COMBINATION THERAPY OF TRANSARTERIAL CHEMOEMBOLIZATION COMBINED WITH RFA VS TRANSARTERIAL CHEMOEMBOLIATION ALONE AMONG PATIENTS WITH INTERMEDIATE HEPATOCELLULAR CARCINOMA.

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Abstract

Introduction: Hepatocellular carcinoma is the sixth most common cancer worldwide and the third most common cause of death from cancer. (1) Hepatectomy is considered as the first line treatment for intermediate or large sized HCC. However, due to poor hepatic reserve in chronic liver disease, only 5% to 40% of patients with HCC's become candidates for hepatectomy. Combination therapy of TACE and RFA has been tried to counterbalance their limitations and enhance efficacy. ([2]) TACE prior to RFA can lead to tumor revascularization which can lead to all the heat generated to be confined to the tumor area. Thus, the devascularization and thermal ablation can synergistically lead to increased tumor necrosis. The aim of this study is to compare the survival among HCC patients treated with a combination of TACE+RFA against those treated with TACE alone.

Method:

Patients who were diagnosed with intermediate sized HCC at Cardinal Santos Medical Center were included. HCC was diagnosed on the basis of positive results in serum AFP level (AFP >20ng/ml) along with positive imaging findings that indicated HCC in high risk patients. Demographics, tumor and tumor related factors were assessed in both groups. The primary endpoint of the study was 1 year survival and the secondary outcome is tumor response.

Results: A total of 22 patients met the inclusion criteria and were included in the study. 9 (40.9%) patients received TACE + RFA and 13 (59.09%) received TACE alone. There were no significant differences in the baseline characteristics and tumor and non tumor variables considered. Mean age for TACE+RFA group is 64.33 and for TACE alone is 62.76. Majority were male in both groups. Eighty eight percent (8/9) of patients in the combination group and fourty six percent (6/13) in the TACE group were HBsag positive. Mean tumor size for TACE+RFA group was 7.244 (cm) and for TACE alone is 9.8 (cm). Majority of the patient in both groups were CPC B. AFP levels in combination group were majority <200ng/ml (7/9) while 7/13 in TACE group alone had AFP >400ng/ml. Mean survival in combined TACE with RFA group is 19.83 (months) and in TACE alone is 9.8 (months)

Conclusion: Combination treatment with TACE+RFA had a longer mean survival rate compared to TACE group alone. The longer mean survival rate in TACE +RFA group may be attributed to lower AFP level and smaller tumor size compared to TACE group alone.

Introduction:

Hepatocellular carcinoma is the sixth most common cancer worldwide and the third most common cause of death from cancer. (1) Hepatectomy is considered as the first line treatment for intermediate or large sized HCC. However, due to poor hepatic reserve in chronic liver disease, only 5% to 40% of patients with HCC's become candidates for hepatectomy. Liver transplantation provides the best curative treatment of solitary HCC 5 or less cm or 3 or less tumor nodules, each 3 or less cm associated with CPC class C cirrhosis. Bridge treatments including resection, percutaneous ablation and TACE are commonly adopted while patients are on a waiting list to prevent tumor progression. Local ablation is an acceptable alternative to resection for small HCC (<3cm in C-P class A cirrhosis, and is a first line treatment of unresectable, small HCC with three or fewer nodules in C-P class A or B cirrhosis. TACE is recommended for patients with unresectable, large/multifocal HCC who do not have vascular invasion or extrahepatic spread. ([1]) Combination therapy of TACE and RFA has been tried to counterbalance their limitations and enhance efficacy. ([2]) TACE prior to RFA can lead to tumor revascularization which can lead to all the heat generated to be confined to the tumor area. Thus, the devascularization and thermal ablation can synergistically lead to increased tumor necrosis.

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Target Population.

Patients who were diagnosed with intermediate sized HCCs at Cardinal Santos Medical Center.

Inclusion criteria.

HCC was diagnosed on the basis of positive results in serum alpha-fetoprotein determination (serum alpha-fetoprotein level >20 ug/L) along with positive imaging findings that indicated HCC in high-risk patients. (1) Child-Pugh liver function class A or B; (2) presence of solitary lesion; (3) maximum tumor diameter of 3.1 to 5.0 cm; (4) the lesion could be detected by ultrasonography; (5) the divergence of the hepatic artery was suitable for TACE; (6) no evidence of portal and/or venous thrombosis, extrahepatic metastasis, or uncontrollable ascites; (7) adequate hematologic function (platelet count >50 x 10^9 cells/L, hemoglobin >8.0 g/dL and prothrombin time <80%); (8) adequate hepatic function (albumin >2.5 g/L, total bilirubin <3 mg/dL, and alanine aminotransferase and aspartate levels <5x the upper limit of the normal range); (9) adequate renal function (serum Creatinine concentration <1.5x the upper limit of the normal range.

Exclusion criteria.

Patients were excluded if they met the criteria for surgical resection.

Definition of procedure.

TACE was performed according to the following protocol: A selective 5-F catheter was introduced, and visceral angiography was carried out to assess the arterial blood supply to the liver and to confirm patency of the portal vein. All patients underwent a distal super-selective catheterization of the hepatic arteries using a coaxial technique and micro catheters (2.9 F; Terumo Corporation,

Tokyo, Japan). Then, the same three chemotherapeutic agents at the same dosages were used throughout the study, regardless of tumor number and size. Hepatic artery infusion chemotherapy was performed using carboplatin 300mg (Bristol-Myers Squibb, New York, NY). Next, chemolipiodolization was performed using epirubicin 50 mg (Pharmorubicin; Pfizer, Wuxi, China), and mitomycin 8mg (Zhejiang Hisun Pharmaceutical, Taizhou, China) mixed with 5mL of lipiodol (Lipiodol Ultra-Fluide; André Guerbet Laboratories, Aulnay-Sous-Bois, France). If the territory of the chemolipiodolized artery did not shown stagnant flow, pure lipiodol was then injected. For all cases, embolization was finally performed with absorbable gelatine sponge particles (Glefoam; Hanzou Alc, Hangzhou, China; 1 to 2 mm in diameter) or polyvinyl alcohol particles (Alicon Pharm SCT&TEC, Hangzhou, China; 350 to 560 μmin diameter) through the microcatheter to achieve stasis in the tumor-feeding artery. After embolization, angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. Patients were observed carefully, and analgesia (morphine or meperidine) was administered if necessary.

RFA was performed according to the following protocol: All patients included in the study were started on intravenous branched-chain amino acids (BCAA) and prophylactic antibiotics (2^{nd} or 3^{rd} generation cephalosporin) the night prior to procedure. During the procedure patient was placed under general anesthesia and the skin of the upper abdomen cleaned with several applications of 70% alcohol and Providone iodine. All patients were treated with the same type of RFA instruments; RADIONICS Cool Tip RF System (RF generator), Radionics™ Cool Tip, single electrode, 3cm x 20cm (electrode needle) and 2 sets of Covidien ground pads (dispersive electrode). Insertion of the Cool Tip needle into the hepatic tumor was done under ultrasound guidance. Each tumor was ablated for a total of 12 minutes for 3 cycles or until 3 breaks have been achieved regardless of the 12-minute set time. All ablations were done in impedance mode and started at a power (RF) of 80W which is increased by 10W every minute until a maximum of 160W or when 3 breaks have been achieved.

Results

I. Baseline characteristics

Characteristic	TACE+RFA	TACE
Age		
Mean	64.33	62.76
SD	6.305	12.3
Gender		
Male	8	11
Female	1	2
Duration of Hepatocellular Carcinoma		
Mean	19.83	9.8
SD	21.563	2.9
Main Tumor Size		
Mean	7.244	9.8
SD	1.8935	6.01
Number of Tumors		
1	7	6
>1	2	7
HBsAg		

Positive	8	6
Negative	1	7
HCV-Ab		
Positive	0	0
Negative	9	13
NASH		
No	9	8
Yes	0	5
ALD		
No	8	11
Yes	1	2
Child-Pugh Score		
A	2	1
B	6	4
C	1	0
AFP (ng/mL)		
<200	7	5
200-400		1
>400	2	7
Platelet		
Mean	204.33	208.166
SD	81.354	93.766
Hemoglobin		
Mean	12.22	12.4
SD	3.456	2.96
Prothrombin Activity (%)		
Mean	6.73844	80.3
SD	18.1369	24.25
INR		
Mean	1.1044	1.196
SD	0.1108	0.186
Albumin		
Mean	27.333	29.725
SD	8.8792	6.42
Total Bilirubin (umol/L)		
Mean	62.6866	26.86
SD	58.1914	14.31
ALT (u/L)		
Mean	52.4389	53.8
SD	25.7249	17.17

AST (u/L)		
Mean	112	119.4
SD	76.857	88.4
Creatinine		
Mean	132.4766	70.56
SD	125.9912	19.93

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Discussion:

A retrospective study was conducted to evaluate the advantages of combining TACE with RFA for treating intermediate sized hepatocellular carcinoma. We identified 22 patients between the years 2009 to 2015 in which 9 belonged to the TACE + RFA group while 13 were from the TACE alone group. Results have shown that the mean survival time in the combination group was longer compared to TACE alone group. Tumor progression in the combination group was significantly lower.

TACE in combination with RFA was postulated to be beneficial than TACE group alone because it is believed that performing chemoembolization occludes the hepatic arterial blood flow thereby reducing the cooling effect of hepatic blood flow on thermal coagulation and thus enhancing the efficacy of RFA-induced ablation. Morimoto et al ([13]) reported that TACE before RFA expanded the short axis of the ablated area resulting to a more spherical ablated area. They postulated that a spherical ablated area was more effective than a nonspeherical ablated area in ensuring local tumor control because a spherical ablated area was more likely to completely cover the target tumor including micrometastasis and reduce the chance of recurrence. The effect of chemotherapeutic agents used in TACE on cancer cells as well as the disruption of the intratumoral septa, which usually result from TACE, also enhances the effects of hyperthermia. Facilitating heat distribution within the tumor, and intratumoral septa fibrosis are considered to hamper heat diffusion within the tumor.

Analysis of the tumoral and non tumoral characteristics of HCC may have contributed to our results. Noteworthy is the low AFP levels in the TACE+RFA compared to the TACE alone group. Alpha feto protein (AFP) is a widely tested biomarker in hepatocellular carcinoma (HCC). However, several aspects linked to level fluctuations made its performance suboptimal in diagnosing HCC. New biomarkers have then been introduced in HCC diagnosis (DCP and AFP-L3). Recently, AFP was proposed as a predictor of patient survival and tumor recurrence after surgery, locoregional therapies and systemic chemotherapies. In our study, AFP may be a tool in recognizing subset of patients that may benefit from combination treatment. However, a larger sample size is needed.

Conclusion:

Combination treatment with TACE+RFA had a longer mean survival rate compared to TACE group alone. The longer mean survival rate in TACE +RFA group may be attributed to lower AFP level and smaller tumor size compared to TACE group alone. This study presents some limitations, however. First, the number of patients in this study is relatively small. Second, this is a single-center experience and the results may not be generalizable to patients with HCCs in other countries.

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