TREATMENT OUTCOMES OF UNRESECTABLE HEPATOCELLULAR CARCINOMA BY TRANSARTERIAL CHEMOEMBOLISATION COMBINED WITH RADIOFREQUENCY ABLATION

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ABSTRACT

Background: *Hepatocellular carcinoma (HCC) is one of the most common cancer and ranks third in terms of cancer related deaths. The majority of patients are not eligible for curative treatment because of local or distal progression of tumor. RFA treatment following TACE has some advantages over TACE alone. The purpose of this study was to evaluate the effectiveness and survival benefits of the TACE+RFA approach to the management of unresectable HCCs in Hue Central Hospital, Vietnam.*

Methods: *A prospective, cohort study on 60 patients, diagnosed with unresectable HCCs and treated with TACE combined with RFA at Hue Central Hospital from 1/2016 – 1/2019. All clinical and paraclinical data and adverse effects of each treatment, tumor response rate assessed by m-RECIST criteria, survival rate and other adverse events from the first treatment were documented.*

Results: *There were no major complications after combined therapy except for two cases (1.4%) of liver failure treated successfully with conservative therapy. Tumor control rate (CR+PR) at three months after the last treatment was 81.6%. All patients were followed-up closely after treatment and additional treatments were decided based on imaging and laboratory results. The mean follow-up time was 19.3 (4 – 30) months. The 1-year and 2-year survival rates were 71.7% and 58.3%, respectively.*

Conclusion: *Combination therapy with TACE and RFA is an effective, safe and feasible option for patients with unresectable HCCs.*

Key words: *Hepatocellular carcinoma (HCC), transarterial chemoembolisation (TACE), radiofrequency ablation (RFA)*

I. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancer and ranks third in terms of cancer related deaths. Vietnam is among the countries with highest incidence of HCC, which can be partly explained by the high prevalence of HBV and HCV infections [2]. Liver resection and transplantation remain the mainstays of curative treatment for HCC. However, the majority of patients are not eligible for curative treatment because of local or distal progression of tumor. Among non-surgical therapies, the most commonly used therapies are Trans Arterial Chemo Embolization (TACE) and Radio Frequency Ablation (RFA).

TACE slows tumor progression and improves survival by combining the effect of targeted chemotherapy with that of ischemic necrosis induced by arterial embolization. However, it is difficult to achieve complete necrosis of liver tumor with TACE alone. RFA is considered the initial curative treatment of choice because of its favorable results in patients with small unresectable HCCs. The five-

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year overall survival and recurrence-free survival were reported about 60% and 20% in patients who received RFA as first-line therapy for HCC [9].

Theoretically, TACE combined with RFA provides additional advantages. TACE reduces vascular supply and also tumor burden in immediate and large HCCs, making ablation by RFA more effective and complete. TACE combined with RFA has been reported to be effective for local control of medium-sized HCC tumors (3-5 cm) [9]. The purpose of this study was to evaluate the effectiveness and survival benefits of the TACE+RFA approach to the management of unresectable HCCs in Hue Central Hospital, Vietnam.

II. SUBJECTS AND METHODS

2.1. Subjects: 60 patients, diagnosed with unresectable HCCs and treated with TACE combined with RFA at Hue Central Hospital from 1/2016 – 1/2019.

• ***Inclusion criteria***

- Unresectable HCCs diagnosed by imaging or pathological examination

- The Child-Pugh grade of liver function was A or B

- The ECOG PS score of 0-2

- Treatment by both TACE and RFA

• ***Exclusion criteria***

- Invasion of main trunks of portal veins or hepatic veins

- Extrahepatic metastases or invasion of adjacent organs

- Unsuitable for interventional treatments due to other serious diseases (coagulation disorder, prothrombin activity < 40%, platelet count < 30 x 10^9/L, severe cardiovascular diseases)

- Denial of treatments

2.2. Study design: a prospective, cohort study.

2.3. Sampling method: consecutive sampling method.

2.4. Study protocol

- Patients diagnosed with HCC were discussed among experienced hepatobiliary surgeons. Decision for treatment choice was made following current updated guidelines (either RFA or TACE).

- After each treatment, patients will be followed after one month. Reevaluation with CTscan and laboratory tests were done routinely. If viable tumor was detected, additional TACE or RFA was indicated depending on the size, location and current patient's condition.

- Tumor response was assessed using CT scan one month after treatment according to the modified response evaluation criteria in solid tumor (m-RECIST) developed by the American Association for the Study of Liver Diseases (AASLD): Complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD).

- All clinical and paraclinical data and adverse effects of each treatment were documented.

- Survival time and other events from the first treatment were documented until the end of the study.

2.5. Statistical analysis

Data analysis was performed with SPSS 22.0 software. A P value < 0.05 (two-tailed) was considered statistically significant.

III. RESULTS

3.1. General characteristics of patients

Table 3.1. General characteristics of patients

Variables	Values
Gender (Male/Female)	56/4
Age	61.2 ± 10.4
Hepatitis B	41 (68.3%)
Hepatitis C	4 (6.7%)
Hepatitis B + C	2 (3.3%)
Child-Pugh grade	
A	57 (95.0%)
B	3 (5.0%)
Serum AST (IU/L)	43.17 ± 12.21
Serum ALT (IU/L)	39.04 ± 11.92
AFP (ng/ml)	
≥ 20	56 (93.3)
<20	4 (6.7%)
Mean number of tumor	1.6 (1- 4)
Tumor position	
Right lobe	53 (88.3%)
Left lobe	2 (3.3%)
Both lobes	5 (8.3%)
Mean maximal tumor diameter (cm)	6.04 ± 0.77 (5.3 – 6.9)

The majority of patients were male, more than 60 years old, having history of hepatitis B. Most patients had liver functions classified as Child A. Liver enzymes were only slightly elevated in most patients. Most tumors were located in the right lobe and were large in size with the mean maximal tumor diameter of 6.04 cm.

3.2. Tumor response after treatment

Table 3.2. Tumor response after treatment

Variables	Values
Mean number of TACE	1.4 (1-3)
Mean number of RFA	2.3 (1-5)
Tumor response 3 months after the last treatment	
Complete response (CR)	39 (65.0%)
Partial response (PR)	10 (16.7%)
Stable disease (SD)	2 (3.3%)
Progressive disease (PD)	9 (15%)

Both TACE and RFA were mini-invasive procedures and could be repeated if necessary if clinical and imaging characteristics justified. Tumor control rates (CR+PR) at three months after the last treatment was 81.6%.

3.3. Adverse effects of treatment

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Adverse effects	TACE	RFA
Right subcostal pain	26 (30.9%)	46 (76.7%)
Fever	65 (77.4%)	13 (9.4%)
Fatigue	11(13.1%)	2 (1.4%)
Nausea, vomiting	7 (8.3%)	2 (1.4%)
Liver failure	2 (2.4%)	0 (0%)
Pleural effusion	6 (7.1%)	8 (5.8%)
Bile duct injury	0 (0%)	0 (0%)
Hemorrhage	0 (0%)	2 (1.4%)
Death	0 (0%)	0 (0%)
Total number of interventions	**84**	**138**

No major complications were recorded following TACE and RFA procedures. Post-embolization and post-ablation syndromes happened with varying extent and severity. Of which, fever was more common in TACE group while right subcostal pain was more frequent in RFA group. Liver failure only happened after two (1.4%) cases of TACE in child B patients which completely responded to conservative management. There were no documented deaths.

3.4. Overall survival

Table 3.4. Overall survival following TACE + RFA

Overall survival rates	Values
1- year	71.7%
2 - year	58.3%
Mean follow-up time (months)	19.3 (4 – 30)

All patients were followed-up closely after treatment and additional treatments were decided based on imaging and laboratory results. The mean follow-up time was 19.3 months. Reasons for death in followed-up patients were advanced cancer, liver failure, gastrointestinal hemorrhage, and tumor rupture.

IV. DISCUSSION

Treatment of unresectable HCCs is multidisplicinary and requires discussion between experienced surgeons, radiologists, interventional radiologists and oncologists. Main treatments include transarterial and local ablation therapies. The long-term outcome for patients with unresectable HCC treated with TACE is unsatisfactory due to the inability to achieve complete tumor necrosis. RFA effectiveness, on the other hand, is limited by the maximal size of ablation zone, heat sink effects and potential complications caused by difficult localization of tumor.

The general characteristics of our study samples were similar to that of previous study in Vietnam with high prevalence of HBV, HCV infections, male predominance and big tumor sizes. The rates of HBV infection in the study of Tran Van Huy was 85% [1], and in the study of Nguyen Tien Thinh et al was 78.6%. HCV infection was also less common than HBV infection in our study [3].

Tumor size was also of great consideration for indication of HCC therapy. In a study of Zhang et al (2014), tumor size > 5cm was one of the prognostic factor related to incomplete tumor response [10]. It is difficult to completely destroy tumors larger than 5 cm by RFA despite multiple overlapping

ablations. However, first-line TACE treatment might reduce the volume of viable tumor thus making complete ablation of the lesions possible. Buscarini et al. treated 14 HCC patients with median tumor diameter of 5.2 cm with TACE followed by RFA and suggested the possibility of treating large HCC with this approach [5]. Lencioni et al. similarly reported a successful outcome (82%) among patients with HCC (lesion size ranging between 3.8 and 8.5 cm) who were treated with TACE prior to RFA [6]. Our post-treatment CR rate of 65.0% and partial response rate of 16.7% in the present study indicate an encouraging benefit for patients with unresectable HCCs.

The rates of post-embolisation and post ablation syndromes were similar to other studies with most the frequent symptoms being fever, pain and nausea and vomiting. The study of Tran Xuan Truong reported a prevalence of post-embolisation syndrome of 45-68% [4]. Similar results were seen in the study of Nguyen Tien Thinh on 121 patients treated with RFA combined with TACE: right subcostal pain (67%), fever>38 degreee (8%), vomiting (3%), dyspnea (1%) [3]. We found that TACE-RFA combined therapy had a low rate of major complications. No permanent adverse sequelae or treatment-related deaths were observed. Thus, combination therapy of TACE followed by RFA appears to be relatively safe.

Our survival rates at 1 year and 2 year were also promising. Vogl suggested that repeated TACE might reduce the size of the treated lesions and helps improve the results of combined therapy compared to TACE or RFA alone [7]. In this study, the 1-, 2-, and 3-year survival rates were 89%, 61%, and 43%, respectively. These rates are consistent with those of other studies. Veltri reported 1- and 2-year survival rates of 89.7% and 67.1% for TACE-RFA combined therapy for unresectable non-early HCC (size 30–80 mm, mean 48.9 mm) [8].

RFA treatment following TACE has some advantages over TACE alone. Embolization during the TACE procedure can block arterial flow, which may reduce heat-sink effects during RFA thus increasing the volume of the zone of ablation and reducing the chance of tumor recurrence. TACE can also control or eliminate micro-metastasis, which cannot always be detected by ultrasonography, CT, or MRI. Thus, the addition of TACE may decrease the chance of micro-metastasis after RFA treatment in HCC patients with unresectable tumors beyond the Milan criteria.

Considering the timing of RFA and TACE, the interval between different sequences of TACE and RFA was normally one month. This is similar to most studies with the timing of RFA being two weeks to one month after TACE. Other authors also tried to do TACE with RFA simultaneously with very good results. Tai-Yang-Zuo conducted a study on 66 patients treated with simultaneous TACE and CT-guided RFA reported the tumor control rates (complete remission + partial remission) were 100.0% (66/66), 92.4% (61/66), 87.9% (58/66), and 70.1% (39/55) at 1, 3, 6, and 12 months after TACE + RFA, respectively. The 1, 3, and 5year survival rates were 93.2% (55/59), 42.5% (17/40), and 27.2% (9/33), respectively [11].

V. CONCLUSION

Combination therapy with TACE and RFA is an effective, safe and feasible option for patients with unresectable HCCs.

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