on lesions up to 5 cm in Child Pugh A-B cirrhotic patients and we performed local ablation following TACE by a maximum of 2 weeks.

In our study, we found comparable complete ablation rates between both lines for tumors less than 3 cm while larger lesions up to 5 cm better responded to TACE-MWA. As mentioned in previous studies, MWA carries the ability to perform larger and faster ablation that can exceed the limitations of RFA due to the guarded and preserved consistent high intratumoral temperatures and the avoidance of the heat sink effect observed with RFA (Poggi et al., 2013). Literally, it was mentioned that adding TACE to local ablation can abolish such differences between RFA and MWA. TACE can block the arterial blood flow to the tumor leading to attenuation of the cooling effect of the tumoral vessels. In addition, iodized oil and gelatin sponge particles that are used in TACE procedures can help in achieving higher coagulation necrosis by going through multiple arterio-portal micrometastases and reduce risk of tumor recurrence (Yi et al., 2014). In our study, we didn`t notice this effect of TACE in larger lesions 3-5 cm.

Regarding our survival rates and recurrence free survival, we found a beneficial survival gain (overall survival and recurrence free survival) for combined TACE and MWA but hopelessly this notice didn`t achieve statistical significance. Even after discriminating lesions according to their size, still no difference was noticed. In a different study, they had striking high success rates of ablation (100%) and complete ablation rates (94%) while much higher local and distal recurrence rates (66.7% and 71.7% respectively) than our study. Also, their 1 year survival was 80% that dropped hardly to 6.7% for the 3 year survival rate. It is clearly evident that the tumor size is a major player in such situations and tumor sizes exceeding 7 cm still leads to high recurrence rates and lower survival even with good apparent original ablation (Fan et al., 2011). Other different prognostic factors include portal vein thrombosis and advanced BCLC stages (Fan et al., 2011, Ni et al., 2014).

In another retrospective study comparing TACE-MWA and TACE-RFA, they had complete response rates 80% and 76.6% for TACE-RFA and TACE-MWA respectively. No significant difference in survival or complication rates was detected. BCLC and Child score significantly differed between both groups and were mentioned as limitations to the study although these confounding factors were corrected by multivariate analysis. Although their maximum median size was 2.9-3.1 cm, their size of tumors ranged 1.6 – 12 cm.

Finally, we conclude that TACE-MWA led to better response rates than TACE-RFA with tumors 3-5 cm. No difference between both lines of treatment for small tumors (less than 3 cm). Better response rates did not efficiently correlated with better survival rates.

Conflict of interest

All included authors declare absence of any financial or personal relationships with other people or organizations that could inappropriately influence and bias the work.

Submission declaration

This work has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

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